AUDIT OF ULTRASOUND GUIDED CORE NEEDLE BIOPSIES OF IPSILATERAL AXILLARY LYMPH NODES IN BREAST CANCER.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Radiology Diagnostic

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Declaration

I, David Akilimali Balolebwami, declare that this research report is my own work. It is being submitted for the degree of MMed (RadD) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

DR DA Balolebwami

On this 06 th day of October 2020

To my dad Didier and the whole family for your endless support.

Publications and presentations

This work has never been published or presented at a congress.

Abstract

INTRODUCTION: The most essential prognostic factor in the management of primary breast cancer patients is the involvement of axillary lymph nodes. Ultrasound-guided core needle biopsy (US-guided CNB) of lymph nodes is a simple and minimally invasive technique used to stage the axilla.

AIM: This study aims to establish the clinical usefulness and the diagnostic accuracy of US-guided CNB in targeting metastatic axillary lymph nodes.

METHOD: This study is a retrospective review of US-guided CNB of ipsilateral axillary lymph nodes in breast cancer patients. Nodal ultrasound findings were considered suspicious for metastases when one of the following features was visualized: nodal enlargement (>2cm), cortical thickening (>3mm), loss of fatty hilum and non-hilar blood flow (NHBF). US-guided CNB histopathological were compared to axillary lymph node dissection (ALND) histology results for diagnostic accuracy.

RESULTS: Axillary nodal metastases were found by US-guided CNB in 120/132 (90,9%) patients. Axillary lymph node dissection was performed in 63/130 (48,4%) patients, 56/63 (88,8%) and 7/63 (11,1%) of these patients had positive and negative US-guided CNB results respectively. In this study, there were no false-positive results, the false-negative result was 1/7.

It was found that NHBF had a PPV of 89,8% (p=0,05), identifying a significant difference between histologically involved and non-involved nodes.

Among the US-depicted abnormalities, thickening of the cortex had the highest sensitivity 91/118 (77,1%), followed by the absence of fatty hilum 84/119 (70.6%) whereas the size of the node had the highest specificity 36/37 (97,3%).

CONCLUSIONS: Axillary lymph nodes in breast cancer patients can be sampled with high accuracy using the US-guided CNB technique.

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List of Abbreviations and Terminology

ALND	Axillary Lymph Node Dissection
BIRADS	Breast Imaging and Reporting Data System
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CNB	Core Needle Biopsy
CT	Computed Tomography
FNA	Fine Needle Aspiration
HIV	Human Immunodeficiency Virus
LMP	Lymphoma
LN	Lymph node
MRI	Magnetic Resonance Imaging
NHBF	Non-Hilar Blood Flow
NHLS	National Health Laboratory System
NPV	Negative Predictive Value
PACS	Picture Archiving and Communication System
PPV	Positive Predictive Value
SLND	Sentinel Lymph node Biopsy
TB	Tuberculosis
TNM	Tumour Node Metastasis
US	Ultrasound
USFNA	Ultrasound-Guided Fine Needle Aspiration

1. Introduction

The knowledge of ipsilateral lymph node status is of great significance in the management of breast cancer (1) (2).

Previously, after ablation of the primary breast tumour, surgeons were performing an extensive axillary lymph node dissection without accurate information on the metastatic status of the primary lesion (3).
The alternative technique of sentinel lymph node biopsy widely accepted may be time-consuming; the surgeon spends a significant amount of time harvesting positive sentinel lymph nodes (4) (5) (6). Also, this method may have some inaccuracies; if no sentinel node is found then an axillary lymph node dissection is required (7).

To reduce the morbidity related to these surgical procedures, radiologists have developed less invasive transcutaneous methods of sampling suspicious lymph nodes in breast cancer (8) (9) (10). Axillary lymph node biopsy minimises the incidence of extensive “axillary lymph nodes dissections” and “sentinel lymph node biopsy” by providing accurate staging information of the lesion (11) (12).

Different techniques are evolving depending on the imaging modality in use.
Ultrasonography has been the foremost widely used modality for this purpose. The practice of “ultrasound-guided Axillary lymph node Fine Needle Aspiration” (FNA) is declining because this recovers only a few cancer cells insufficient for detailed study such as receptor profiles which “Ultrasound-guided Core Needle Biopsy” can provide (13) (14).

1.1. Anatomical relevance of axillary lymph nodes in metastatic breast cancer

Breast cancer is one of the common neoplasms in the female population. Axillary lymph nodes status is an important prognostic factor and a great indicator of long-term survival in breast cancer (15) (16) (17). It provides relevant information and a guide to systemic therapy.

Even though the therapy choice also depends on the age of the patient, the size of the tumour, the histological grade, the receptors for oestrogen, progesterone and HER 2-neu; the axillary lymph nodes mirrors the interaction of the primary lesion's aggressiveness and the host response (18).

Other important prognostic factors are the number lymph nodes, the extent of involvement, the anatomical location of concerned axillary lymph node and whether there is micro or macrometastasis.

Axillary lymph nodes receive 75% of lymph from the breast via a well-established anatomic pathway; hence, compose the principal lymphatic drainage of the breast. Anatomically, there are five axillary lymph nodes sets, the anterior (pectoral), the posterior (subcapsular), the lateral (humeral), the medial and apical (posterior and superior to the pectoralis minor) nodes. The final common pathway for all the nodes is constituted by the apical group. Surgeons categorises axillary lymph nodes according to their location relative to the pectoralis minor muscle. Three surgical levels of axillary lymph nodes are acknowledged (19):

- Level I: located lateral or below the margin of the pectoralis minor muscle.
- Level II: located deep to the pectoralis minor muscle
- Level III: located medially or superficially to the upper margin of the pectoralis minor

Breast cancer metastasis spread to the ipsilateral axilla in predictable fashions. Level I nodes are primarily affected, followed by Level II (20) (21). Occasionally, Level I nodes are spared. Thus, Level II nodes are chiefly involved in 25 % of cases (22). Level III nodes are rarely affected without prior involvement of Level I and II; hence, the latest levels are more addressed by axillary dissection.

1.2. Ultrasonogram of an axillary lymph node

Axillary lymph nodes can be examined by different imaging modalities such as CT scan, MRI and nuclear medicine; ultrasound is the gold standard modality for this purpose. This detects, localises and further characterizes axillary lymph nodes metastasis (23) (24). Previously, patients underwent routine axillary lymph node dissection for both diagnostic and metastatic disease management. The evolution of screening ultrasound of the axilla in breast cancer subsequently gave rise to ultrasound-guided fine-needle aspiration (USFNA) of axillary lymph nodes and then to ultrasound-guided core needle biopsy of axillary lymph nodes.

To perform an axillary ultrasound, the patient is placed in the supine position her/his hands joined above the head, or in an oblique position, concerned side up with the ipsilateral hand placed above the head ("bathing beauty" position). A high-frequency transducer (7.5-17 MHZ linear probe) provides better special resolution and details visualization for adequate characterization of lymph nodes. Grey-scale, colour Doppler and power doppler are mainly used during the study. The operator interrogates the axilla, which is the zone of interest, focusing on its lower aspect especially in the region adjacent to the lateral edge of the pectoralis major muscle including the axillary fossa (25). The update of the TNM classification no longer considers supraclavicular lymphadenopathy as metastases (26). Lymph nodes are scattered throughout the axillary fat. The axillary tail is also scanned. Level III nodes are not routinely examined. The aim is to detect at least one lymph node (27). Ultrasonographically, axillary lymph nodes are assessed according to the following criteria:

1.2.1. Size and shape

Classically, benign axillary lymph nodes measure 2 cm or less in the maximal diameter; however, size is not a reliable criteria for discriminating benign from suspicious lymph node since metastatic deposits have been documented in small axillary lymph nodes (< 1cm of diameter) (28) (13). Conversely, reactive lymph node can be large enough to be misguiding. A normal or benign- appearing axillary lymph node is oval in shape, frequently wider than taller with long to short axis ratio greater than 1. Benign lymph node hypertrophy involves the lymphatic follicles and sinuses, preserving the oval form. Any changes in shape and long to short axis ratio are of suspicious appearance (29).

1.2.2. Cortex and margins

A benign-appearing node should have regular margins. The cortex is hypoechoic with almost homogenous thickness not exceeding 3 mm. The lymphatic channels enter the lymph node via the cortex. Metastatic cells deposits expand the cortex of the node. The focal cortical bulge is one of the early morphologic changes in the presence of metastasis. Diffuse cortical thickening is highly associated with malignancy however eccentric cortical thickening is more suspicious especially in known malignant primary lesion. As the cortex expands, the surface of the lymph node becomes lobulated. However, in patients with HIV, reactive hyperplasia of the axillary nodes is not uncommon and the cortex may be greater than 3 mm in thickness.

1.2.3. Hilum

Vascular supply of lymph node enters the hilum, hence normal lymph node has an echogenic fatty hilum. A normal hilum is elliptical in shape, and the preservation of this form is a sign found in 90% of benign lymph nodes. Compression and total replacement of the fatty hilum from inward bulging of the cortex due to metastatic deposit is frequently observed in involved cortex. Hence the hilum becomes compressed and absent in an involved lymph node.

1.2.4. Colour Doppler

Colour Doppler is used for detecting abnormal blood flow. Low filter and low-velocity setting are conventional. The colour gain is also slightly increased to detect minimal flow without causing noise artefact. The hilar vasculature in normal lymph nodes was described in early 1988 by Morton (30). Because of this notion, a characterization by the morphological description of the angioarchitecture is described:

- Where central vessels of hilar topography are found connected in a regular fashion along the hilar vascular axis with the appearance of intra-nodular vascular spots, a benign condition is suggested.
- The presence of peripheral vessels in conjunction with tumour neo-vessels, displaced or amputated hilar vessels, aberrant vessels of perforating-type, and absence of focal vascularization favour malignancy (29).

Colour Doppler is not specific if used separately as a diagnostic criterion; its value increases with the number of morphological signs present, and when all the criteria of

angioarchitecture are met, the positive predictive value is high reaching 94% (vs 67% for a single criterion) (31).
Associated with other criteria previously described (cortical hypertrophy, absent fatty hilum), the specificity of colour doppler increases and the value of the two methods combined reaches 87% (29). Other practical advantages of colour ultrasound are the visualisation of vascular markers during internal mammary exploration and US-guided CNB sampling.

1.2.5. Contrast enhancement

Involved axillary lymph nodes demonstrate enhancement after injection of contrast material (microbubbles) in the peri-areolar region. This technique improves the detection of malignant peripheral vascularisation. Hence, suspicious lymph nodes can be successfully identified and biopsied (32).

1.3. Biopsy of lymph nodes.

Suspicious lymph nodes are identified with axillary screening ultrasound in newly diagnosed breast cancer. These lymph nodes are sampled by core needle biopsy technique.

1.3.1. Biopsy device

Core needle biopsy is performed habitually with an “automated 14-gauge core biopsy needle”. A “Tru-Cut biopsy needle” can also be used. By firing a stylet, a cutting cannula captures the tissue sample in a quick sequence. Advanced echogenic technology offers better ultrasound visibility of the stylet needle and the cutting cannula. Manoeuvring must be done with care; the cutting cannula must not be advanced very far beyond the lymph node to avoid vessels, nerve or other tissue damage.
Automated needles have the advantage of the easy-to-use benefit, good quality specimens, and a higher sampling rate (33).

1.3.2. Technique

The biopsy procedure is fully explained to the patient, and his\her consent gained. The patient is placed in an oblique position, concerned side up with the ipsilateral hand placed above the head. A wedge pillow is used to immobilize the patient in that position.

The area of interest is cleaned and draped.

Once a target lymph node is distinctly identified on ultrasound, the next step is to assess the local vasculature with the mean of the colour Doppler. Large vessels in the vicinity of the target lymph node must be avoided. Guided by the ultrasonogram, the operator plans an optimal needle approach for the puncture. The skin and deeper soft tissues along the future biopsy track are numbed with a local anaesthetic. The operator incises the skin with a #11 scalpel.

The biopsy needle is then advanced under real-time ultrasound guidance; the tip of the cannula must remain visible and uncorked. Once the outer cortex of the lymph node is reached, the cutting cannula is smoothly advanced manually through the centre of the target or the operator can fire the trocar and cutting cannula automatically without advancing the needle tip. The needle throw image position is saved for documentation. Under ultrasound control, the needle is withdrawn, and the operator or the assistant applies his hand or finger on the biopsy site for pressure haemostasis.

The specimen is assessed before being placed into formalin 10%. An excellent specimen has target tissue that appears white or brown-tan, and the adjacent fat to the lymph node is yellow. A sample composed of fat only will float on the formalin surface because of its low density or partially sink. Specimen with nodal tissue replaced by tumour will sink to the bottom of the formalin container. If these conditions are not satisfied, further sampling is advised (33).

1.3.3. Complications

Active haemorrhage and bruising are consequences of puncturing a blood vessel. Another serious complication is the pain, indicating that the needle has been inserted into a nerve. The mastery of the anatomy and adequate expertise in handling biopsy equipment are necessary tools to prevent complications. Minimal haemorrhage can be managed with manual pressure haemostasis. Pneumothorax is very rare (2).

1.3.4. Histopathology

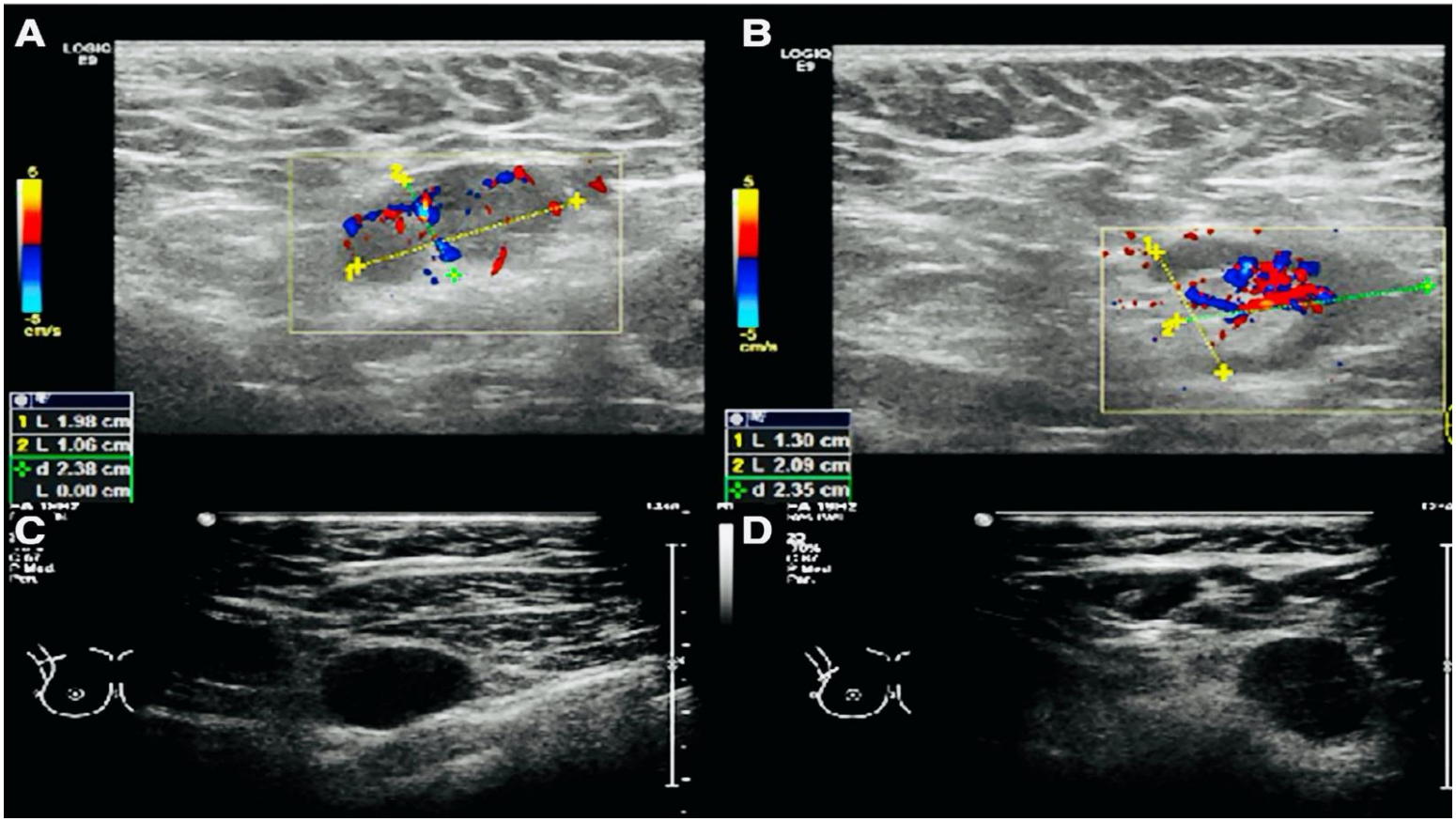
It is essential for the pathologist to identify metastasis in submitted biopsy samples accurately. Special expertise and immunohistochemical stains are required to identify isolated tumour cells. Categorization of nodal metastasis has been stated by both the Union

for international Carcinoma Control Tumour Node Metastasis and The American Joint Committee on Carcinoma (AJCC).

The size of the metastatic deposit in millimetre along the greatest axis of a lymph node or the number of cancer cells within the lymph node help to distinguish the pathologically node-positive disease from node-negative (pN0).

Micrometastasis range in size from 0.2 to 2 mm or (>200 cells in one lymph node section).

Macrometastasis is tumour deposits of >2 mm (34).



(A) Suspicious axillary lymph node with thickened cortex and early loss of hilar vascularity

(B) Normal axillary lymph node.

Figure 1.1. Axillary lymph node ultrasonogram (CMJAH mammography department)

1.4. Aim

This study aims to establish the clinical usefulness and performance of US-guided core needle biopsy in targeting metastatic axillary lymph nodes.

1.5. Study objectives

To:

- Determine the diagnostic frequency of US-guided core needle biopsies of suspicious ipsilateral axillary lymph node in a cohort of newly diagnosed and treatment naïve breast cancer patients.
- Determine the false positive and false negative results associated with US-guided CNB.

2. Materials and Methods

2.1. Research paradigm

This is a retrospective review of patient's radiological images, histopathological reports of sampled primary breast tumour/axillary lymph nodes and axillary lymph nodes dissection as well as medical notes.

2.2. Sample

This study was conducted on patients that attended the breast clinic and the mammography department at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from July 2017 to December 2018.

2.2.1. Inclusion criteria

Patients that presented with clinically suspicious invasive breast cancer and involved ipsilateral axillary lymph node(s) if:

- They were treatment naïve.
- They underwent US-guided core needle biopsy of both primary tumour and suspected metastatic lymph node(s).
- They had available radiology and histology results.

2.2.2. Exclusion criteria

Patients were excluded where:

- The breast lesion was found to be benign
- They have had previous radiotherapy and chemotherapy.
- The radiology and/or histology results were unavailable or equivocal.

2.3. Materials and Methods

Were considered, core needle biopsies performed in the mammography department using either an automatic Pro Mag TM 14G biopsy needle or semi-automatic Super Core 14G biopsy needle (supplied by Argon Medical Device).
All core needle biopsies have been visualised under ultrasound guidance using a high-frequency probe 18MHz of a Toshiba Xario 100 US-machine and all the specimens processed according to the South African National Health Laboratory System (NHLS) standards.
UG-core needle biopsies have been performed by a single team of two senior radiologists and histopathological results interpreted and/or reviewed by a single senior consultant, all having more than 17 years of experience in their respective fields.

2.4. Data collection

Data was collected from, breast clinic (patients record), patients files (to determine surgical outcomes), Picture Archiving and Communicating System (PACS) in the radiology department and from the National Health Laboratory System (NHLS) database.
The data have been entered on a Microsoft Excel spreadsheet and include:

- Age
- Breast laterality
- BIRAD
- Clinical TNM
- Suspicious sonographic features of biopsied lymph nodes included: Size (cm) and shape (oval or lobulated) cortical thickness in mm, hilum (present or absent), doppler (non-hilar blood flow).
- Primary tumour histology and grade (as per revised Bloom-Richardson grading system)
- Lymph node histopathology
- Associated comorbidities: HIV, lymphoma, tuberculosis.
- Neoadjuvant chemotherapy/radiation.
- Histopathological results of axillary lymph nodes dissection.

2.5. Data analysis and statistics

Statistical calculations were performed by using STATA 15 versions 11.0, software. The statistical significance level gives the p value ≤ 0.05.

Ultrasound features were compared to histopathological results using the Yates $\chi 2$ test.

Lymph nodes size of 20 mm and cortical thickness of 3 mm were considered as the cut-off point.

Positive and negative US-guided CNB histopathological results were confirmed on ALND histology results.

2.6. Ethics

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand, approval number M190293. This certificate is attached as Appendix A.

3. Results

3.1. Baseline characteristics of the participants

Between July 2017 and December 2018, a total of 140 patients presented at CMJAH with clinically suspicious invasive breast cancer and involved ipsilateral axillary lymph node(s). Of the patients excluded, 2 patient specimens were histologically not representative, 5 patients presented with one of the following lesions: breast abscess, lymphoma, fibroadenomas, autoimmune mastitis, phyllodes tumour. One patient had no data on PACS. Therefore 132 patients constituted the inclusion group as illustrated in Flow diagram 3.1. The age varied from 28 to 80 years, the mean age was 53 years.

The BIRADS categories of the primary breast tumour are as follow:

- 3/132 (2,3%) patients presented with BIRAD 4,
- 126/132 (95,4%) patients presented with BIRAD 5 and
- 3/132 (2,3%) patients presented with BIRAD 6

The right breast was involved in 71/132 (53%) patients than left breast 61/132 (46,2%) patients.

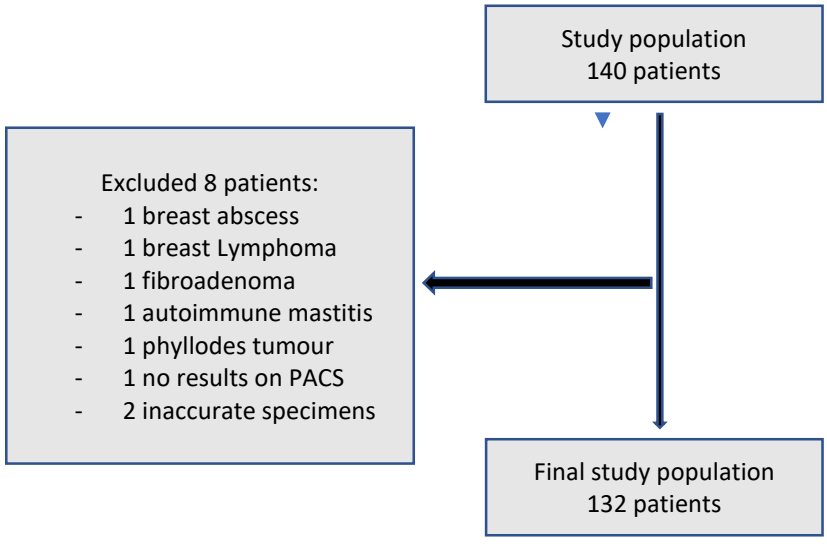


Figure 3.1. Flow diagram of the constitution of the final study group.

3.2. Histopathological results

Axillary nodal metastases found by US-guided CNB in 120/132 (90,9%) patients are illustrated in Table 3.1.

Table 3.1. Prevalence of US-guided CNB.

Lymph node status	*Frequency (n)*	*Percentage (%)*
Malignant	120	90,9
Benign	12	9,1
Total	132	100.00

After admission, axillary lymph node dissection (ALND) was only performed in 63/132 (47,7%) patients, 69/132 (52,2%) haven't benefited from axillary lymph node dissection; 2 patients had had a SLNB with no further documentations, 2 patients had other distant metatastatic foci from advanced cancers. The remaining 65/69 (94,2%) did not undergo ALND for diverse raisons: refusal of treatment, lack of follow-up, death, changes in management upon cleanical review.

Of those 63 patient that had ALND, 56/63 (88,8%) patients had metastatic nodes on US-guided CNB and 7/63 (11,1%) of them had non- metastatic nodes on histopathological results.

The final histopathological results on ALND were as follow: 48/56 (85,8%) positive patients on US-guided CNB remained positive and 8/56 (14,2%) patients were negative for nodal metastatic disease on final histopathological assessment. However, all these negative patients had had neoadjuvant chemotherapy which cleared the axillary metastases. Therefore the true positive group was 56/56 (100%) patients with no false-positive results.

The analysis of the 7/63 (11,1%) negative patients on US-guided CNB that undergone ALND revealed 6/7 to be negatives whereas 1/7 patient deemed to be positive on ALND histopathological results despite having had the neoadjuvant chemotherapy. This represents the true negative and false negative respectively.

In total, ALND revealed metastases in 48/48 (100%) US-guided CNB positive patients and 6/7 US-guided CNB negative patients were determined to be negative, yielding a high sensitivity of 98,2% and specificity of 100,0 % for US-guided CNB, shown in Table 3.2.

Table 3.2. Sensitivity and Specificity of US-guided CNB in correlation with ALND histological results.

		ALND				
		Malignant	*Benign*	*Total*	*Sensitivity(%)*	*Specificity(%)*
US-CNB	*Malignant*	**56** (98,2)	**0** (0,0)	**56** (88,8)		
	Benign	**1** (1,8)	**6** (100,0)	**7** (11,2)	**98,2**(56/57)	**100,0**(6/6)
Total		**57** (100,0)	**6** (100,0)	**63** (100,0)		

Note: ***frequency*** *(column percentage)*

The calculated positive and negative predictive values of US-guided CNB were 100 % and 85,7% respectively denoting a relatively high probability of disease positivity or negativity given the corresponding test results, displayed in Table 3.3.

Table 3.3. Positive and negative predictive value of US-guided CNB in correlation with ALND histological results.

		ALND				
		Malignant	*Benign*	*Total*	*PPV (%)*	*NPV(%)*
US-CNB	*Malignant*	**56** (100,0)	**0** (0,0)	**56** (100,0)		
	Benign	**1** (14.3)	**6** (85,7)	**7** (100.0)	**100 (56/56)**	**85,7(6/7)**
Total		**57** (90,5)	**6** (9.5)	**63** (100.0)		

Note: ***frequency*** *(row percentage)*

All 132 patients demonstrated at least one suspicious US feature which excluded negative ultrasound results.

No hilar blood flow (NHBF) and absence of fatty hilum shared the same highest frequency of 199/132 (90,1%) in comparison to other US features.

It was found that NHBF had a PPV of 89,8% (p=0,05), identifying a significant difference between histologically involved and non-involved nodes.

Among the US-depicted abnormalities, thickening of the cortex had the highest sensitivity 91/118 (77,1%), followed by the absence of fatty hilum 84/119 (70.6%) whereas the size of the node had the highest specificity 36/37 (97,3%).

Thickening of the cortex and the absence of fatty hilum had high positive predictive value, 91/101 (90,1%) and 84/93 (90,3%) respectively. However, there were statistically no significant differences between metastatic and non-metastatic lymph nodes (p>0,05), considering those two criteria.

The highest positive and negative predictive values were represented by the size of the node (36/37) 97.3% and 12/95 (12.6%) respectively, however, there were no significant differences with metastatic and non-metastatic lymph nodes, p>0,05.

Table 3.4. Correlation between ultrasound features and US-guided CNB histology.

	Histopathological results					
US Features	*Malignant (n)*	*Benign (n)*	*Sensitivity %(n)*	*Specificity %(n)*	*PPV %(n)*	*NPV %(n)*
Size	**37**	**95**	**30.3 (36/119)**	**92.3 (12/13)**	**97.3 (36/37)**	**12.6 (12/95)**
NHBF	**119**	**13**	**66.4 (79/119)**	**30.8 (4/13)**	**89.8 (79/88)**	**9.09 (4/44)**
Hilum	**119**	**13**	**70.6 (84/119)**	**30.8 (4/13)**	**90.3 (84/93)**	**10.3 (4/39)**
Cortex	**118**	**14**	**77.1 (91/118)**	**28,5 (4/14)**	**90.1 (91/101)**	**13 (4/31)**

4. Discussion

Breast cancer is known to be the most frequently seen malignancy in the South African population (35).
Sentinel lymph node biopsy and ALND have been used to examine and stage the ipsilateral axillary lymph node. Both of these procedures are time-consuming and associated with significant morbidity (8) (9) (10).

US-guided CNB is a minimally invasive technique with few complications. Staging of the ipsilateral axilla in breast cancer patients using US-guided CNB has been acknowledged to have a sensitivity and specificity which varies from 90-94% and 100% respectively (14) (36).

In this study, US-guided CNB in targeting axillary metastasis had an overall sensitivity and specificity of 98,2% and 100% respectively.
All 8 false-positive results were most likely due to a complete response to neoadjuvant chemotherapy which cleared the lymph nodes in the axillary dissection specimen. There were no false-positive US-guided CNB results in this series.

The single false-negative US-guided biopsy result showed a metastatic deposit in 1 of the 14 nodes submitted for histopathological tests after ALND. This patient was known to have received neoadjuvant chemotherapy for breast cancer. A retrospective analysis revealed this: it may have resulted from biopsying an uninvolved area in this node (13).

Experience with US-guided CNB is known to be of great value in lymph nodes sampling, however, in our series, all lymph nodes have been sampled by two mammography sub-specialized radiologists with more than 15 years of professional experience.

The positive predictive value in the current series was 100%. US-guided CNB technique should enable breast surgeons to safely perform ALND when a US-guided CNB is positive, eliminating the need for sentinel lymph node biopsy (SLNB). In addition a positive US-guided CNB will be a reliable indicator for neoadjuvant chemotherapy (36) (37).

Fine needle aspiration is an alternative technique that was extensively performed and investigated on before the era of US-guided CNB.
Several comparative accuracy surveys of FNA versus US-guided CNB has shown that FNA has a lower sensitivity fluctuating between 57-76% and a relatively lower positive predictive value ranging from 87,1-100%. By contrast, US-guided CNB in those studies had an overall sensitivity and positive predictive value reaching 90 % and 100% respectively (38) (39) (40) (41).
Therefore, surgical management based on negative FNA results cannot reduce the risk of positive axillary nodes. Furthermore, FNA had been reported to often be limited by the lack of sufficient cytological material with a limitation rate of 0-54% (14) (40).
Conversely, US-guided CNB provides more tissue than FNA and so has become a standard procedure, less operator-dependant.

Minor haemorrhage controlled with finger pressure haemostasis was the main consequence observed in this series of US-guided CNB. There were no observed major complications such as vessels or nerve damages and pneumothorax. Most authors reported puncture site haemorrhage as a minor complication associated with US-guided CNB technique. It has been reported that US-guide CNB is safe and reproducible (36) (14).

The role and the accuracy of ultrasonography of the axilla in breast cancer had been investigated by many authors. An oval shape, smooth margins, a maximal cortical thickness of 3 mm, discernible fatty hilum and presence of hilar blood flow are characteristic of a normal lymph node. Any alterations within any of these listed characteristics are predictive of metastatic disease (42).
The literature confirms that ultrasound can be used to predict axillary nodal metastatic disease: the overall sensitivity ranges from 26% to 76% with specificity ranging from 88% to 98% (42) (43).

In this study, all 132 patients demonstrated at least one suspicious US feature. Therefore no benign node was sampled.
The total absence of fatty hilum, has been reported as a reliable positive-result indicator (44), had the highest positive predictive value of 90,3%. Statistically, there was no statistically significant difference between benign and malignant nodes ($p>0,05$) in the

current study. This meant that in some cases, partial effacement of the fatty hilum was found to be metastatic in the current series.

Thickening of the cortex due to metastatic deposits via the lymphatics had the highest sensitivity 77,1% that contrasts with its low specificity of 28,8 %, the thickness cut-off set at 3 mm. This finding is almost similar to Deurloo and al study results. However, these workers suggested that the thickness of the cortex of at least 2.3 mm was a good indicator of metastatic involvement (25). In this series, the cortical thickness was measured perpendicularly to the lymph node surface.

The absence of hilar blood flow had a positive predictive value of 89,8%, p=0,05. This ultrasound feature, less used in the majority of studies was considered to be an important indicator of metastases spread in the current study (14). It is believed to result from the cortical neo-vessels formation with displacement or amputation of hilar vessels. This phenomenon is also seen in inflammatory and reactive processes. However, in this series, there was a statistically significant difference between benign and malignant lymph nodes using this criterion. The current study found that this was an important additional indicator of metastasis.

The size of the lymph is the less important criteria in the identification of nodal metastasis (36) (45). Axillary lymph node with short-axis measuring >2cm was supposed to facilitate metastatic deposits. This criterion had the lowest sensitivity of 30.3 % contrasting with the highest positive predictive value of his series 97.3% with p>0,05. In the current study, the smallest sampled positive lymph node measured 0,9 cm and the largest measured 4 cm (short axis). There was no strong correlation between the histopathological lymph node status and its size in the current study.

4.1. Limitations of the current study

Limitations of the study include the fact that:

- A significant amount of US-guided CNB patients did not undergo a confirmatory ALND. This may have been due to patients declining the procedure, neoadjuvant chemotherapy preceding during the study and patients lost to follow-up. These are

factors which limit the size of the ALND group. Despite the small group of ALND subjects, the results were found to be statistically representative.

- The correlation between the biopsied lymph nodes and the harvested lymph nodes on ALND is uncertain because all suspicious nodes were not sampled with US-guided CNB. This could explain the false-negative rate (even if it was not significant).

4.2. Future applications

The introduction of an image-based chart in the examination rooms would standardize the ultrasound evaluation of axillary nodes to be sampled referring to:

- Size of the lymph node,
- Cortex thickness,
- Absence and/or distortion of fatty hilum and,
- Absence of the hilar blood flow on colour Doppler imaging.

Additionally, this would facilitate and systematize the inter-examiner evaluation and comparison of results for lesions follow up.

5. Conclusion

This study supports the evidence of the use of US-guided CNB as a staging tool of the ipsilateral axilla in breast cancer patients at presentation. It was proven to be a highly accurate first-line diagnostic tool. Where neoadjuvant chemotherapy is considered, the finding of a positive US-guided CNB will support the selection of this therapy.

The absence of nodal fatty hilum is a good indicator of metastatic deposits due to its high positive predictive value. Thickening of the cortex and absence of hilar blood flow are additional ultrasound features that increase the accuracy of the axillary ultrasound in metastases detection.

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Appendix A: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr David Akilimali Balolebwami

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190293

NAME: (Principal Investigator)	Dr David Akilimali Balolebwami
DEPARTMENT:	Radiology Diagnostics Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Audit of ultrasound guided core needle biopsie of ipsilateral axillary lymph nodes in metastatic breast cancer
DATE CONSIDERED:	Ad hoc
DECISION:	Aproved unconditionally
CONDITIONS:	Sub-study under primary study M170425 Dr Carolina Nel et al
SUPERVISOR:	Prof A Mannell
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	08/07/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed June and will therefore be due in the month of June each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

10-08-2019.
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: CMJAH CEO approval letter

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. X Dhlamini
Office of the Clinical Director
Email: Xolisane.Dhlamini@gauteng.gov.za
Tell: (011): 488-3710
15 July 2019

Dear Dr. Akilimali

STUDY TITLE: Audit of Ultrasound Guided Core Needle Biopsies of Ipsilateral Axillary Lymph Nodes in Metastatic Breast Cancer

Permission to conduct the above-mentioned study is provisional approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your Ethics Clearance Certificate as soon as the study is approved by the Ethics Committee for the CEO's office to give you the final approval to conduct the study.

Supported / ~~not supported~~

Dr. M.I. Mofokeng
Clinical Director
DATE:

Approved / not approved

Ms. C. Bogoshi
Chief Executive Officer
DATE: 15.07.2019

Appendix C: Mammography unit approval letter

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

10 JULY 2019

Dear Dr Akilimali

I am aware of and support your research to be conducted in the Breast Imaging Unit at CMJAH, investigating core needle biopsy of ipsilateral axillary lymph nodes of metastatic breast cancer at CMJAH.

Please ensure that you have informed and have permission from the CEO of CMJAH to conduct this research in the hospital.

Thank you

Dr J Smilg

Head Breast Imaging Unit , CMJAH

Appendix D: Data collection sheet

Patient Number	Age	Breast L/R	BIRAD & Histology	Clinical Staging			Ultrasound features				LN Histology	HIV TB LMP	NA Chemo	ALND
				T	N	M	Size	Cortex	Hilum	Doppler				

Appendix E: Plagiarism declaration

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS
SENATE PLAGIARISM POLICY: APPENDIX ONE

I _____DA BALOLEBWAMI_____ (Student number: _1003024_____)
am a student registered for the degree of __MMed RAD (DIAG)_____ in the academic year __2020__.
I hereby declare the following:

- - I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- - I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- - I have followed the required conventions in referencing the thoughts and ideas of others.
- - I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the

source of the ideas or words in my writing.

- - I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection)

software indicating the level of plagiarism in my research document.

Signature: _____ Date: _____

Appendix F: Note on referencing style

Please note that the referencing in this thesis is a modification of the Vancouver Referencing style, done according to the Faculty of Health Sciences Style Guide as set out by the Wits Health Sciences Library.

The information on this WHSL Vancouver Citation Style Guide for Theses, Dissertations and Research Reports is available from http://libguides.wits.ac.za/whsl-vancouver updated on 8 August 2017.