Comparison of ^{18}F -Fluorodeoxyglucose positron emission tomography/computed tomography and conventional imaging for locally advanced breast cancer staging: A prospective study from a tertiary hospital cancer centre in the Western Cape

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Background: Breast cancer is the second most common cancer in adults and the most frequent cancer diagnosed in women. In South Africa, breast cancer accounts for 38.5% of cancers diagnosed in women. Since the presence, extent and location of distant metastases is one important prognostic factor in locally advanced breast cancer (LABC), accurate staging at diagnosis is crucial to ensure that patients receive the appropriate treatment. Increasing evidence shows that the use of ^{18}F -Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) for disease staging of LABC may improve diagnostic sensitivity.

Aim: The aim of this study was to prospectively assess the difference in diagnostic accuracy between whole-body PET/PET-CT and conventional imaging (CI) for staging LABC.

Setting: The breast cancer outpatient clinic at Groote Schuur Hospital in Cape Town, South Africa.

Methods: A total of 42 participants with clinical stage III and a select few stage II breast cancer underwent both ^{18}F -FDG PET/CT and CI.

Results: The ^{18}F -FDG PET/CT found significantly more ($p = 0.0077$) distant metastatic sites than CI (36% vs. 21%). The ^{18}F -FDG PET/CT upstaged 9 (21.4%) of patients from clinical stage IIIa to stage IIIc, and changed in management of 54% of patients. Thirty-eight per cent of the patients had their clinical stage unchanged. One of five suspected metastatic sites ^{18}F FDG PET/CT on biopsy was positive for malignancy.

Conclusion: The ^{18}F -FDG PET/CT is useful for staging locally advanced non-inflammatory infiltrating ductal carcinoma of the breast. Use of ^{18}F -FDG PET/CT was superior to conventional imaging in assessing metastatic mediastinal lymphadenopathy, but with a poor specificity. The use of ^{18}F -FDG PET/CT in LABC is useful, with the biopsy of isolated suspicious lesions for metastasis increasing its accuracy.

Keywords: locally advanced breast cancer; NACT; ^{18}F -FDG PET/CT; conventional imaging; staging; South Africa; LMICs.

Introduction

Breast cancer is the second most common cancer in adults and is the most frequently diagnosed cancer in women globally.¹ In South Africa, breast cancer is the commonest type of cancer affecting women accounting for 26% of all female cancers, excluding non-melanoma skin cancers.² Like most other African countries, many patients are diagnosed at a later stage with locally advanced disease, which may account for the higher mortality in comparison to the high income countries (HICs).^{3,4,5,6}

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Approximately 40% of patients with locally advanced breast cancer (LABC) will develop metastasis within 5 years after treatment.^{7,8} The presence or absence of distant metastases is the single most important prognostic factor in LABC patients and plays a critical role in the determination of appropriate therapy.⁹ Accurately staging this group of patients is crucial in disease management and prognostication.

At Groote Schuur Hospital (GSH) in the Western Cape, patients diagnosed with LABC were previously staged with conventional imaging (CI) comprising chest X-ray, abdominal ultrasonography and bone scintigraphy. This has since changed to the use of contrast-enhanced computed tomography (CECT) of chest and abdomen, and bone scintigraphy. A clinical argument has existed for over two decades concerning the need to use more sophisticated technology in the accurate staging of women with LABC in order to correctly exclude patients with metastatic disease from aggressive therapies.¹⁰ Existing evidence has demonstrated superior diagnostic accuracy of ¹⁸F-Fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET-CT) in comparison to CI in staging and restaging of most cancers.^{3,11,12,13,14} The use of ¹⁸F-FDG PET/CT for disease staging of patients with LABC may improve diagnostic sensitivity.

However, most studies assessing the clinical utility of ¹⁸F-FDG PET/CT for LABC staging have emerged from HICs.^{9,12,15,16,17,18} A limited number of studies conducted in low and middle income countries (LMICs) comparing ¹⁸F-FDG PET/CT with CI have shown superior accuracy of ¹⁸F-FDG PET/CT in the detection of distant metastasis in LABC.^{3,14} Two international guidelines, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO), agree regarding the clinical utility of ¹⁸F-FDG PET/CT in breast cancer and recommend its use when CI modalities are equivocal or suspicious in locally advanced inoperable, non-inflammatory breast cancer.^{19,20} However, there remains some uncertainty regarding the diagnostic superiority of ¹⁸F-FDG PET/CT compared with CI in LABC in South Africa.

The use of PET/CT services in South Africa was introduced in 2007. The College of Nuclear Physicians (CNP) of South Africa cautioned that because of the high tuberculosis (TB) prevalence in the South African population, and endemic prevalence in the Western Cape specifically, care is needed to be taken over interpretation of fluorodeoxyglucose (FDG)-avid lesions, because of the risk of false positive lesions.²¹ The generalisation of evidence from developed countries on PET/CT was not recommended by the CNP at the time, stating that diagnostic accuracy depends in part on the prevalence of disease in the population, and such data might not be accurate for South Africa.²² Findings from the local context would be important to provide evidence of the clinical utility of ¹⁸F-FDG PET/CT in LABC and dispel concern of over-reporting of metastasis in high TB prevalence areas. The study aimed to assess the difference in diagnostic accuracy between whole-body ¹⁸F-FDG PET/CT and CI for staging of LABC in our local setting.

Materials and methods

Study design

Female patients presenting with LABC at the breast cancer outpatient clinic at GSH in Cape Town, South Africa were recruited between January 2017 and December 2017.

Study setting

Groote Schuur Hospital, a large tertiary-level state and academic hospital, is one of the two hospitals providing oncology care in the Western Cape. Staging for LABC at GSH historically relied on chest radiograph, ultrasound scan of the abdomen and whole-body bone scintigraphy (targeting the three common sites for breast metastasis). Locally advanced breast cancer (T₃, N₁₊, T₄, N₀₊) cohorts undergo a CECT of chest and abdomen and a whole-body bone scintigraphy.

During the study period, all infiltrating ductal carcinoma (IDC) and LABC patients were staged with ¹⁸F-FDG PET/CT and managed radically or palliatively accordingly. All patients were diagnosed by a multidisciplinary team (MDT), and appropriate decisions were made depending on ¹⁸F-FDG PET/CT findings and/or subsequent biopsy results.

Study sample

All consecutive female patients presenting with LABC at GSH during the relevant period were offered enrolment into the study, with the target of recruiting a total of 48 participants. Participants were eligible for participation if they were over 30 years of age, able to undergo radical treatment, and if they had newly diagnosed IDC stage III or LABC found to be unresectable upfront, good performance status (ECOG 0-2) and no comorbidities that would restrict the use of ¹⁸F-FDG PET/CT and IDC. For the purpose of this study, LABC was defined clinical stage III disease, which is a heterogeneous group of advanced primary and/or nodal disease without clinically evident systemic metastases.⁷

Patients with previous malignancies and patients younger than 30 years were excluded (higher risk for radiation-induced malignancies). Patients with HIV or AIDS and/or tuberculosis, diabetics, early breast cancer, pregnant or lactating, male patients, breast cancer recurrence and if consent was withheld were excluded.

Sample size was estimated based on previous similarly designed studies, with an expected 40% difference in detection of metastasis between use of ¹⁸F-FDG PET/CT and CI for LABC, using an alpha value of 0.05 and a power of 80% to estimate a required sample size of 38 participants.^{23,24} On the advice of the statistician, 10 extra participants were recruited to account for the possibilities of failure to complete investigations, ineligibilities and consent withdrawals.

Procedures

Patients meeting eligibility criteria were identified at the breast cancer clinic of the surgical out-patient department (SOPD) at GSH and assessed by a surgical consultant. All participants underwent clinical examination, fine needle aspiration cytology (FNAC) and a core biopsy of the tumour for histological confirmation, immunohistochemistry (IHC) for hormone receptor status and HER₂/neu amplification status as per GSH breast cancer protocol guidelines. The Ki67 and Bright-Field HER₂ dual *in situ* hybridisation (B-DISH) tests, performed for equivocal IHC HER₂/neu amplification (scored at 2), were only requested if the MDT deemed them important for the management of the patient. This was because almost all LABC, irrespective of Ki67, would receive the same neo-adjuvant chemotherapy (NACT) combination regimen and anti-HER₂/neu therapy was not available on protocol because of cost constraints. The work-up included haematology and chemistry, breast mammogram and ultrasonography. Conventional imaging comprised chest radiographs, abdominal-pelvic ultrasonography and ^{99m}Tc-MDP bone scan.

¹⁸F-FDG PET/CT scans were performed on a GEMINI TF Big Bore PHILIPS whole-body scanner using the European Association of Nuclear Medicine (EANM) procedure guidelines for tumour imaging: version 2.0 (2015).²⁵ Images were interpreted by two nuclear medicine physicians and a radiologist who were blinded to results by the use of participant study generated numbers. All sites of abnormal ¹⁸F-FDG uptake (except normal physiological uptake) were recorded. For all sites, maximum standard uptake value (SUV_{max}), size and CT characteristics were recorded. If the SUV_{max} within the lesion was greater than that of the liver and CT findings were characteristic of metastasis, the lesion was scored as 3. The reason for choosing liver intensity is because of its low variability in metabolic activity.²⁶ If either the SUV_{max} or CT findings were characteristic of metastasis, the lesion was scored as 2. If neither the SUV_{max} nor the CT findings were characteristic of the lesion scored as 1. Disagreements in scores were resolved through consulting a third nuclear physician and a second radiologist.

The conventional investigations were performed as follows:

- ^{99m}Tc MDP Bone scans were performed on a Siemens eCam Signature 2006 dual head gamma cameras. SPECT/CT, when required was performed on a Symbia True Point 2012 SPECT/CT camera. All patients were prepared, injected and imaged in accordance with the EANM practice guidelines for bone scintigraphy.²⁷ Images were viewed using HERMES Gold version 4.15.
- Liver and abdominal ultrasound using a Toshiba TUS X100 2017 model, using a 6 MHz frequency probe.
- Plain chest radiographies using a General Electric (GE) 6000 X-ray machine, 2008 model.

Conventional imaging and ¹⁸F-FDG PET/CT were performed within a 3-week period of each other to avoid treatment

delays and minimise reported differences in disease stage. Patients with isolated metastases in distant lymph nodes or visceral organs on ¹⁸F-FDG PET/CT were subjected to biopsy for cytologic or histologic confirmation. When biopsy of the isolated lesions was deemed too risky by the MDT, the patient was treated as non-metastatic with a planned follow-up imaging. Isolated lung lesions were biopsied via CECT-guided biopsy or endobronchial ultrasound (EBUS)-guided with trans-bronchial needle aspiration (TBNA), depending on location. Biopsy of other suspicious lesions on ¹⁸F-FDG PET/CT were site dependent; liver lesions for ultrasound-guided biopsies and peripheral lymph nodes were subjected to surgical biopsy (Trucut or FNA). We had no access to bone-related biopsy procedures, and treatment decision was made by MDT on ¹⁸F-FDG PET/CT findings. After the staging investigations, patients were discussed in an MDT and treatment was based on ¹⁸F-FDG PET/CT report.

Data collection

Demographic information was extracted from participants' clinical folders, information included: clinical stage (2010 AJCC TNM staging system, 7th edition), histopathologic subtype, IHC markers (ER/PR and HER₂ status), B-DISH results in patients found to have equivocal HER₂ results on IHC, Ki-67 in luminal disease, mammogram, breast ultrasound scan, CI findings, ¹⁸F-FDG PET/CT findings, liver functions and full-blood count.

Data analysis

Statistical analysis utilised Stata version 15.1 (StataCorp. 2017). Continuous variables were summarised as mean and standard deviation whilst nominal and ordinal variables were summarised as counts and percentages. The McNemar test for matched pairs was used to evaluate whether there was a difference between proportions of positive ¹⁸F-FDG PET/CT and CI findings. A $p < 0.05$ was used to assess statistical significance.

Ethical consideration

The study was approved by the Human Research Ethics Committee of the University of Cape Town. All participants provided written consent. Data were anonymised using a study participant number stored in a Microsoft (MS) Excel spread sheet on a password protected computer (HREC REF: 900/2016). Ethical Clearance was received on 06 Jan. 2017.

Results

Forty-eight participants were recruited. The final analysed sample consisted of 41 participants (Figure 1).

Clinical and demographic characteristics of patients with newly diagnosed LABC are summarised in Table 1. The mean

($\pm$ SD) age of the participants was 51.5 ($\pm$ 12.71) years, (range: 27 to 77 years). Slightly more patients were post-menopausal (51.2%) than pre-menopausal (48.8%), based on a history of 1 year of uninterrupted absence of menstruation. Stage at presentation was mainly stage IIIB (56.1), with the majority (52.38%), having clinical T4b disease (skin ulceration, peau d'orange or satellite nodules; or palpable nodal disease (90.48%).

The ^{18}F -FDG PET/CT upstaged 9 (21.4%) of patients from clinical stage IIIa to stage IV and changed management decision in 54% of the patients (Table 2); three of the nine

FIGURE 1: Study subject recruitment and inclusion for analysis.

TABLE 1: Demographic and clinical characteristics of participants ($N = 41$).

Variables	<i>n</i>	%
Menopausal status		
Pre-menopausal	20	48.8
Post-menopausal	21	51.2
Smoking history, pack years		
Nil	27	65.9
< 10	5	12.2
≥ 10	9	21.9
Sidedness of the breast cancer		
Right	24	58.5
Left	17	41.5
Clinical Stage (AJCC/TNM 7th Ed)		
Stage IIIA	12	29.3
Stage IIIB	23	56.1
Stage IIIC	6	14.6
Histology		
Invasive ductal cell carcinoma	41	100
Molecular subtype		
Luminal	10	24.4
Luminal HER ₂ overexpressed	5	12.2
Luminal HER ₂ equivocal	12	29.3
HER ₂ /neu over-expressed	3	7.3
TNBC	11	26.8

AJCC, American Joint Committee on Cancer; TNM, tumour, node, metastasis; HER₂, human epithelial growth factor receptor 2 based on IHC; TNBC, triple negative breast cancer.

TABLE 2: The ^{18}F -Fluorodeoxyglucose positron emission tomography/computed tomography versus conventional imaging cross-tabulation.

Conventional imaging	^{18}F -FDG PET/CT		
	Regional uptake (negative), <i>n</i>	Metastatic (positive), <i>n</i>	Total, <i>n</i>
Negative, <i>n</i>	24	8	32
Positive, <i>n</i>	0	9	9
Total, <i>n</i>	24	17	41

^{18}F -FDG PET/CT, ^{18}F -Fluorodeoxyglucose positron emission tomography/computed tomography.

patients had a biopsy of the nodes, with two having negative results for cancer cells resulting in their down-staging. The ^{18}F -FDGPET/CT ($n = 17$, 401.5%) detected significantly more distant metastasis than CI ($n = 9$, 22%) ($p = 0.005$).

Chest X-ray showed evidence of lung metastasis in eight patients, ultrasonography of the abdomen detected liver metastasis in five patients, whilst bone scintigraphy showed skeletal metastasis in five patients (Table 3). Some of the patients had multiple sites detected on CI. Most detected metastases on ^{18}F -FDG PET/CT were in mediastinal lymph nodes (26%).

The ^{18}F -FDG PET/CT detected ipsilateral supraclavicular lymphadenopathy in 10 (23.8%) patients, which was clinically detected in only 5 (11.9%) patients. The ^{18}F -FDG PET/CT detected internal mammary lymphadenopathy (IMN) in 11 (26.1%) patients, 4 (9.5%) of whom had bilateral IMN. Overall, N3b or N3cdisease, which was not recognised by either clinical examination or CI, was identified on ^{18}F -FDG PET/CT in an additional 11 (26.1%) patients. Three of the patients with supraclavicular nodal disease detected on ^{18}F -FDG PET/CT were subjected to a biopsy, two of these were found to be negative on histopathology and/or cytology (Figure 1). All the N3 diseases detected on ^{18}F -FDG PET/CT were clinically at least T4b and/or N2 or N3.

Comparison of 99mTc-MDP bone scan with ^{18}F -FDG PET/CT (Table 3): The bone scan detected bone metastases in five (12%) patients, with the common sites being thoracic and lumbar vertebrae. The bone scan missed two osteolytic osseous metastatic lesions in the thoracic and lumbar vertebrae that were detected on ^{18}F -FDG PET/CT. All the lesions detected on bone scan were also detected on ^{18}F -FDG PET/CT. However, the ^{18}F -FDG PET/CT detected more numerical sites than the bone scan in all patients with bone metastases, with one patient having 12 different bone sites detected on ^{18}F -FDG PET/CT compared with 7 on bone scan. All the patients in this study but one had abnormal haematological blood results, with no correlation found between an abnormal blood results and metastatic bone disease.

TABLE 3: Metastatic sites† on conventional imaging and ^{18}F -Fluorodeoxyglucose positron emission tomography/computed tomography.

Metastatic site	CI, <i>n</i>			^{18}F -FDG PET/CT, <i>n</i>	Total
	Bone scan	CXR	USG		
Bone	5	-	-	7	7
Lungs	-	8	-	8	8
Liver	-	-	5	4	5
Distant LN	-	-	-	12	12
Brain	-	-	-	0	0

LN, lymph node; CXR, chest X-ray; USG, ultrasonography; ^{18}F -FDG PET/CT, ^{18}F -Fluorodeoxyglucose positron emission tomography/computed tomography.

†Certain patients had metastasis in multiple sites.

Comparison of chest X-ray with ^{18}F -FDG PET/CT (Table 3): Pulmonary metastases were detected in eight patients (19%) on plain chest X-ray, which was equal to the number detected on ^{18}F -FDG PET/CT, but two were not in the same patients or in the same anatomical locations. The two patients with suspected lung metastasis on chest X-ray were not detected on the ^{18}F -FDG PET/CT. The patient with an isolated lung metastasis detected on ^{18}F -FDG PET/CT was subjected to an EBUS guided biopsy, with a negative result (Figure 4). This lesion was not detected on chest X-ray.

Comparison of abdominal ultrasonography with ^{18}F -FDG PET/CT (Table 3): The USG detected 5 suspicious metastatic liver lesions, with ^{18}F -FDG PET/CT detecting 4. The one

patient with a suspected liver lesion detected on abdominal ultrasound, and not detected on ^{18}F -FDG PET/CT, was too small to characterise to biopsy. The ^{18}F -FDG PET/CT liver findings correlated well with abnormal liver function tests.

^{18}F -FDG PET/CT detected 12 distant lymph nodes (Table 3): The majority (9/12) of distant metastatic lymph nodes were mediastinal. The isolated para-aortic lymph node detected on ^{18}F -FDG PET/CT was not biopsied, procedure too risky for the benefit, and elected to treat the patient as non-metastatic, and to repeat the ^{18}F -FDG PET/CT at completion of the NACT.

Patients with isolated metastases detected on ^{18}F -FDG PET/CT were to be subjected to biopsy (Figures 2–4).

FIGURE 2: A 32-year-old with triple negative breast cancer with suspicious right supraclavicular node on fluorodeoxyglucose positron emission tomography/computed tomography. SUVmax primary tumour = 24.7, suspected metastatic supraclavicular node = 3.5. Biopsy results were negative for malignancy.

FIGURE 3: A 55-year-old with luminal disease with a station two mediastinal lymph node suspicious of metastasis on fluorodeoxyglucose positron emission tomography/computed tomography was subjected to endobronchial ultrasound guided biopsy. SUVmax primary breast tumour = 8.4, suspected station 2 node = 3.4. Biopsy results were negative for malignancy.

FIGURE 4: A 43-year-old with luminal disease with a left lung non-spiculated lesion suspicious of fluorodeoxyglucose positron emission tomography/computed tomography was subjected to a computed tomography – guided biopsy. SUVmax primary breast tumour = 16.4, suspected lung lesion 4.8. Biopsy results were negative for malignancy.

Discussion

The study aimed to assess the difference in diagnostic accuracy of ^{18}F -FDG PET/CT and CI in detecting metastases in patients with LABC at GSH. The ^{18}F -FDG PET/CT was superior to the selected CI in detection of distant metastases ($p = 0.005$), resulting in the upstaging of disease in 22% of patients from stage IIIa to stage IV and altered management in 54%. Of the five suspected metastatic sites that were biopsied, one was positive for malignancy, indicating the limited specificity of ^{18}F -FDG PET/CT to distinguish malignant from benign lesions.

The CNP of South Africa recommend use of PET/CT in breast cancer in selected cases as an adjunct to CI when such modalities are equivocal and in disease recurrence staging.²² The NCCN recommends ^{18}F -FDG PET/CT as a category 2B option for diagnostic staging work-up; utilise it in LABC with equivocal or suspicious findings on conventional staging modalities.¹⁹ The reason for not recommending upfront use of ^{18}F -FDG PET/CT is lack of data showing a clear clinical benefit.

The existing data comparing ^{18}F -FDG PET/CT and CI modalities have shown the superior sensitivity of ^{18}F -FDG PET/CT in the detection of occult metastasis, extra-axillary nodal disease and has the added advantage of being a full-body examination in a single session.^{3,12,14} However, there exists scarcity of prospective data from developing countries, where in addition to late presentation, infectious diseases remain a big challenge.³ Patients from HICs present with earlier stages of disease (stage IIB or IIIA),¹² in comparison with LMIC where more advanced stages (IIIB or IIIC) are the majority.¹⁴ This prospective study of 41 LABC patients found 70% of patients staged as IIIB or IIIC.

Overall, our findings suggest that ^{18}F -FDG PET/CT was able to detect more metastases than the selected CI, and resulted in upstaging of disease, which was similar to previous

studies.^{3,9,12,14} However, it was not possible to determine sensitivity and specificity because of the limited number of patients who underwent biopsies.

The apparent superiority of ^{18}F -FDG PET/CT over CI as a staging modality was in the detection of mediastinal lymphadenopathy. In the other common sites of breast metastases (lung parenchyma, liver and bone), there was no difference detected between ^{18}F -FDG PET/CT and CI. Our data are consistent with the earlier studies similarly designed by Schirmeister et al. and Dose et al. who found that ^{18}F -FDG PET/CT was superior for the detection of distant metastasis, particularly the presence of mediastinal and thoracic lymph node metastases.^{9,18,28} The ^{18}F -FDG PET/CT upstaged the nodal status in five patients by detecting IMN. This had an impact on the target delineation and radiotherapy fields. Inclusion of involved IMN in radiotherapy field has shown a trend towards improved disease-free survival and overall survival.^{29,30} Riegger et al. showed in a retrospective study that ^{18}F -FDG PET/CT had an impact on both surgical procedures and the delineation of radiotherapy targets in breast cancer.³⁰

Concern regarding the use of ^{18}F -FDG PET/CT in areas where infectious diseases are prevalent is an important consideration. In this study, our patients came from communities with high tuberculosis prevalence, known to be a PET-avid infectious disease.^{31,32} The uptake of ^{18}F -FDG in lymph nodes should ideally be confirmed to be metastatic by biopsy, because of the known low specificity of the radiopharmaceutical, raising concern for the possibility of false positives.¹⁰ Patients with isolated solitary metastatic lesions on ^{18}F -FDG PET/CT had a biopsy for histopathological confirmation if considered safe (Figures 2–4). The low positive biopsy results of only 20% agreed with the known poor specificity of ^{18}F -FDG PET/CT. There is a possibility of biopsy yielding spurious results in certain cases. Therefore, co-registration of suspected lesions on

^{18}F -FDG PET/CT with imaging used in the biopsy is suggested, including both nuclear physician and the physician performing the directed biopsy for maximal yield.

The ^{18}F -FDG PET/CT upstaged 10 patients (24%) in the ipsilateral supraclavicular lymphadenopathy, which were clinically palpable in only five (11.9%) patients. All patients with ^{18}F -FDG PET/CT-detected ipsilateral supraclavicular lymphadenopathy or isolated mediastinal lymphadenopathy had clinically advanced T₄-disease (skin ulceration or oedema). There is a risk of super-imposed infection in these lesions, and a corresponding inflammatory response in the draining lymph nodes. Unlike developed countries, our patients (>60%) commonly present with advanced disease.³ We recommend that breast ultrasound, including axilla be extended to the supraclavicular areas, to help distinguish between inflammatory and metastatic lymph nodes.

The ^{18}F -FDG PET/CT is an important diagnostic tool in the identification of non-regional distant metastatic lymphadenopathy in LABC, especially mediastinal, as shown by our study. The non-regional lymphadenopathy assumes more significance when it is not accompanied by other distant metastases. Therefore, the use of ^{18}F -FDG PET/CT in LABC should be used in centres with the biopsy capability, avoiding falsely up-staging of disease.

The study highlighted the superiority of ^{18}F -FDG PET/CT over CI in our LABC cohort, useful for selection of patients that would derive the most benefit from this staging investigation, when coupled with access to tissue confirmation of the 'hot spots' found on ^{18}F -FDG PET/CT. The ^{18}F -FDG PET/CT was superior to CI mainly for mediastinal lymphadenopathy and patients with isolated mediastinal lymphadenopathy tissue confirmation before staged metastatic.

The ^{18}F -FDG PET/CT has limited specificity distinguishing malignant from benign lesions, both of which demonstrate increased glucose utilisation.¹² The low number of tissue confirmations of all imaging findings was one of the main limitations of this study. The study was also limited by its design as a single institutional prospective study. Most quoted studies used CT scan of the chest and abdomen as a part of CI, whereas we used chest X-ray and ultrasound of the abdomen as was the prevailing policy at our institution at the time. The addition of CT chest scans has been shown to improve the sensitivity of CI.^{12,14} Although the current study was suitably powered to answer the research question, we acknowledge that small sample sizes may lack generalisability because of lack of sufficient randomisation and stratification. Future research should include larger samples recruited from multiple centres. The availability of PET/CT in most state-funded cancer centres might require a cost analysis in LMIC settings, which may be prohibitive.³³

Conclusion

The ^{18}F -FDG PET/CT is more accurate than CI for the initial staging of LABC, frequently upstaging clinical disease and requiring modification of loco-regional management. It was also beneficial in identification of mediastinal lymphadenopathy. It provides the convenience of examining the whole body in a single session. The use of ^{18}F -FDG PET/CT in comparison with CI showed a clinical difference in the evaluation of LABC staging, increasing its utility in this clinical group of LABC. The use of ^{18}F -FDG PET/CT for breast cancer staging is recommended in LABC, with a better accuracy of biopsy of isolated suspected metastatic lesions. Larger multicentred prospective studies are required to ascertain the significance of isolated solitary lesions on ^{18}F -FDG PET/CT.

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Competing interests

The authors have declared that no competing interests exist.

Authors' contributions

P.M.C. and D.A. conceived the idea. P.M.C. wrote manuscript under the supervision of JP. R.G. and G.H. reported CI of chest X-rays and USG. R.S. and S.M. reported on ^{18}F -FDG PET/CT and bone scans. F.M. was the consultant surgeon for the clinical staging confirmation. L.M. performed endobronchial biopsies. K.M. provided writing assistance, feedback on drafts and final formatting and language editing. A.H. and A.J.H. performed the statistical analysis. All authors were involved in study protocol formulation.

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Data availability statement

The data analysed in this study are openly available in the metadata submitted to the journal and are available within the article.

Disclaimer

The views and opinions expressed in this article are those of authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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