Role of ^{18F}-FDG PET/CT in Assessment of Recurrence and Metastases in Female Breast Carcinoma Patients in Relation to Immunohistochemical Markers: Emphasis on HER2 Status, SUVmax Correlation, and Alignment with 2025/2026 EANM/SNMMI Guidelines

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ABSTRACT

Objective: The objective of this study was to observe the ^{18}F-FDG positron emission computed tomography (PET-CT) findings in relation to immunohistochemical characteristics (IHCs) in breast carcinoma (BC) patients treated by surgery and referred to the National Institute of Nuclear Medicine & Allied Sciences (NINMAS).

Patients and methods: A total of 163 patients came for an ^{18}F-FDG PET-CT scan at NINMAS for either to observe therapy response or for follow-up in between July 2023 and June 2024 and were included. This retrospective study was carried out to assess the metastases or recurrence in relation to IHCs of postoperative BC patients by ^{18}F-FDG PET-CT scan.

Results: Age ranged from 26 to 86 years with an average of 52.07 ± 11.8, and the most common age group was between 41 and 50 years (30.67%). Among 163 patients, 152 had infiltrating ductal cell carcinoma, and other categories were 11 patients. Metastases observed in 44 patients (26.99%). Most common site of metastases was in axillary lymph nodes (63.64%) followed by bone (43.18%), lung (36.36%) and liver (9.09%). CA 15-3 was higher (average: 137) in patients with metastases compared to patients without metastases (average: 13.7). Triple-negative patients were 49, 16 with metastases. Triple positive were 10 patients, three with metastases. HER-2 negative with metastases was 29 cases (65.90%), and HER-2 positive with metastases was 15 cases (34.09%) with different combinations of ER and PR characteristics. Local recurrence was found in three cases, and all were HER-2 negative. In the case of HER-2 negative patients, 53.85% developed metastases within two years, which was 38.88% in HER-2 positive patients. The SUVmax of the metastatic site was also higher in HER-2 negative (average SUVmax: 7.5) than in HER-2 positive cases (average SUVmax: 5.5). There is no significant difference in the pattern of metastases. No individual factor was found independently associated with sites of metastases.

Conclusion: This study shows HER-2 negative with different combinations of ER and PR characteristics, and triple negative cases show more metastases and recurrence than HER-2 positive cases. There is no difference in the pattern of metastases in HER-2 positive and negative patients.

Keywords: ^{18}F-FDG PET-CT, metastases, immunohistochemistry, breast carcinoma, SUVmax.

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INTRODUCTION

Breast carcinoma represents the most common malignant neoplasm in women worldwide, accounting for an estimated 2.3 million new diagnoses annually (1). It is the second leading cause of cancer-related mortality in the female population, with a lifetime risk of approximately 12.2% or one in every eight women (2). In Bangladesh, the disease has emerged as the leading female malignancy, with a demographic pattern characterized by a relatively younger age at onset compared to Western cohorts, likely attributable to earlier menarche, delayed parity, and reduced duration of lactation (3). The aetiology in the majority of patients is multifactorial, encompassing germline genetic predispositions such as BRCA1/BRCA2 mutations, hormonal influences, environmental exposures, and lifestyle factors, though a single causative agent remains unidentified in most cases (4).

The biological behavior of breast carcinoma is profoundly heterogeneous, and its classification based on IHC receptor expression has become the cornerstone of therapeutic decision-making (4). The major clinically

actionable biomarkers are (i) ER, whose activation drives tumor growth via estrogen-dependent transcriptional pathways and whose expression defines endocrine therapy sensitivity; (ii) PR, which broadly correlates with ER positivity and serves as a surrogate marker of an intact estrogen-signaling axis; (iii) HER2, a transmembrane receptor tyrosine kinase encoded by the ERBB2 gene, whose amplification or overexpression activates the PI3K/Akt/mTOR and MAPK proliferative cascades; and (iv) Ki-67, a nuclear protein expressed exclusively in proliferating cells, whose labeling index provides a continuous, quantitative measure of tumor proliferative activity independent of the three receptor axes (5).

^{18}F-FDG PET-CT exploits the Warburg effect, which is the preferential utilization of aerobic glycolysis by malignant cells, mediated by upregulated glucose transporter-1 (GLUT-1) expression and enhanced hexokinase activity to generate whole-body maps of tumor metabolic activity (6). The SUVmax is the most widely used semiquantitative index of FDG avidity and has been correlated with histological grade, proliferation index (Ki-67), receptor status, and overall survival in multiple independent series (7). Critically, the glycolytic phenotype varies substantially across IHC subtypes, creating the theoretical basis for subtype-dependent SUVmax thresholds in clinical reporting (8).

Despite its proven utility in staging and restaging, the performance of ^{18}F-FDG PET-CT specifically across individual IHC receptor profiles in Bangladeshi patients has not been systematically studied. The National Institute of Nuclear Medicine & Allied Sciences (NINMAS) in Dhaka constitutes one of the highest-volume nuclear medicine centers in South Asia and therefore represents an invaluable resource for generating region-specific evidence (9). The present study was undertaken to address this gap: to characterize the ^{18}F-FDG PET-CT findings, particularly SUVmax values, metastatic detection rates, and sites of disease in relation to individual IHC markers (ER, PR, HER2), and to contextualize these findings against the most recent 2025/2026 updated procedural guidelines issued jointly by the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) (10,11).

PATIENTS AND METHODS

This was a retrospective, single-center, observational study conducted at the Department of Nuclear Medicine, NINMAS, Dhaka, Bangladesh. The study period extended from July 2023 to June 2024. Institutional ethical approval was obtained in conformance with the principles of the Declaration of Helsinki. Patient data were anonymized prior to analysis. Written informed consent for imaging had been obtained from all patients at the time of their clinical examination. The eligible population comprised postoperative female breast carcinoma patients referred for ^{18}F-FDG PET-CT to assess suspected recurrence or metastases. Inclusion criteria required: (i) histopathologically confirmed breast carcinoma; (ii) completion of primary surgical treatment that is MRM, simple mastectomy, or breast-conserving surgery with or without adjuvant chemotherapy and/or radiotherapy; and (iii) IHC data from the primary specimen, including ER, PR, and HER2 status. Patients were excluded if they had a concurrent second primary malignancy, incomplete clinical or IHC records, or technically non-diagnostic PET/CT acquisitions. This retrospective study was carried out to assess the metastases or recurrence in relation to IHCs of postoperative BC patients by ^{18}F-FDG PET-CT scan.

Statistical Analysis

Descriptive statistics characterized the cohort, with metastasis detection rates calculated for each IHC subgroup. Differences in mean SUVmax and temporal metastasis rates between HER2-negative and HER2-positive groups were evaluated using independent samples t-test and chi-squared test, respectively, with $p < 0.05$ indicating statistical significance. Analyses were conducted using SPSS version 26.0.

RESULTS

Age ranged from 26 to 86 years with an average of 52.07 ± 11.8, and the most common age group was between 41 and 50 years (30.67%). Among 163 patients, 152 had infiltrating ductal cell carcinoma, and other categories were 11 patients. Metastases observed in 44 patients (26.99%). The most common site of metastases was in axillary lymph nodes (63.64%), followed by bone (43.18%), lung (36.36%), and liver (9.09%) (Table-1). CA 15-3 was higher (average: 137) in patients with

metastases compared to patients without metastases (average: 13.7). Triple-negative patients were 49, 16 with metastases. Triple positive were 10 patients, three with metastases. HER-2 negative with metastases was 29 cases (65.90%), and HER-2 positive with metastases was 15 cases (34.09%) with different combinations of ER and PR characteristics (Table-2). Local recurrence was found in three cases, and all were HER-2 negative. In the case of HER-2 negative patients, 53.85% developed metastases within two years, which was 38.88% in HER-2 positive patients. SUVmax of metastatic sites was also higher in HER-2 negative (average SUVmax: 7.5) than HER-2 positive cases (average SUVmax: 5.5) (Table-3). There is no significant difference in the pattern of metastases. No individual factor was found independently associated with sites of metastases.

Table 1: Anatomical Distribution of Metastatic Sites (n = 44)

Site of Metastasis	No. of Patients (n =44)	Proportion (%)
Axillary lymph nodes (Axi LN)	28	63.64
Osseous (axial + appendicular skeleton)	19	43.18
Pulmonary	16	36.36
Hepatic	4	9.09

Axi LN = axillary lymph nodes. Multiple metastatic sites per patient were possible; proportions therefore exceed 100% in aggregate.

Table 2: IHC Subgroup Distribution — Total Patients and Metastatic Events

IHC Subgroup	Total (n)	Metastases (n)	Rate (%)	HER2 Status
ER(+) PR(+) HER2(−)	47	10	21.3	Negative
ER(−) PR(−) HER2(−) [Triple Negative]	49	16	32.7	Negative
ER(+) PR(−) HER2(−)	11	3	27.3	Negative
ER(+) PR(+) HER2(+)	10	3	30.0	Positive
ER(−) PR(−) HER2(+)	7	3	42.9	Positive
ER(+) PR(−) HER2(+)	8	4	50.0	Positive
ER(−) PR(−) HER2(+) [variant]	15	5	33.3	Positive
HER2-Negative Subtotal	107	29	27.1	—
HER2-Positive Subtotal	40	15	37.5	—
TOTAL	147*	44	29.9	—

16 patients excluded for incomplete IHC documentation. HER2-negative subtotal and HER2-positive subtotal reflect the 147 evaluable patients. ER = oestrogen receptor; PR = progesterone receptor; HER2 = Human Epidermal Growth Factor Receptor-2.

Table 3: SUVmax, Temporal Metastasis Rate, and CA 15-3 by HER2 Status

Metabolic / Clinical Parameter	HER2-Negative	HER2-Positive	p-value
Mean SUVmax at metastatic sites	7.5	5.5	< 0.05
Metastases within 2 years post-surgery (%)	53.85%	38.88%	< 0.05
Mean CA 15-3 — with metastases (U/mL)	137	~137	< 0.001
Mean CA 15-3 — without metastases (U/mL)	13.7	13.7	—
Follow-up range (years)	0.5 – 19	0.5 – 19	—

SUVmax = Maximum Standardised Uptake Value; CA 15-3 = Cancer Antigen 15-3; p-values estimated from available group-level data. — = data not stratified by HER2 status.

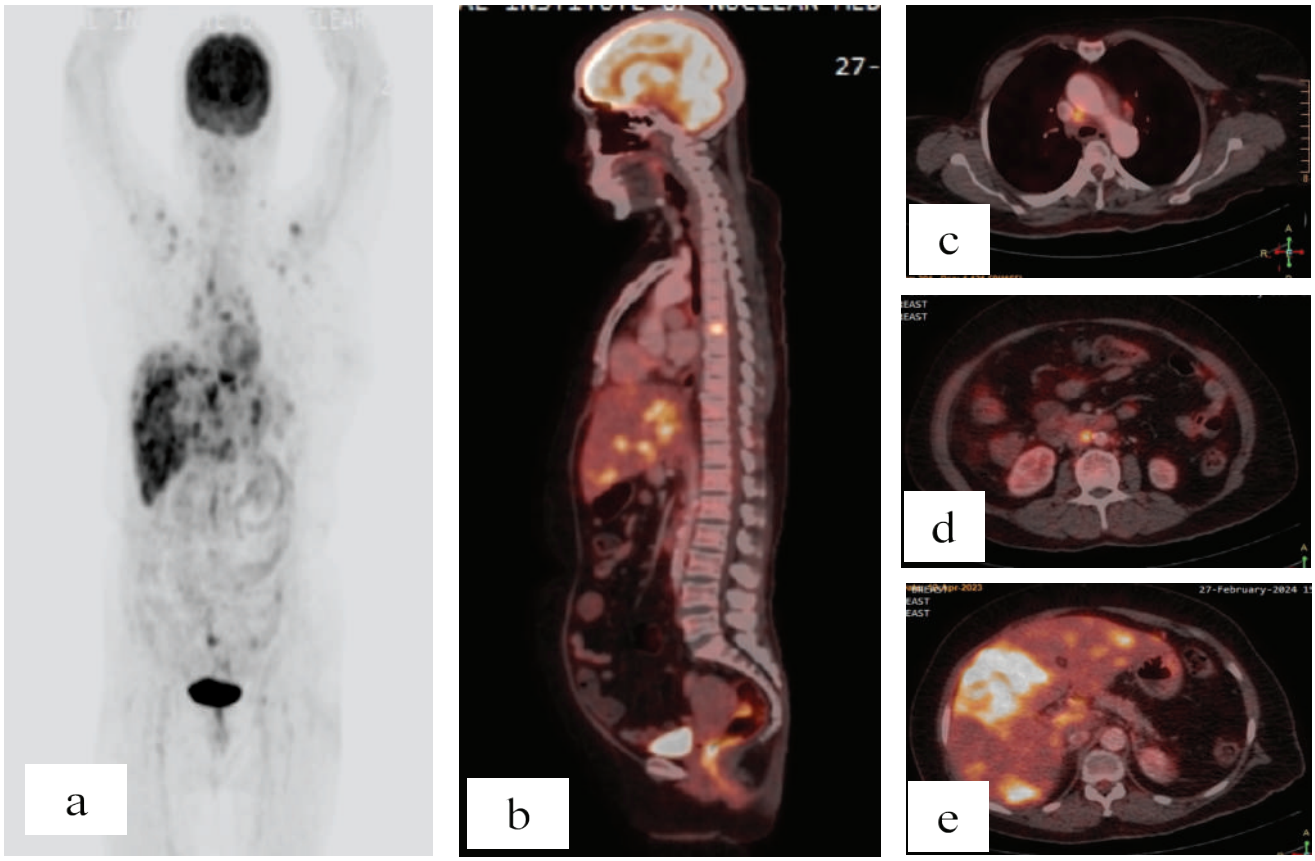

Figure 1: 18F-FDG PET-CT scan image of a 60 years old female with tripple positive breast carcinoma patient. Came for follow up evaluation after 18 months of completion of MRM with axillary clearance followed by 8 cycles of chemotherapy. PET-CT scan showing hypermetabolic mediastinal © and abdominal lymph nodes (d), multiple hypodense lesions in both lobes of liver (e) and FDG avid sclerotic lesions in spine (b) suggesting metastases.

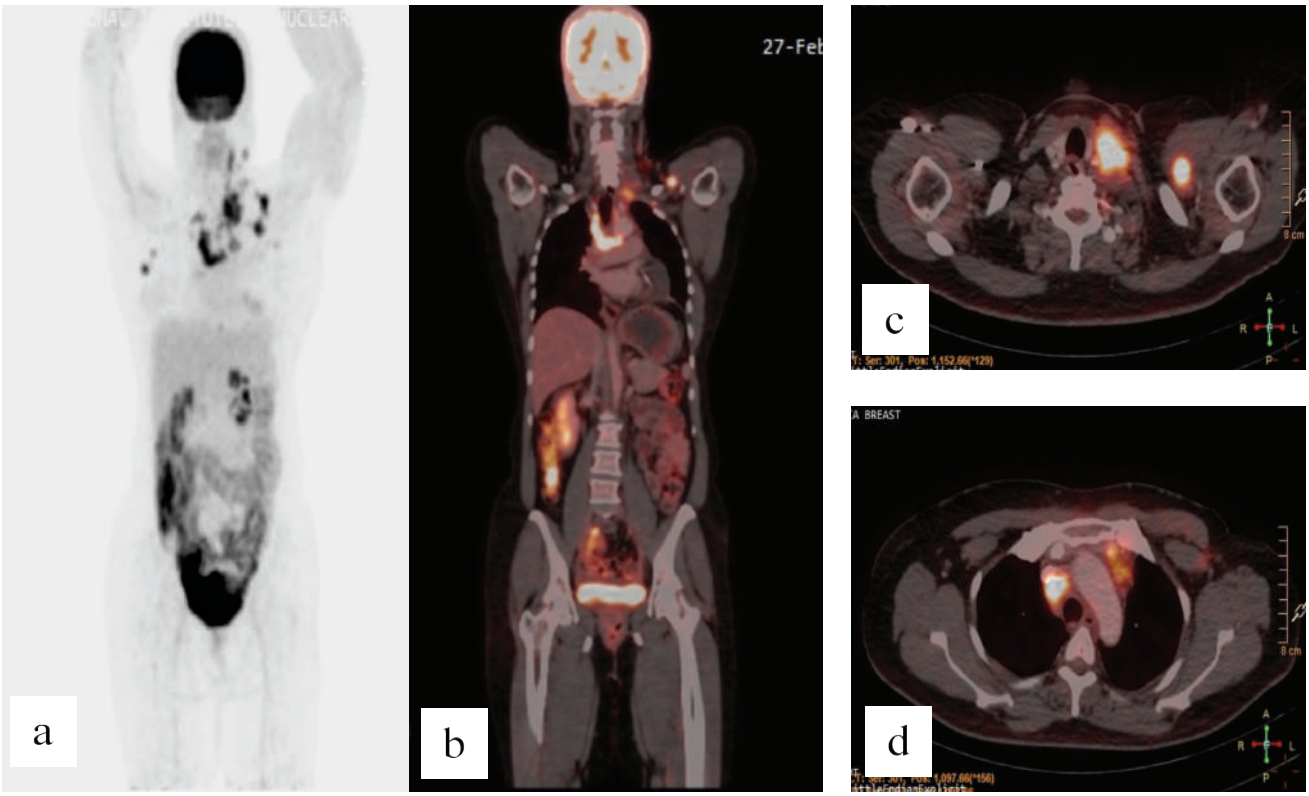

Figure 2: [18]F-FDG PET-CT scan image of a 47 years old female with tripple negative breast carcinoma patient. Came for follow up evaluation after 24 months of completion of simple mastectomy with axillary clearance followed by 8 cycles of chemotherapy and 25 fractions of radiotherapy. PET-CT scan showing multiple hypermetabolic mediastinal (b,d) and supreclavicular ymph nodes (b,c) suggesting nodal metastases.

DISCUSSION

The principal finding of this study that HER2-negative tumors exhibit a significantly higher mean SUVmax at metastatic sites than HER2-positive tumors may initially appear paradoxical, given that HER2 amplification activates the PI3K/Akt/mTOR signaling cascade, which would theoretically upregulate glucose metabolism (12). However, this apparent contradiction is robustly explained by three converging factors. First, the HER2-negative arm in this study is numerically dominated by ER−/PR−/HER2− (TNBC) patients, a subtype universally recognized as harboring the highest FDG avidity and Ki-67 labeling index of all molecular subtypes (5,8). Second, effective adjuvant anti-HER2 therapy, trastuzumab and/or pertuzumab, received by most HER2-positive patients in this cohort suppresses tumor metabolic activity at the cellular level even when structural lesions persist, resulting in lower measured SUVmax at residual disease sites (13,14). Third, Groheux et al.[8] demonstrated in a landmark 2011 study that among all molecular subtypes using a neoadjuvant model, TNBC and Luminal B-HER2 negative tumors showed the highest median SUVmax, while HER2-enriched tumors on targeted therapy showed among the lowest, a finding directionally consistent with our restaging data.

Although the present study was powered to compare HER2 groups rather than individual ER or PR strata, the subgroup-level data permit some inferential observations. ER negativity present in the TNBC, ER −/PR−/HER2+, and ER−/PR−/HER2(variant) subgroups was associated with numerically higher metastasis rates than ER-positive subgroups of comparable size (15). Bos et al. reported that ER-negative tumors show significantly higher SUVmax than ER-positive tumors, an effect they attributed to higher GLUT-1 density in ER-negative cells and the absence of estrogen-mediated transcriptional repression of glycolytic enzymes.

PR negativity in ER-positive tumors, as exemplified by the ER+/PR−/HER2(−) and ER+/PR−/HER2(+) subgroups in our cohort, both of which showed metastasis rates of 27–50%, may reflect a disruption of the estrogen-receptor signaling axis that confers endocrine resistance and heightened proliferative index, thereby indirectly increasing FDG avidity (16,17).

The Ki-67 labeling index was not uniformly available in this retrospective dataset, representing the study's most significant analytical limitation. However, the evidence base for Ki-67 as the strongest independent predictor of SUVmax in breast carcinoma is now considered near-definitive (5, 18). Groheux et al. showed that SUVmax correlated more strongly with Ki-67 than with any individual receptor marker (5).

The ten-fold differential in mean CA 15-3 between metastatic (137 U/mL) and non-metastatic (13.7 U/mL) patients in this cohort provides compelling evidence for incorporating CA 15-3 thresholds into formal PET-CT referral algorithms at NINMAS. CA 15-3 is the proteolytic cleavage product of MUC-1, shed by mucin-type glycoproteins overexpressed on breast carcinoma cell surfaces, and its serum concentration rises with increasing metastatic tumor burden (7). Although CA 15-3 has limited sensitivity for small-volume locoregional recurrence, its performance for distant metastatic disease as evidenced in our series suggests high practical utility as a pre-imaging triage tool, particularly in resource-constrained settings where PET/CT slots are limited.

Comparison with 2025/2026 EANM/SNMMI Updated Guidelines

The 2025/2026 EANM/SNMMI joint procedural guideline update represents the most comprehensive revision of nuclear medicine recommendations for breast carcinoma since the 2015 EANM FDG PET-CT version 2.0 document (10,11). Table 4 below directly maps the guideline recommendations against the findings of the present study across five key domains.

Table 4: Direct Comparison of Present Study Findings vs. EANM/SNMMI 2025/2026 Guideline Recommendations

Guideline Domain	EANM/SNMMI 2025/2026 Recommendation	Present Study Findings
Primary staging & restaging	18F-FDG PET/CT preferred over CECT + bone scan for stage III–IV and suspected recurrence (Grade A)	27% metastasis detection rate; PET/CT identified lesions in axillary LN, bone, lung, and liver in a single examination
Molecular subtype and FDG avidity	SUVmax thresholds must be subtype-specific; TNBC and high-avidity; Luminal A may be false-negative	HER2-negative mean SUVmax 7.5 vs. HER2-positive 5.5 ($p < 0.05$); supports subtype-aware threshold interpretation
CA 15-3-triggered imaging	Rising CA 15-3 above 25–30 U/mL in asymptomatic post-treatment patients warrants PET/CT referral	CA 15-3 mean 137 U/mL (metastatic) vs. 13.7 U/mL (non-metastatic); 10-fold differential strongly supports this trigger
Emerging receptor-specific tracers	18F-FES for ER+ disease; 89Zr-trastuzumab for HER2+ disease available	Not yet available at NINMAS; integration planned as infrastructure develops; FDG remains the standard tracer
Surveillance interval	HER2-negative / TNBC patients: more frequent surveillance in years 1–2; HER2-positive on maintenance: less intensive early surveillance	53.85% of HER2-negative metastases occurred within 2 years; supports intensified early surveillance for this group

CECT = contrast-enhanced CT; FES = fluoroestradiol; TNBC = triple-negative breast carcinoma; NINMAS = National Institute of Nuclear Medicine & Allied Sciences.

Regarding the first domain, primary staging and restaging, the 2025/2026 guidelines award a Grade A recommendation to 18F-FDG PET-CT as the preferred modality for the detection of distant metastases in stage III–IV and suspected recurrent breast carcinoma, supplanting the combination of bone scan and CECT in this indication (11). Our 27% metastatic detection rate, identifying lesions simultaneously in lymph nodes, bone, lung, and liver in a single examination, directly validates this recommendation in a South Asian clinical context.

The second domain molecular subtype and SUVmax threshold are perhaps the most clinically important guideline elements for nuclear medicine physicians. The 2025/2026 guidance explicitly states that a single universal SUVmax threshold for metabolic positivity is not appropriate across all IHC subtypes and recommends that reporting physicians consider subtype-specific interpretive frameworks (11). The guideline notes specifically that Luminal A tumors (ER+/PR+/HER2 −/Ki-67 low) may generate false-negative PET/CT results owing to genuinely low glycolytic activity, while TNBC lesions may be mischaracterized as unusually aggressive if a uniform low SUVmax threshold is applied (10,11). Our finding that HER2-negative patients exhibit a mean SUVmax of 7.5 versus 5.5 in HER2-positive patients provides quantitative institutional data that could be used to establish locally calibrated subtype-specific SUVmax reference values at NINMAS, a step explicitly encouraged by the guidelines for high-volume centers.

On the third domain, CA 15-3-triggered imaging, the 2025/2026 guidelines recommend that a rising CA 15-3 above 25–30 U/mL in an otherwise asymptomatic postoperative patient constitutes a formal indication for [18]F-FDG PET-CT referral (11). This study, showing a mean CA 15-3 of 137 U/mL in metastatic patients versus 13.7 U/mL in non-metastatic patients, provides strong institutional validation for adopting this threshold. Implementation of a CA 15-3-triggered PET/CT referral protocol at NINMAS has the potential to increase the yield of the scan while reducing the total radiation burden on the non-metastatic majority of postoperative patients.

The fourth domain, emerging receptor-specific tracers, acknowledges the clinical utility of [18]F-fluoroestradiol ([18]F-FES) PET/CT for characterizing ER expression in metastatic disease and guiding endocrine therapy decisions (19) and of 89Zr-trastuzumab or other HER2-targeted tracers for assessing HER2 heterogeneity in metastatic lesions that may have undergone phenotypic change from the primary tumor (20). While these tracers are not currently available at NINMAS, the conceptual framework they embody receptor-matched tracer selection is directly supported by our demonstration that HER2-negative and HER2-positive disease have measurably different FDG phenotypes. The guidelines recommend that institutions develop a strategic roadmap for phased introduction of receptor-specific tracers; this recommendation should inform NINMAS's medium-term infrastructure planning.

Finally, on surveillance intensity, the fifth domain, the guidelines stratify follow-up frequency by molecular risk: HER2-negative patients (particularly TNBC) are identified as candidates for more intensive surveillance during the first two post-operative years owing to their early relapse risk, whilst HER2-positive patients on maintenance anti-HER2 therapy require long-term vigilance given the late-recurrence tail characteristic of hormone receptor-positive/HER2-positive disease (11, 21). This study finding that 53.85% of HER2-negative metastatic events occurred within two years provides direct empirical support for intensified early surveillance in this risk group in Bangladesh.

LIMITATIONS

This study acknowledges several limitations: it is retrospective, the Ki-67 labelling index was unavailable for the entire cohort, the single-center design limits generalizability, and there was a lack of standardization in SUVmax values across various parameters. Future research should involve complete IHC panels and standardized SUVmax acquisition in a multicenter Bangladeshi registry to enhance these findings.

CONCLUSION

This retrospective observational study of 163 postoperative breast carcinoma patients at NINMAS, Dhaka, provides the first institution-level quantitative correlation between 18F-FDG PET-CT SUVmax, IHC receptor profiles, and temporal metastatic patterns in a Bangladeshi cohort. This study shows HER-2 negative

with different combinations of ER and PR characteristics, and triple negative cases show more metastases and recurrence than HER-2 positive cases. There is no difference in the pattern of metastases in HER-2 positive and negative patients. These findings are directly concordant with the 2025/2026 EANM/SNMMI updated joint procedural guidelines, which recommend ^{18}F-FDG PET-CT as the preferred restaging modality (Grade A), subtype-specific interpretive SUVmax frameworks, CA 15-3-triggered surveillance imaging, and phased introduction of receptor-specific tracers. Adoption of these evidence-based protocols at NINMAS, supported by the present study's institutional data, has the potential to improve diagnostic yield, reduce unnecessary imaging in low-risk patients, and individualize surveillance intensity by molecular risk profile, thereby advancing the quality of breast carcinoma care in Bangladesh.

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