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Ultrasound-detected BI-RADS 3 breast lesions at a quaternary institution in Johannesburg: initial features and audit of follow up findings

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ULTRASOUND- DETECTED BI-RADS 3 BREAST LESIONS AT A QUATERNARY INSTITUTION IN JOHANNESBURG: INITIAL FEATURES AND AUDIT OF FOLLOW UP FINDINGS

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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 Diagnostic Medicine

Johannesburg, 2020

Declaration

I, Dr Foriwah Obeng-Adjei, 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 Foriwah Obeng-Adjei

On this 26th November, 2020

This work is dedicated to my husband, Akwasi Obeng-Adjei and my children, Nana Kofi and Kaycee Obeng-Adjei. Thank you for every smile you put on my face and for the warm hugs. I love you to the moon and back.

Publications and presentations

This work has never been published.

This research was presented as a poster at the Breast Imaging Congress of South Africa in Cape Town from 15-16th of August 2019.

Abstract

INTRODUCTION

The American College of Radiology (ACR) recommends short term follow up in the management of probably benign breast disease diagnosed on ultrasound, mammography, and breast MRI, although the criteria for each imaging modality varies. This recommendation eliminates unnecessary and extensive workup for these patients considering that the risk of malignancy associated with this category is < 2%. Studies in South Africa on BI-RADS 3 breast disease and their outcomes are limited.

METHOD

The study was conducted at Charlotte Maxeke Johannesburg Academic hospital (CMJAH) mammogram department in South Africa on 308 women. The study covered a period of 2 years between 1 January 2016 and 31 December 2017 . Inclusion criteria were: Women between the ages 18 and 40 years old; and BI-RADS 3 breast lesion/s diagnosed primarily on ultrasound. Exclusion criteria were: Patients with incomplete records. The outcome of the follow up at each visit was documented for each patient as well as their initial imaging findings.

RESULTS

Out of the 308 patients whose data were analysed, 159 (52%) defaulted, 16 (5%) opted for surgical excision biopsy, 8 (3%) were upstaged at 6 months follow up and 6 (2%) were upstaged at 12 months follow up and had core biopsy. None of the lesions biopsied was found to be malignant. 115 (37%) were downstaged. 4 (1%) had breast abscess for which they had ultra-sound guided aspiration.

CONCLUSION

No malignancy was found in this study which is in line with international findings of 0-2% malignancy rate in patients with BI-RADS 3 breast disease.

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My parents and siblings, thank you for all the prayers.

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List of Abbreviations and Terminology

ACR	American College of Radiology
BI-RADS	Breast Imaging-Reporting and Data System
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
LLIQ	Left lower inner quadrant
LLOQ	Left lower outer quadrant
LUIQ	Left upper inner quadrant
LUOQ	Left upper outer quadrant
MMG	Mammogram/Mammography
PACS	Picture Archiving and Communication system
PASH	Pseudoangiomatous stromal hyperplasia
RLIQ	Right lower inner quadrant
RLOQ	Right lower outer quadrant
RUIQ	Right upper inner quadrant
RUOQ	Right upper outer quadrant

1. Introduction

1.1. Background

The breast undergoes various changes during the lifetime of a woman. These physiological changes may result in the development of benign breast disease (1, 2). Benign breast disease is the most prevalent breast condition affecting young women but there is limited data available in Sub-Saharan Africa (1, 3). In a study conducted by Rayne et al., more than 50% of the patient population had benign breast diseases, while 14% had breast cancer. The study emphasised that breast cancer is not the only motivation for comprehensive breast care (3).

Benign breast diseases encompass all non-malignant breast pathologies, which vary on a broad spectrum. Clinicians must understand these disorders to alleviate the anxieties and missed emotions experienced by these patients (2). The current diagnosis of breast pathologies employs the triple test approach, which involves a clinical examination, imaging, and histopathology. Clinical examination alone cannot distinguish malignant from non-malignant breast pathologies, and one cannot do biopsies based on palpation of a lump. The role of imaging in the diagnosis of breast disease can, therefore, not be overemphasised (4, 5). Breast cancer is leading cancer among women worldwide, and it is also the leading cause of cancer-related death in many countries. According to the Global cancer statistics in 2018, there will be 2.1 million new cases of breast cancer worldwide representing 1 in 4 cancer cases in women. It has been projected that breast cancer will be responsible for 6.6% of all cancer-related deaths (6). According to the National cancer registry, it was the leading cancer in women in South Africa. It was responsible for 0.7% of deaths in women (7). Early detection, diagnosis, and treatment of breast cancer are paramount in preventing cancer-related deaths (4).

Risk factors for breast cancer include gender, age, race, family history of breast cancer, previous benign breast disease or prior history of breast cancer, radiation, hormone replacement therapy and lifestyle (8, 9).

1.2. Role of Imaging in breast cancer diagnosis and management

1.2.1. Screening

The World Health Organization defines screening as the application of simple tests to a seemingly healthy set of people to identify those with risk factors or early signs of a particular disease but are asymptomatic for the disease. The principle underpinning screening is that identifying people at risk at an earlier stage of the disease is beneficial for the clinical or overall good of the population (10).

For a condition to meet the criteria for screening, it should have the following requirements as developed by Wilson and Junger in 1968 (10)

- The condition sought should be an essential health problem;
- There should be an acceptable treatment for patients with recognised disease;
- Facilities for diagnosis and treatment should be available;
- There should be an appropriate test or examination;
- The test should be acceptable to the population;
- The natural history of the condition, including development from latent to declared disease, should be adequately understood;
- There should be an agreed policy on whom to treat as patients;
- The cost of a case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced with possible expenditure on medical care as a whole; and
- Case-finding should be a continuing process and not a "once and for all project.

Breast cancer screening identifies women who are asymptomatic for breast cancer to avoid aggressive treatments to improve the outcome for the patient. There are essential factors to consider when it comes to screening women for breast cancer, including who to screen when to start, frequency, and modality or modalities to use (10).

Who should be screened and how often should screening be done?

The guidelines for who should be screened for breast cancer varies from one country to the other and region to region within countries. Most importantly, women who undergo screening for breast cancer should be made aware of the potential benefits, limitations, and related problems. From the age of 45 years, women with an average risk of breast cancer should undergo regular screening as follows (11):

- Annual screening should be performed in women aged between 45 and 54 years;
- Those aged 55 years and older should have screening every other year or once yearly;
- Women who are aged between 40 and 44 years should have the opportunity to begin annual screening;
- Screening mammography should be offered to women who are expected to live for 10 years or more and are in good health; and
- The American Cancer Society does not recommend clinical breast examination for breast cancer screening among average-risk women at any age.

There is no national mammography screening program for breast cancer in South African public health centres due to the high cost involved (4, 12). Women are encouraged to perform breast self-examination and to report to their clinic if they develop any symptoms (mass, nipple discharge, pain, itchiness). They are then referred to a specialist breast unit in their catchment area (4). The mammography unit of the Charlotte Maxeke Johannesburg Academic Hospital offers yearly mammogram screening with adjunct ultrasound examination to patients referred by clinicians for example post- menopausal women on hormone replacement. From the age of 40 until 75 for women with no previous history of breast cancer. If they have a history of breast cancer, they have imaging follow up for the rest of their lives.

1.2.2. Follow-up for women with previous breast cancer

All surveillance programs recommend mammography, but there is controversy about when to start, number of times, and when to stop surveillance (13). In a study conducted amongst breast surgeons and radiologists across the United Kingdom, it was established that the most common practice was yearly mammography commencing twelve months after surgery (14). Some doctors support shorter follow up periods of two times yearly, and this reasoning is

based on findings that the majority of disease recurrences take place within the first five years after treatment. Therefore, two times annual follow-up is more likely to detect a higher number of disease recurrence at an earlier stage than once yearly (15). Having said this, more frequent surveillance for women previously treated for early-stage breast cancer may not be beneficial. A meta-analysis on two-arm studies conducted by Kokko et al. in 2005, one comparing data for patients who followed up every three months to those who followed up every six months and the other arm comparing routine testing versus testing when indicated clinically, found more intensive surveillance (either frequent or multiple testing) to be costly with no benefit to overall patient survival (13, 16).

1.2.3. Diagnosis

One of the most common findings of breast pathology is a palpable breast mass. The clinical examination cannot differentiate benign from malignant lesions (4, 5). Imaging before either incision or excision biopsy is helpful in the characterisation of breast masses. The ACR Appropriateness Criteria, 2017 recommends ultrasound as the first imaging tool in evaluating patients with no added risk for breast cancer (17). Currently, in CMJAH, women less than 40 years of age presenting for the first time are offered breast sonar. However, some patients may be further evaluated with single view mammography (mediolateral oblique) depending on their risk factors, history, and ultrasound imaging findings. Patients older than 40 years receive mammography and adjunct breast ultrasound.

The Breast Imaging Reporting and Data System (BI-RADS) was developed by the ACR in 2015 to categorise imaging findings and risk stratification (18). Patients are classified as having either benign or malignant disease based on imaging. BI-RADS 1 and 2 indicate normal and benign findings, respectively, BI-RADS 4 and five indicative suspicious and highly suspicious results, respectively. BI-RADS 3 category is a grey area that can be a source of much anxiety for patients, clinicians, and radiologists and evokes lots of reactions, including surgery and core biopsy. It has different meanings for mammography, ultrasound and MRI (19). BI-RADS allows for standardisation in the management of breast cancer and risk stratification for malignancy. It also helps to avoid confusion in image interpretation and enable effective communication to clinicians and also improve patient care. The BI-RADS classification is summarised in Table 1.1. below (19).

Table 1. 1. The BI-RAD system

BI-RADS	Description
0	Needs additional mammographic/sonographic information and/or prior mammogram for comparison. This should only be used when such a comparison is needed to make the diagnosis
1	Negative. Breasts are normal. Plan: annual follow up
2	Benign finding e.g. typical nodes, calcified fibroadenomas and scattered microcalcifications. Plan: annual follow up
3	Probably benign finding with < 2% chance of malignancy. These include non-palpable non calcified circumscribed solid masses, focal asymmetry and a cluster of round/punctuate calcifications. Plan: 6 months follow up.
4	Suspicious abnormality. Plan: biopsy. 4a findings needing intervention, low suspicion of malignancy (>2- ≤ 10 %) 4b: lesions with intermediate suspicion for malignancy (>10- ≤ 50%) 4c: lesions with moderate concern not classic for malignancy (>50 - 95%)
5	Highly suggestive of malignancy. ≥ 95% chance of malignancy including spiculate lesions. Plan: biopsy or excision
6	Known biopsy proven malignancy but patient hasn't yet undergone definitive treatment.

The ACR recommends short term follow up for probably benign breast masses. According to the ACR, lesions are to be followed up at 6 months, 12 months, 18 months, and 24 months, and if the lesion remained stable patient can be discharged. This is not followed stringently, and the follow-up duration varies from country to country and one practice to another. Studies have shown that the first 6 months is the most critical period and that if the masses remained stable during this review, patients could be safely discharged from imaging follow up (20). BI-RADS was not intended to be static. It continued to evolve over the years with new editions. In 2001, an ultrasound lexicon was developed by the ACR as an adjunct in breast cancer screening and as a diagnostic and interventional tool in breast imaging. The ultrasound lexicon 5th edition is summarised in Table 1.2 (18, 21).

Sonographic features of benign breast masses include (21, 22).

- Well circumscribed oval, round or macrolobulated mass;
- Mass oriented parallel to the chest wall;
- Hypoechoic mass;
- 3 or less gentle lobulations;
- A horizontal length greater than the vertical length; and
- Homogeneous hyperechogenicity relative to breast fat.

Role of Elastography in diagnosis of breast lesions

Breast imaging modalities have a high sensitivity in detection of breast cancer, however, studies have shown that about 75% of breast masses which are biopsied have benign histopathology reports (23, 24). Ultrasound elastography which evaluates the stiffness of the breast mass in increasing being used in this regard. Ultrasound elastography assesses the elasticity of soft tissues which is the ability of soft tissues to resist deformation when force is applied. Malignant processes change the elasticity of soft tissues due to specific processes which affects the stiffness of the tumour as well as the surrounding tissues (24, 25).
There are two techniques used to determine the elasticity of masses on ultrasound. These include the strain elastography in which the operator uses the probe to induce pressure or patient is asked to breath, and shear elastography in which a special sound wave is used to produce the pressure (24, 25).

Table 1.2. Breast imaging reporting and data System (BI-RADS) categories – ultrasound lexicon 5th edition.

Ultrasound Lexicon		
Breast composition	Homogenous – fat Homogenous – fibroglandular Heterogenous	
Mass	Shape	oval- round- irregular
	Margin	Circumscribed or Not circumscribed: indistinct, angular, microlobulated, spiculated
	Orientation	Parallel Not parallel
	Echo pattern	Anechoic Hyperechoic Complex cystic/solid Hypoechoic Isoechoic Heterogenous
	Posterior features	No features Enhancement Shadowing Combined
Calcification	In mass Outside mass Intraductal	
Associated features	Architectural distortion Duct changes Skin thickening Skin retraction Oedema Vascularity (absent, internal, rim) Elasticity	
Special cases *(cases with a unique diagnosis)*	Simple cyst Clustered microcysts Complicated cyst Mass in or on skin Foreign body (including implants) Intramammary lymph node AVM Mondor's disease Postsurgical fluid collection Fat necrosis	

The ACR recommends short term follow up for patients with probably benign breast lesion Clinical follow up is recommended in women with palpable breast masses which turns out to be benign breast on targeted ultrasound (e.g., simple cysts, reactive node, lipoma, sebaceous cyst, clustered cysts or duct ectasia). These women do not require short term imaging follow up, needle aspiration, or biopsy. They may return for imaging follow up or biopsy if there is a need (5). Other benign breast pathologies including mastitis and breast abscess are typically managed clinically but may have ultrasound guided aspiration (26-28).

At CMJAH, women younger than 40 years diagnosed with BI-RADS 3 disease are followed up at 6 months and 12 months with ultrasound. Empirical studies have shown that very few audits have been conducted on BI-RADS- ultrasound 3 breast lesions about initial and follow up imaging findings in South Africa in women aged between 18- 40 years. This makes the study valuable to bridge the gap in knowledge .

1.3. Study objectives

This was an audit of BI-RADS 3 breast lesions diagnosed on ultrasound in women between the ages of 18 and 40 years. The study was aimed at determining the malignancy rate in this category of patients in the local South African population and also to determine if there is a need for these patients to follow up at 6 and 12 months in our setting.

The objectives of the research were to:

- To document the sonographic features of BI-RADS 3 lesions at initial, 6 months and 12 months follow up; and
- To determine the histology findings of patients who underwent biopsy.

2. Materials and Methods

2.1. Patient selection

Data on all female patients aged between 18 and 40 patients seen at CMJAH between 1 January 2016 and 31 December 2017 with BI-RADS 3 breast masses were obtained from the hospital's PACS. There were a few patients with hand-written reports which were accessed from their folders.

2.2. Imaging

Breast ultrasound images and reports on these patients were obtained for the period of the study. Imaging and reporting were done by two consultant radiologists both of whom have specific interest in breast imaging with several years of experience. Readers were not used for the study. The practice in our facility is to evaluate women younger than 40 years with ultrasound. Patients between the ages of 40 and 75, routinely come for an annual mammogram and adjunct breast ultrasound if necessary and for life, if they had a personal history of breast cancer.

The decision to employ other imaging modalities like mammography and magnetic resonance imaging (MRI) were made depending on the ultrasound findings. Some of the patients were evaluated with limited mediolateral oblique mammograms to exclude pathology that might only be visible on MMG, eg microcalcifications". The follow- up imaging for these patients was done with ultrasound only. The images were obtained with either Toshiba istyle (using a 12MHz pixel linear probe) or Toshiba Xario 100 (using a 14 MHz linear probe). The lesions identified on sonar were classified according to the ACR BI-RADS atlas 5th edition. Only patients with sonographic imaging findings that fit the category of BI-RADS 3 were included in this study. In our institution, patients are seen at 6 months and 12 months after the initial visit and then either down-staged according to the imaging features or biopsied. These patients are advised to continue breast self-examination and follow up at their local facilities if they have any concerns. Lesions were evaluated mainly based on

whether or not they changed in size on subsequent imaging, their echogenicity and the numbers of lesions in each breast.
All the women had been referred from the surgical breast unit where they had undergone breast examination by the breast surgeons. The ultrasound images, reason for excision biopsy and the histology of the biopsied samples were analysed.

On their first visit to the MMG department, patients fill in a questionnaire to document their symptoms and assess their breast cancer risk. Information pertinent to the study was extracted from this questionnaire. All data was entered on a data collection sheet (Appendix A). Images of patients who had biopsies were saved on a disc for editing and inclusion in the research report. The length and width were recorded for each lesion and the length to width ratio was calculated for each lesion. Lesions with length to width ratio less than 1 were categorised as 1, and those with ratios greater than 1 were categorised as 0.

2.3. Inclusion and exclusion criteria

The criteria for selecting the sample was limited to:

- women between the ages 18 and 40 years old; and
- BI-RADS 3 breast lesion/s diagnosed primarily on ultrasound

The following patients were excluded from the study:

- patients with incomplete records

2.4. Statistical analysis

Demographic and clinical characteristics of the study participants, frequencies and percentages were reported for all categorical variables. The ages of the patients were expressed as means, median, and range. The total number of lesions in the patients were tallied. The lesions in patients who defaulted were not included in the data analysis. The outcomes on each visit were recorded per patient, and these were further analysed in terms of frequencies. The number of lesions whose BI-RADS category changed were analysed as frequencies and percentages of the total number of lesions evaluated. This data was recorded for each of the subsequent visits. The number of patients, as well as the lesions found in the patients who had excision biopsy, were analysed as frequencies and

percentages. The histology results of patients who had core biopsy and excision biopsy were analysed in terms of frequencies and percentage of the total number of lesions.

2.5. Reliability and Validity

The use of BI-RADS to classify breast imaging findings and to plan management is well published and accepted as an international standard of reporting and management. The BI-RADS grading of the patients in this study is considered to be reliable, as all the studies are either performed by a consultant radiologist or supervised and co-signed by one.

2.6. Bias

CMJAH is a level four hospital with the majority of referrals from Johannesburg and surrounding regions, so the number of patients seen may not be a true reflection of the South African population. Also, all the patients were symptomatic and had already been assessed at the breast clinic.

2.7. Ethics

Approval to perform the study was granted by the Ethics Committee at the University of the Witwatersrand. Approval number is M190408. This certificate is attached as Appendix B.

3. Results

Table 3. 1. Patient demographics and risk assessment

	Frequency	Percentage (N=308)
Age 18- 26 27- 34 35-40	 180 120 8	 58.4% 39.0% 2.6%
Risk Assessment 1. Family history Breast cancer Other cancers 2. Previously documented Benign breast disease or breast surgery 3. Contraceptive 4. Lifestyle Smoking Caffeine 5. Pregnancy history 1 2 3 or more	 18 12 6 13 9 48 42 11 13	 5.8% 3.9% 1.9% 4.2% 2.9% 15.6% 13.6% 3,6% 4.2%
6. Symptoms Palpable mass only Pain only Nipple discharge only Pain with breast mass Pain with nipple discharge Mass with nipple discharge All three symptoms Symptoms not documented Total	 208 7 2 47 2 8 6 28 308	

A total of 308 patients were included in the study. The ages ranged from 18 to 40, with a mean age of 25 and a median age of 25.

The demographics of our study population as well as risk factors and clinical presentation is represented in Table 3.1 above.

Table 3.2. Break down according to ultrasound findings

Benign breast pathology	Number	Percentage
Solid masses	569	99.0%
Abscess	4	0.7%
Duct ectasia with intra ductal lesion	2	0.3%
Total	575	100%

The ultrasound findings at the initial visit are represented in Table 3.2. The majority of the patients that were seen had solid breast masses, with a total of 569 (99%) solid masses, 4 (0.7%) patients had breast abscesses and 2 (0.3%) was diagnosed with duct ectasia duct ectasia with intra ductal lesion.

Table 3.3. Imaging features of the solid masses

Imaging features (N=575)		**Number reported**	**Not reported**
Margin	Circumscribed	49	526
	Indeterminate	1	574
Shape	Ovoid	64	511
Echogenicity	Hypoechoic	49	526
	Isoechoic	1	574
Calcifications	None	16	559
	Present	2	573
Posterior features	Posterior acoustic enhancement	22	553
	Shadowing	2	573
	No posterior	19	556

A summary of the imaging features are represented in Table 3.3 above. The majority of the solid masses were ovoid, hypoechoic with no calcifications and well-circumscribed margins. Most of the lesions had posterior acoustic enhancement.

Table 3.4. Size of the solid masses

	Number N =575	Percentage %
Length		
<10mm	109	19%
10-20mm	416	72.3%
20-30mm	36	6.3%
>30mm	14	2.4%
Width		
<10mm	386	67.1%
10-20mm	151	26.3%
20-30mm	27	4.7%
>30mm	11	1.9%
Length to width ratio		
<1	0	
>1	575	
Ranges		
Length	1-56 mm	
Width	1-32 mm	

Table 3.4 above represents the sizes of the solid masses on first visit. All the masses evaluated longer than wide.

Table 3.5. Biopsy results

	Histology results	Number
Core biopsy only	Fibroadenoma	6
	Benign phyllodes	1
	Lactating adenoma	1
	Usual ductal hyperplasia	1
	PASH	2
	Tuberculosis	1
	Intraductal papilloma	1
	Atypical cells	1
Total		14
Surgical excision biopsy only	Fibroadenoma	13
	Hamartoma	1
	Lactating adenoma	1
	PASH	1
	Tubular adenoma	1
Total		17

The results of the patients that underwent **either** core biopsy of excision biopsy are shown in table 3.5. The most prevalent histology result in these cases was that of a fibroadenoma.

Table 3.6. Patients who had surgical excision after **core biopsy**

	Histopathology result on core biopsy	Histopathology result on excision biopsy
Patient 1	Fibroadenoma	Fibroadenoma
Patient 2	Intraductal papilloma	Negative

Table 3.6. Represents the two patients that had surgical excision after core biopsy. Patient 1 had excision of a giant fibroadenoma (5.3 x 3.8cm). The excision histology confirmed a fibroadenoma. Patient 2 had an intraductal papilloma diagnosed on ultrasound guided core biopsy, but the histology of the excision did not demonstrate any intraductal lesion.

4. Discussion

4.1. Results in context

4.1.1. Imaging features

One of the objectives was to determine the sonographic features of BI-RADS 3 breast lesions at initial, 6 months and 12 months follow up. According to literature, to increase the sensitivity of ultrasound in discriminating benign from malignant lesions, the imaging descriptors should be used in conjunction with one another. The most consistent features are the shape and margins. The imaging features as shown in Table 3.3 are discussed below.

- Margin

Benign breast masses typically have well-circumscribed, smooth, macrolobulated (< 3 lobulations). Poorly defined, Irregular, microlobulated lesions with 4 or more lobulations is suggestive of malignancy (29). This has been found to be one of the most important determining factors in differentiating a benign from a malignant mass.
Out of the 575 solid lesions evaluated, 50 had reports detailing their margins. Of these 49 lesions were well circumscribed with macrolobulated margins. Only one lesion had an indeterminate margin which resulted in biopsy but no malignancy was found.

- Shape

Studies have shown that the shape is one of the most important features in determining benignity of a breast mass. Ovoid masses with long axis oriented parallel to the chest wall are more likely to be benign (29). Reports on 64 lesions had a description of the shape. The only shape reported was oval with the long axis oriented parallel to the chest wall. This is considered a feature of benignity. Malignant lesions tend to be taller than wide, with a positive predictive value of 81.2 percent for malignancy (30).

- Sizes

Study conducted by Chala et al found that a Length -Anterior posterior ratio (L/AP) is far more sensitive than the absolute dimensions of the mass. An L/AP ratio of less than 1.0 suggest malignancy and has high specificity but low sensitivity. The study further reported that a cut off of value of 2.5 increased the sensitivity to 100% (29).

Other studies have argued the interval growth of a mass to be a more sensitive indicator of risk of malignancy and such lesions should be biopsied (31). Majority of the lesions analysed in this study has a L/AP ratio of >1 which represents 72.3%. It was found that interval growth of a mass was a very important determinant for biopsy at our institution. Most of the lesions analysed fell had lengths of between 10-20mm and width of less than 10. This is summarized in Table 3.4 and Figure D.3.

- Echogenicity

In the study conducted by Dogan *et al*, ultrasound images of 39 patients were retrospectively evaluated, 74.4% of the lesions were reported to be hypoechoic while 25.6 % were reported to be isoechoic (26). Similar findings were found in the study conducted by Namazi *et al* on 92 patients in which 91.3 % of the patients had hypoechoic lesions (32). According to the study conducted by Chala *et al* (29), the echotexture of the lesions was found to be of limited value in differentiating between benign and malignant lesions. In this study, 50 lesions had their echogenicity reported. Of these, the commonest echogenicity reported was hypoechoic. Only one lesion was reported to be isoechoic. This was not found to be a strong determining factor on the management of the masses.

- Calcifications

The presence of calcifications, especially micro calcifications increases the chance of lesion being malignant and is an indication for biopsy (31). Eighteen lesions had reports on the presence or absence of calcifications. 16 masses had no calcifications while 2 masses had calcifications. The rest of the masses had no description of whether or not there were calcifications.

- Posterior acoustic features

Posterior features are related to how much the mass attenuates the sound waves. Masses with high attenuation of sound waves demonstrate posterior acoustic shadowing whiles those with less attenuation of the sound waves demonstrate posterior acoustic enhancement. Posterior shadowing is seen in fibroadenomas as they begin to hyalinize. According to Gohklae (30), the presence of dense posterior shadowing has a positive predictive value of 64.9% for malignancy but Adarsh *et al* and Chala *et al* reported posterior shadowing alone as a poor predictor for malignancy (33).

According to Weinstein *et al*, the pattern of shadowing might help differentiate benign from malignant masses. Posterior acoustic shadowing in benign masses may be seen at the periphery which gives it a somewhat different appearance compared to that seen in malignant masses which tend to be located centrally. Also benign masses do not cast dense shadows compared to malignant masses (33). Forty- three lesions had details on their posterior acoustic imaging features. Twenty-two masses had posterior acoustic enhancement, 2 had shadowing and 19 had no posterior features. Our study found only two masses which were reported to have posterior acoustic shadowing.

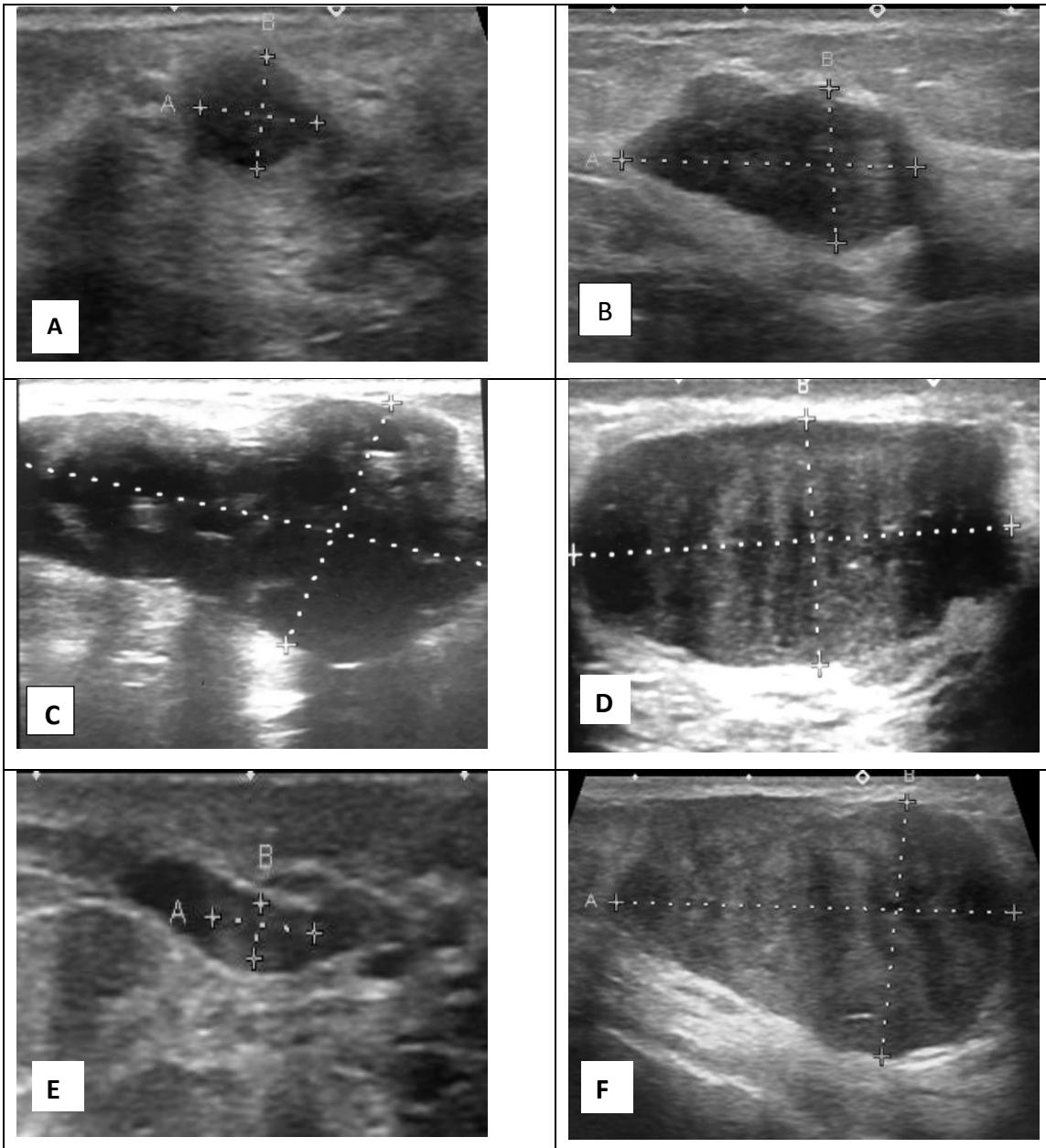
The analysis above indicates that the echogenicity, margin, shape, posterior acoustic enhancement, presence or absence of calcifications were only reported on the first visit. Across all the population analyzed, the size of the lesions was consistently reported on at each visit and was the main determining factor for either downstaging or upstaging a patient.

4.1.2. Histology findings of lesions that were biopsied and reasons for biopsy

A retrospective review by Moon *et al* (31) of 214 lesions evaluated with ultrasound demonstrated that 22 of the lesions (10.3 %) showed interval growth and were also found to be malignant on biopsy. The study also found a malignancy rate of 18.2% in lesions that had demonstrated at least one suspicious feature on ultrasound (e.g., round or irregular, microlobulated, spiculated, echogenic halo, amongst others). The study, therefore, concluded that probably benign breast lesions which demonstrated interval growth or suspicious features should be biopsied. The outcome of the study conducted by Dogan et al. in 2017 was different. In this study, the commonest reason for biopsy was suspicious lesion shape (15 patients) followed by 13 patients with interval growth of lesion (26).

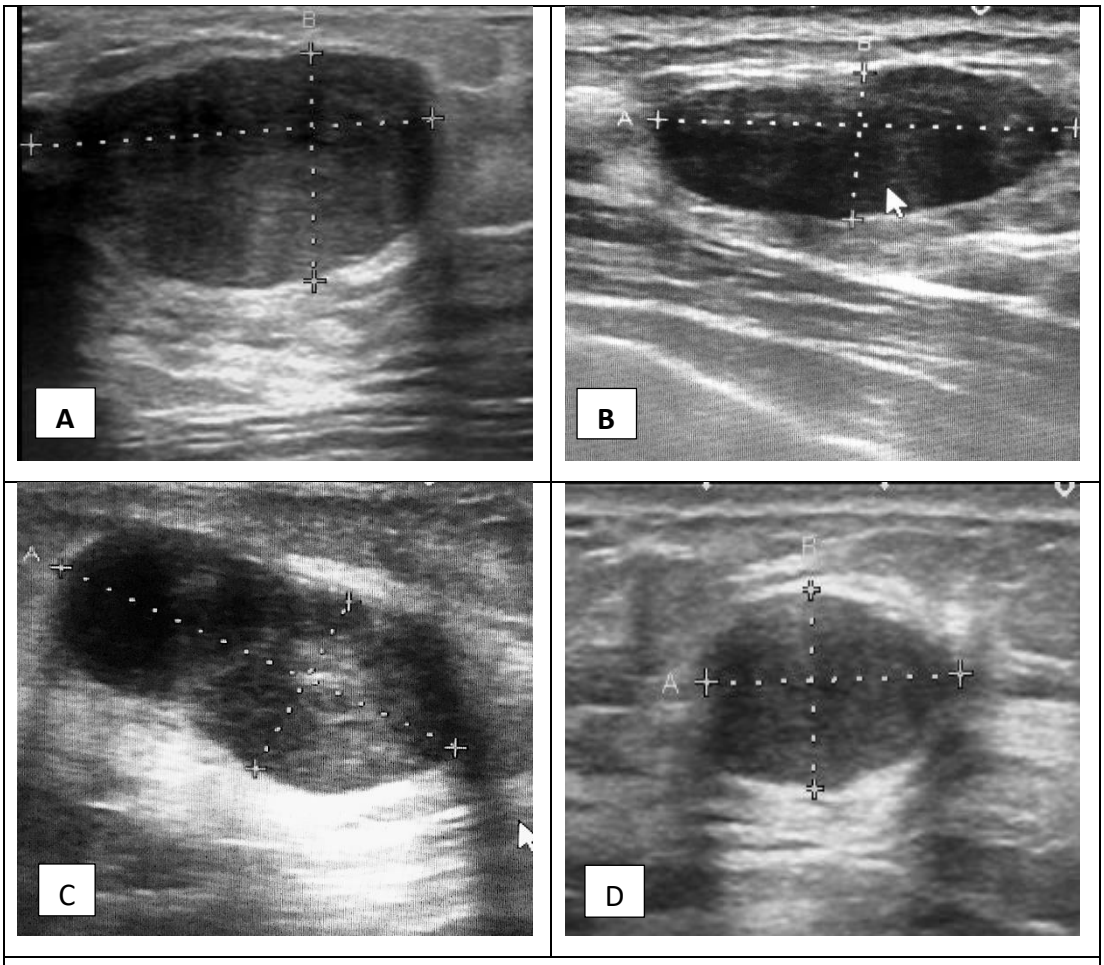
As per Table 3.5 and flow chart in Figure D.1, a total of 14 patients representing 4.5% of the study population were upstaged and had biopsy. The average age of these patients was 25.4 years. Out of these, 7 were upstaged to BI-RADS 4a and one to BIRADS 4b on the second visit. Six (6) patients were upstaged to BI-RADS 4a on the third visit. The reasons for core biopsy in these patients included: an objective increase in size on subsequent follow up visit (12 patients), subjective increase in size as reported by patient (1 patient), suspicious

ipsilateral axillary adenopathy with benign-appearing breast mass (one patient). The histology results of patients who had core were as follows: fibroadenoma-six, benign phyllodes-one, lactational adenoma-one, usual ductal hyperplasia-one, PASH-two, intraductal papilloma-one, tuberculosis of the breast-one and atypical cells with no features of malignancy- one. Of the 14 patients who had core biopsy, one had surgical excision because of histology report of intraductal papilloma and the other had surgery due to discomfort related to the breast mass.



A and B. 31 year old female with multiple breast lesions. All remained stable except for one which demonstrated interval growth. Biopsy revealed TB of the breast.
C. 29 year old seen with biopsy proven benign phyllodes.
D. 34 year old with positive family history of breast cancer, seen with a palpable mass which showed interval growth. Biopsy revealed a usual ductal hyperplasia.
E. 29 year old female, seen with mastalgia. Dilated retro areolar duct with intra ductal lesion with interval growth. Core biopsy results revealed intra ductal papilloma.
F. 28 year old female seen with biopsy proven PASH.

Figure 4. 1. Representative images of BI-RADS 3 lesions which underwent core biopsy



A-D. Circumscribed ovoid, hypoechoic mass with smooth macrolobulated border, no calcifications. Masses demonstrates posterior acoustic enhancement.
These masses remained stable with no interval growth at 6 and 12 months. Patients were down staged and discharged.

Figure 4. 2. Representative images of some of the BI-RADS 3 lesions that remained stable on follow up

4.1.3. Patients who had excision biopsy

The study set out to evaluate histology results of the patients who had core biopsy, but it was noted that a proportion of patients who defaulted imaging follow up had requested surgery (11.6%), and so it was essential to analyse their histology results. A total of 36 patients opted to have an excision biopsy. Twenty of them had not undergone surgery at the time of the study, and no further data was available on these patients. A flow chart

summarizing the outcome of patients who presented with BI-RADS 3 breast disease during the study period is summarized in Figure D.1. below.

A total of 16 patients had surgical excision biopsy, this includes two patients who had core biopsy because the reports were inconclusive. The histology report revealed fibroadenoma as the most frequent histopathological finding (7 lesions). One patient had two lesions in the right breast, one turned out to be a tubular adenoma, and the other was a fibroadenoma. None of the patients who had excision biopsy had risk factors for breast cancer. The reasons for surgery were: increase in size of the masses (7), retro areolar location of the mass (3) and patients' request for operation (6). No malignancy was found in the patients who had an excision biopsy.

Asymptomatic fibroadenomas – stable size with no deformity to the breast should be managed conservatively. Surgery is warranted if the fibroadenomas are larger than 5cm, rapidly growing, painful or result in significant deformity. Surgery may be offered to patients without clinical grounds if it is causing considerable anxiety to the patient due to the fear of malignancy which is very rare in a woman less than 40 years of age (34). In the study conducted by Loving et al., 59 patients representing 29% of the population had surgical excision, and of this number 36 was based on patients' preference. None of the lesions were found to be malignant (27).

Excision biopsy is an expensive alternative to short term ultrasound follow up, or core biopsy and where possible, clinicians and radiologists should be able to allay patients' fears and concerns as this is based on suspicion of malignancy developing in a fibroadenoma. Studies have shown that the risk of malignancy arising from a fibroadenoma is about 0.002 to 0.125% and in such cases, the malignancies are found at very early stages and tend to be carcinoma in situ which has a favourable prognosis (35).

4.1.4. Comparison with other studies conducted on BI-RADS 3 breast lesions

A total of 30 patients (31 lesions) had biopsy representing 9.7 percent of the total study population. No malignancy was found . Various studies conducted between 2008 and 2014 by different researchers on the risk of malignancy in BI-RADS– ultrasound 3 breast disease

found a low risk of malignancy (< 1%) in these patients (5, 27, 35-38). The findings are summarised in table 4.1 below, together with the results of this study.

Table 4. 1. Comparison with other studies conducted on BI-RADS 3 breast lesions

Reference	Year	Age (Years)		Total number of patients in study	Number of symptomatic lesions	Number biopsied	Number found to be malignant	Percentage Of malignancy
		Mean	Range					
This study	2019	25	18-40	308	274	31	0	0
Patterson et al (36)	2014	NA	18-81	487	197	117	0	0
Barr et al (37)	2013	54	25-86	2662	745	124	6	0.8
Giess et al (38)	2012	31	15-68	381	440	295	3	0.9
Loving et al (27)	2010	24	12-19	830	140	202	0	0
Harvey et al (35)	2009	34	12-88	320	375	109	1	0.3
Shin et al (39)	2009	43	25-75	352	288	367	7	3.2
Park et al (40)	2008	34	12-64	274	312	305	2	0.6

A detailed analysis of the comparative results of prior studies with results obtained in this review has been provided below.

Age

The average age of patients in this study was 25. Although this is slightly below the average age of patients used in prior studies, a review of the range of 18-40 years is consistent with those used by previous researchers as depicted in Table 4.1. Furthermore, in my department, patients who fall within this age range are primarily investigated with ultrasound with further imaging dictated by the findings.

Total number of patients

This study set out to evaluate masses in young patients (aged between 18 and 40 years) who had breast ultrasonography as a primary investigation. A total of 308 patients met the inclusion criteria for the study. In order to confirm the adequacy of the sample size of the patients, this number was compared to other similar studies and it was identified that this study population did not materially differ from four out of the seven similar studies".

Total number of symptomatic lesions

Three hundred and eight (308) patients with 575 masses fulfilled the criteria for the study. Four patients had breast abscesses and were discharged to the breast clinic for further management. Two hundred and seventy- four (274) solid breast masses were followed up at a 6-month interval (i.e. masses in patients who did not default). There were varying numbers of lesions evaluated by the studies represented in Table 4.1. To compare the results of this study to the studies referenced in Table 4.1, the average of their lesions was determined to be 307. The variance between the average of the comparative studies, and this study was circa 33, which is not a significant deviation. Further, the lesions in the comparative study ranged from 64 to 745. The number of masses evaluated in this study falls within the range of comparative studies.

Number biopsied

The total number of patients who had biopsy in this study was 30 (with 31 lesions), which included both core and excision biopsy. This number is much smaller than the numbers observed with the other reviews. The study was conducted over two years, which is

relatively shorter compared to the period of the other researches. Since patients needed to be followed up at 6 months and 12 months, it implied that any patient seen after February 2017 was not included in the study so essentially the study was conducted in patients seen and followed up in a year.

Number found to be malignant

No malignancy was found in this study (0%) which is consistent with the findings in most of the studies except in the study conducted by Shin, Han, Ko, et al. in 2009 which reported a high malignancy rate of 3,2% (40). The study was conducted among a subdivision of patients with probably benign breast masses who had a biopsy. This was attributed to the sampling method. The research was done on all masses and not just probably benign masses. The high rate of malignancy was attributed to the sampling method (5). Considering the comparative analysis performed, the data used in this review can be relied upon to draw a reasonable conclusion on the research objectives. Specifically, the research aimed to investigate the malignancy rate in patients in the local South African population and also to determine if there is a need for these patients to follow up at 6 and 12 months in our setting.

4.1.5. Background history

Demographics

A total of 308 female patients were seen between the period 1 January 2016- 31 December 2017. The geographical composition of the patients were mainly inhabitants of Johannesburg and its surrounds. CMJAH is a referral centre that provides public health services to patients in this catchment area. The demographics of this population consisted of females between the ages of 18-40 years. In this age range, the average age was 25 years. The median age was 25 years, which indicates that half of the population lies below the age of 25, and the other half lies above this age. The modal age was 19 years, which means there were more 19 years old patients within the study population, which is a very young population group. These findings are summarized in Table 3.1 and Figure D.2.

Risk factors and clinical background of the sample population

A woman has an increased risk for breast cancer if she has a first degree relative with breast cancer (8). Table 3.1 provides a summary of the risk factors of the study population. Thirty

patients representing 9.7% of the study population had a family history of cancer. Of this number, 18 had a positive family history of breast cancer, and 12 had a family history of other cancers. None of the patients with positive family history for malignancy were upstaged.

Studies have shown that women with benign breast disease are at a slightly increased risk for developing breast cancer, but this risk is not significant (26, 41). Only 6 patients had a history of prior diagnosis of breast disease, and they were all reported as benign according to the patients. None of these patients were upstaged.

Research has shown that women who are on oral contraceptives or have stopped for less than 10 years are at a slightly increased risk for breast cancer (5). In this study, only 13 patients had reported using any form of oral contraceptives. None of these patients were upstaged on follow up visits.

Controversies exist about the link between breast cancer and smoking, but some studies have shown that smoking, especially before the age of adolescence, increases the risk of breast cancer (9, 42). Only 9 patients had a positive smoking history and all had stable disease.

There is no link between the use of caffeine and breast cancer, however, caffeine use is implicated as cause of mastalgia (42). Forty-eight patients reported caffeine use. Of this number, 11 reported mastalgia associated with a breast mass. All these patients had stable disease and were discharged.

The most prevalent presenting complaint in the patient population was finding a mass in the breast. This was reported by 269 patients, representing 87% percent of the patients. Mastalgia was reported by 62. Nipple discharge was reported by 18 patients and 6 patients reported all three symptoms. These results are detailed in the Appendix D Figure D.4. These findings are consistent with the study conducted by Rayne *et al* and Janaki *et al* where a large number of their respondents reported finding a mass in the breast, followed by pain and fewer patients reporting nipple discharge (3, 41). These findings are summarized in Figure D.4.

4.2. Limitations of the current study

A lot of patients defaulted follow up, and as such, few masses were analysed. South Africa being one of the strongest economies in Africa and has better health care systems and therefore it was no surprise that people from other countries migrate to South Africa mostly

for jobs and better health care, amongst other reasons. Johannesburg has the majority of internal migrants as well as people coming from neighbouring African countries. This greatly affects the continuation of health care in these patients. A study conducted by Vearey in 2016 found that the majority of the respondents who were women were surveyed in a province different from where they were born. The study also found that a higher proportion of migrants from other countries used urban clinics (43, 44). Also, the high default rate may be related to the fact that our patients are reassured about the findings and may be a contributing factor for them missing the subsequent visits.

The reported analysed did not have details regarding the imaging features of most of the lesions and less so on the follow up visits which made achievement of the first objective difficult.

Further, the patient data analysed was based on records obtained from one referral hospital in Johannesburg and may not be representative of the overall patient population with probably benign breast masses.

4.3. Future applications

The introductory section of this research indicated that one of the motivations for this research was the minimal empirical study performed in the area in the South African context. This study bridged that gap in knowledge as far as the breast lesions study is concerned. Further, the research output will provide a basis for future studies to be performed.

5. Conclusion

The study was a retrospective study of BI-RADS 3 breast lesions in women aged 18-40 years. By analysing the patient's imaging data at the initial visit, 6 months and 12 months follow up visits revealed no malignancy in the local South African population and that these findings are comparable to existing international data of research conducted among women with this category of breasts lesions.

5.1. Recommendation for future studies

Few of the lesions had a detailed report on the imaging findings on the masses evaluated on ultrasound. This may be explained by the high patient numbers seen at our facility. Because of this, consideration can be made for the use of tick sheets in the mammogram unit for reporting.

A high default rate was observed in this study in the first 6 months of follow-up. In view of this, we recommend that elastography be included in the evaluation of breast masses at CMJAH. This could result in more lesions classified as BI-RADS 2 and fewer lesions as BI-RADS 3. This will reduce the economic burden on patients and also reduce the stay away time from work as a follow up visit in 6 months would not be needed. The benefits of elastography to the facility will include less patient burden as we will eliminate follow ups and it will also reduce the cost of biopsy and management of unintended biopsy related complications.

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Appendix A: Data collection sheets

Case number			
Age at first presentation			
Number of lesions			

	Lesion A	Lesion B	Lesion C etc.
Site of lesion			
Size of lesion, Visit 1			
Shape (1)			
Margin (2)			
Internal echogenicity (3)			
Calcifications (4)			
Through transmission (5)			
Orientation to chest wall (6)			
Size of lesion, Visit 2			
Size of lesion, Visit 3			
Size of lesion, Visit 4			
Other changes on follow up			

Outcome at 6 and 12 months	Discharged (0)
	Down staged (1)
	Biopsied (2)
Histology results	Recorded for each patient

Number of pregnancies	0	1	2	≥ 3
Age at first pregnancy	Before age 30	After age 30		
Presenting Symptoms	Nipple discharge	Lump	Discomfort, pain, tenderness	
Previous breast benign breast disease or surgery	Yes	No	Right breast	Left breast
Relatives with breast cancer	Yes	No		
Contraceptive use	Yes	No		
Smoker	Yes	No		
Caffeine	Yes	No		

Appendix B: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr Foriwah Obeng-Adjei

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190408

NAME: (Principal Investigator)	Dr Foriwah Obeng-Adjei
DEPARTMENT:	Diagnostic Radiology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Ultrasound-detected bi-rads 3 breast lesions at a tertiary institution in Johannesburg: Initial features and audit follow up findings
DATE CONSIDERED:	26/04/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Trevor Nefale and Dr Susan Lucas
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/04/2019

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 on the 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 in **April** and will therefore be due in the month of **April** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 14/05/2019

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C: Note on referencing style

Please note that the referencing in this reseach report 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 thesis, Dissertations and Research Reports is available from https://libguides.wits.ac.za/c.php?g=145382&p=952469

Appendix D: Diagrams and graphical presentation of results

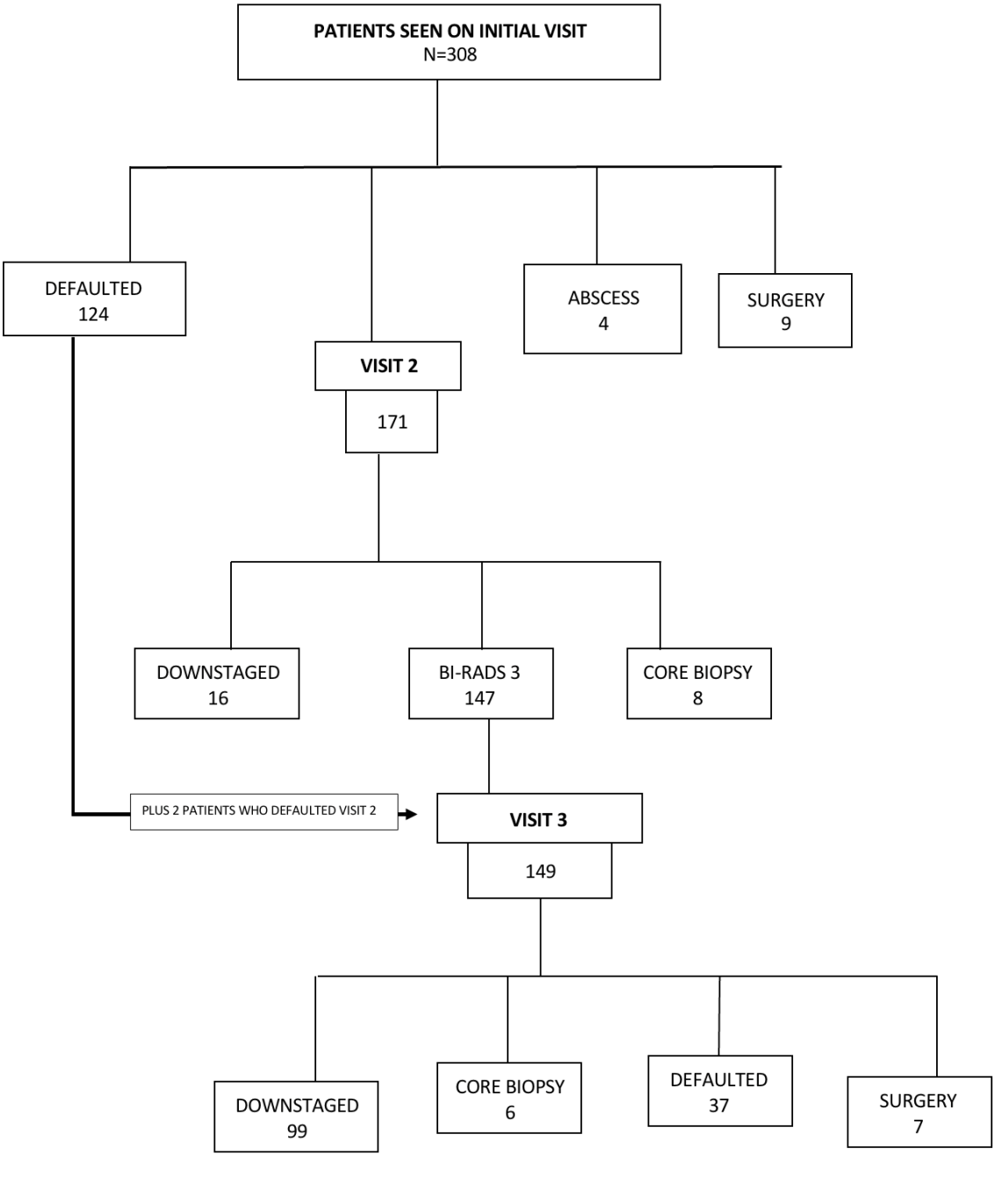


Figure D. 1. Outcome of follow-up

The outcome of patients with BI-RADS 3 lesions who visited the breast imaging unit of the CMJAH from 1 January 2016 to 31st December 2017

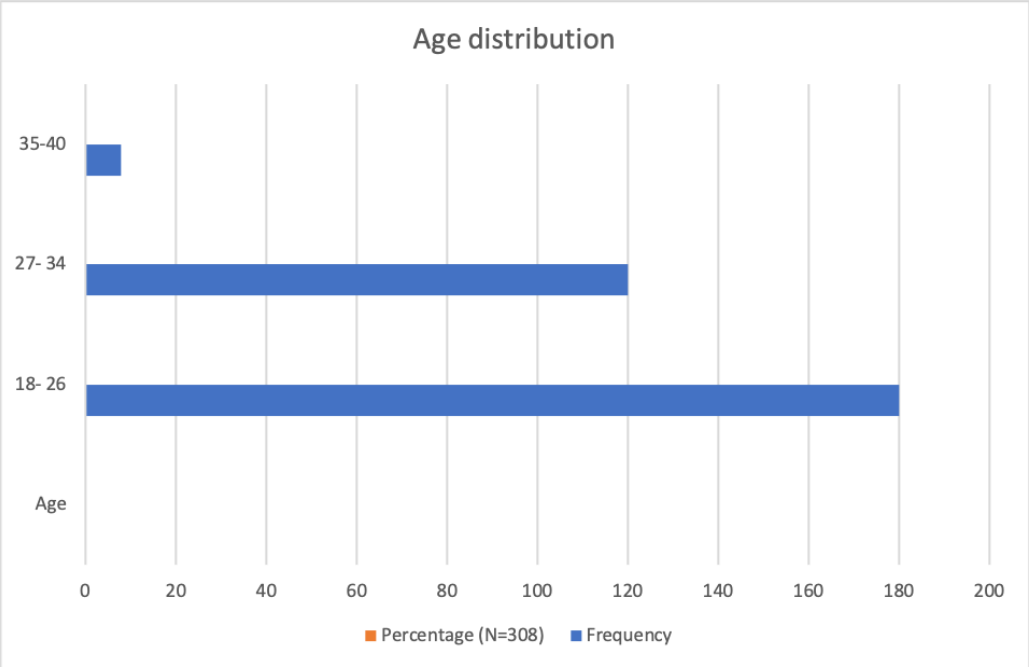


Figure D. 2. Age distribution

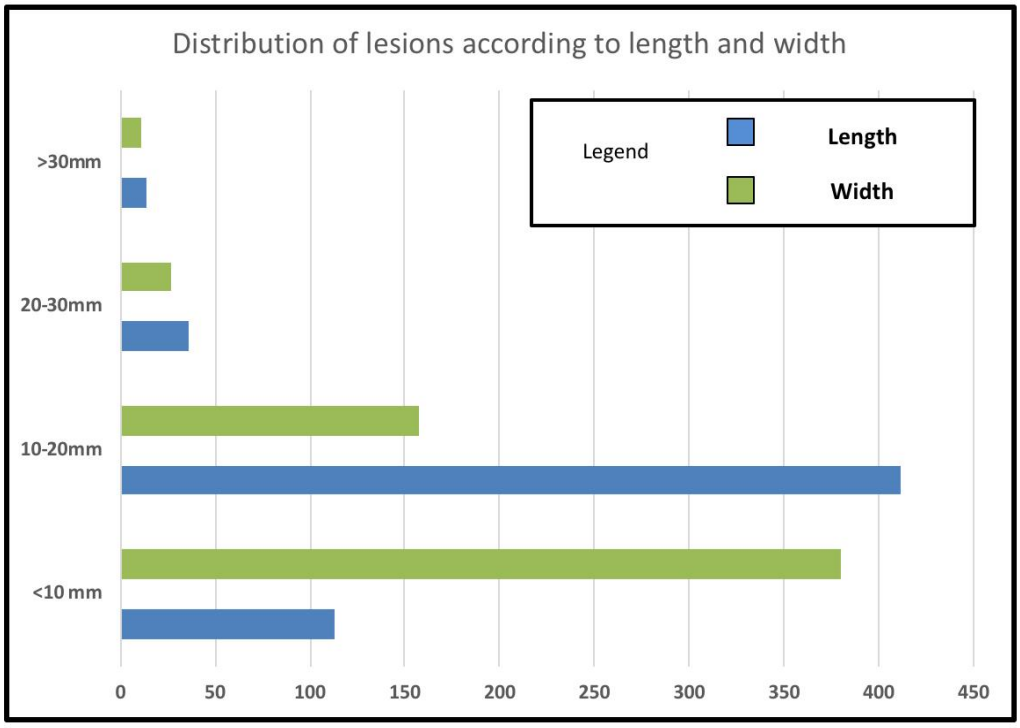


Figure D. 3. Distribution of lesions according to length and width

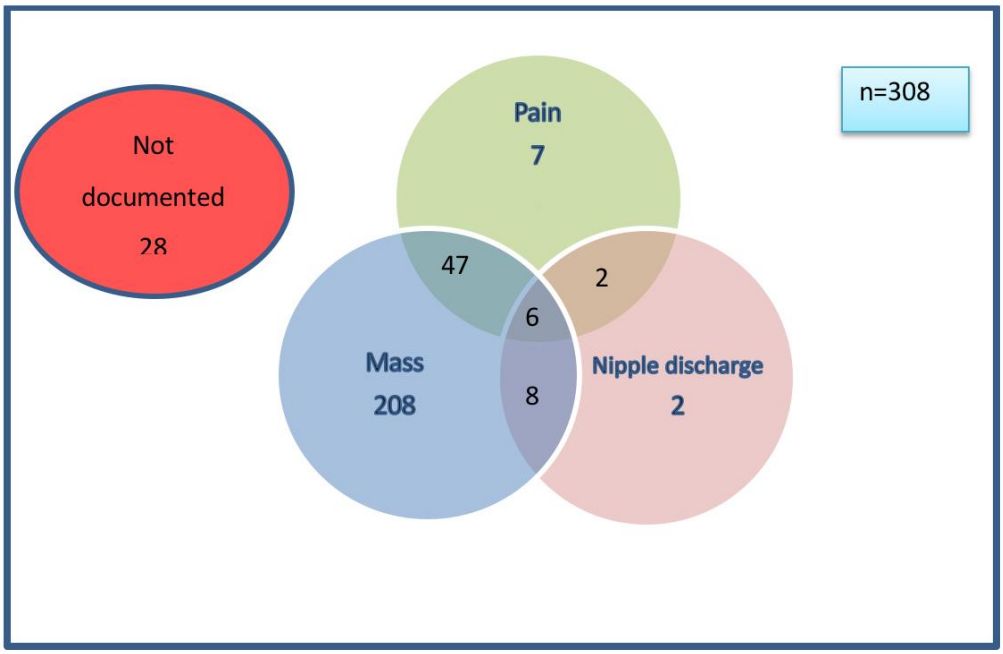


Figure D. 4. Patient presenting complaints