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

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In fulfilment of the degree

Master of Medicine (MMed)

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June 2019

DECLARATION

I **Paul Mambwe Chilwesa** declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by the University of Cape Town will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification. I hereby declare that the work on which this dissertation is based on my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, or is to be submitted for another degree in this or any other University.

Signed: Signed by candidate

Date: /07/2019

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ABBREVIATIONS

ABC	Advanced breast cancer
CECT	Contrast-enhanced computed tomography
CI	Conventional Imaging
CNP	College of Nuclear Physicians
CT	Computed tomography
CXR	Chest x-ray
ESMO	European Society for Medical Oncology
^{18}F-FDG PET/CT	^{18}fluorine-fluorodeoxyglucose positron emission tomography/computed tomography
FDG	Fluorodeoxyglucose
GSH	Groote Schuur Hospital
HIC	High income country
LABC	Locally advanced breast cancer
LMIC	Low and middle income country
NACT	Neo-adjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
SOPD	Surgical Out-Patient Department
USG	Ultrasonography
WHO	World Health Organization

Chapter 1
Study protocol

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

Research protocol

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Master of Medicine (MMed)
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Final version, December 2016

1.1.Background

Breast cancer is the second most common cancer in adults and the most frequent cancer diagnosed in women.[1] However, breast cancer mortality rates are higher in low and middle income countries (LMICs).[2,3] In South Africa, Breast cancer accounts for more than 20% of cancers diagnosed in women.[1] One of the biggest challenges of breast cancer management in LMICs is lack of access to new and improved treatment and staging technologies. Staging is defined as an assessment of tumour spread in an untreated patient with confirmed cancer.[4] Staging is also important for disease prognosis as well as accurate inter-institutional comparison of survival and mortality.

Breast cancer prognosis has improved globally over the last decade nearing 80% at 5 years, owing to the improvement in early detection and treatment: Survival rate decreases to less than 60% and 20% in cases of locally advanced breast cancer and metastatic disease, respectively.[5] For accurate inter-institutional comparison of survival and mortality, accurate standardized staging is important.

In LMICs, breast cancer patients tend to present late (especially in the public sector), usually with locally advanced or metastatic disease. There is no consensus on the definition of 'locally advanced breast cancer (LABC)',[6] but most commonly this term refers to clinical stage III disease, which is a heterogeneous group of advanced primary and/or nodal disease without clinically evident systemic metastases(table 2). Approximately 40% of patients with LABC will develop metastasis within five years post treatment.[7, 8]

Neo-adjuvant chemotherapy (NACT) is the standard of care in LABC,[9] and is increasingly used in patients with larger operable breast cancer and/or with axillary lymph node metastases.[10,11] Administration of NACT follows radiological exclusion of metastasis. Presence of distant metastases is the single most important prognostic factor in patients with breast cancer, and plays a critical role in determination of therapy.[12] The presence of non-regional nodal (ipsilateral) metastases in breast cancer patients immediately excludes them from radical treatment,[6,13,14] which consists of sequential combination of NACT, radical breast surgery, and radiotherapy with or without endocrine therapy. Patients with metastatic breast cancer receive palliative treatment to improve quality of life, consisting of either endocrine therapy or single agent chemotherapy in the majority of patients. Hence, it is crucial to accurately stage LABC at first presentation.

NACT for LABC consists of at least six cycles of combination chemotherapy and, according to the European Society for Medical Oncology (ESMO),[15] and St. Gallen International Expert Consensus, it should include an anthracycline and a taxane.[16] Therefore accurate staging at diagnosis is crucial to ensure that appropriate treatment is offered to patients, and to prevent the unnecessary overtreatment of patients harbouring metastases.

LABC require complete staging before initiation of therapy. Assessment of metastasis via conventional imaging (CI) ideally include whole body CT and bone scans, but at GSH we use a chest radiograph, an ultrasound scan of the abdomen (targeting the 3 common areas for breast metastasis), and a bone scan at due to resource constraints and long waiting times for the whole body CT scan. However, several studies demonstrate the sensitivity of CI to be lower than 60%.[7,10,12] When used appropriately in oncology, PET/CT can provide useful clinical information and has been postulated to lead to significant cost savings in patient management(such as avoiding expensive intervention; surgery, chemotherapy, radiotherapy).[17, 18] Strong evidence has demonstrated superior diagnostic accuracy of PET-CT in comparison to conventional imaging in staging and restaging of most cancers.[19] The use of ^{18}F-FDG PET/CT for disease staging of patients with locally advanced breast cancer may improve diagnostic sensitivity,[20] However, we're still unsure of the diagnostic superiority of ^{18}F-FDG PET/CT over CI in LABC.

Previously, Schirrmeister *et al*(2001) found as high as 20% false-negative rate for detection of lymph node metastases in breast cancer when using ^{18}F-FDG PET,[21] but this was a heterogeneous group of participants that included early breast cancer, and also included invasive lobular carcinoma that is known to be poorly ^{18}F-FDG PET avid. Research suggests that the merit of this technology for screening and work-up is questionable because no large prospective studies have been done, and the high false negative sclerotic bone lesions on ^{18}F-FDG PET, but has superior detection rates once combined with CT.[19] In addition, although some studies have compared whole-body PET/PET-CT with conventional imaging, most of the results have been criticised:[7] The limitation of many of these studies is they were retrospective, and were without histologic confirmation of suspected metastases.[5,22] In addition, very few prospective studies have been conducted in the developed world,[10,23] limited by their bias for breast cancer recurrence or metastatic disease,[24] and lack of histopathological stratification.[25]

Nevertheless, the use of ^{18}F-FDG-PET/CT for staging in a selected group of high-risk breast cancer patients has been shown to be accurate in identifying metastases.[15,16,26,27] Therefore,

based on this evidence, as well as recommendations from the National Comprehensive Cancer network (NCCN),[13,14] and ESMO[15], ^{18}F-FDG PET/CT was introduced for the staging of invasive ductal carcinoma(IDC) LABC at Groote Schuur Hospital (GSH) since May 2015. The South African College of Nuclear Physicians (CNP) recommends the use of ^{18}F-FDG PET/CT as an adjunct to CI when studies are equivocal in LABC staging or metastatic breast cancer.[28]

Accurate detection of metastases can reduce the number of radical treatments and alter course of disease. On the other hand, failure to detect metastases can lead to poor quality of life. Poor inter-institution concordance of breast cancer staging implies inconsistent diagnosis and treatment, and may be reflected in higher mortality in institutions where it is systematically inaccurately staged.[11] No studies have investigated whether the use of ^{18}F-FDG PET/CT in IDC LABC at Groote Schuur Hospital is appropriate. Furthermore, the cost of breast cancer treatment, as well as whole-body ^{18}F-FDG PET/CT for staging purposes, may be prohibitive in health care systems with limited resources. The initial ^{18}F-FDG PET/CT recommendation in breast cancer staging was for multifocal disease or suspected disease recurrence.[29] This study may provide to evidence to oncology treatment teams on the most appropriate staging modality in IDC LABC staging in the local context.

1.2. Aim

To assess the difference in the sensitivity in detecting metastases between whole-body ^{18}F-FDG PET/CT and conventional imaging (CI) for staging in participants with locally advanced irresectable invasive ductal carcinoma (IDC) of the breast treated at Groote Schuur Hospital.

1.3. Hypothesis

^{18}F-FDG PET/CT has a greater sensitivity than conventional imaging with CXR, bone scan and abdominal ultrasound in locally advanced irresectable invasive ductal carcinoma of the breast.

1.4. Objectives

1. To compare the potential differences in the detection rate of distant metastases in locally advanced breast cancer between whole-body ^{18}F-FDG PET/CT PET/CT and conventional imaging modalities used at GSH.
2. To establish if whole-body ^{18}F-FDG PET/CT should replace CI at GSH for the staging of IDC locally advanced breast cancer.
3. To describe the clinical impact on patient management of the study outcomes.

4. To determine ^{18}F-FDG PET/CT specificity in isolated lymph nodes beyond normal breast cancer lymphatic drainage.

1.5.Methods

1.5.1. Design:

This will be a prospective study of forty (40) participants diagnosed with irresectable locally advanced breast cancer at GSH. Participants will be staged with CI (CXR, Abdominal ultrasound and bone scan) in addition to ^{18}F-FDG PET/CT. Participants found to have isolated mediastinal lymph nodes will have cytological confirmation performed. The detection rate of metastases between ^{18}F-FDG PET/CT and CI will then be compared.

1.5.2. Sample:

The number of study participants required was derived using the chi-square test. A detection rate of 60% for PET/CT and 18% for CI for clinical T_3/T_4 disease, irrespective of nodal status, was estimated in the breast clinic at Groote Schuur Hospital.

1.5.2.1. Inclusion Criteria:

1. Newly diagnosed IDC LABC found to irresectable to upfront surgery (Appendix 2).
2. No previous malignancies or treatment thereof, and not known to GSH Oncology unit.
3. Performance status and co-morbidities; ECOG 0-2, participants must be candidates to undergo radical treatment.
4. Histology: infiltrating ductal carcinoma (IDC).[22]

1.5.2.2. Exclusion Criteria:

1. Early breast cancer (stage I and II)
2. Pregnant or lactating participants
3. Breast cancer recurrence
4. HIV/AIDS positive participants
5. Confirmed active tuberculosis, and/or on treatment
6. Age below 30 years,[30] for radiation protection considerations
7. Male gender
8. Diabetic participant
9. Surgery in last 3 months

1.5.3. Procedures:

Participants will be identified at the walk-in breast cancer clinic at SOPD GSH. Suspected LABC participants will be assessed by a surgical consultant. Participants will undergo routine examination, FNAC (fine needle aspiration cytology) and Tru-cut biopsy, as per current protocol guidelines.

Participants who meet the eligibility criteria will be identified by the oncologist (registrar) at SOPD and consented for the study. CI (mammogram, chest x-ray, abdominal ultra-sound scan, bone scan) in addition to PET/CT will be requested. CI and PET/CT will be performed within a three week period, estimated from the turn-around time for LABC patients in our department. The study will not interfere with standard of care, all LABC would have PET/CT done as per GSH protocol. No additional slots for scans will be requested outside the standard procedure. Two qualified Nuclear medicine physicians will read the PET and the bone scans separately. The CT part of the ^{18}F-FDG PET/CT and the CI will be read by a qualified radiologist. The radiologist reporting the CI and the nuclear medicine physician reporting the PET/CT will be blinded to the findings of each other.

1.5.3.1. PET/CT

^{18}F-FDG PET CT imaging will be done using a GEMINI TF Big Bore PHILIPS whole-body scanner. Participants will be prepared, injected and imaged in accordance with the FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0 (2015).

Propranolol 20mg will be administered orally 30 minutes prior to 18F-FDG injection to each participant to decrease the amount of brown fat uptake. Participants in whom propranolol is contraindicated will not receive it and the reasons clearly documented. The participants will be positioned supine in the PET CT scanner and acquisition from base of skull to mid-thigh will be started 60 minutes after tracer injection. Images will be acquired in 3- dimensional mode and reconstructed with attenuation correction using a 5-node quad core CPU computer cluster provided by PHILIPS. For whole body PET a relaxed list mode ordered subsets expectation maximization algorithm (BLOB-OS), with spherically symmetric basis functions on a body centred cubic grid to represent the emission object will be used. Images will be viewed with Hermes Hybrid Viewer PDR v.2.2C.21 and interpreted by a Nuclear Medicine Physician and Radiologist. Low dose uncontracted CT will be performed. The CT portion of PET/CT provides the anatomic information useful for accurate interpretation of PET signal. It also provides a map used for attenuation correction of PET images.

The FDG PET CT images will be interpreted by a Nuclear Medicine Physician and a Radiologist who are blinded to other imaging results and clinicopathological findings other than the presence of breast cancer. All sites of abnormal 18F FDG uptake (areas that do not conform to normal physiological 18 F FDG uptake) will be listed. Each area will be scored as 1 = negative for metastasis; 2 = equivocal for metastasis; and, 3 = consistent with metastasis.

Standard uptake values for each area will be calculated using the following formula $SUV_w = A \times W/D \times 1000$ g/c where SUV_w= Normalization to body Weight, A= Activity Concentration in Becquerel/cubic centimetres (Bq/cc), W= Participant weight in kg and D= Injected dose in Bq decay corrected. The SUV_{max} defined as the highest SUV in the pixel for within the region of interest (ROI) will be recorded.

1.5.3.2. Bone Scintigraphy

All participants will be scanned on a Siemen's eCam Signature series dual head gamma camera (200^). If a SPECT CT is required, the participant will be transferred to a Symbia hybrid SPECT-CT for the SPECT CT acquisition. Examinations will be processed and viewed on the HERMES physicians' workstations.

Participants will be prepared, injected and imaged according to SNM guideline procedure guidelines[31]. Each participant will be injected with 740 MBq-1110 MBq of Technetium-99m-methylene diphosphonate (MDP) (according to the body weight). Planar images will be acquired using a low energy high-resolution collimator.

SPECT images will be obtained using a 128 x 128 matrix with 25 seconds per step acquiring 64 projections with 180degree rotation for each gamma camera head. Images will be reconstructed using Flash 3D ordered subset expectation maximization (OSEM) iterative reconstruction algorithm in 4 subsets and 8 iterations.

CT images will be acquired using a low dose protocol without intravenous contrast administration. The low dose CT parameters will be: 2.5-30mAs, 120 kV, slice thickness of 1.25-5mm and pitch of 1.5. Images will be reconstructed using high-resolution reconstruction algorithms (B08s kernel).

The planar images will be interpreted by a Nuclear Medicine Physician, SPECT/CT, if acquired, will be read together with a radiologist, both the Nuclear Medicine Physician and Radiologist are blinded to other imaging results and clinicopathological findings other than the presence of breast cancer. All sites of abnormal ^{99m}Tc- MDP uptake (areas that do not conform to normal physiological uptake will be listed. Each area will be scored as 1 = negative for metastasis; 2 = equivocal for metastasis; and, 3 = consistent with metastasis.

1.5.3.3. Abdominal Ultrasound scan (USS)

USS studies will be performed according to routine practice using the Toshiba Nemeo XGI machine, with a convex (3-6MHz) transducer and when necessary a linear (7-12 MHz) transducer as well as Doppler imaging. USS of the liver will be performed with conventional B-mode and metastases will be identified according to conventional imaging criteria. USS findings will be recorded by number, size, and location of the lesions. Each lesion will be scored as 1 = negative; 2 = equivocal; and 3 = consistent with metastases.

1.5.3.4. Chest X-ray (CXR)

CXR will be performed according to routine practice at our institution: PA and lateral views (125 Kv and 2-5 mas) to identify metastases in the lung, mediastinum, or visualized thoracic spine. CXR findings will be recorded as 1 = nodules/mass lesion either infective or suspicious for metastases; 2 = opacification, fibrosis, of nodules/mass; 3 = septal thickening suggestive of lymphangitis carcinomatosis; and, 4 = mediastinal, supraclavicular, or hilar nodes.

Chest X-rays that are reported as suspicious for metastases will be subjected to diagnostic CT scans, as per standard of care. Should participants be found to have isolated metastases on ^{18}F-FDG PET/CT, they will be subjected to biopsy for histologic confirmation[21], as per standard of care. After the staging investigations, participants will be treated as per current departmental guidelines.

1.5.3.5. Biopsy of isolated metastases on FDG PET CT

Biopsy will be performed using endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration is a technique (TBNA). EBUS is a technique that uses ultrasound along with bronchoscope to visualize airway wall and structures adjacent to it. The clinical application and diagnostic benefit of EBUS have been established in many studies. EBUS has been incorporated into routine practice in many centres because of its high diagnostic informative value and low

risk.[32, 33] It may replace more invasive methods for staging lung cancer or for evaluating mediastinal lymphadenopathy and lesions in the future.

In the proposed study we will use EBUS-TBNA to access and cytologically confirm the presence of invasive ductal cell breast cancer in intrathoracic nodes that show increased activity on ^{18}F-FDG PET scanning. These lesions will be identified following a combined reading of the CT and PET scan by both qualified radiologists and nuclear medicine physicians. In conjunction with the pulmonologist a procedure will be planned.

EBUS will be performed under procedural sedation using both fentanyl and midazolam. Participants will be nil per os (NPO) for at least 6 hours prior to the procedure. Participants will be positioned supine with operator standing on head end of bed: The bronchoscopist should have clear view of monitor. The monitoring devices will be placed onto the patient, supplemental oxygen will be administered by nasal cannula, and intravenous access established before starting the procedure. Participant's eyes will be covered to prevent splashing the normal saline, secretion, or blood into them. Curved probe-EBUS will be performed orally, as ultrasound probe in it prevents using nasal route. Once in the airways, a syringe filled with sterile water will be attached to the balloon channel of the scope and the balloon filled with water to achieve contact with the airways. Lymph nodes that show increased activity on ^{18}F-FDG PET scanning will be identified with its typical sonographic appearance. Aspirated specimen will be smeared onto glass slides and fixed so that a cytopathologist can evaluate the specimen. Histological cores (if obtained) will be fixed with formalin and sent to the pathology department for cell block.

Continuous monitoring of cardiac rhythm, heart rate, respiratory rate, oxygen saturation, and blood pressure will be done after the procedure until the effects of sedation and upper airway anaesthesia have resolved. Eating and drinking can be resumed once the gag reflex returns. A chest radiograph will be performed only if clinically indicated. Outpatients must have stable vital signs, be alert and oriented with baseline ambulation status before discharge.

1.5.4. Data collection:

The following data will be prospectively collected: Age; co-morbidities; clinical stage (AJCC TNM staging system); histopathologic subtype; immunohistochemistry markers (ER/PR and HER2 status); B-DISH results in participants found to have equivocal HER2 results on IHC; Ki-67 in participants with luminal disease; CI results (including mammogram [BIRADS score

1-6, presence of lymph nodes], breast ultrasound scan if done, CXR, bone scan, abdominal ultrasound, CT chest if needed); PET/CT results; liver function blood test results; time interval between the last CI test and the PET/CT; waiting period from diagnosis to completion of CI vs PET/CT; if metastases were pathologically confirmed; number of metastatic sites detected by both techniques; site of metastases; presence of regional (lymph node) metastases; and, treatment plan from the multi-disciplinary team.

1.5.5. Data analysis

The primary end point of this study is the sensitivity difference between ^{18}F-FDG PET/CT and CI in the detection of metastases in irresectable IDC LABC. Estimated specificity will be calculated for the biopsies of the ^{18}F-FDG PET/CT isolated metastases. The number of study participants required was derived using the chi-square test. A detection rate of 60% for PET/CT and 18% for CI for clinical T_3/T_4 disease, irrespective of nodal status, was estimated in the breast clinic at Groote Schuur Hospital. Assuming a 40% difference in the sensitivity between ^{18}F-FDG PET/CT and CI groups, minimum of 38 participants will be required for the final analysis with 95% statistical power to detect sensitivity difference using a chi-square test at an alpha level of 5%. Data will be collected and stored on a Microsoft excel spreadsheet. Stata and R will be the statistical software employed for the analysis.

1.6. Ethical considerations

The clinical standard of care management of the participant will not be affected by the study. According to current standard departmental clinical protocols, IDC LABC patients are staged with ^{18}F-FDG PET/CT and are managed radically or palliatively accordingly. While CI is used in early breast cancer as standard of care at GSH, it is not employed in LABC.

In this prospective study, in addition to ^{18}F-FDG PET/CT which is GSH standard of care, participants will be exposed to CI, which will be employed specifically for research purposes . This poses potentially a small increase in risk from the excess radiation exposure from the bone scan. The total radiation dose to the participant will be taken into account in accordance with the ALARA (as low as reasonably acceptable) principles of Radiation protection.[34] There is no risk from an abdominal ultrasound. From the table below, the excess radiation received will be approximately 3-6 mSv.

Cancer induction is both dose and age related: the higher the dose the higher the likelihood of cancer induction, and exposure to radiation before the age of 30 increases the induction of

second cancers.[30] Effective doses are the parameters used for benefit/risk assessment in the approximation of the detriment of ionization radiation, and compares the detriment from cancer and hereditary effects (Stochastic effects). The risk for leukaemia and solid tumours (especially breast and lung cancer) induction is 1.7%/Sv and 0.275%/Sv respectively, if exposed before the age of 30, affected too by smoking, with a risk reduction in later life exposure. The above added dose (3-6 mSv) bone scan predisposes one to cancer induction by under 0.05% (Appendix 1).[35] The risk associated with a biopsy, in the case of usual isolated metastases, must be weighed against the benefit of obtaining a definitive stage and appropriate treatment. The main risk from biopsy is bleeding and post procedural pain in the participant. The gold standard of confirming an isolated suspicious metastasis is to have tissue diagnosis by biopsy: Some studies have shown the misdiagnosis of metastasis in indolent infectious state,[36,37] and Cape Town population is highly endemic for Tuberculosis.[38] The biopsy result will give a definite answer as to whether the participant should be managed radically or palliatively. A separate consent will be sought for the biopsy, and risks explained in full. As discussed above, this difference has significant implications for the participant and the benefit of a biopsy far outweighs the risks that are associated with it. The benefit to the participant will be that the extra test will add to the positive and negative predictive value of their staging.

The workflow in Nuclear medicine and radiology will not be affected by this study. Imaging slots will be booked through the routinely used 2-week slots at GSH in time for the MDT: All investigations, nuclear medicine and radiology, will be arranged according to normal scheduling, with no additional slots requested. The study will not at any point disadvantage non-participating patients with LABC who are investigated with ^{18}F-FDG PET/CT as per standard of care.

Informed consent will be sought from the participant for study participation by non-coercive methods. It is understood that diagnosis of cancer leaves one vulnerable, and are at risk of making rushed decisions towards information that seems to offer a better disease outcomes: The radiation oncology registrar taking consent will make it clear to the potential participant that taking part in the study does not confer therapeutic gain, nor change the current standard of care. We endure to make it clear that this study will not delay or derail standard of care for the participant, but may be of benefit for future patients. Consent will specifically explain the extra radiation dose the participant will receive. The imaging modalities will be at no added cost to the participant and any transport costs associated with extra hospital visits will be covered by the study.

Electronic information will be stored on a password protected laptop as well as a password protected cloud server. The participants will be informed that the results of this study will be used for research, and the department will store the anonymised information for future research. The cost of this study will be absorbed by the department of radiation oncology, Groote Schuur Hospital.

1.7. Resources

Published journal articles; PubMed; Google Scholar; University of Cape Town FHS library databases; EBSCOhost; Clinicalkey; Web of Science; Africa-Wide; EndNote X7; Microsoft Excel; and, Stata.

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1.9. Appendices

1.9.1. Appendix 1: Effective Doses per modality

DIAGNOSTIC IMAGING MODALITY	RADIATION EFFECTIVE DOSE (mSv)[34, 39, 40]
Mammogram	0.4 (0.10-0.60)
Chest x-ray	0.1 (0.04-0.24)
Chest CT scan	7.0 (4.0-18.0)
Ultra-sound scan	0
Bone Scan	3-6.3 (0.0057mSv/MBq)
PET/CT Scan	4-5.6 (0.02mSv/MBq)
TOTAL EXPECTED DOSE/PARTICIPANT	10-30

1.9.2. Appendix 2: Breast Cancer TNM Staging[4]

Nodal status/Metastasis	T stage			
	T_1	T_2	T_3	T_4
N_0	I	IIa	IIa	IIIb
N_1	IIb	IIb	IIIa	IIIb
N_2	IIIa	IIIa	IIIa	IIIb
N_3	IIIc	IIIc	IIIc	IIIc
M_1	IV	IV	IV	IV

Shaded boxes constitute the heterogeneous group of clinically-determined LABC.

1.9.3. Appendix 3: Study consent form

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

PARTICPANT INFORMATION SHEET AND CONSENT FORM

INVESTIGATION OF BREAST CANCER IMAGING: A COMPARISON OF PET/CT SCAN AND CONVENTIONAL IMAGING

Investigators: Dr Paul Chilwesa, Radiation Oncology, Groote Schuur Hospital
We would like to invite you to take part in a research study. Research is a way of finding out new knowledge that may help us develop better treatments for patients in the future.
You are attending Groote Schuur Hospital breast cancer clinic for treatment of your breast cancer. As part of your care, you will undergo some scans to assess whether your cancer has spread. This is important because it allows doctors to decide on the best treatment for you. We are still uncertain which type of scan is the best to use, so we would like to scan you for research purposes using different machines and techniques so that we can compare them. As part of your standard care, you would receive a PET/CT scan. A PET/CT is a special type of scan that uses a radioactive dye that may allow the identification of tumour cells in different places in your body if the tumour has spread. For research purposes, we would like to request that you agree to have some additional scans, namely, a chest x-ray, an ultrasound scan, a bone scan and a CT scan.

What will the study involve?
PET/CT
This scan, which is part of your routine care, will take place at Tygerberg Hospital so transport will be provided to take you there. The procedure will involve injection of a radioactive dye into your arm and your whole body will be scanned using the PET/CT machine. This may take between 5 and 40 minutes. If the PET/CT reveals images that are not clear, we may need to take a biopsy, which involves taking a small sample using a needle in an area shown on the scan to test if tumour is present. Such biopsies would also be part of your standard care if required.

Bone scan
A bone scan is a nuclear imaging procedure. In nuclear imaging, tiny amounts of radioactive dye (tracers) are injected into a vein and taken up in varying amounts at different sites in the body. Areas of the body where cells and tissues are repairing themselves most actively take up the largest amounts of tracer. Nuclear images highlight these areas, suggesting the presence of abnormalities associated with disease, such as cancer, or injury. A bone scan includes both an injection and the actual scan.

Chest x-ray
Chest x-ray is a non-invasive procedure, with invisible rays directed at your chest, with a digital image taken. You will be asked to keep still when the image is taken. It is a short procedure, lasting not longer than 5 minutes.
Ultrasound scan

The ultrasound image is created by first transmitting sound waves into the body and then interpreting the intensity of the reflected echoes. This is achieved using a hand held probe which contacts the body via a water based gel.

CT scan
The CT scanner looks like a giant thick ring. Within the wall of the scanner there is an X-ray source. Opposite the X-ray source, on the other side of the ring, are X-ray detectors. You lie on a couch which slides into the centre of the ring until the part of the body to be scanned is within the ring. The X-ray machine within the ring rotates around your body. As it rotates around, the X-ray machine emits thin beams of X-rays through your body, which are detected by the X-ray detectors. The CT scan requires preparatory dye to be taken by mouth (instruction will be given), and some will be injected shortly before the procedure itself.

Risks
PET/CT
You will be receiving a PET/CT scan as part of your routine care so there will be no additional risks from taking part in this research from this procedure. Your doctor will discuss these risks with you.

Chest x-ray, CT scan and Bone Scan
These scans involve a small amount of radiation. Although radiation can cause cancer, the risk from such small doses is extremely low. The doses received from the bone scan may increase the risk of cancer by approximately 0.05% (5 in 1000 patients if exposed before age of 30), considered very low risk. CT scan and bone scan requires an injection to be given before the scans are done. The dye we use can cause a reaction in people who have seafood allergies or people who have had a previous reaction to it. This information will be asked of you before the procedure.

Ultrasound
Ultrasound does not use radiation and carries no radiation risk.
You might require an extra visit to complete all the above investigation, and we will give you transport refund for that. This additional visit will not any planned treatment.

Benefits
There are no benefits to you from participation, but the information obtained may benefit others in the future.

Will I be paid for participating?
You will not be paid to participate. However, you will be provided with R50 to cover transport costs for an additional visit for research purposes.

Are there any costs for participation?
There are no costs for participation in the research but the visits and procedures forming part of your regular care will need to be paid for as usual.

Do I have to be in the study?
You have the right to refuse to participate and may withdraw whenever you like. If you initially decide to take part and then decide to change your mind that is okay. If you decide not to take part in the research, your treatment will not be affected and you will not be penalised in any way.

Who will see the information that is collected about you during the study?
Only those involved in the study will see the information. We may want to publish the results in the future, but we will not use any names.

What will happen to my personal information?
Your personal information will remain confidential.

Future use of data in additional research projects
In addition to the above described research, we would like to store your clinical information and results from this study for research in the future, subject to approval by the Human Research Ethics Committee. **If you give permission for storage of your data for future research, please indicate your acceptance on the signature page.**

What happens if I get hurt taking part in this study?
While it is unlikely that you will be hurt taking part in this research, the study is covered by an insurance policy taken out by the University of Cape Town in case you suffer a bodily injury because you are taking part in the study.

The insurer will pay for all reasonable medical costs required to treat your bodily injury, according to the SA Good Clinical Practice Guidelines 2006, which are based on the Association of the British Pharmaceutical Industry Guidelines. The insurer will pay without you having to prove that the research was responsible for your bodily injury. You may ask the study doctor for a copy of these guidelines.

The insurer will *not* pay for harm if, during the study, you

- Use medicines or other substances that are not allowed
- Do not follow the study doctor's instructions
- Do not tell the study doctor that you have a bad side effect from the study procedures
- Do not take reasonable care of yourself

If you are harmed and the insurer pays for the necessary medical costs, usually you will be asked to accept that insurance payment as full settlement of the claim for medical costs. However, accepting this offer of insurance cover does not mean you give up your right to make a separate claim for other losses based on negligence, in a South African court.
It is important to follow the study doctor's instructions and to report straightaway if you have a side effect from the procedure.

Contact details
If you have any questions about the study, please contact Dr Paul Chilwesa (Tel. 021 404 4286)
If you would like to ask any questions about your rights as a research participant, please contact Professor Marc Blockman at the Faculty of Health Sciences Human Research Ethics Committee (Tel. 021 406 6338)

CONSENT

Kindly mark box (×) if you agree to the following;

- ☐I have read and understood the patient information sheet.
- ☐I give consent to be part of this locally advanced breast cancer PET/CT vs Conventional imaging study
- ☐I understand that my personal information will be anonymous when the study is published
- ☐I understand that, personally, I will not benefit from this study
- ☐I understand that I can opt out of the study at any point
- ☐I give permission for storage of my information provided for future research purposes.

_____	_____	_____
Participant signature	**Participant name**	**Date**
_____	_____	_____
Witness signature	**Witness name**	**Date**
_____	_____	_____
Investigator signature	**Investigator name**	**Date**

1.9.4. Appendix 4: PET/CT data entry form

Technical quality: Optimal ☐ **Suboptimal** ☐

Reason for suboptimal quality _____

AREA	1	2	3	SUV max	Size	CT characteristic	Metastasis
Brain							
R Breast							
L Breast							
L Axilla level 1							
L Axilla level 2							
L Axilla level 3							
L Internal mammary							
[Etc.]†							

† The datasheet continues to include the following areas: L Cervical; L Mediastinal: Level 1; L Mediastinal: Level 2; L Mediastinal: Level 3; L Mediastinal: Level 4;L Mediastinal: Level 5; L Mediastinal: Level 6; L Mediastinal: Level 7; L Mediastinal: Level 8; L Mediastinal: Level 9; L Mediastinal: Level 10; R Axilla level 1; R Axilla level 2; R Axilla level 3; R Internal mammary; R Cervical; R Mediastinal: Level 1; R Mediastinal: Level 2; R Mediastinal: Level 3;R Mediastinal: Level 4; R Mediastinal: Level 5; R Mediastinal: Level 6; R Mediastinal: Level 7; R Mediastinal: Level 8; R Mediastinal: Level 9; R Mediastinal: Level 10; L Lung; R Lung; Liver; L Adrenal; R Adrenal; Cranium; Mandible; L Clavicle; L scapula; L Manubrium; L Sternum; L Ribs; L Humerus; L Radius; L Ulna; L Pelvis; L Femur; L Tibia; L Fibula; C Spine; T Spine; L Spine; Sacrum; R Clavicle; R scapula; R Manubrium; R Sternum; R Ribs; R Humerus; R Radius; R Ulna; R Pelvis; R Femur; R Tibia; R Fibula; Skin; GIT; GUT; Other

1.9.5. Appendix 5: Bone scan data entry form

Technical quality: Optimal ☐ **Suboptimal** ☐

Reason for suboptimal quality _____

AREA	1	2	3	SUV max	Size	CT characteristic	Metastasis
Cranium							
Mandible							
L Clavicle							
L scapula							
L Manubrium							
L Sternum							
L Ribs							
[Etc.][†]							

[†] The datasheet continues to include the following areas: L Humerus; L Radius; L Ulna; L Pelvis; L Femur; L Tibia; L Fibula; C Spine; T Spine; L Spine; Sacrum; L Ulna; R Clavicle; R scapula; R Manubrium; R Sternum; R Ribs; R Humerus; R Radius; R Ulna; R Pelvis; R Femur; R Tibia; R Fibula; Skin; GIT; GUT; Other

1.9.6. Appendix 6: Human ethics research committee study approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: lamees.emted@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

06 January 2017

HREC REF: 900/2016

Dr D Anderson
Radiation Oncology
L Block
NGSH

Dear Dr Anderson

PROJECT TITLE: COMPARISON OF THE SENSITIVITY OF 18F-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY (18F-FDG PET/CT) AND CONVENTIONAL DIAGNOSTIC IMAGING IN DETECTING METASTASES IN LOCALLY ADVANCED BREAST CANCER STAGING AT GROOTE SCHUUR HOSPITAL: A PROSPECTIVE STUDY (MMed Candidate, Dr P Chilwesa)

Thank you for submitting your request to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th January 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period. (Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledges that the following MMed Candidate, Dr P Chilwesa, **will** also be involved in this study.

Please add to the informed consent document that all future use of their stored data **will** be approved by the HREC.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 900/2016

Chapter 2

Literature review

Table of Contents

2.1. Introduction

Breast cancer is the second most common cancer in adults, second to lung cancer, and is the most frequent cancer diagnosed in women globally (figure 1).[1] Breast cancer mortality rates are higher in low and middle income countries (LMIC).[1,2] In South Africa, breast cancer accounts for more than 20% of cancers diagnosed in women (figure 2).[3] Like most other African countries, patients are thought to present late, which accounts for the higher mortality in comparison to the high income countries (HICs).[4]

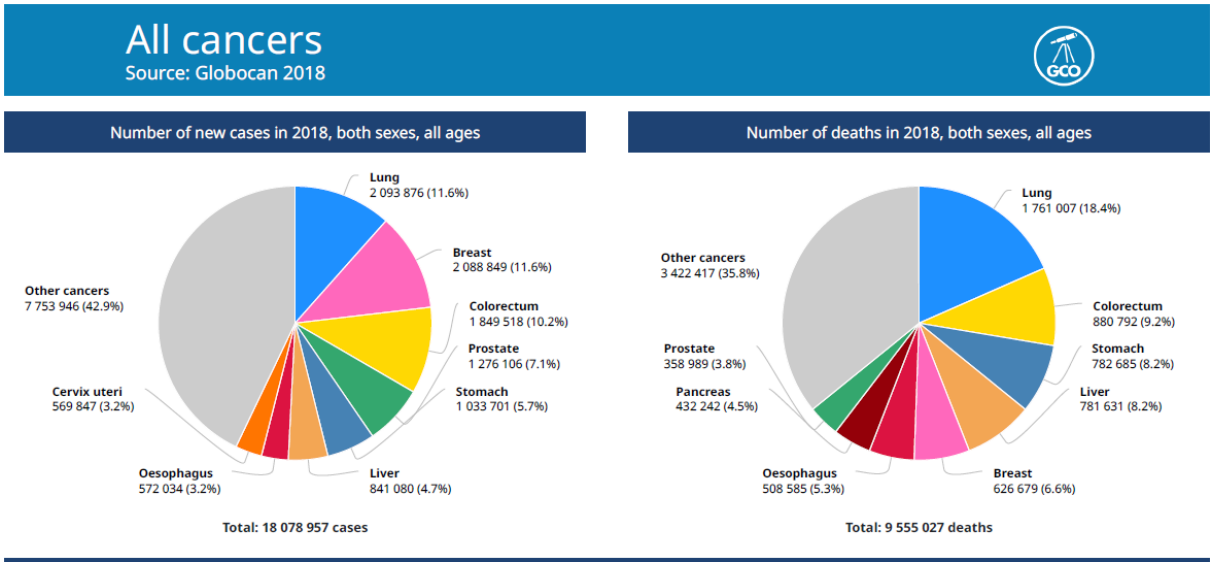

Figure 1: Global cancer burden at a glance

Source: WHO, 2018[1]

Breast cancer survival rate decreases to less than 60% and 20% in cases of locally advanced and metastatic disease, respectively.[5] Staging is defined as an assessment of tumour spread in an untreated patient with confirmed cancer[6] and is important for disease prognosis. One of the biggest challenges of breast cancer management in LMICs is the lack of access to new staging technologies, drug availability and modern radiotherapy facilities.

There exists no consensus on the definition of "locally advanced breast cancer (LABC)",[7] but most commonly this term refers to clinical stage III disease, which is a heterogeneous group of advanced primary and/or nodal disease without clinically evident systemic metastases. Approximately 40% of patients with LABC will develop metastasis within five years post treatment.[8,9]

Neo-adjuvant chemotherapy (NACT) is the standard of care in LABC[10] and is increasingly used in patients with operable breast cancer with or without axillary lymph node metastases.[11,12] The administration of NACT must follow clinical and radiological exclusion of metastasis. The presence of distant metastases is the single most important prognostic factor in patients with breast cancer, and plays a critical role in determination of therapy.[13] The importance of accurate staging at diagnosis of LABC is crucial to ensure that appropriate treatment is offered to patients, and to prevent the overtreatment of patients harbouring metastases.

The three most common sites of metastasis in breast cancer are the lungs, liver and bones.[14] Historically, these subsites were targeted in the staging processes for breast cancer using conventional imaging (CI) of bone scintigraphy, chest plain radiography, and abdominal ultrasonography. Assessment of metastasis via conventional imaging (CI) should ideally include whole body CT and bone scans,[15] however, at Groote Schuur Hospital (GSH) (Cape Town, South Africa) we use a chest radiograph, an ultrasound scan of the abdomen and a bone scan. The choice of these CI modalities at GSH is due to resource and time constraints. However, the sensitivity of these methods has been criticised, and previous studies have shown the limitations of the use of CI in the accurate staging of locally advanced breast cancer.[11,13,14,16-19]

The use of ^{18}F-FDG PET/CT in cancer care is thought to provide useful clinical information and has been postulated to lead to significant cost savings in patient management (such as avoiding expensive intervention; surgery, chemotherapy, radiotherapy).[20,21] Strong evidence has demonstrated superior diagnostic accuracy of ^{18}F-FDG PET/CT in comparison to conventional imaging in staging and restaging of most cancers.[22] The use of ^{18}F-FDG PET/CT for disease staging of patients with locally advanced breast cancer may improve diagnostic sensitivity.[23] However, we are still unsure of the diagnostic superiority of ^{18}F-FDG PET/CT over CI specifically in LABC in the South African population.

2.2. Search strategy

A comprehensive literature search was performed by using electronic bibliographic databases (i.e. PubMed, MEDLINE, Scopus, Web of Science, Google Scholar, Clinical Key, Clinical Evidence and Cochrane Library) using the following keywords: Breast Cancer; ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography; ^{18}F-FDG PET/CT; Conventional Imaging; Breast cancer Staging; Locally Advanced Breast cancer; South Africa; Low and middle income Countries; LMICs. Studies with breast cancer and ^{18}F-

fluorodeoxyglucose (FDG) positron emission tomography/computed tomography were retrieved without restriction to language.

2.3.Literature Review

2.3.1. Breast cancer incidence and mortality

Breast cancer is the second most common cancer in adults, second to lung cancer, and is the most frequent cancer diagnosed in women globally.[1] Breast cancer mortality rates are higher in low and middle income countries (LMIC).[1,2] The high cancer-related mortality rates in Africa are linked to multiple related factors with late presentation and diagnosis, and lack of adequate treatment facilities cited as the main reasons.[2,4] The mortality to incidence rate of breast cancer in SA is 46%.[24]

2.3.2. Incidence and mortality in South Africa

In South Africa, breast cancer accounts for approximately 38.5% of cancers diagnosed in women.[3,25] Like most other African countries, patients are thought to present late, which accounts for the higher mortality in comparison to the high income countries(HICs).[4] Globally breast cancer typically comprises approximately 25% of the total patient caseload.[7] The workload of the oncology unit at Groote Schuur hospital comprise 22% breast cancer related work (according to the unpublished Radiation Oncology Groote Schuur hospital & University of Cape Town Audit of activities conducted in 2017 for the period 2013 to 2016), with the majority of the intake been locally advanced at presentation. The second tertiary hospital in the Western Cape (Tygerberg Academic Hospital) estimates the patients presenting with advanced breast cancer at 60% (unpublished). The breast cancer mortality rate is considered higher than recorded (46%) in South Africa due to unreported cases.[24] This is in part due to the cancer registry being a pathology based registry. The age-standardized mortality rate is reported as 15.6 per 100,000 population, and a 5-year net survival of just over 50%.[24] In comparison, the United States averages at 90%.[26] The ASR for mortality is seen to be getting worse, reported in 2015 as 11.7 for the period spanning 2008 to 2012 to the current 15.6, which might be a reflection of an improvement in the reporting to the National cancer registry.[26,24]

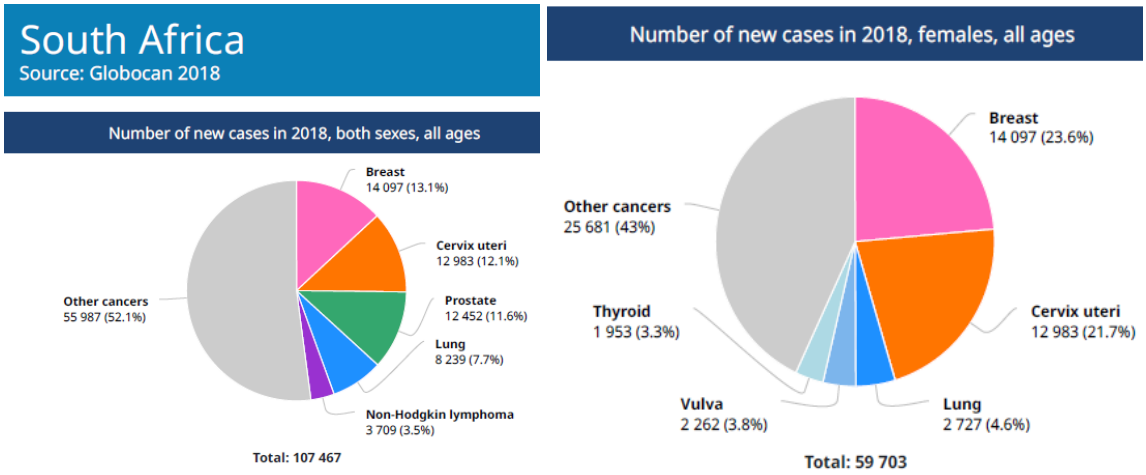

Figure 2: South African cancer burden at a glance

Source: WHO, 2018[1]

2.3.3. Importance of early detection of breast cancer

Breast cancer survival rates decrease to less than 60% and 20% in cases of locally advanced breast cancer and metastatic disease, respectively.[5] Staging is defined as an assessment of tumour spread in an untreated patient with confirmed cancer,[6] and is important for disease prognosis. Owing to the improvement in early detection and treatment, breast cancer prognosis has improved globally over the last decade nearing 80% at 5 years.[5] However this is not the case in LMICs, with the majority of cancer patients presenting at advanced or late stage.[27]

2.3.4. Problem in low and middle income countries (LMICs)

One of the biggest challenges of breast cancer management in LMICs is the lack of access to new and improved treatment and staging technologies, as well as that patients tend to present late.[2,4] It is well reported that a large proportion of women with breast cancer seek medical care late, thereby presenting with advanced disease.[4] This situation is made worse with the limited access to cancer treatment facilities, with most Sub-Sahara African countries lacking radiotherapy services, and the ones that do have face the challenges of limited access to affordable and quality services.[26,28]

2.3.5. Locally-advanced breast cancer

There is no consensus on the definition of "locally advanced breast cancer (LABC)",[7] but most commonly this term refers to clinical stage III disease, which is a heterogeneous group of advanced primary and/or nodal disease without clinically evident systemic metastases. Approximately 40% of patients with LABC will develop metastasis within five years post

treatment.[8, 9] The presence of distant metastases is the single most important prognostic factor in patients with breast cancer, and plays a critical role in determination of therapy.[13]

2.3.6. Locally advanced Breast cancer and Neo-adjuvant chemotherapy

Neo-adjuvant chemotherapy (NACT) is the standard of care in LABC.[10] This makes the surgical breast cancer operation (usually a mastectomy and axillary node clearance) safer and more successful. More recently it is also used for the conversion from a radical mastectomy to a breast conserving therapy. In both accounts it is only administered after exclusion of metastasis. Typically, NACT treatment for LABC consists of at least six cycles of combination chemotherapy and, according to the European Society for Medical Oncology (ESMO) and St. Gallen International Expert Consensus, it should include an anthracycline and a taxane component.[29,15,30]

In contrast, combination chemotherapy does not provide an overall survival benefit when used in metastatic disease, but has a role in treatment when a rapid response is desired.[15] This comes with a cost of increased toxicity. These drugs are highly toxic, especially when used in combination or sequentially when administered over 6 cycles or more. In addition there is a higher financial cost. Combination chemotherapy is thus not the appropriate treatment in metastatic disease.

Radical treatment in breast cancer refers to the use of various treatment modalities (with acceptable toxicities) with the aim of the complete cure of the disease. In LABC this typically consists of the sequential combination of multi-agent NACT, breast surgery, and radiotherapy with or without endocrine therapy.[15] The extent of disease is important for deciding the loco-regional treatment. The stage of the disease is determined by the initial clinical assessment and radiographic findings. The diagnosis of metastatic disease immediately excludes these patients from radical treatment options because no curative treatment exists yet for metastatic breast cancer.[7, 31, 32] Therefore, instead of receiving radical treatment, patients with metastatic breast cancer receive palliative treatment to improve quality of life. This non-curative option consists of targeted and/or endocrine therapy, single agent chemotherapy, and the use of radiotherapy for local and symptomatic control. It is therefore important that all clinically LABC patients be staged comprehensively before treatment is begun.

2.3.7. Breast cancer and common sites of metastasis

Breast cancer is inherently heterogeneous in nature, both in intra- and inter-tumoral variability.[33] As a consequence of this, metastatic disease varies between different molecular subtypes, although most commonly occur in bone, lungs and liver, in that decreasing frequency respectively.[34] Historically, the 3 subsites namely bone, lungs, and liver were targeted in the staging processes for breast cancer using conventional imaging (CI) of bone scintigraphy, chest plain radiography, and abdominal ultrasonography. Previous studies have shown the limitations of the use of CI in the accurate staging of locally advanced breast cancer.[11,13,14,16-19]

2.3.8. Bone Scintigraphy use in breast cancer

A search of literature showed that bone is the most common site of metastases for breast carcinoma, accounting for on average 40% to 60% of all breast cancer metastases.[7,14,17-19,35-37] Garg *et al.* in a prospective study of LABC staging with FDG PET/CT compared to CI reported bone metastases as the most common picked up metastases, accounting for 50% and 45% on CI and PET/CT, respectively.[17] This is in keeping with the most common molecular luminal subtype (approximately 85%) that is known to metastasize to bone early in the course of the disease.[33]

Osteolytic bone lesions are more common for metastatic breast cancer,[38] with some authors reporting a few mixed lytic-sclerotic,[36] however the reviewed literature does not go into the details of the type of bone lesions. This could limit the utility of bone scintigraphy with a technetium based agent, which is dependent on blood flow and osteoblastic activity: This has been shown to reduce the sensitivity in the more common osteolytic metastases, which has led to significant differences in the pick up between PET/CT and bone scintigraphy.[14]

Bone scintigraphy still remains a reasonably good option with comparable sensitivity in osteoblastic and mixed lytic-sclerotic lesions to PET/CT, despite the scarcity of these type of lesions.[14,36,39] Surprisingly, Damle *et al* (2013) showed a better sensitivity of ^{99m}Tc-MDP bone scans of 91% compared to ^{18}F-FDG PET/CT of 73%, and Groheux *et al.* also showed a lower FDG PET/CT sensitivity in purely sclerotic bone metastases: This literature offers contradictory findings about the superior sensitivity of FDG PET/CT in detection of bone metastases in breast carcinoma, and retains the utility of ^{99m}Tc-MDP bone scintigraphy in this subset of patients.[36,18] A retrospective study conducted by Morris *et al*. specifically addressed this issue that has dominated the field of breast cancer staging.[40] When he assessed if an 'integrated positron emission tomography/computed tomography *could* render bone scintigraphy unnecessary to

investigate suspected metastatic breast cancer', he found a consistency in both modalities, and concluded that PET/CT replacing bone scintigraphy in this setting remained unknown.

2.3.9. Chest X-ray use in breast cancer

Data on plain chest radiography, the chest X-ray (CXR), utility in the staging of LABC are very limited. The few available studies have shown a low yield of lung metastases, high false positive results, and inferior sensitivity in comparison to chest computed tomography.[14,41,42] The problem with thoracic metastases assessment is that most patients remain asymptomatic, unless they are complicated by a pleural effusion.

Less than a quarter of all breast cancer patients present with lung metastasis.[14] Unlike bone metastases, thoracic metastases are said to be clinically asymptomatic and uncommon at initial breast cancer diagnosis. Almost 3 decades ago, Ciatto *et al.* argued that the use of CXR for thoracic assessment and staging of breast cancer was limited and inadequate with a low sensitivity of less than 30%.[43]

Another consideration is that the positive findings on CXR usually requires the use of contrast-enhanced computed tomography (CECT) for correlation and characterization due to many breast cancer thoracic false positives. Despite the limitations with use of CXR, Puglisi *et al.* in their prospective study on baseline staging investigations for all clinical stages of breast cancer showed some patients are upstaged from early breast cancer to stage IV using CI for work-up, stating that CXR can still be useful in 'patients with a priori high risk of metastases', viz-a-viz clinical T4 and high nodal burden.[37] In most high- and middle income countries, this modality has been done away with in preference for CECT in the routine assessment for lung metastasis in LABC, which has been the preferred modality of choice for over 3 decades.[15,29,44,45]

2.3.10. Abdominal ultrasonography uses in breast cancer

Liver and abdominal metastases are rare in breast carcinoma at initial diagnosis.[14,37] The initial work for liver metastases with the help of liver enzymes or imaging remains very non-specific and is thought to be of low diagnostic yield. The correlation of deranged liver enzymes and diagnostic imaging remains poor.

Most recent evidence shows very similar pick-up in lung and liver metastases on both CI (ultrasonography abdomen, CECT) and whole body PET/CT.[17-19] This can be attributed to advancements made in image resolution on the latest generation of ultrasonography machines

(the evolution of transducers has changed our ability to visualize anatomy), and an increase in the slice number and image reconstruction of computed tomography (CT). The preferred modality to investigate for symptomatic liver metastases is a contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI).[15,46] The use of abdominal ultrasonography has been recommended as an alternative in the absence of CECT or MRI, in the characterization of small lesions identified on CECT.[47] There is a paucity of evidence on the recommended use of abdominal ultrasonography (USG) in the initial staging for breast cancer. To date no large-scale studies have been performed to investigate the utility of abdominal USG in LABC. Puglisi *et al (*2005) thought abdominal USG still had a role in the staging of breast cancer with high risk for metastasis, in locally advanced disease.[37] Considering there has also been advancement in the USG scanner and transducer capabilities since Puglisi *et al.* study, its utility in LABC requires more research and exploration.

2.3.11. Molecular subtypes and metastases

The limitations of the use of CI in accurately staging LABC has been further highlighted by the molecular classification of breast cancer which has dispelled the notion that all breast cancers have a well-defined pattern of metastasis: The molecular classification into the 4 distinct subtypes (luminal A, luminal B, HER_2/neu, Basal-like), has led to breast cancer no longer being considered a single disease, but rather diseases characterized by different molecular signatures.[14,33] Hormone receptor positive disease is generally thought to have a predilection for bone metastasis before visceral metastasis, while the triple negative and HER_2/neu subtypes are known to send metastatic deposits early in the course of disease to lymph nodes and viscera respectively.[14,34] Therefore, the use of CI in the staging of breast cancer creates a lot of opportunities for error in the restricted work-up of site and/or organ specific metastasis.

2.3.12. Positron emission tomography/computed tomography (PET/CT) and breast cancer

Positron emission tomography (PET) was introduced into clinical services in the mid-1970s for the purpose of brain and cardiac research. The use of PET in oncology came to the fore at the beginning of the 21st century, with almost 98% of all indications been staging and re-staging of tumours.[48] PET involves the topographic assessment of biochemical processes associated with the process in question. The biochemical process can be a dysfunction, for example an inflammatory disease process, or an association of the tumour biology. The common radiopharmaceutical used, ^{18}Fluorine-Fluorodeoxyglucose (^{18}F-FDG), takes advantage of the differential utilization of glucose at the cellular level between normal tissue and malignant

tumour cells. Tumours have been shown to have a higher tumour cell uptake of ^{18}F-FDG secondary to increased tumour cells glycolysis.[49] ^{18}F-FDG PET/CT measures the accumulation of the radiopharmaceutical (^{18}F-FDG) in tumour cells picked up on PET and co-registered with the CT component for anatomical localization, a hybrid technology.

Given the problems and limitations of site specific staging investigations (conventional imaging) in breast cancer, PET was considered and introduced as a suitable alternative. One of the first studies aimed at comparing the use of PET with CI in breast cancer, showed the benefit of PET in the upstaging of patients and it had superior accuracy in the detection of distant metastasis, thus influencing a change of management of patients. The Schirrmeister *et al*. study of ^{18}F-FDG PET in pre-operative staging of breast cancer in comparison with standard procedures (conventional imaging) made a conclusion that PET was better at the detection of distant metastasis, with the presence mediastinal and thoracic metastases being the highest.[16] The limitations of this study was that it was retrospective, comprised a heterogenous breast cancer histologies, and only 10% of all patients had clinically advanced (stage III) disease. They did not, however, recommend the use of PET in staging of breast cancer at initial presentation due to the low incidence of metastases at initial presentation, and due to its limited availability. Their findings were also confirmed by Dose *et al.* who found and concluded that FDG PET was superior in the detection of pulmonary metastases, and more so of mediastinal lymph node metastases in comparison to CXR, while the its sensitivity for liver and bones was similar to abdominal USG and bone scintigraphy respectively.[13] The recommendation was then made for FDG PET in locally advanced disease, i.e. clinical high tumour stage or axillary node positive disease.

The clinical stage of breast cancer at which the use of ^{18}F-FDG PET/CT could be performed with a good balance of cost and clinical superiority to CI remained unclear for almost a decade since its introduction in oncology. Reviewed literature has shown ^{18}F-FDG PET/CT utility to be maximal after clinical stage IIB, with the American (NCCN- National Comprehensive Cancer Network) and French (NCI- National Cancer Institute) making protocol adjustment of recommending ^{18}F-FDG PET/CT use in identification of unsuspected regional lymph nodal disease or distant metastases in LABC when used in addition to standard imaging studies (CI) and as a single procedure as an option in LABC, respectively.[32,50,51,52]

The use of ^{18}F-FDG PET/CT for staging in a selected group of high-risk breast cancer patients has been shown to be accurate in identifying metastases.[18,49] Groheux *et al.* found ^{18}F-FDG

PET/CT to be more superior to CI, stating that the maximal utility of ^{18}F-FDG PET/CT in breast cancer lies in the staging of locally advanced and inflammatory breast cancer, with an advantage over CI of allowing the examination of extra-axillary nodes as well as chest, abdomen, and bone in a single session.[18] This study also highlighted the importance of breast cancer histological and molecular subtype stratification for ^{18}F-FDG PET/CT indications, as they found variability in ^{18}F-FDG uptake, and recommended its use in locally advanced non- lobular breast cancers.

Similar studies conducted in India, comparing ^{18}F-FDG PET/CT and CI, designed in settings similar to ours are in agreement with the findings by Groheux *et al.*[18] Garg *et al*. prospectively found that ^{18}F-FDG PET/CT detected ipsilateral supraclavicular and internal mammary nodes, thereby upstaging patients, and outperformed all CI modalities in the detection of distant metastases. The shortfall of this study was the lack of histopathologic confirmation of metastatic lesions. They recommended the addition of CT to CI, hypothesizing that its addition was likely to improve sensitivity of CI and lead to more accurate staging. A prospective study by Gajjala *et al.*[18] conducted in India, designed in accordance with the recommendations of Garg *et al*. and with the addition of CECT to CI, found ^{18}F-FDG PET/CT to be more accurate than CI for staging and modification of stage and treatment of LABC.[19] CECT of the chest was however, more superior over ^{18}F-FDG PET/CT for the detection of pulmonary metastasis. The ^{18}F-FDG PET/CT had more false positives in the lung in comparison to CECT, with one case reported to be a lung abscess on biopsy. In agreement with previous studies, ^{18}F-FDG PET/CT outperformed CI despite the addition of CECT.

When used appropriately in oncology, ^{18}F-FDG PET/CT has been shown to provide useful clinical information and has been postulated to lead to significant cost savings in patient management (such as avoiding expensive intervention; surgery, chemotherapy, radiotherapy).[20,21] Strong evidence has demonstrated superior diagnostic accuracy of ^{18}F-FDG PET/CT in comparison to conventional imaging in staging of locally advanced breast cancers. The use of ^{18}F-FDG PET/CT for disease staging of patients with locally advanced breast cancer may improve diagnostic sensitivity.[23]

The use of ^{18}F-FDG PET/CT in breast cancer needs to be done cautiously. Breast cancer is a heterogenous disease, with proven variable radiopharmaceutical uptakes. Tagliabue *et al.* gives an important caution on the use of ^{18}F FDG PET/CT in breast cancer stating the requirement for the knowledge of its potentials and limitations as some of the findings may be misleading.[48]

The uptake of ^{18}F-FDG by lymph nodes should always be confirmed due to the known low specificity of this radiopharmaceutical.[53] Despite Schirrmeister *et al.* study been retrospective, they found as high as 20% false-negative rate for detection of lymph node metastases in breast cancer when using ^{18}F-FDG PET, but this was a heterogeneous group of participants that included early breast cancer, and also included invasive lobular carcinoma which often cannot be accurately staged by ^{18}F-FDG PET.[16] Furthermore, research suggests that the merit of this technology for screening and work-up is questionable because no large prospective studies have been done and due to the high rate of false negative sclerotic bone lesions on ^{18}F-FDG PET.[22] However PET does have superior detection rates once combined with CT. In addition, although some studies have compared whole-body PET/CT with conventional imaging, most of the results have been criticised: The limitation of many of these studies is they were retrospective, and without histologic confirmation of suspected metastases.[8,5,18] Very few prospective studies have been conducted in the developed world, and those that have, have been limited by their bias for breast cancer recurrence or metastatic disease and lack of histopathological stratification.[11,54,55,56]

The use of ^{18}F-FDG PET/CT in breast cancer remains a controversial argument, with two commonly referenced professional communities, NCCN and ESMO, not categorically recommended its use in the upfront staging procedures. NCCN in the last 2 clinical versions recommend the use of ^{18}F-FDG PET/CT in breast cancer staging in circumstances where conventional imaging remains suspicious or is equivocal in locally advanced disease,[32,46] FDG PET/CT is most useful in situations where standard imaging results equivocal or suspicious' because a few studies support its potential role for this indication. The panel further recommend consideration for biopsy of these equivocal or suspicious sites for accurate staging.

In 2013 ESMO recommended that, if PET/CT is available, it may be used (instead of and not on top of standard staging procedures) in LABC staging, but this was a weak recommendation (IIB).[29] The 2018 ESMO recommendation on the staging of LABC is non-committal, 'minimal staging work-up for ABC (advanced breast cancer) includes a history and physical examination, haematology and biochemistry tests, and imaging of chest, abdomen and bone', it is without a clear direction of what imaging technique(s) are to be employed. ABC is a heterogenous group comprising locally advanced and metastatic breast cancers.[15]

The use of PET/CT services in South Africa was introduced in 2007. A caution by the College of Nuclear Physicians (CNP) of South Africa was given, due to the high TB prevalence in the

South African population care needs to be taken over FDG-avid lesions, with such lesions creating a risk of a considerable number of false positive scans.[57] The extrapolation of evidence gathered from developed Countries on PET/CT was not recommended by the CNP at the time of it been introduced in South Africa, stating that diagnostic accuracy depends in part to prevalence of disease in the population, and such data might not be as accurate for the majority of the South African population. In consonance with NCCN recommendations, the CNP stance on the PET/CT indications for LABC is in select cases as an adjunct to conventional imaging when CI modalities used are said to be equivocal.[58]

Accurate detection of metastases can reduce the number of radical treatments and alter course of disease. On the other hand, failure to detect metastases can lead to poor quality of life. The initial ^{18}F-FDG PET/CT recommendation in breast cancer staging was for multifocal disease or suspected disease recurrence.[59] It is clear that more evidence, preferably level I, on the indications of ^{18}F-FDG PET/CT in breast cancer staging is warranted.

2.4. Conclusion

Based on information and evidence presented above, the importance of accurate staging at diagnosis of LABC is clear and crucial to ensure appropriate treatment is offered to patients, and for prevention of unnecessary overtreatment of patients harbouring metastases. Assessment of metastases via conventional imaging (CI) ideally include whole body CT and bone scans.[15] However, at Groote Schuur Hospital we used a chest radiograph, an ultrasound scan of the abdomen and a bone scan (targeting the three common areas for breast metastasis). The choice of CI at GSH was due to resource and time constraints for the use of whole body CT scan against the high volume of patients in the breast cancer clinic.

In May 2015, PET/CT became available for use in the combined breast MDT. Based on the available evidence given above from the NCCN,[44,60] CNP, and ESMO,[29] and clinical experience by the local GSH breast cancer MDT, ^{18}F-FDG PET/CT was introduced for the staging of invasive ductal carcinoma (IDC) LABC in HIV negative patients at Groote Schuur Hospital (GSH).

Evidence has pointed out that, there is considerable biologic variability within breast cancer,[33,61] which results from factors that influence the development of the disease. These factors include, but are not limited to, environmental causes, genetic factors and race.[62] PET/CT is a hybrid investigation that focuses on biological and anatomical localization of disease, thus breast

cancer biology differences might have a role to play.[18] Results from other studies cannot always be extrapolated to our settings without a consideration for the differences in the causal factors between various geographical regions. To the best of our knowledge there is no existing prospective data comparing the use of ^{18}F-FDG PET/CT with conventional imaging in IDC LABC in the South African or African population. Therefore, the focus of this research project is to develop an understanding of the diagnostic accuracy and superiority of ^{18}F-FDG PET/CT, in comparison to conventional imaging modalities, in the staging of locally advanced breast cancer. The outcomes of this research will provide evidence that may inform the local clinicians on the appropriate use of ^{18}F-FDG PET/CT in locally advanced breast cancer in South Africa.

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Chapter 3

Publication-ready manuscript

Table of Contents

The following manuscript been prepared and formatted according to author guidelines for The South African Journal of Oncology (SAJO). Author guidelines are provided in Appendix A.

1.1. Title page

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

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Word count: 4491

1.2. Abstract

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 patients receive the appropriate treatment. Increasing evidence shows that the use of ^{18}F-FDG PET/CT for disease staging of LABC may improve diagnostic sensitivity.

Aim: To prospectively assess the difference in diagnostic accuracy between whole-body PET/PET-CT and conventional imagine (CI) for staging LABC.

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: ^{18}F-FDG PET/CT found significantly more (p=0.0077) distant metastatic sites than CI (36% vs. 21%). ^{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. Thirsty-eight percent (38%) of the patients had their clinical stage unchanged. One of 5 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. (Words: 247)

1.3.Keywords

Locally advanced breast cancer; NACT; ^{18}F-FDG PET/CT; Conventional imaging; Staging; South Africa; LMICs

1.4. Introduction

Breast cancer is the second most common cancer in adults, second to lung cancer, and is the most frequently diagnosed cancer in women globally.[1] In South Africa, breast cancer is the commonest type of cancer affecting women and accounts for 26% of all female cancers, excluding non-melanoma skin cancers.[2] Like most other African countries, many patients present late with locally advanced disease (clinical stage III),[3-5] which may account for the higher mortality in comparison to the high income countries(HICs).[6]

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

At Groote Schuur Hospital in the Western Cape, patients diagnosed with LABC were previously staged with conventional imaging (CI) consisting of a 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 exists 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 ^{18}F-FDG PET-CT in comparison to CI in staging and restaging of most cancers.[3, 11-14] The use of ^{18}F-FDG PET/CT for disease staging of patients with LABC may improve diagnostic sensitivity.

Most studies assessing the clinical utility of ^{18}F-FDG PET/CT for LABC staging have emerged from high income countries.[9, 12, 15-18] A limited number of studies conducted in LMICs comparing ^{18}F-FDG PET/CT with CI have shown superior accuracy of ^{18}F-FDG PET/CT in the detection of distant metastasis in LABC.[3, 14] Two international guidelines, the National Comprehensive Cancer Network (NCCN) from North America and European Society for Medical Oncology (ESMO), agree regarding the clinical utility of ^{18}F-FDG PET/CT in breast cancer, and recommend its use when conventional imaging modalities are equivocal or suspicious in locally advanced inoperable, non-inflammatory breast cancer.[19-21] However, there remains some uncertainty regarding the diagnostic superiority of ^{18}F-FDG PET/CT compared to 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 due to the high TB prevalence in the South African population, and endemic prevalence in the Western Cape specifically, care needed to be taken over interpretation of FDG-avid lesions, due to the risk of false positive lesions.[22] The extrapolation 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.[20] Findings from the local context would be important to provide evidence of the clinical utility of ^{18}F-FDG PET/CT in LABC, and dispel the concern of over-reporting of metastasis in high TB prevalence areas. The aim of this study was to assess the difference in diagnostic accuracy between whole-body ^{18}F-FDG PET/CT and CI for staging of LABC in our local geographical setting.

1.5.Materials and methods

1.5.1. Study design

This prospective single-blinded study involved female patients presenting with locally advanced breast cancer (LABC) at the breast cancer outpatient clinic at Groote Schuur Hospital (GSH), Cape Town South Africa between January 2017 and December 2017.

1.5.2. Study setting

Groote Schuur Hospital (GSH) is a large tertiary-level state and academic hospital. It is one of two tertiary hospitals providing oncology care to the population of the Western Cape province.

Staging for LABC at GSH has typically relied on a chest radiograph, an ultrasound scan of the abdomen and whole-body bone scintigraphy (targeting the 3 common sites for breast metastasis). Early clinical stage breast cancer (T_1N_0, T_2N_0) does not routinely have radiologic staging investigations, except a plain chest radiograph. The intermediate group of patients (T_1N_1, $T_2N_1T_3N_0$) undergo a plain chest radiograph and abdomen-pelvis ultrasonography, or a CECT of the chest and abdomen as well as a whole-body bone scintigraphy if symptomatic and/or if elevated alkaline phosphatase is noted. The rest of the LABC (T_3, $N_{1+}T_4$, N_{0+}) cohort undergo a CECT of chest and abdomen, and a whole-body bone scintigraphy.

During the study period, all IDC LABC patients were staged with ^{18}F-FDG PET/CT and managed radically or palliatively accordingly. All patients were discussed in an MDT, and appropriate decisions were made depending on ^{18}F-FDG PET/CT findings and/or subsequent biopsy results.

1.5.3. 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 irresectable upfront, good performance status (ECOG 0-2), and no co-morbidities that would restrict use of ^{18}F-FDG PET/CT, and infiltrating ductal carcinoma (IDC) on histology.

Patients who had previous malignancies, and patients younger than 30 years were excluded because of the higher risk for radiation-induced malignancies. Patients who had known HIV/AIDS and/or tuberculosis were excluded, as were patients with early breast cancer (stage

I or II), those who were pregnant or lactating, male patients, patients with breast cancer recurrence, and those who did not give consent.

Sample size was estimated based on previous similarly designed studies, with an expected 40% difference in detection of metastasis between use of ^{18}F-FDG PET/CT and CI for clinical T_3/T_4 disease, irrespective of nodal status. We used an alpha value of 0.05 and a power of 80% to estimate a required sample size of 38 participants.[23, 24] An extra 10 participants were recruited to account for the possibilities of failure to complete investigations, ineligibilities, and consent withdrawals.

1.5.4. Procedures

Patients meeting eligibility criteria were identified during routine examination at the breast cancer clinic of the surgical out-patient department (SOPD) at GSH. Suspected LABC patients were assessed with the help of a surgical consultant. All participants underwent routine clinical examination, fine needle aspiration cytology (FNAC) and a core biopsy of the tumour for histological confirmation and type, as well as immunohistochemistry (IHC) for hormone receptor status, and HER_2/neu amplification status as per GSH breast cancer protocol guidelines. The Ki67 and Bright-Field HER_2 Dual In-Situ Hybridization (B-DISH) test, 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 NACT combination regimen, and because anti-HER2/neu therapy (trastuzumab) was not available on protocol due to cost constraints. The conventional investigations included serum haematology and chemistry, breast mammogram and ultra-sonography, chest radiographs, abdominal-pelvic ultrasonography, and ^{99m}Tc-MDP bone scan. Patients with known HIV and diabetes were excluded.

^{18}F-FDG PET/CT scans were performed on a GEMINI TF Big Bore PHILIPS whole-body scanner. Participants were prepared, injected and imaged in accordance with the FDG PET/CT: 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 all imaging results. All sites of abnormal ^{18}F-FDG uptake (areas that did not conforming to 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 finding were characteristic for metastasis, the lesion was scored as 3. If either the SUV_{max} or CT findings were characteristic for metastasis, the lesion was scored as 2. If neither the SUVmax or CT findings were characteristic the lesion was scored as 1. Thus, each site was scored by consensus as 1=negative for metastasis; 2 =equivocal for metastasis; 3=consistent with metastasis. Disagreements in scores were resolved through consultation with a third Nuclear Physician and a second Radiologist who then made the final decision. If there was no consensus among the 2 nuclear physicians and the diagnostic radiologist, a third nuclear physician opinion was sought.

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/CTs, when required were performed on a Symbia TruePoint 2012 SPECT/CT camera. All patients were prepared, injected, and imaged in accordance with the EANM practice guidelines for bone scintigraphy.[26] 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 ^{18}F-FDG PET/CT were performed within a three-week period of each other to avoid treatment delays and minimise reported differences in disease stage. Regardless of imaging protocol used, patients thought to have isolated metastases in distant lymph nodes or organs beyond the drainage area of the breast were subjected to biopsy for cytologic or histologic confirmation. When biopsy of the isolated lesions was deemed by the MDT to be too risky for the patient, the patient was treated as non-metastatic, and a planned follow-up scan was requested. Isolated lung lesions were biopsied via CECT-guided biopsy or endobronchial ultrasound (EBUS)-guided with trans-bronchial needle aspiration (TBNA), depending on which modality was deemed safer. The EBUS-TBNA was used to cytologically confirm the presence of IDC breast cancer in intrathoracic nodes that showed increased activity on ^{18}F-FDG PET scanning. These lesions were identified following a combined reading of the CT and PET scan by both radiologists and nuclear medicine physicians. In conjunction with the pulmonologist a directed biopsy procedure was planned. After the staging investigations, patients were discussed in an MDT and treated as per departmental guidelines, based on ^{18}F-FDG PET/CT findings.

1.5.5. Data collection

Relevant demographic information was extracted from participants' clinical folders. Information included: comorbidities, clinical stage (2010 AJCC TNM staging system, 7th edition), histopathologic subtype, immunohistochemistry markers (ER/PR and HER2 status), B-DISH results in patients found to have equivocal HER2 results on IHC, Ki-67 in patients with luminal disease if this had an impact on treatment decision making, mammogram (BIRADS score 1-6, presence of lymph nodes), Breast ultrasound scan (if done), CXR, bone scintigraphy, abdominal ultrasound, ^{18}F-FDG PET/CT, liver functions and full-blood count results. All sites of abnormal ^{18}F FDG uptake (areas not conforming to normal physiological ^{18}F-FDG uptake) and areas of ^{99m}Tc-MDP bone scan abnormalities were documented in a specifically designed standard case report form for each participant. The CXR and USG were generated from the radiologist reports. Each area had a designate score (1 = negative for metastasis, 2 = equivocal for metastasis, 3 = consistent with metastasis).

1.5.6. Data analysis

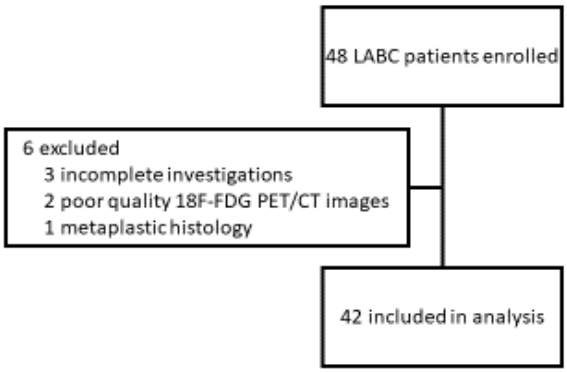
Statistical analysis was done using Stata version 15.1 (StataCorp. 2017.). Continuous variables were summarized as mean and standard deviation while nominal and ordinal variables were summarized as counts and percentages. The McNemar test for matched pairs was used to evaluate whether there was a difference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

1.6.Ethical considerations

The study was approved by the Human Research Ethics Committee of the University of Cape Town (HREC REF: 900/2016). All participants provided written consent. Data was anonymized using a study number to code for each folder number and stored in a Microsoft (MS) Excel spreadsheet on a password protected computer.

1.7. Results

Forty-eight participants were recruited; however, 6 were excluded; 2 because of poor quality ^{18}F-FDG PET/CT scans, 1 because of metaplastic histology, and 3 because they did not complete the investigations for analysis. The final analysed sample consisted of 42 participants.



The clinical and demographic characteristics of patients with newly diagnosed LABC are summarised in Table 1. The mean (±SD) age of the participants was 51.5 (±12.71) years, (Range: 27 to 77 years). Slightly more patients were post-menopausal (52.4%) than pre-menopausal (47.6%), based on a history of one year of uninterrupted absence of menstruation. More patients had cancer in the right breast (57.1%) than the left. The patients were predominantly of luminal type disease (66.7%). The stage at presentation was mainly stage IIIB (54.8), with the majority (52.38%), having clinical T4b disease (skin ulceration, peau d'orange or satellite nodules; or palpable nodal disease (90.48%).

Table 1. Demographic and clinical characteristics of participants (N=42).

Variables	**n (%)**
Menopausal status	
Pre-menopausal	20 (47.6)
Post-menopausal	22 (52.4)
Smoking history, pack years	
Nil	28 (66.7)
<10	5 (11.9)
≥10	9 (21.4)
Sidedness of the breast cancer	
Right	24 (57.1)
Left	18 (42.9)
Clinical Stage (AJCC/TNM 7th Ed)	
Stage IIB	1 (2.4)
Stage IIIA	12 (28.6)
Stage IIIB	23 (54.8)
Stage IIIC	6 (14.3)
Histology	
Invasive ductal cell carcinoma	42 (100)
Molecular subtype	
Luminal	11 (26.2)
Luminal HER_2 overexpressed	5 (11.9)
Luminal HER_2 equivocal	12 (28.6)
HER_2/neu over-expressed	3 (7.1)
TNBC	11 (26.2)
AJCC, American Joint Committee on Cancer; TNM, tumour, node, metastasis; HER_2, human epithelial growth factor receptor 2 based on IHC; TNBC, triple negative breast cancer	

^{18}F-FDG PET/CT upstaged 9 (21.4%) of patients from clinical stage IIIa to stage IIIc (Table 2), and changed management decision in 54% of the patients. Three of the 9 patients had a biopsy of the nodes, with 2 having results negative for cancer cells resulting in their down-staging. ^{18}F-FDG PET/CT (n=17, 40.5%) detected significantly more (p=0.0077) distant metastasis than CI (n=9; 21.4%; Table 3).

Table 2. Detection of metastasis by ^{18}F-FDG PET/CT compared to CI in 42 patients

Case	Clinical stage	^{18}F-FDG PET/CT	CI	Biopsy	Stage after ^{18}F-FDG PET/CT	Stage after biopsy	Management change
1	T2N1	Negative	Negative	Not applicable	T2N1	Not applicable	No
2	T4bN1	Negative	Negative	Not applicable	T4N3 (IMN)	Not applicable	Upstaged
3	T4bN2	Positive	Positive	Not done (multiple areas)	T4N3M1	Not applicable	Yes
4	T4bN2	Positive	Negative	Not done (too risky, close to vessels)	T4N2M1(lung)	Not applicable	Yes
5	T4bN1	Positive	Negative	Not done, declined	T4N3M1(mediastinal node)	Not applicable	Yes
6	T4bN1	Negative	Negative	Not applicable	T4N1	Not applicable	No
7	T4bN2	Negative	Negative	Not applicable	T4N3(IMN)	Not applicable	Upstaged
8	T4aN0	Negative	Negative	Not applicable	T4N0	Not applicable	No
9	T4bN1	Negative	Negative	Not applicable	T4N1	Not applicable	No
10	T4bN3	Positive	Positive	Not done (multiple areas)	T4N3M1	Not applicable	Yes
11	T4bN1	Positive	Negative	Station 2 node	T4N1M1	T4N1M0	No, biopsy negative
12	T3N1	Positive	Positive	Not done (multiple areas)	T4N3M1	Not applicable	Yes
13	T4bN0	Negative	Negative	Not applicable	T4N1	Not applicable	Upstaged
14	T4bN2	Negative	Negative	Not applicable	T4N2	Not applicable	No
15	T4bN1	Negative	Negative	Not applicable	T4N1	Not applicable	No
16	T4aN1	Negative	Negative	Not applicable	T4aN1	Not applicable	No
17	T3N1	Negative	Negative	Supraclavicular node	T3N3	T3N1	No
18	T4bN3	Positive	Negative	Not done, declined	T4N2M1(lung)	Not applicable	Upstaged
19	T2N2	Negative	Negative	Not applicable	T2N3(IMN)	Not applicable	Upstaged
20	T3N1	Positive	Negative	Thyroid	T3N0, second primary	T3N0	No
21	T3N2	Positive	Positive	Not done, multiple areas	T3N3M1(multiple)	Not applicable	Yes
22	T3N1	Positive	Negative	Too risky	T3N1M1(PALN)	Not applicable	Yes
23	T4bN2	Positive	Positive	Not done (bilateral lung)	T4N2M1	Not applicable	Yes
24	T3N1	Negative	Negative	Not applicable	T3N1	Not applicable	No
25	T3N1	Negative	Negative	Not applicable	T3N0	Not applicable	Down-staged
26	T4cN3	Positive	Positive	Not done (multiple)	T4N3M1	Not applicable	Yes
27	T3N1	Negative	Negative	Not applicable	T3N1	Not applicable	No
28	T4bN2	Negative	Negative	Not applicable	T4N3M0	Not applicable	Upstaged
29	T4bN3	Positive	Positive	Not done (multiple)	T4N3M1	Not applicable	Yes
30	T4bN0	Negative	Negative	Axilla	T4N1	T4N0	No
31	T2N2	Positive	Positive	Not done (multiple)	T2N3M1	Not applicable	Yes
32	T4aN1	Negative	Negative	Not applicable	T4N3(IMN)	Not applicable	Upstaged
33	T3N3	Negative	Negative	Supraclavicular node	T3N3	T3N3	Yes
34	T3N1	Negative	Negative	Not applicable	T3N1	Not applicable	No
35	T4bN1	Negative	Negative	Not applicable	T4N3(IMN)	Not applicable	Upstaged
36	T3N2	Positive	Negative	Lung	T3N0M1	T3N0M0	Down-staged
37	T4bN2	Negative	Negative	Not applicable	T4N2	Not applicable	No
38	T2N3	Negative	Negative	Not done (Rx started before biopsy of node)	T2N3	Not applicable	No
39	T3N2	Negative	Negative	Not applicable	T3N3	Not applicable	Upstaged
40	T4bN1	Positive	Positive	Not done (multiple areas)	T4N3M1	Not applicable	Yes
41	T4bN2	Positive	Negative	MDT decision not to biopsy	T4N2M1(station 2)	Not applicable	Yes
42	T4bN0	Positive	Negative	Not done, spine	T4N1M1	Not applicable	Yes

Table 3. ^{18}F-FDG PET/CT versus CI cross-tabulation

Conventional imaging	**^{18}F-FDG PET/CT**		
	Regional uptake (Negative), n	**Metastatic (positive), n**	**Total, n**
Negative, n	25	8	33
Positive, n	0	9	9
Total, n	25	17	42

Chest X-ray showed evidence of lung metastasis in 8 patients, ultrasonography of the abdomen detected liver metastasis in 5 patients, while bone scintigraphy showed skeletal metastasis in 5 patients (Table 4). The majority of detected metastases on ^{18}F-FDG PET/CT were in mediastinal lymph nodes (26%).

Table 4. Metastatic sites*on CI and ^{18}F-FDG PET/CT

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

Abbreviations: LN, lymph node; CXR, chest X-ray; USG, ultrasonography
*Certain patients had metastasis in multiple sites.

^{18}F-FDG PET/CT detected axillary uptake in 37 (88%) patients while clinical examination detected axillary lymphadenopathy in 38 (90%) patients. Of the 4 patients without clinical nodal disease, 3 had FDG-avid nodes. Of the 5 patients without significant ^{18}FDG PET/CT uptake, 4 had clinical N1 disease and 1 had clinical N2 disease. The negative ^{18}F-FDG PET/CT in a patient with clinical N2 disease had an isolated left lung nodule seen on ^{18}F-FDG PET/CT.

^{18}F-FDG PET/CT detected ipsilateral supraclavicular lymphadenopathy in 10 (23.8%) patients, which was clinically detected in only 5 (11.9%) patients (Table 2). ^{18}F-FDG PET/CT detected internal mammary lymphadenopathy (IMN) in 11 (26.1%) patients, 4 (9.5%) of whom had bilateral IMN. Overall, N3 disease, which was not recognized by either clinical examination or conventional imaging, 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 by MDT recommendation, and 2 of these were found to be negative on histopathology and/or cytology (Figure 1). All the N3 disease detected on ^{18}F-FDG PET/CT was clinically at least T4b and/or N2 or N3 (Table 2).

Comparison of ^{99m}Tc-MDP bone scan with ^{18}F-FDG PET/CT (Table 4): The bone scan detected bone metastasis in 5 (12%) patients, with the common sites being thoracic and lumbar vertebrae. The bone scan missed 2 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 bone metastatic 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 to 7 on bone scan. All the patients in this study but one had abnormal haematological blood results, with correlation found between an abnormal blood results and metastatic bone disease.

Comparison of chest X-ray with ^{18}F-FDG PET/CT (Table 4): Pulmonary metastasis was detected in 8 patients (19%) on plain chest X-ray, which was equal to the number detected on ^{18}F-FDG PET/CT, but 2 were not in the same patients nor in the same anatomical locations. The 2 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 endobronchial ultrasound (EBUS) guided biopsy. This lesion was not detected on chest X-ray. The result of the EBUS guided biopsy was negative.

Comparison of abdominal ultrasonography with ^{18}F-FDG PET/CT (Table 4): The abdominal ultrasound detected 5 suspicious metastatic liver lesions, with ^{18}F-FDG PET/CT picking up 4. The one patient with a suspected liver lesion picked up on abdominal ultrasound, and not detected on ^{18}F-FDG PET/CT, was too small to characterize or to biopsy. The ^{18}F-FDG PET/CT liver findings correlated well with abnormal liver function tests.

^{18}F-FDG PET/CT detected 11 distant lymph nodes (Table 4): The majority (9/11) of distant metastatic lymph nodes were mediastinal. The isolated para-aortic lymph node detected on ^{18}F-FDG PET/CT was not biopsied as the MDT considered the procedure too risky for the benefit and elected to treat the patient as having metastases, and to repeat the ^{18}F-FDG PET/CT at completion of the Neo-adjuvant chemotherapy (NACT).

Patients with isolated metastases detected on ^{18}F-FDG PET/CT were supposed to be subjected to biopsy according to protocol. An isolated station 2 mediastinal lymph node was subjected to an endobronchial ultrasound (EBUS) guided biopsy and was found to be negative on cytology and cell-block (Figure 2). The isolated lung metastasis detected on ^{18}F-FDG PET/CT was subjected to a CT-guided biopsy (Figure 3), in a 43-year-old luminal non-HER_2 disease patient. The radiologist performing the biopsy was availed the PET/CT images prior to the CT-guided biopsy procedure. The histopathology results were negative for metastatic or infectious diseases.

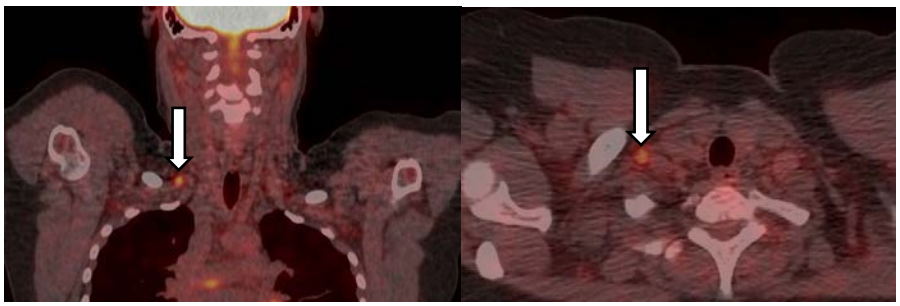


Figure 1: A 32-year-old with TNBC with suspicious right supraclavicular node on FDG PET/CT. SUV_{max} Primary disease 24.7, Supraclavicular node 3.5. Biopsy results were negative for malignancy.

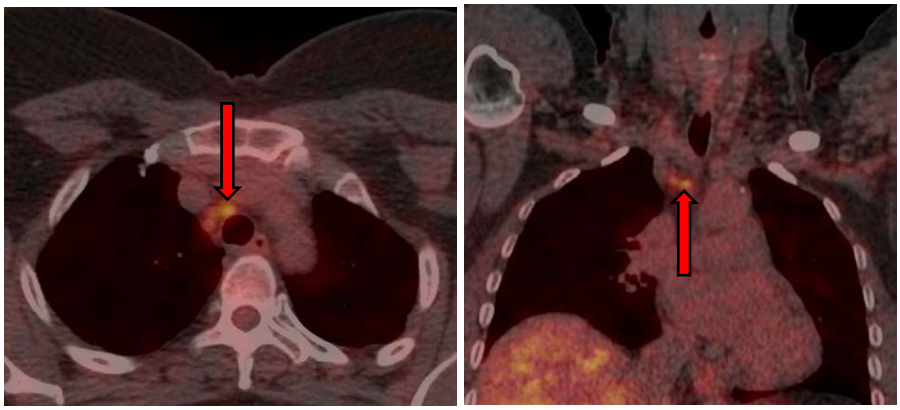


Figure 2: A 55-year-old with luminal disease with a station 2 mediastinal lymph node suspicious for metastasis on FDG PET/CT. Subjected to endobronchial ultrasound guided biopsy. SUV_{max} breast primary 8.4 node 3.4. Biopsy results were negative for malignancy.

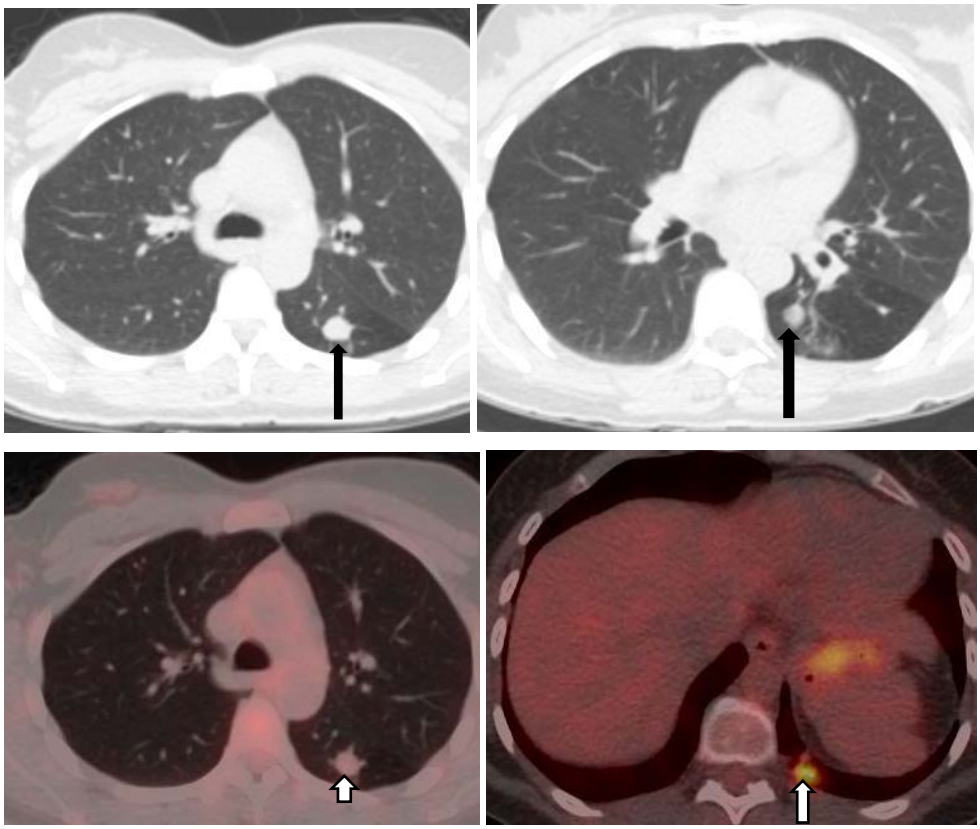


Figure 3: A 43-year-old with luminal disease with a left lung non-spiculated lesion suspicious on FDG PET/CT. Subjected to a CT-guided biopsy. SUV_{max} Primary breast 16.4 lung lesion 4.8 Biopsy results were negative for malignancy.

The SUV_{max} tended to differ across different molecular subtypes, with a 2-fold difference between minimum and maximum values (Table 5). The SUV_{max} findings of the patients who had metastases were analysed against their respective molecular subtypes (on surrogate markers). Patients with HER2 disease demonstrated the highest values (SUV_{max}=20.2) while patients with luminal disease demonstrated lower values (SUV_{max}=10.19).

Table 5: SUV values against molecular subtypes in metastatic disease

Molecular subtype	**N**	**minimum**	**maximum**	**median**	**IQR**
Luminal	4	3.4	10.19	4.11	3.54
HER_2 over-expressed	2	3.7	12.99	8.35	9.29
Triple Negative	7	2.97	14.5	6.2	9.06
Luminal HER_2 positive	2	6	20.2	13.1	14.2
Luminal HER_2 equivocal	6	3.49	10.4	7.75	2.93

Abbreviations: IQR, inter-quantile range

1.8.Discussion

The study aimed to assess the difference in the sensitivity of ^{18}F-FDG PET/CT and CI in detecting metastases in patients with locally advanced invasive ductal carcinoma (IDC) of the breast treated at Groote Schuur Hospital. ^{18}F-FDG PET/CT was superior to the selected CI (CXR, USG, bone scan) in the detection of distant metastases(p=0.0077), resulting in the upstaging of disease in 21.4% of patients from clinical stage IIIa to stage IIIc, and changed management in 54 % of patients. Of the 5 suspected metastatic sites that were biopsied, only one was positive for malignancy. This indicates the limited specificity of ^{18}F-FDG PET/CT to distinguish between malignant and benign lesions.

The CNP of South Africa recommend the use of PET/CT in breast cancer in select cases as an adjunct to CI when such modalities are equivocal, as well as in disease recurrence for staging.[27] The NCCN guidelines recommend ^{18}F-FDG PET/CT as a category 2B (weak evidence) option for diagnostic staging work-up.. The NCCN also advocates for its use in LABC particularly in patients with equivocal or suspicious findings on conventional standard staging modalities.[19, 28] The main reason for not advocating for upfront use of ^{18}F-FDG PET/CT is the lack of data showing a clear clinical benefit.

The existing data comparing ^{18}F-FDG PET/CT and CI modalities has 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 is a scarcity of any prospective data from developing countries, where in addition to late presentation, infectious diseases remain a big challenge.[29] International literature has most patients presenting with earlier stages of disease (stage IIB or IIIA),[12] in comparison to LMIC where more advanced stages (IIIB or IIIc) are the majority.[14] This prospective study of 42 LABC patients who were simultaneously staged with ^{18}F-FDG PET/CT and conventional imaging, found 70% of patients staged as IIIB or IIIC.

The study aimed to assess the difference in sensitivity in detecting metastases between whole-body ^{18}F-FDG PET/CT and conventional imaging (CI) in patients with locally advanced invasive ductal carcinoma (IDC). Overall, our findings suggest that ^{18}F-FDG PET/CT was able to detect more metastases than the selected CI (CXR, USG, bone scan), and resulted in upstaging of disease, which was similar to previous studies.[3, 9, 12, 14, 30] However, it was not possible to determine sensitivity and specificity due to the limited number of patients who underwent biopsies as indicated in Table 2.

The apparent superiority of ^{18}F-FDG PET/CT and 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 is consistent with the earlier studies conducted by Schirrmeister *et al.* and Dose *et al.* who found that ^{8}F-FDG PET/CT was superior for the detection of distant metastasis, particularly the presence of mediastinal and thoracic lymph node metastases.[9, 30]

^{18}F-FDG PET/CT upstaged the nodal status in 5 patients by detecting internal mammary nodes (IMN). This had an impact on the target delineation and field of radiotherapy. Including involved IMN in the radiotherapy field has shown a trend towards improved disease-free survival, and overall survival. [31, 32] 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.[32]

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. Tuberculosis is known to be a PET-avid infectious disease.[34, 35] The uptake of ^{18}F-FDG in lymph nodes should ideally be confirmed to be metastatic by biopsy, due to the known low specificity of the radiopharmaceutical, raising concern for the possibility of false positives.[3, 10] In accordance with our study protocol, patients with isolated solitary metastatic lesions on ^{18}F-FDG PET/CT were subjected to a biopsy for histopathological confirmation if considered safe (Figures 1-3). The low positive biopsy results of only 20% was in agreement with the known poor specificity of ^{18}F-FDG PET/CT. Histopathological confirmation must therefore not be omitted in cases of isolated solitary lesions found on ^{18}F-FDG PET/CT as these may lead to incorrect upstaging and treatment. There may be 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.

^{18}F-FDG PET/CT detected ipsilateral supraclavicular lymphadenopathy in 10 (23.8%) patients, which was clinically detected in only 5 (11.9%) patients. All patients with ^{18}F-FDG PET/CT-detected ipsilateral supraclavicular lymphadenopathy or isolated mediastinal lymphadenopathy had clinically advanced T_4-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 such advanced disease. We would recommend that breast ultrasound, including axilla be extended to the supraclavicular areas, to help distinguish between inflammatory and metastatic lymph nodes.

^{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 routinely used in centres with the capability of biopsy of such sites, in order to avoid up-staging of disease.

The majority of distant metastatic disease (60%) seen on ^{18}F-FDG PET/CT is of the aggressive subtype. This is consistent with international studies, where the amount of FDG uptake is determined by the presence of glucose metabolism and hypoxia in breast cancer cells.[13, 14] In the present study, SUV_{max} values tended to differ across different molecular subtypes. However,

confirmation in larger studies with similar use of subtyping via molecular surrogate markers should be done.

The study has highlighted the superiority of ^{18}F-FDG PET/CT over CI in our LABC cohort. Clinically this is useful for selection of patients that would derive the most benefit from this staging investigation, especially if coupled with access to histologic confirmation of the 'hot spots' found on ^{18}F-FDG PET/CT. ^{18}F-FDG PET/CT was superior to CI mainly for mediastinal lymphadenopathy. Patients with isolated mediastinal lymphadenopathy based on ^{18}F-FDG PET/CT warrant further confirmatory investigation before they can be classified as having metastatic disease.

^{18}F-FDG PET/CT has limited specificity in its ability to distinguish between malignant and benign lesions, both of which demonstrate increased glucose utilization.[12] The low number of histological confirmations of all imaging findings by biopsy 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 generalizability due to lack of sufficient randomization and stratification. Future research should include larger samples recruited from multiple centres.

1.9. Conclusion

^{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 also provided more accuracy in detection of distant metastases. It was most useful in the 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 to CI in this study, therefore, showed a clinical difference in the evaluation of LABC staging, increasing its utility in this clinical group of breast cancer. The use of ^{18}F-FDG PET/CT for breast cancer staging is therefore recommended in LABC, with a better accuracy if biopsy of isolated suspected metastatic lesions can be performed safely and timeously. Larger multi-centred prospective studies are required to ascertain the significance of isolated solitary lesions on ^{18}F-FDG PET/CT. Further research into the genetic profile of breast cancer patients and its correlation to quantitative PET/CT parameters is warranted. (Words: 4244)

1.10. Acknowledgements

We acknowledge the Groote Schuur Hospital and its departments involved in the provision of diagnostic tools for this study, at no cost to the enrolled patients.

1.11. Funding sources: Departmental MMED fund was used to pay for the statistical analysis.

1.12. Author contributions

PMC and DA conceived the presented idea. PMC wrote the manuscript under the supervision of JP. RG and GH reported the conventional imaging of chest X-rays and abdominal ultrasounds. RS and SM reported on the ^{18}F-FDG PET/CT and bone scans. FM was the consultant surgeon for the clinical staging confirmation. LM performed endobronchial biopsies of the isolated mediastinal nodes. KM providing writing assistance, critical feedback on drafts and final formatting and language editing. AH and AJH performed the statistical analysis. All authors were involved in the formulation of the study protocol.

1.13. Conflict of interest disclosures

None to the best of our knowledge.

1.14. References

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Appendices

1.15. Appendix A: SAJO manuscript guidelines

Original Research Article full structure

Title:

- Full title: Specific, descriptive, concise, and comprehensible to readers outside the field. Max 95 characters (including spaces).
- Tweet for the journal Twitter profile: This sentence/statement will be used on the journal Twitter profile to promote your published article. Max 101 characters (including spaces). If you have a Twitter profile, please provide us your Twitter @ name. We will tag you to the Tweet.

Abstract: The Abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. The Abstract should not exceed 250 words. Please minimize the use of abbreviations and do not cite references in the abstract. Refer to the relevant article type's guideline you are submitting for the abstract sections.

Introduction: The Introduction should put the focus of the manuscript into a broader context and explain its social and scientific value. Address this to readers who are not experts in this field and include a brief review of the key literature. If there are relevant controversies or disagreements in the field, they should be mentioned. Conclude with a brief statement of the overall aim of the experiments and a comment about whether that aim was achieved. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

Methods: The Methods section should provide clarity about how and why a study was done in a particular way. It should provide enough detail for reproduction of the findings. Protocols for new methods should be included, but well-established methodological procedures may simply be referenced. A full description of the methods should be included in the manuscript itself rather than in a supplemental file. Only information that was available at the time the plan or protocol for the study was being written must be included; all information obtained during the

study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.

The methods section should include:

- The selection and description of participants or description of materials.
- The aim, design and setting of the study.
- The description of the processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses.
- The type of statistical analysis used, including a power calculation if appropriate.

The Methods section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

Results: Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods Section. Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as “random” (which implies a randomizing device), “normal,” “significant,” “correlations,” and “sample.” Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

Conclusion: It is useful to begin the discussion by briefly summarizing the main findings, and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Discuss the influence or association of

variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses, when warranted and label them clearly.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named.

Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our policy on competing interests.
- Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.
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References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

Word limit	3500-4000 words (excluding the structured abstract and references)
Structured abstract	250 words to include a Background, Aim, Setting, Methods, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate