An Audit of Patients Clinically Deemed as High Risk or for Immediate Intervention at the Helen Joseph Hospital Breast Clinic, Johannesburg

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A research report submitted in format of a submissable article 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 Radiology

Johannesburg, 2021

Declaration

I, Heila-Mari Brink, 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 Heila-Mari Brink
On this 3rd day of March 2021

Abstract

BACKGROUND:

The Helen Joseph Hospital Breast Clinic has implemented a clinical triage system for patients presenting with a variety of breast concerns. The goal of this system is to expedite the process from initial presentation to radiological assessment of patients with suspected breast malignancy or breast abscess in a resource limited setting.

OBJECTIVES:

To assess the clinical, imaging and histological diagnoses of breast disease in these patients with malignancy and sepsis.

METHODS:

A retrospective audit of patients clinically deemed high risk for malignant breast pathology referred to the Breast Imaging Unit (BIU) in 2018. Patients were triaged based on strict clinical criteria: presence of a breast mass with or without lymph nodes or a breast abscess. Patients that were subsequently referred for mammography/ultrasound were identified using the patient files in the BIU. Results were recorded on Microsoft Excel and analysed using SAS version 9.2.

RESULTS:

There were 325 patients included in this study. A total of 87 (26.8%) were diagnosed with breast cancer and 236 (72.6%) with benign disease. The most common presenting complaint was a palpable mass (n=227; 69.9%). Of the BI-RADS 5 patients, 95% had malignant disease. The majority of malignancies (55.8%) diagnosed on ultrasound had locally advanced disease. The most common histological diagnosis of malignancy was invasive ductal carcinoma (n=67, 77%). The most commonly diagnosed benign disease was breast abscess (n=42, 17.8%).

CONCLUSION:

BI-RADS findings correspond to similar studies, however a large number of benign breast disease was diagnosed. This may indicate heightened clinical awareness of breast cancer diagnosis and early detection. A significant percentage of malignancies presented as locally advanced. Except for a lower number of invasive lobular carcinoma, the histological spectrum of malignant disease is similar to comparative studies.

Acknowledgements

To my supervisors, Drs Grace Rubin and Susan Lucas. Thank you for your guidance and patience through this process.

Thank you to the staff at the Helen Joseph Breast Imaging Unit. Every single staff member was always willing to help and did so with a smile on their face. Conducting my research in this department was an absolute pleasure.

Thank you to my husband, Darren Rattray, for endless support, encouragement and proofreading.

Table of Contents

List of Figures

List of Tables

List of Abbreviations and Terminology

BIU	Breast Imaging Unit
BI-RADS	Breast Imaging – Reporting and Data System
DCIS	Ductal carcinoma-in-situ
IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma
MC&S	Microscopy culture and sensitivity
NHLS	National Health Laboratory Services

1. Introduction

The Helen Joseph Hospital Breast Clinic has implemented a clinical triage system for patients that present at the breast clinic. This is an open access clinic where any patient with a breast concern is seen. Patients are triaged into 3 groups according to strict clinical criteria: High-, intermediate-, and low- risk cases.

Low risk includes patients with no clinical suspicion of breast disease - asymptomatic patients presenting for screening. Intermediate risk includes patients with unilateral breast pain, a breast mass deemed clinically benign, non-spontaneous nipple discharge, or palpable lymph nodes but no breast involvement.

High risk includes any patient with a breast mass that has a clinical suspicion of malignancy, with or without palpable axillary lymph nodes, or an acute breast collection/abscess. Even though patient age is not part of the triage protocol, patients with increased age are deemed more likely to have malignant breast disease and are more often referred in this high risk category. This is at the referring clinician's discretion. These patients are referred to the Helen Joseph Breast Imaging Unit (BIU) for urgent imaging and if necessary intervention within seven days from presentation. The goal of this triage system is to expedite the process from initial presentation to diagnosis and the timeous management for any patient with a suspicion of breast malignancy. It also aims to decrease the patient burden on the BIU in a resource limited setting and it standardizes the referral criteria for clinicians across varying levels of experience. Breast abscesses and other acute breast collections are added to this group as they require urgent intervention.

The aim of this study was to conduct an audit to assess the spectrum of breast disease clinically deemed high risk for malignant breast pathology, their clinical and imaging features, and their final histological diagnosis.

1.1.This study in context

Even though the incidence of breast cancer in Africa is low in comparison to other countries, the related morbidity and mortality is as high, or even higher, than developed countries (1).

A recent Ghanaian study reviewed 330 histologically proven breast cancer patients. The peak incidence of diagnosis of breast cancer was in the age group of 40-49 years (2). This is in

keeping with multiple other studies done in Sub-Saharan Africa (3-5), which showed that patients in this region present at the pre- and perimenopausal stage, versus high income countries where the majority of patients present postmenopausal (6, 7). The different presenting complaints that were subsequently diagnosed as histologically confirmed breast malignancy were also noted. The most common presenting complaint was a breast lump (75.2%)(2).

Invasive ductal carcinoma (IDC) was the most common histological subtype identified (82.1%). This is in keeping with the trend elsewhere in Africa, Europe and worldwide (8).

The Breast Imaging – Reporting and Data System (BI-RADS) of reporting for breast disease aims to standardize mammography and ultrasound reports (9). An American study done in 2018, which focused on a majority African American demographic, studied the correlation between the mammographic BI-RADS category compared to the histological diagnosis. Breast cancer was diagnosed in 0.03% of patients with a BI-RADS grade of 1 – 3, 29% of patients reported as BI-RADS 4, and 89.7% of patients reported as BI-RADS 5 (10).

No previous research has been done to assess this population's specific burden of disease, highlighting the need for the study in this context.

1.2. Primary Objective

To analyse the spectrum of imaging findings of the patients triaged as high risk for malignant breast pathology at the Helen Joseph BIU.

1.3. Secondary Objectives

To document the associated clinical and relevant laboratory findings, including HIV status.

2. Materials and Methods

2.1.Research paradigm

A retrospective audit of imaging findings of patients clinically deemed high risk and for immediate breast imaging.

2.2. Sample

Patients referred to the Helen Joseph BIU from 1 January to 30 June 2018.

2.2.1. Inclusion criteria

Patients clinically deemed as high risk for malignant breast pathology and seen at the Helen Joseph Hospital BIU.

2.2.2. Exclusion criteria

Patients with illegible records or missing imaging findings.

2.3. Materials and Methods

Files and records at the Helen Joseph Hospital BIU were accessed. The National Health Laboratory Services (NHLS) online database was accessed in order to obtain the relevant histology/HIV results.

2.4. Data collection

The data was collected using a pre-formulated data collection sheet and entered into a Microsoft Excel spreadsheet. Each patient was allocated a study number and only this number was linked to the patient's personal identifiable information.

A triage book is kept at the Helen Joseph Hospital BIU which contains the names and hospital numbers of each patient that is booked at the imaging unit as well as their triage status.

Each patient has a corresponding file which contains their imaging request form, imaging report, history questionnaire and a biopsy information sheet.

The triage book was used to identify the patients seen and triaged as high risk from 1 – 30 June 2018. The corresponding mammography files were then accessed to obtain their demographics, clinical history, imaging findings and histology results. This unit's practise is that every patient should receive a mammogram, except in the following cases: Patients that are younger than 35 years of age start with ultrasound imaging and only if deemed necessary and appropriate are then referred for mammography; patients with painful or ulcerative breast pathology where mammography would cause too much discomfort for the patient; and patients who are physically unable to be positioned for mammography, for instance bed-ridden patients.

The patient's HIV status was documented either from the request form, the history questionnaire or the NHLS online database. If no results were found for a 6-month window period prior to the patient's clinic date, the patient was determined to be HIV "unknown".

2.5. Data analysis and statistics

Data was captured electronically in Microsoft Excel. Further analysis was done using SAS Version 9.2. Descriptive statistics namely frequencies and percentages were calculated for categorical data. Means and standard deviations or medians and percentiles were calculated for numerical data. The Shapiro-Wilk test was used to investigate if numerical data followed a normal distribution. A significance level (p) value of 0.05 was used.

2.6. Ethics

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand, approval number M190675.

3. Results

A total of 760 patients were identified as high risk from the triage book, however multiple patient files were not found. The large number of missing patient files could be due to multiple factors: If patients presented for follow up appointments subsequent to their initial booking date, they were given a new file number which made the tracing of these patients' information difficult. A large number of patients also defaulted on their appointment dates, and some files were erroneously labelled as high risk, but were in fact patients presenting for annual screening – these patients were also excluded. Of these 760 patients, 334 patients with imaging were identified during the study period and nine patients were excluded from the study due to indecipherable imaging reports. The total number thus included was 325.

3.1. Demographics and presenting complaints

Table 1 depicts the patient demographics. Added are their presenting complaints and type of imaging obtained. Percentages of benign versus malignant disease are given. Two patients were not confirmed to have either malignant or benign disease as there was no histology for correlation, but these patients were suspected to have malignant disease based on their imaging features. These patients are added in the 'unknown' column.

Table 1. Patient demographics.

		Malignant	Benign	Unknown	Total (%of total patients)
Sex	Male	0	11 (100%)	0	11 (3.4%)
	Female	87 (27.7%)	225 (71.7%)	2 (0.6%)	314 (96.6%)
Age (median)	Median = 46	57	41	54	
HIV status	Negative	32 (23.7%)	102 (75.6%)	1 (0.7%)	135 (41.5%)
	Positive	7 (13.5%)	45 (86.5%)	0	52 (16%)
	Unknown	48 (34.8%)	89 (64.5%)	1 (0.7%)	138 (42.5%)
Presenting complaint	Palpable mass	80 (35.3%)	146 (64.3%)	1 (0.4%)	227 (69.9%)
	Nipple discharge	1 (10%)	9 (90%)	0	10 (3.1%)
	Lump in armpit	1 (11.1%)	8 (88.9%)	0	9 (2.8%)
	Breast pain	5 (7.9%)	58 (92.1%)	0	63 (19.6%)
	Breast erythema	0	2 (100%)	0	2 (0.6%)
	Skin thickening	0	1 (100%)	0	1 (0.3%)
	Metastatic disease	0	5 (83.3%)	1 (16.7%)	6 (1.9%)
	Breast cancer in remission	0	5 (100%)	0	5 (1.5%)
	Other	0	2 (100%)	0	2 (0.6%)
Type of imaging	Mammography	76 (35.7%)	136 (63.9%)	1 (0.5%)	213 (65.5%)
	Ultrasound	87 (26.8%)	236 (72.6%)	2 (0.6%)	325 (100%)

The majority of patients were female (96.6%). All male patients were diagnosed with benign disease. The most common presenting complaint was a palpable mass for both benign and malignant disease.The median age of malignancies was 57, which was higher than for benign disease of 41.

3.2. Imaging findings

Tables 2 and 3 demonstrate the different imaging findings on mammography and ultrasound with comparison between malignant and benign disease. Of the patients that had masses present on mammography, 58.6% were malignant. This accounted for 78.2% of the total number of malignancies. All of the patients who had malignant masses on mammography (54/87 of malignancies) also presented with identifiable masses on ultrasound. Of the 87 proven malignancies, 86 had masses on ultrasound. The one patient with biopsy proven malignancy that did not have an identifiable mass on ultrasound presented with suspicious microcalcifications on mammography and no mass.

Table 2. Imaging findings on mammography

		Malignant	Benign	Total
Mass present		68 (58.6%)	48 (41.4%)	116
Number of masses	1	50 (60.2%)	33 (39.8%)	83
	2	7 (63.6%)	4 (36.4%)	11
	3	1 (100%)	0	1
	>3	9 (50%)	9 (50%)	18
Mass size	<20mm	4 (57.1%)	3 (42.9%)	7
	20 - 50mm	10 (83.3%)	2 (16.7%)	12
	>50mm	5 (83.3%)	1 (16.7%)	6
Mass shape	Round	2 (14.3%)	12 (85.7%)	14
	Oval	0	1 (100%)	1
	Irregular	3 (100%)	0	3
Breast Density	a	16 (32%)	34 (68%)	50
	b	20 (37.7%)	33 (62.3%)	53
	c	11 (25.6%)	32 (74.4%)	43
	d	2 (25%)	6 (75%)	8
Calcifications	No suspicious	24 (22.6%)	82 (77.4%)	106
	Suspicious	40 (93%)	3 (7%)	43
	Benign	4 (8.3%)	44 (91.7%)	48
	None	1 (25%)	3 (75%)	4
Borders	Circumscribed	6 (17.7%)	28 (82.3%)	34
	Obscured	5 (71.4%)	2 (28.6%)	7
	Microlobulated	14 (87.5%)	2 (12.5%)	16
	Indistinct	14 (82.4%)	3 (17.6%)	17
	Spiculated	21 (95.5%)	1 (4.5%)	22
Architectural distortion	Yes	33 (66%)	17 (34%)	50
	No	11 (10.4%)	95 (89.6%)	106
Associated features	Trabecular thickening	1 (50%)	1 (50%)	2
	Skin thickening	46 (68.7%)	21 (31.3%)	67
Intramammary nodes	Yes	2 (22.22%)	7 (77.78%)	9
	No	74 (36.5%)	129 (63.5%)	203
Axillary nodes	Yes	22 (81.5%)	5 (18.5%)	27
	No	54 (29.2%)	131 (70.8%)	185

Spiculation was the most common border characteristic of the malignant masses (30.9%) on mammography. Suspicious microcalcifications were seen in 40 (52.6%) of malignancies on mammography.

In table 3 we can see that 86 (51.5%) of masses seen on ultrasound proved to be malignant.

Table 3. Imaging findings on ultrasound

		Malignant	Benign	Total
Mass present		86 (51.5%)	81 (48.5%)	167
Mass size	<20mm	16 (28.6%)	40 (71.4%)	56
	20 - 50mm	37 (61.7%)	23 (38.3%)	60
	>50mm	12 (75%)	4 (25%)	16
Number of masses	1	62 (53%)	55 (47%)	117
	2	10 (62.5%)	6 (37.5%)	16
	3	3 (60%)	2 (40%)	5
	>3	9 (36%)	16 (64%)	25
Margin	Circumscribed	8 (14.8%)	46 (85.2%)	54
	Not circumscribed	60 (88.2%)	8 (11.8%)	68
Echo pattern	Anechoic	0	1 (100%)	1
	Hyperechoic	4 (25%)	12 (75%)	16
	Complex cystic/solid	3 (42.9%)	4 (57.1%)	7
	Hypoechoic	44 (57.1%)	33 (42.9%)	77
	Isoechoic	0	2 (100%)	2
	Heterogenous	5 (55.6%)	4 (44.4%)	9
Posterior features	None	0	2 (100%)	2
	Enhancement	0	6 (100%)	6
	Shadowing	15 (83.3%)	3 (16.7%)	18
	Combined	2 (100%)	0	2
Vascularity	Yes	1 (100%)	0	1
	No	4 (80%)	1 (20%)	5
Collection	Yes	1 (2.3%)	42 (97.7%)	43
	No	84 (30.6%)	191 (69.4%)	275
Calcifications	Yes	9 (69.2%)	4 (30.8%)	13
	No	2 (11.1%)	16 (88.9%)	18
Architectural distortion	Yes	2 (50%)	2 (50%)	4
	No	1 (5.9%)	16 (94.1%)	17
Oedematous	Yes	6 (20%)	24 (80%)	30
	No	3 (27.3%)	8 (72.7%)	11
Axillary LN	Yes	57 (70.4%)	24 (29.6%)	81
	No	30 (12.5%)	210 (87.5%)	240

Only 65 out of these 86 patients with malignant masses had a size documented on ultrasound, of which 49 (75.3%) were larger than 2cm and 12 (18.5%) larger than 5cm. Thus 61 out of 65 (93.8%) of presenting masses were larger than 2cm. The majority of poorly circumscribed masses identified on ultrasound were malignant (88.2%).

Axillary adenopathy was present on ultrasound in 57 of the 86 (66.2%) patients presenting with malignancy. Of these 57 patients, 48 had malignant infiltration of their ipsilateral axillary

nodes on ultrasound. Thus 55.8% of patients presenting with breast carcinoma had ipsilateral malignant axillary nodal involvement. Of note is that most patients with malignant lymphadenopathy (35/48; 72.9%) presented with multiple suspicious ipsilateral axillary lymph nodes.

Figure 1 compares the BI-RADS imaging findings with malignant versus benign disease. Of the breast lesions that were assessed as BI-RADS 5, 95% proved to be malignant. The 2 patients with BI-RADS category 5 imaging and reportedly benign histology had suboptimal biopsy results with no representative histology of the lesion.

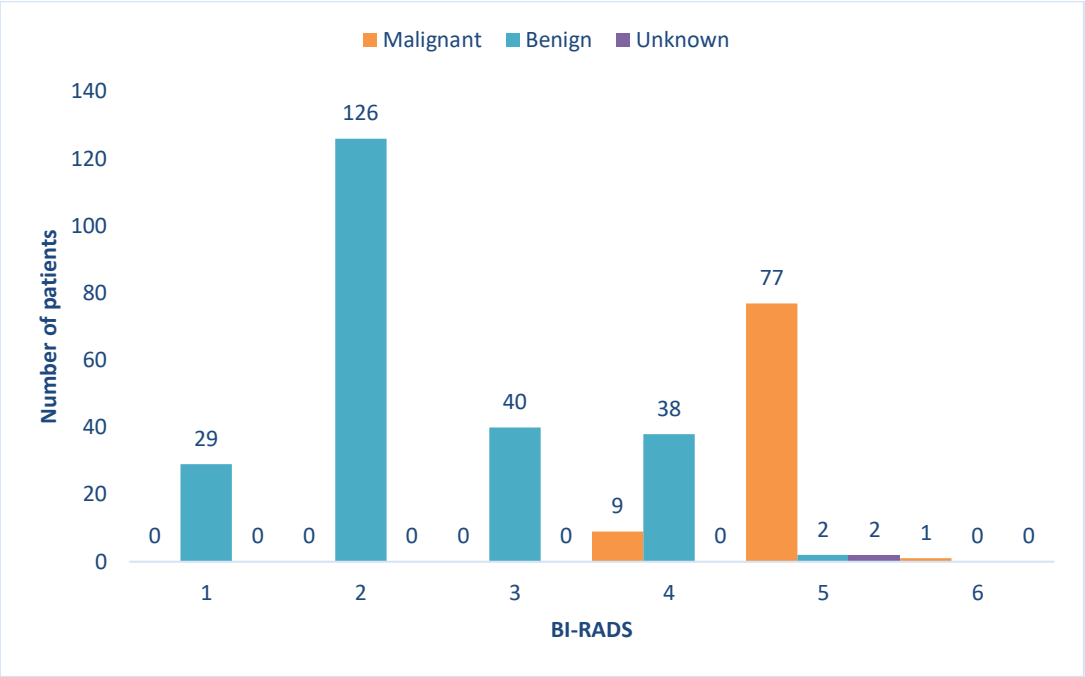

Figure 1. BI-RADS imaging findings

3.3. Spectrum of disease

Figure 2 depicts the histological spectrum of malignant disease. IDC formed the majority of the malignancies (77%).

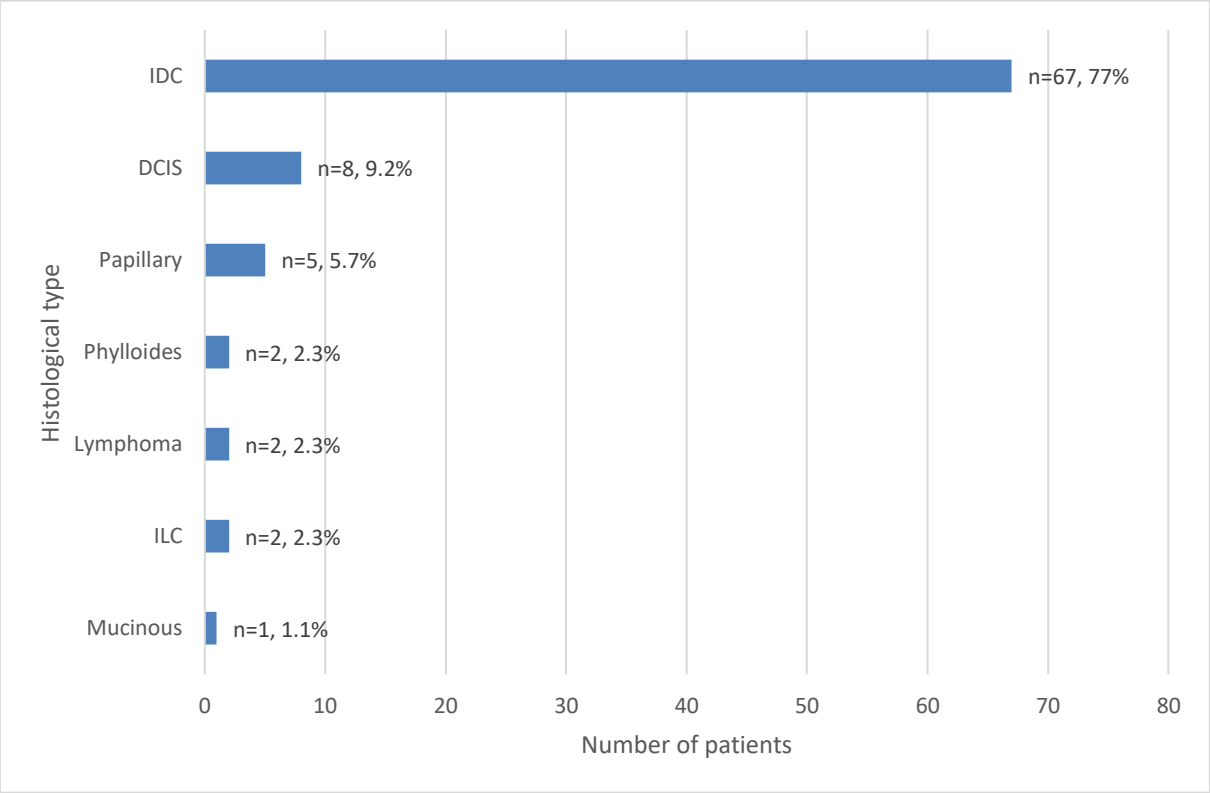

Figure 2. Histological spectrum of malignant disease

The most commonly diagnosed benign breast disease was breast abscesses (n=42, 17.8%) followed by normal imaging findings (n=35, 14.8%) and fibroadenomas (n= 29, 12.3%).

Of the 42 diagnosed breast abscesses, 19 (45.3%) patients were HIV negative, 6 (14.3%) patients were HIV positive, and 17 (40.5%) patients had unknown HIV status.

4. Discussion

The Helen Joseph Hospital Breast Clinic has a triaging system allowing for timeous breast imaging referral and management of patients with suspected breast cancer. This aims to standardise the referral criteria for any clinician examining a patient with a breast concern. We initially expected to see a large majority of malignancies in this study, however the majority proved to have benign disease. This is likely due to a high concern and awareness of the early diagnostic value of breast cancer as well as an indication of the spectrum of clinical experience in an academic teaching hospital. There are also a large number of patients suspected of having a breast abscess attending the breast clinic, and these are referred for imaging and immediate management.

4.1. Results in context

The majority of patients included in the study were females (n=314, 96.6%). Only 11 males were included, of which 100% were diagnosed with benign disease. Global and local trends show that male breast cancer comprises less than 1% of diagnosed breast malignancies (11, 12). The lower rate in this study may be due to the low number of male patients that were seen during the study period.

The median age of patients diagnosed with breast malignancy was 57 with the largest number of patients presenting between 60 – 69. Interestingly, this is out of keeping with findings in multiple other Sub-Saharan African studies where the peak incidence of breast cancer was in pre-and perimenopausal patients (3 - 5). This appears more in keeping with peak incidences in high income countries (6, 7) where women were of post-menopausal ages.

The most common presenting complaint was a breast lump. This included 69.9% of all patients and 92% of malignancies. This is in keeping with a recent study done in Kumasi, Ghana in which they showed that of 330 patients with histologically proven malignancies, 75.2% presented with breast lump (2).

The majority of patients with breast malignancy had a mass present on ultrasound and mammography. It is worth noting that of the 65 malignant masses measured on ultrasound, 49 (75.3%) were greater than 2 cm. Metastatic nodes were seen on ultrasound in 48/86 (55.8%) of malignancies and 35 (40.7%) had multiple ipsilateral metastatic nodes. This would indicate that

at least 55.8% of malignancies diagnosed on ultrasound had locally advanced disease based on imaging features.

Of the patients characterised as BI-RADS 5, 95% proved to have malignant disease, and 20.8% of patients characterised as BI-RADS 4 proved to have malignant disease. This is in keeping with an American study that was done in 2018 which focused on a majority African American demographic. The study compared the correlation between the mammographic BI-RADS category given in reports versus the final histological diagnosis. It was found that 29% of patients reported as BI-RADS 4, and 89.7% of patients reported as BI-RADS 5 were diagnosed with malignancy (10). This also corresponds to another recent Ghanaian study, where out of 54 histologically proven malignancies, 85.2% of patients had findings in keeping with BI-RADS 4 and 5 (13).

IDC (67, 77%) comprised the majority of diagnosed breast malignancies, followed by DCIS (8, 9.2%). This is in keeping with the previously mentioned study done in Kumasi, Ghana where the different histological types of breast cancer were given (2). Out of 340 patients, 82.1% proved to have IDC. Another study done in the Central African Republic in 2018 also showed IDC to be the most common tumour at 64.9%, followed by ILC (9.8%) (14). ILC constituted only 2.3% of patients in our study which was lower than in the above comparison studies.

Breast abscesses were the most common benign condition. This was expected as these patients are referred for immediate intervention. A large number of patients presented with lactational breast abscesses. A recent Zambian study found that HIV infection was a significant risk factor for developing lactational breast abscesses (15). In our study only 14.3% of the total number of breast abscesses were known to be HIV positive. This could be due to a large number of the patients (40.5%) presenting as HIV unknown. The second most common finding was normal imaging. This highlights the difficulties faced in assessing breast disease if clinical examination alone is used.

4.2. Limitations of this study

A large amount of patients had unknown HIV status due to difficulty in tracing results.

The majority of benign breast disease results are not biopsy proven, as BI-RADS 1 – 3 diagnoses commonly do not require biopsy, according to the BI-RADS management guidelines. Some imaging occult malignancies may have been missed.

Self-identified race was not available from the patient files at the BIU – this limits the appropriate comparison to patient groups in comparison studies.

Another limiting factor is the low number of biopsy-proven malignant disease. This could partly be due to the large number of missing files from the initially identified number of high risk patients.

4.3. Future applications

It was interesting to note that all of the masses that were seen mammographically were also identified on ultrasound. This would be valuable for a further study considering ultrasound as a possible screening tool for clinically suspicious masses in resource limited settings.
There were multiple missing files from the initially identified study sample. A large percentage of this is due to the filing system in the department as new file numbers are given to follow up patients. This can be further assessed to possibly keep original file numbers regardless of number of visits to aid future research in this department. Many patients also defaulted on their mammography appointments. Patients should be counselled regarding the importance of follow up appointments at the initial clinical assessment. A large number of imaging reports did not comment on the relevant BI-RADS imaging categories. This can be highlighted and encouraged in mammography training. This is a study of a single centre breast unit triage system. Subsequent studies, with comparison to other triage systems, are needed and may highlight changes that should be implemented. This triage system does however significantly decrease the burden of the radiology department in a resource limited setting and can be considered for implementation in other centres.

5. Conclusion

This is an index study of a breast clinic triaging system. BI-RADS imaging findings largely correspond to other similar studies, however a large number of benign breast disease was diagnosed in this study. This requires ongoing evaluation of the triaging system, however it highlights that clinical evaluation of breast disease requires imaging and biopsy. Clinical presentation of breast malignancy at our centre corresponds to other comparative studies with the majority of patients presenting with palpable breast masses. A large number of our patients presented with locally advanced breast malignancy based on imaging. The histological spectrum of malignant breast disease is similar to the available literature, however we saw a lower number

of ILC. A large number of imaging reports did not report on the relevant BI-RADS imaging categories. This should be further encouraged during mammography training.

Publications and presentations

This article has been accepted for publication in the South African Journal of Surgery.
It has never been presented at a congress.

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Appendix A: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Heila-Mari Brink

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190675

NAME: (Principal Investigator)	Dr Heila-Mari Brink
DEPARTMENT:	Diagnostic Radiology Helen Joseph Hospital
PROJECT TITLE:	An audit of patients clinically deemed as high risk or immediate intervention at the Helen Joseph Hospital Breast Clinic, Johannesburg
DATE CONSIDERED:	28/06/2019
DECISION:	Approved unconditionally
CONDITIONS:	Change of Title
SUPERVISOR:	Dr G. Rubin and Dr S. Lucas
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/07/2019 (Initial Approval), 13/08/2020 (Change of Title)

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 **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 Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: Turnitin Report

2057440:Final_Turnitin_report_Heila_Brink.docx

ORIGINALITY REPORT

4%	3%	3%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	journals.co.za Internet Source	1%
2	Shaomin Hu, James Szymanski, Zeina Khairy, Yungtai Lo, Yanhua Wang. "Breast pathology and mammography BI-RADS category correlation study - A single institute experience", Annals of Diagnostic Pathology, 2018 Publication	1%
3	journals.sagepub.com Internet Source	1%
4	HHC Tsang, JWC Wai, JLF Chiu, OK Wong. "Mucocele-like Lesions of the Breast: Mammographic, Sonographic, and Pathologic Findings and Upgrade Rate", Hong Kong Journal of Radiology, 2017 Publication	<1%
5	Susan G. Orel, Nicole Kay, Carol Reynolds, Daniel C. Sullivan. "BI-RADS Categorization As a Predictor of Malignancy", Radiology, 1999 Publication	<1%

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9	"30th Annual San Antonio Breast Cancer Symposium – December 13–16, 2007", Breast Cancer Research and Treatment, 2007 Publication	<1 %
10	"Breast Diseases", Springer Science and Business Media LLC, 2019 Publication	<1 %

Appendix C: Protocol

An Audit of Patients Clinically Deemed as High Risk or for Immediate Intervention at the Helen Joseph Hospital Breast Clinic, Johannesburg

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Table of Contents

1. Rationale

Breast cancer is one of the leading causes of cancer deaths among females in the world (1). The incidence of breast cancer in African women is the lowest worldwide, however the mortality caused by this disease is as high, or even higher than in developed countries (2).
A recent systematic review in sub-Saharan Africa (3) showed that a high proportion of females in this region are diagnosed at a late stage of breast cancer which has been proven to poorly affect the survival rate of these patients (4).

The Helen Joseph Hospital Breast Unit has implemented a triage system for each patient that is seen at the breast clinic. The patients are triaged into 3 groups: High risk/for immediate intervention, intermediate risk, and low risk cases.
The patients triaged as high risk/for immediate intervention include any patient with a breast mass with or without palpable lymph nodes that have a suspicion of malignancy, or an acute collection/breast abscess, in both males and females. The goal of this triage system is to expedite the process from initial presentation to appropriate diagnosis and management for any patient with a suspicion of breast malignancy. This aims to achieve the best clinical outcome for patients. We will therefore expect the largest proportion of the patients in this group to be diagnosed with breast malignancy, rather than benign conditions. Breast abscesses and acute breast collections are added to this group as they require urgent intervention.

These patients are to be seen at the mammography unit within 1 – 7 days for imaging and appropriate further investigations, such as fine needle aspiration or core biopsy.
There have been no previous studies to assess the disease burden within this unique subset of patients and thus the aim for this study is to conduct an audit on this group of patients to assess the spectrum of breast disease, their clinical and imaging features, as well as their final histological diagnosis.

2. Introduction

2.1. Epidemiology of breast cancer

Breast cancer is the one of the most common malignancies, as well as one of the primary causes of death due to cancer among females worldwide. As mentioned above, there is a significant difference in the breast malignancy survival rates of developed countries versus developing countries with the 5 year survival rates being 80% and 40% respectively (1).

Breast cancer is the most common female cancer in South Africa, responsible for approximately 22% of all cancers with a lifetime risk 1 in 27 women (5). Male breast cancer however, is extremely uncommon, accounting for less than 1% of all male malignancies and less than 1% of all breast cancers (6, 7).

2.2. Clinical presentation of breast cancer

Breast cancer is diagnosed on tissue histology, however the following are the most common clinical features of breast malignancies:

1. Breast mass: The classic characteristics of a malignant breast lesion include a hard, fixed single lesion with irregular borders. These features can however not reliably distinguish a benign from a malignant mass.
2. Locally advanced disease: Signs of locoregional disease include axillary lymphadenopathy.
3. Inflammatory changes: Skin findings such as erythema, thickening and dimpling of the overlying skin are suggestive of inflammatory breast cancer.
4. Metastatic disease: Signs and symptoms of metastatic disease are dependent on the organ system involved. The most common sites of metastatic involvement include bone (e.g. back or leg pain), liver (e.g. abdominal pain, nausea, jaundice), and lungs (causing for instance shortness of breath or cough) (8).

2.3. Imaging findings suggestive of breast cancer

2.3.1 Mammography

Mammographic features of breast cancer can be broadly divided into two categories including soft tissue masses and microcalcifications (9):

Soft tissue masses: A large group of noncalcified malignancies (approximately one third) present as spiculated mass lesions; approximately a quarter present as ill-defined round, lobulated or oval masses; less than ten percent as well defined lobulated or oval masses; and as little as 5 percent as architectural distortion (10).
Microcalcifications: Of the group of cancers that are detected on mammogram, approximately 60% present with microcalcifications (9). Linear branching microcalcifications have a higher risk for malignancy than coarse heterogenous microcalcifications, particularly for high-grade ductal carcinoma in situ (DCIS) (11). Microcalcifications present as the only mammographic finding in approximately 20% of invasive cancers (12). Of all the invasive breast malignancies, approximately one third present with microcalcification – this includes cancers with or without soft tissue masses. Soft tissue masses without microcalcifications are present in ten percent of intraductal cancers (11).

2.3.2 Ultrasound

Breast ultrasound is used together with breast mammography to further classify lesions as benign or suspicious for malignancy. Ultrasound features that increase the likelihood of underlying malignancy include hypoechogenicity, microlobulation, spiculation, shadowing, internal calcifications, a lesion that is taller than wide, and ill-defined angular margins (13).

2.3.3 Intramammary and axillary lymphadenopathy

The presence and characteristics of lymph node involvement is evaluated with both ultrasound and mammography (9). These modalities are useful in distinguishing benign from malignant lymph nodes based on imaging characteristics, however the definitive diagnosis is based on histopathologic correlation (14).

2.4. BI-RADS imaging classification of breast cancer

The American College of Radiology Breast imaging Reporting and Data System (BI-RADS) imaging classification system was initially developed in 1993. The lexicon aims to standardize breast imaging reports, provide a quality assurance tool and to improve the referral system and communication with referring clinicians (15).

The lexicon uses multiple descriptors such as breast composition and imaging morphology characteristics to formulate an assessment category for ultrasound and mammographic imaging features (See Appendix A: BI-RADS 5 easy reference card for imaging characteristics and discriminators) (16).

See Table 1 for the assessment categories for the BI-RADS 5 system (16).

Table 1: BI-RADS assessment categories

BI-RADS ASSESSMENT CATEGORIES	
Category 0	Needs additional imaging/prior examinations.
Category 1	Negative
Category 2	Benign
Category 3	Probably benign
Category 4	4A: Low suspicion for malignancy 4B: Moderate suspicion for malignancy 4C: High suspicion for malignancy
Category 5	Highly suggestive of malignancy
Category 6	Known biopsy-proven malignancy

2.5. Histological classification of different types of breast cancer

The histological classification of breast malignancies is divided into two broad categories: In situ and invasive carcinomas. In situ carcinomas can then be further divided into ductal and lobular types with the differentiating features between these two entities including growth patterns as well as cytological features. Ductal carcinoma in situ is significantly more common than lobular carcinoma in situ. This group includes a large variety of tumours. The architectural features of the tumours classified as ductal carcinoma in situ is the basis for a further subclassification into five subtypes which include solid, cribriform, papillary, micropapillary and comedo types (17). See figure 1 (18).

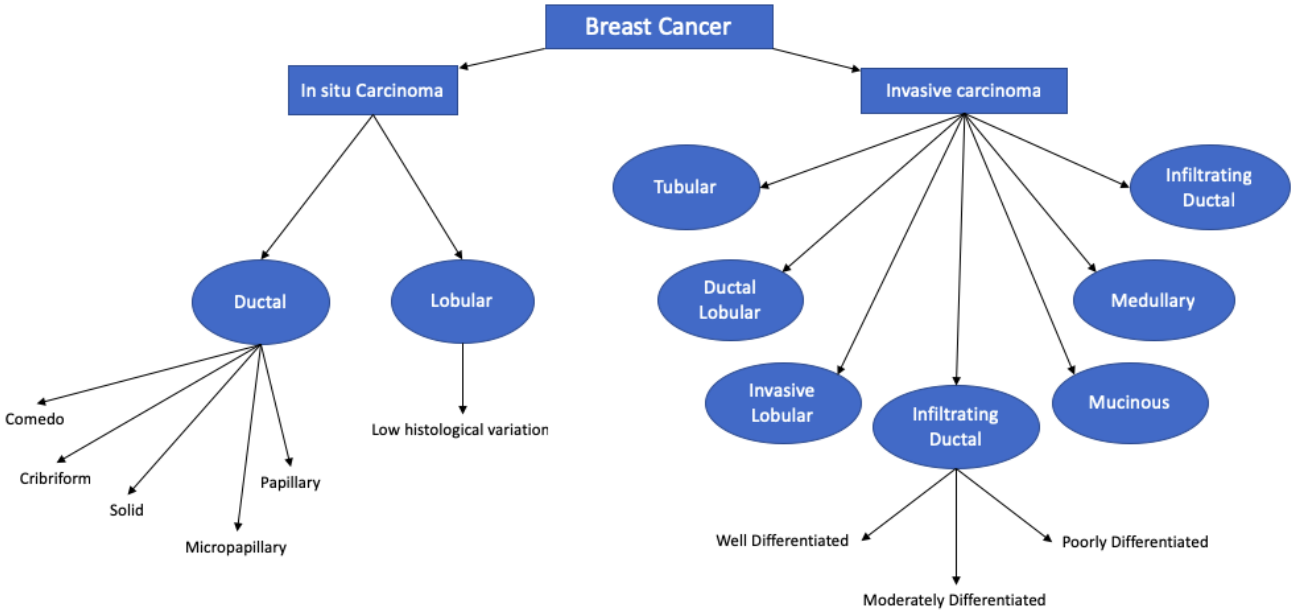


Figure 1: Schematic presentation of histological classification of breast malignancies

The invasive types of breast carcinomas are also divided into major histological subtypes and include invasive ductal carcinoma (IDC), invasive lobular, mixed ductal and lobular, papillary, colloid, medullary and tubular types (Fig.1). 70 – 80% of all invasive carcinomas are of the invasive ductal subtype (19). The invasive ductal type can also be sub-divided into grade 1 (well differentiated), grade 2 (moderately differentiated), or grade 3 (poorly differentiated). This sub-classification is based on the tumour's assessed nuclear pleomorphism, mitotic index, as well as tubule or glandular formation (20).

2.6. Breast abscesses

Breast abscesses can develop as a primary entity with no causative disease or it can occur as a complication of another disease process (i.e. secondary) such as periductal mastitis, skin infection over the breast, or granulomatous lobular mastitis (21). In a study of 89 patients with primary breast abscesses that required surgery, the large majority of breast abscesses were caused by *Staphylococcus Aureus* (22). A Zambian study found that HIV infection is a significant risk factor for the development of breast abscesses in lactating women (23).

The clinical presentation of a breast abscess includes a tender and inflamed breast, fever, as well as a palpable tender mass which is warm and fluctuant (24). The diagnosis is usually confirmed with ultrasound demonstrating fluid collection. Ultrasound can also be used for guided aspiration of the collection (25).

The differential for breast abscess includes the following:
In lactating women:

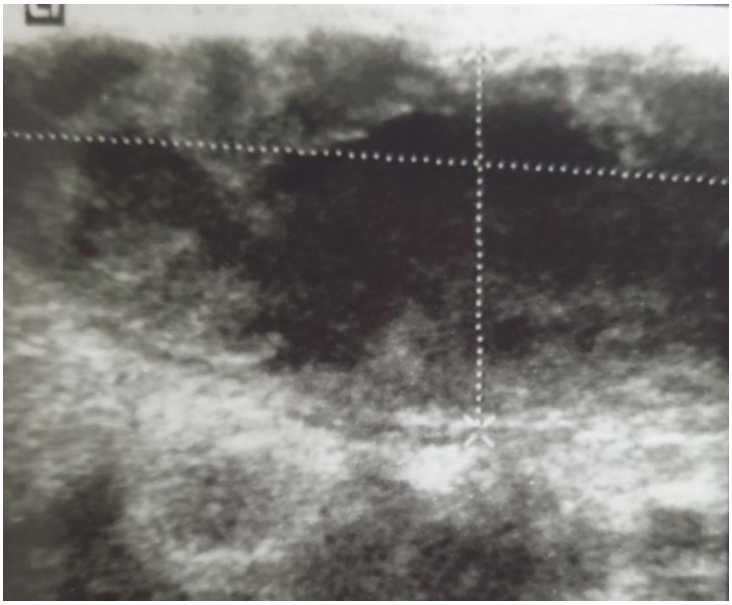
- Plugged duct – localized area of milk stasis within the ductules causing distention of the mammary tissue.
- Milk retention cyst – also known as galactocoele. This is caused by obstruction of a milk duct and presents as a fluid collection or a cystic mass.

In any woman with a breast abscess:

- Inflammatory breast cancer – This entity can be difficult to differentiate from a breast abscess or infection due to similar presenting features. Clinical features include skin thickening and inflammation (21).

See figure 2 below for an example of a breast abscess on ultrasound.

Figure 2: Transverse ultrasound image of a woman who presented with a painful and inflamed breast. Ultrasound shows a large complex fluid collection which proved to be an abscess on aspiration.



2.7. Other common benign breast conditions

There are multiple benign breast conditions that can mimic breast carcinoma on clinical examination and on mammography/ultrasound. Irregular hypoechoic breast masses on ultrasound are characterised as BI-RADS 4, however a large variety of benign conditions can have this appearance (26). These conditions are commonly seen in daily practice at the Helen Joseph Breast Imaging Unit. These include, but are not limited to, atypical fibroadenomas, fat necrosis, fibrocystic changes, sclerosing adenosis and granulomatous mastitis. A brief summary of commonly seen entities are given below:

2.7.1 Fibroadenomas

Fibroadenomas are benign tumours with mixed epithelial and stromal components. Their usual appearance on sonography is that of an oval circumscribed mass with lobulated contours which is iso- or hypoechoic and with homogenous low internal echogenicity. Some of these tumours however present with intratumoral calcifications as well as irregular margins and can be confused for a suspicious mass with a BI-RADS imaging category of 4.

2.7.2 Fat necrosis

Fat necrosis is a common entity that occurs after injury to the adipose tissue of the breast. It is a benign inflammatory condition and the associated imaging features can range from a completely benign appearance (homogenous and well defined) to features that mimic that of a malignant process. These lesions can even present as irregular masses with suspicious calcifications. They clinically present as palpable breast masses which is clinically difficult to distinguish from more aggressive mass lesions (27).

2.7.3 Foreign body reaction

Foreign body reactions can mimic malignancies on mammography and can present as microcalcifications, calcifications or even and ill-defined mass. These masses can also appear suspicious on ultrasound and can present as spiculated or irregular hypoechoic masses.

2.7.4 Fibrotic scars

If the history of previous breast surgery or trauma is not available, it can be difficult to diagnose fibrotic scars in the breast. Imaging features on mammography include architectural distortion with lesions of variable density. Ultrasound can show an irregular hypoechoic lesion.

2.7.5 Sclerosing Adenosis

This disease is common among perimenopausal women and is a benign proliferative disorder. It can often be confused with carcinoma as it presents with overlapping clinical and imaging findings. The clinical presentation is of a firm breast mass. The radiological features are variable on both ultrasound and mammography. Mass borders can range from well circumscribed to spiculated with associated architectural distortion and calcification. The most common ultrasound presentation is of a well circumscribed hypoechoic mass, however they can also present with heterogeneity and an antiparallel orientation.

2.7.6 Fibrocystic change

This is also a very common benign breast condition that includes a large variety of different histological findings. Similarly, imaging findings are also varied. Sonographic features can include simple or complicated cysts, solid lesions and calcifications. Mammographic findings range from an indistinct mass with calcification to a benign appearance/well circumscribed mass (26).

This emphasizes the importance of clinical examination and imaging combined with guided histological diagnosis for accurate diagnosis and subsequent patient management.

2.8. This project in context

As mentioned above, even though the incidence of breast cancer in Africa is low in comparison to other countries, the morbidity and mortality due to this disease is as high or even higher than developed countries with a unique demographic composition (2). It

is therefore imperative to assess the spectrum of disease and the unique characteristics thereof to ensure timely diagnosis and appropriate treatment in our setting.

In a recent Ghanaian study where they looked at 330 histologically proven breast cancer patients, the peak incidence of diagnosis of breast cancer was in the age group of 40-49 years old (28). This finding is in keeping with multiple other studies done in Sub-Saharan Africa (29-31), which showed that patients in this region present at the pre- and perimenopausal stage, as opposed to high income countries where the majority of patients present at postmenopausal ages (32, 33).

A Ugandan study which looked at histologically diagnosed breast disease at a tertiary institution over a nine year period showed that the male to female breast cancer was 1:48 (34), which is in keeping with the global picture where male breast cancer comprises of less than 1% of breast cancer diagnosed worldwide (7).

In the abovementioned Ghanaian study, the different presenting complaints that were subsequently diagnosed as histologically confirmed breast malignancy were noted. The most common presenting complaint by far was that of breast lump (75.2%). See table 2 (28).

Table 2: The frequency of different presenting complaints in percentage in histologically diagnosed breast cancer.

Presenting complaint	Percentage (%) of patients
Breast lump	75.2
Swelling of the breast	18.5
Breast pain	3.6
Bloody nipple discharge	1.5
Lump in armpit	1.2

The different histological types of breast cancer were also noted in this study with invasive ductal carcinoma being the most common at 82.1%. This is in keeping with the trend elsewhere in Africa, Europe and the world at large for the most frequently diagnosed breast cancer type (35). Another study done in the Central African Republic in 2018 also showed invasive ductal carcinoma to be the most common tumour at

64.9%, followed by invasive lobular carcinoma (9.8%), and ductal carcinoma in situ (5.7%) (36).

As previously mentioned, the BI-RADS system of reporting for breast aims to standardize mammography and ultrasound reports (15). An American study that was done in 2018, which focused on a majority African American demographic studied the correlation between the mammographic BI-RADS category given in reports compared to the final histologic diagnosis. This study found that the diagnosis of breast cancer in the benign to probably benign mammography reports (BI-RADS 1-3) was 0.03%. 29% of patients reported as BI-RADS 4, and 89.7% of patients reported as BI-RADS 5 were diagnosed with malignancy (37).

This is in keeping with a recent Ghanaian study, where out of 62 cases that were reported as BI-RADS 4 and 5, only 16.1% were diagnosed as benign on histology. This study also showed that the sensitivity for diagnosing breast cancer was higher with ultrasound than mammography, however the specificity is similar (38).

The subset of patients identified for this study is completely unique with a unique demographic distribution, clinical features and spectrum of disease. An audit of the burden of disease of these patients is crucial in order to identify and improve on any unique or previously missed clinically diagnostic or imaging problems. The data collected in this study can also serve as a basis for further study and research in this area.

3. Primary Objective

This study aims to analyse the spectrum of imaging findings of the patients deemed as high risk/for immediate intervention at the Helen Joseph Breast Imaging Unit.

4. Secondary Objectives

- To document the associated clinical findings
- To document the relevant laboratory findings in these patients.

5. Methods

5.1. Research paradigm

This is a retrospective audit of imaging findings of patients clinically deemed as high risk/for immediate breast imaging/intervention.

5.2. Sample

The study population will be patients that are referred to the Helen Joseph Breast Imaging Unit from 1 January 2018 to 30 June 2018.

5.2.1. Inclusion criteria

Patients that were clinically deemed as high risk/for immediate intervention and seen at the Helen Joseph Hospital Breast Imaging Unit will be considered for inclusion into the study.

5.2.2. Exclusion criteria

Any patients with illegible records or missing imaging findings.

5.3. Materials and Methods

I will access the patient files and records at the Helen Joseph Hospital Breast Imaging Unit. I will also access the National Health Laboratory Services (NHLS) online database in order to obtain histology/MC&S results.

5.4. Data collection

The data will be collected using a pre-formulated data collection sheet and entered into a Microsoft Excel spreadsheet. Each patient will be allocated a study number and only this number will link the patient's personal identifiable information.
This data collection sheet is included as Appendix B and C.

A triage book is kept at the Helen Joseph Hospital mammography unit. This book contains the names and hospital numbers of each patient that is booked at the mammography unit, as well as their triage status.

Each patient has a file in the mammography unit which contains their imaging request form, their imaging report, a history questionnaire completed by the radiographers, as well as a biopsy sheet. This biopsy sheet contains a summary of the imaging findings as well as the specimen reference number for the biopsy/MC&S.

I will use the triage book to identify the patients seen and triaged as high risk/for immediate intervention starting from the first of January 2018. From there I will access their mammography files to get the demographics and clinical history, as given on the X-ray request form. If this history is incomplete or illegible, I will obtain the patient's presenting complaint from the history questionnaire.

The patient's HIV status will be documented, either from the request form, questionnaire or LabTrack. If no HIV results are found for a 6 month window period, the patient will be determined HIV "unknown".

Imaging (mammogram and/or ultrasound) findings and BI-RADS classification will be collected from the imaging report and collected on this data collection sheet. No mammograms will be reviewed for the purpose of this study.

I will then access the NHLS database and use the specimen reference in the file to obtain the final histology or MC&S results for each patient.

5.5 Bias

The study population is a resource limited community and thus we will expect to see more advanced disease.
Accuracy should not be a problem in this study as each imaging report included in this study is approved by a qualified radiologist.

6. Data analysis and statistics

Data from the data collection sheet will be entered into a Microsoft Excel Spreadsheet. Analysis of this data will then be done by a statistician using the program SAS version 9.2. Frequencies and percentages (descriptive statistics) will be calculated for categorical data. Numerical data will be analysed by calculating standard deviations/means or percentiles and medians. The Shapiro-Wilk test will be used to investigate if numerical data follow a normal distribution. A significance level (p) of 0.5 will be used.

7. Ethics

This study has been approved by the Human Resources Ethics Council (HREC) of the University of Witwatersrand, Johannesburg.

7.1. Data safety

Data will be collected anonymously by allocating a study number to each patient. The key to this code will only be available to the primary investigator and supervisors. No personal identifiable information will be collected. The patient data and information gained from this study will be kept in a double password protected database (computer and database passwords).

8. Timing

Month of the Year	1	2	3-5	6-7	7-9	9-10	11-14	15	16-18
Literature search									
Reading literature									
Summarising literature									
Preparing Protocol									
Protocol Assessment									
Ethics application									
Collecting data									
Data analysis									
Writing up thesis/paper									
Submit: marking									
Writing up paper									

9. Budget

Statistician	R1000
Stationary	R500
Travel and congress	R1000

10. Anticipated problems

Data collection and problems with access of files could cause delays in this study. Multiple online backups of the data, as well as the study itself will be made so as to prevent loss of data.

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Appendix A: BI-RADS easy reference card

ACR BI-RADS® Atlas Fifth Edition

QUICK REFERENCE

ACR AMERICAN COLLEGE OF RADIOLOGY
QUALITY IS OUR IMAGE

ULTRASOUND

Tissue composition *(screening only)*	a. Homogeneous background echotexture – fat b. Homogeneous background echotexture – fibroglandular c. Heterogeneous background echotexture	
Masses	Shape	Oval
		Round
		Irregular
	Orientation	Parallel
		Not parallel
	Margin	Circumscribed
		Not circumscribed - Indistinct - Angular - Microlobulated - Spiculated
	Echo pattern	Anechoic
		Hyperechoic
		Complex cystic and solid
		Hypoechoic
		Isoechoic
		Heterogeneous
	Posterior features	No posterior features
		Enhancement
		Shadowing
		Combined pattern
Calcifications	Calcifications in a mass	
	Calcifications outside of a mass	
	Intraductal calcifications	
Associated features	Architectural distortion	
	Duct changes	
	Skin changes	Skin thickening
		Skin retraction
	Edema	
	Vascularity	Absent
		Internal vascularity
		Vessels in rim
	Elasticity assessment	Soft
		Intermediate
		Hard
Special cases	Simple cyst	
	Clustered microcysts	
	Complicated cyst	
	Mass in or on skin	
	Foreign body including implants	
	Lymph nodes – intramammary	
	Lymph nodes – axillary	
	Vascular abnormalities	AVMs (arteriovenous malformations/ pseudoaneurysms)
		Mondor disease
	Postsurgical fluid collection	
	Fat necrosis	

MAMMOGRAPHY

Breast composition	a. The breasts are almost entirely fatty b. There are scattered areas of fibroglandular density c. The breasts are heterogeneously dense, which may obscure small masses d. The breasts are extremely dense, which lowers the sensitivity of mammography	
Masses	Shape	Oval
		Round
		Irregular
	Margin	Circumscribed
		Obscured
		Microlobulated
		Indistinct
		Spiculated
	Density	High density
		Equal density
		Low density
		Fat-containing
Calcifications	Typically benign	Skin
		Vascular
		Coarse or "popcorn-like"
		Large rod-like
		Round
		Rim
		Dystrophic
		Milk of calcium
		Suture
	Suspicious morphology	Amorphous
		Coarse heterogeneous
		Fine pleomorphic
		Fine linear or fine-linear branching
	Distribution	Diffuse
		Regional
		Grouped
		Linear
		Segmental
Architectural distortion		
Asymmetries	Asymmetry	
	Global asymmetry	
	Focal asymmetry	
	Developing asymmetry	
Intramammary lymph node		
Skin lesion		
Solitary dilated duct		
Associated features	Skin retraction	
	Nipple retraction	
	Skin thickening	
	Trabecular thickening	
	Axillary adenopathy	
	Architectural distortion	
	Calcifications	
Location of lesion	Laterality	
	Quadrant and clock face	
	Depth	
	Distance from the nipple	

Appendix B: Data collection sheet

Data collection sheet							
Study number		Sex	M	F	Age		
HIV	POS	NEG	UNKNOWN				
Clinical presentation:							
Palpable mass	Nipple discharge	Breast pain	Swelling of the breast	Lump in armpit	Breast erythema	Hardness of the breast	Other
Histology/MC&S							
Tumour type	DCIS	IDC	ILC	IDC + DCIS	Other		
MC&S result	Gram stain positive		TB positive				
Imaging findings							
Mammogram findings							
Mass size	cm						
Mass shape	Round	Oval	Irregular				
Breast density	High density	Equal density	Low density	Fat-containing			
Calcifications	Macro	Micro		Obviously benign	Suspicious		
Borders	Circumscribed	Obscured	Micro-lobulated	Indistinct	Spiculated		
Architectural distortion	Y	N					
Associated features	Trabecular thickening	Skin thickening					

Appendix C: Data collection sheet continued

Ultrasound findings							
Mass size	cm						
Mass shape	Round	Oval	Irregular	No comment			
Margin	Circumscribed		Not circum-scribed		No Comment		
Echo pattern	Anechoic	Hyperechoic	Complex cystic and solid	Hypoechoic	Isoechoic	Heteroge-nous	No comment
Posterior features	No posterior features	Enhancement	Shadowing	Combined pattern	No Comment		
Vascularity present	Y	N	No comment				
Collection	Y	N	No comment				
Calcifications	Y	N	No comment				
Architectural distortion	Y	N	No comment				
Oedematous breast	Y	N	No comment				
BI-RADS	1	2	3	4	5	6	