UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

An Audit of the Spectrum of Male Breast Pathology imaged at CMJAH Breast Imaging Department

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Declaration

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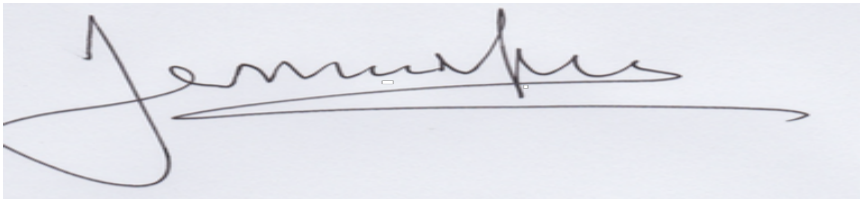

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MMED in publication ready research article submission format guidelines recommended by SAMJ, with extended literature research

Dedication

Ouma Moekoe and Marlene Murfin: To my Grandmother and Mother who have always loved, supported and had faith in my abilities. Thank-you for being my amazing role models in life, I am grateful and in awe.

To my family: For your continual understanding support, patience and love in times of long hours. You amaze me every day.

Presentations/Publications from this study:

No current publications or presentations but there will be in the foreseeable future.

ABSTRACT

Background:

Breast pathology awareness is generally a characteristic of the female population due to greater incidence of malignant disease and the implications of morbidity and mortality.

Male breast pathology receives less attention, although referrals of men to Breast Imaging units are increasing. In lower-middle income countries such as South Africa, a higher rate of HIV disease and growing number of men receiving HAART, an identifiable risk factor for male breast disease, is present. Clinical, mammographic and ultrasonographic review of male breast disease is of increasing importance, to assess both hospital prevalence and spectrum of disease.

Objectives:

The primary objective is to evaluate both the prevalence and spectrum of male breast disease referred to a tertiary Breast Imaging Unit. The secondary objective is to identify aetiological risk factors for different male breast diseases .

Methods:

This is a descriptive retrospective cross sectional audit of males presenting to the Breast imaging unit at Charlotte Maxeke Johannesburg Academic Hospital, South Africa, over the 3 year period (1st January 2016 to 31st December 2018). Both Imaging, histology, MC&S and serology were documented for retrospective statistical analysis.

Results:

The study group consisted of 261 of which the mean age was 46 years (range 13 -83). Benign breast disease with gynaecomastia predominating (85.44%), infectious diseases (2.29%) and miscellaneous group of benign disease (5.37%).

Malignant disease of the breast (5.3%) or adjacent tissue (1.4%) accounted for a total of 6.9% of cases. Male breast cancer has similar histopathology and molecular subtype in comparison to Female breast cancer in recent reports.

In young and middle age South African men, gynaecomastia is most frequently associated with HIV where in this study 35% of the patients were seropositive. Further investigation of viral load and CD4 counts were infrequently performed. In the elderly men with gynaecomastia, obesity, diabetes and liver disease were not infrequent co-morbidities. However, liver function and endocrine tests were rarely done. Scrotal ultrasonography is mandatory in adolescent boys to exclude both oestrogen-producing tumours and varicoceles.

Conclusions:

In this retrospective audit of 261 men referred to a tertiary Breast Imaging Unit, there was a wide spectrum of benign and malignant disease. However, the finding that 5.4% of men had male breast cancer was unexpected. This highlights the importance of histological biopsy of any radiologically suspicious pathology.

The 34,87% (91/261) HIV seropositive subgroup of male patients displayed similar spectrum and distribution of both benign and malignant male breast disease, as that of their HIV seronegative and non-tested majority within this study group. Consistent HIV serological testing is required as the patients did not reflect that they originate from a high HIV positive referral population group. This would allow for both HIV seropositivity and HAART regimes effects on male breast disease to be better evaluated and concluded upon.

This review audit highlights the necessity for multidisciplinary team follow-up and audits, as a critical part of approach and management of both benign and malignant male breast disease. It's imperative that patients are counseled to highlight the importance of their diagnosis, implications of treatment and the need to attend follow-up appointments. Where short falls are noted, a reviewed protocol orientated towards better approach and management plans is required to maximize the efficacy of a multidisciplinary team in Clinical Male breast disease overall.

Acknowledgements:

Dr. J. Haberfeld: Dr. Haberfeld was my unwavering co-supervisor, she has continued to be my bottomless support, positive influence and constant inspiration in life, career and all its pursuits.

Dr R. Minné: Dr. Minné for supporting a total unknown entity and prompt response, even in times of total stress with utter professionalism.

Prof A. Mannell: For her consistent professionalism, eloquence and command of the English language and professional insight with a touch of old school Lady-like class.

Maryna Viljoen: Her contribution in restructuring of the data audit sheets and statistical analytical guidance and utter patience with 'data cleaning', commanding total respect of her professional title.

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List of Abbreviations:

1. Mbc Male breast cancer
2. FBC Female breast disease
3. Mbd Male breast disease
4. BIU Breast Imaging Unit
5. CMJAH Charlotte Maxeke Johannesburg Academic Hospital
6. LMICs Low-middle income Countries
7. HIV Human Immunodeficiency Virus
8. HAART Highly Active Antiretroviral Treatment

INTRODUCTION

Breast pathology awareness, investigation and management generally pertains to females, due to greater incidence, yet male breast pathology awareness is poorly highlighted. [1,2] There are many causes of male breast disease (Mbd), and in low-middle income countries (LMICs), Human Immuno-deficiency virus (HIV) disease and its corresponding treatment regime Highly active Antiretroviral Therapy (HAART) are identifiable risk factors. [1-3] Routine mammographic and ultrasonographic review of male breast pathology outcomes require further evaluation, in both relative frequency and spectrum of male breast disease (Mbd); gynaecomastia and male breast carcinoma (Mbc) representing the opposite ends of the spectrum [2-6]

Gynaecomastia:

Gynaecomastia normally has an age related trimodal distribution of neonatal, pubertal & elderly groups.[7-9] Neonatal period gynaecomastia is asymptomatic and estimated incidence is that of 60 to 90 %.[9]

The pubertal incidence of gynaecomastia, recently updated in a large cross sectional study, is noted to be 4%. [10] Higher BMI's within the adolescent group has resulted in conflicting statistics for gynaecomastia. [10-14] A recent study has also suggested gynaecomastia to be more common in adolescent boys with left-sided varicocoele. [10] In adolescents ages 10 to 13-year-old, gynaecomastia was significantly correlated with left varicoceles. Varicoceles can be associated with a progressive decline in testicular function [10]

Senescent gynaecomastia, incidental peak ranging from 50 - 85 years of age, has a reported prevalence of 70%.[10] Bilateral gynaecomastia is more common than unilateral gynaecomastia; unilateral gynaecomastia ranges approximately 35-45 % [10,14] The HIV & HAART affected subset of male population alters the trimodal age distribution, particularly in low-middle income countries [3,5,8,15].

Multifactorial aetiological causes are noted for gynecomastia which include hormone imbalances from oestrogen excess to testosterone dearth, prolactin hormone excess and low sex hormone binding globulin. Additional causes include renal and liver dysfunction, diabetes mellitus type 2, Human Immune Deficiency Virus (HIV) positivity or other chronic illness subsets. A broad spectrum of medications or drugs can stimulate gynaecomastia or lipomastia . These range from co-morbid disease treatment such as those used in systemic hypertension, prostate disease and psychiatric disorders, to drug abuse such as marijuana, alcohol, heroin or amphetamines. Management of short term gynaecomastia may follow that of a 'wait and see' approach, medical therapy alteration or commencement. For long term gynaecomastia, greater than 1 year duration, surgical management ranging from liposuction, breast reduction, to mastectomy is recommended.[1,2,25]

Other benign male breast pathologies need to be mentioned:
Benign non neoplastic disease such as male breast intramammary lymph node, sebaceous cyst, diabetic mastopathy, mastitis (acute or chronic), haematoma, fat necrosis and

subareolar abscesses are seen. Venous malformations, nodular fasciitis and secondary syphilis are more rarely encountered.[4,16]

Benign neoplasms such as a lipoma, intraductal papilloma, angiolipoma and uncommonly schwannoma may be noted.[4,16]

Male Breast Cancer (Mbc)

Male breast cancer (Mbc) follows a similar age standardised incidence for country, both high & low risk countries, to that of their female counterparts, although the reproductive risk factors do not play a role (2). Non-reproductive risk factors that play a role in this population group must be that of advanced age, environmental, genetic predisposition & hyperoestrogenemic factors. [1-3,5,16-17]

Male breast cancer (Mbc) also follows female breast cancer (FBC) in age distribution and variation in hormone receptor status. [6] Mbc correlates with FBC in age groups over 50 years of age, however under 50 years of age, breast cancer incidence peaks later than that of their female counterparts.[6] The oncogenetics that play a role in MbC are a different distinct disease morphology to that of FBC, which are not routinely screened for and yet are noted to relate to higher incidence of male breast cancer. The list of known genetic markers noted to increase the risk for MbC are *BRCA2* & *BRCA1* androgen receptor genes, *EMSY* gene, *PALB2* gene, [16,17], *PTEN* (Cowden syndrome), *CHEK2* protein kinase truncation mutation, the oestrogen biosynthesis gene *CYP17,* the haemochromatosis gene mutation *HFE* and mismatch repair genes (*hMSH2, hMLH1,hPMS2*). [18]

Mbc is a predominantly unilateral disease, with bilateral disease uncommon. [16]

Mbc follows a similar histological type distribution to FBC, however molecular marker subtype and tumour grade do not correlate with survival in comparison to FBC.[17]

See table 1 : Comparative table of Male vs Female Breast Carcinoma spectral percentage of histologic, molecular markers and tumor grade.

Another consideration for neoplastic disease in male breast pathology would be extramammary and metastatic malignant disease. The median age of diagnosis of Mbc is 70 years in men, so that the presence of other malignancies at this advanced age is not unlikely. [17]

Low-middle income countries (LMICs)

Low-middle income countries (LMICs) are at higher risk of disease due to social, cultural, educational and economic factors. In LMICs, disease incidence rates are rapidly increasing in previously low incidence areas. HAART role out is more prevalent in middle-income countries than low due to financial constraints on public health systems, although high-income countries subsidise HAART regimes.[5,19]LMICs are prone to higher disease burden due to advanced stage at diagnosis, lack of breast cancer awareness and multifactorial socioeconomic barriers to early diagnosis & treatment in the health sector infrastructure.[5,19]

OBJECTIVES

This was a formal audit of male attendees at the Diagnostic Radiology Breast Imaging Unit (BIU), a tertiary governmental hospital Charlotte Maxeke Johannesburg Academic Hospital (CMJAH,) South Africa, a LMIC country. The primary objective was to evaluate the prevalence of male breast disease (MbD) spectrum and secondary objective was to evaluate the causal risk factors, documented for retrospective statistical analysis for a 3 year time span, from 1st January 2016 to 31st December 2018.

METHODS

Study Design

This was a descriptive retrospective cross sectional audit of the specific population subset of males presenting to the Breast imaging unit (BIU) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), over the 3 year period (1st January 2016 to 31st December 2018), with both quantitative and qualitative observation as a means of data capture and analysis.

Participants selection was based on male gender attending the CMJAH BIU between 1st January 2016 to 31st December 2018 and exclusion of female and gender neutral attendees.

Mammograms were routinely performed on a Selenia Dimensions AWS mammographic machine. Routine tomography with bilateral mediolateral-oblique views and *2D* C-view tomographic reconstructions were performed. Tomography with 2D reconstruction only is routinely performed on all patients in this department.
Breast ultrasounds were routinely performed on a TECMED Xario 100 ultrasound machine, with 18 Mhz ultrasound probe.

Patient attendance and personal information were accessed via documented handwritten data capture format in date-stratified departmental books at CMJAH, as well as the Picture Archiving and communication system (PACS) and National Health Laboratory Service (NHLS) results, according to patients hospital number and printed sticker.

The lead researcher captured the relevant data on a standardized Microsoft Excel spread sheets data sheet for further analysis by a biostatistician

Data Collection

The lead researcher captured the relevant data on a standardized Microsoft Excel spread sheet for further analysis by a biostatistician. The variables on the data collection sheet had to be augmented from the original protocol to accommodate the wide spectrum of male breast pathology variables and the multifactorial nature of male breast pathologies.

The age (based on document birthdate), sex and race allocation, were not allocated by the lead researcher, but self-identified by the participants themselves on entering the hospital

data capturing system, which is both patient and hospital clerk dependant. The hospital stickers available to both the BIU, PACS & NHLS assign the age, sex and race.

The spectrum of Male Breast pathology identified on breast multimodal assessment (clinical, mammography and breast ultrasound) was allocated to Gynaecomastia (GCM), lipomastia (LPM), mastitis, breast abscess, skin infection, nipple discharge, lipoma, fat necrosis, intramammary or axillary adenopathy and pectoral muscle asymmetry (Poland Syndrome). Side allocation (left or right, both or L>R, R>L) for each was noted.

Biopsy of masses or areas of inflammation as well as microscopy, culture & sensitivity were noted if done and results conclusive.
For breast cancers histology, molecular receptors and grade were noted.

Assessment of HIV status, on HAART treatment, CD4 count and viral load (non/detectable) was also checked for on NHLS website.

Other serological markers investigated for were: Prolactin hormone levels, sex hormone binding globulin, liver function tests, Diabetes Hb1Ac %.

Mastectomies or breast reduction, with side (left or right) allocation.
Other concomitant cancers or co-morbid diseases were noted if confirmed on clinical history or laboratory results.

Bias:
The bias lay in the non-representative population, as it was biased by multidisciplinary clinical referral, to a single tertiary government hospital BIU, over a specific 3 year time period.

Statistical analysis:
The biographical data underwent quantitative and qualitative descriptive analysis into both categorical (summarised as frequency and percentage tabulation) and continuous variables (summarised by mean, standard deviation, median, interquartile range, and their distribution by means of a histograms). Their frequency procedure was calculated on a univariate or multivariate frequency procedure along with p value to evaluate if skewed or non-skewed distribution curve.

RESULTS

During the 3 year period, a total of 261 males presented to the CMJAH BIU of which 246 (94.25%) were first time attendees and 15 (5.75%) were follow up patients. The frequency procedure showed a trend of an increasing number of male attendees from year to year totals, with 80 males in 2016, 86 males in 2017 and 95 males in 2018.

The age univariate frequency analysis, showed a skewed distribution (p value < 0.05), median age was 46 years old, lower quartile 33 years and upper quartile 59 years. Minimum age of 13 years of age and maximum age of 83 years was noted.

Ethnic distribution showed 224 (85.82%) predominance of African men, with 35 (13.41%) Caucasian males and mixed race 2 (0.77%).

Table 2. Spectrum of Male Benign Breast Disease presenting to CMJAH BIU

Table 3: Spectrum Male Breast Disease based on core biopsy histology results.
*No bilateral breast disease documented

There was a total of 28(10.73%) patients with Male Breast Disease (MbD) that warranted core biopsies while 6(2,30%) patients underwent microscopy, culture & sensitivity (MC&S) investigation.

The MC&S results for the 6 patients showed inflammatory reactions ranging from mixed, acute, chronic, non-necrotising & necrotising granulomatous disease. Two thirds showed gram positive cocci and a further 50% of which were subcategorised as staphylococcus aureus. No specimen showed Ziehl-Neelsen positivity or TB culture positive results. Only one case confirmed TB from an excision biopsy of an axillary lymph node 3 months later.

Of the 261 study populace nineteen patients progressed to surgical mastectomies, with unilateral left 6(31.58%), unilateral right 8(42.11%) and bilateral mastectomies 5(26.32%) patients operated on. The post-surgical mastectomy histology specimens confirmed gynaecomastia.

Only 6 (2.30%) patients underwent breast reductions. Unilateral left disease 1(16.67%) patient, unilateral right 3(50%) patients and bilateral in two(33.33%) patients. Gynaecomastia was confirmed on post-surgical histology specimens.

Concomitant disease and extramammary cancers were noted on both clinical history and laboratory results.

Table 4. Concomitant Disease and Extramammary Cancers noted in Male Breast disease (MbD) - Based and Confirmed on NHLS Laboratory Results.

Laboratory investigatory results were grouped into two main groups. HIV investigatory serology and hormonal-endocrine abnormalities, with prolactin, Sex Hormone Binding Globulin, (SHBG), liver function tests (LFT) and diabetic HB1Ac values.

HIV status was only performed in 155(59%) of the male patients, with 64 (41%) proven to be negative and 91(59%) patients positive. Of the 91 positive patients, a total of 100% were on a HAART treatment regime. CD4 T cell count was only requested in 41(45%) of the 91 HIV patients . The p value showed a normal CD4 count distribution curve, with mean 5.4(2.2), and log values for CD4 distribution curve mean 357.3(230.0).Viral load was not regularly requested with only 20(22%) of the 91 patients with request and results noted. There was a 50% detectable viral load and a 50% non-detectable viral load in the 20 patients, hence only half the patient were HIV controlled on HAART regimes.

The HIV positive subset spectrum presented in the following manner: The majority presented with benign male breast disease 98,90% (90/91), with gynaecomastia predominating with 94,51%(86/91), and 4 separate singular cases of unilateral breast abscess, unilateral intramammary lymph node, unilateral gynaecomastia with a unilateral fibroadenoma and a bilateral lipomastia being noted. Only one HIV positive patient presented with current malignant male breast cancer , invasive ductal carcinoma of no specific type (ER positive, PR positive , HER2 negative & Ki 40% , DCIS positive with solid subtype with comedo necrosis). One HIV positive patient had concomitant acute

pancreatitis with bilateral gynaecomastia. One patient previously had malignant male breast cancer in 2015 (Invasive papillary carcinoma with both ER & PR positive, HER2 negative & Ki 20%) and a simultaneous left shoulder abscess in 2015. Other concomitant cancers noted in HIV positive patients were two patients with Kaposi sarcoma, one with multiple myeloma.

Prolactin (PRL) levels were requested in 56 patients, only 9(3,45%) patients were noted to have elevated levels, 47 (18.01%) normal levels and 205 (78.54%) with no PRL serology requested.

Sex Hormone Binding Globulin (SHBG) levels were requested in 11(4.21%) of male patients, with 7(2.68%) elevated, 3(1.15%) decreased and 1(0.38%) normal. Non-measurement in 250(95.79%) of patients.

Liver Function Tests were requested in 34 (13%) of male patients, 18(6.92%) were elevated, 16(6.15%) normal range and non-measurement in 226(86.92%) of the male attendees.

Diabetic type1 & II HB1Ac was measured in 14(5%) patients who attended the clinic. Five patients (36%) were uncontrolled. The mean value of Hb1Ac was 6.5(1.4), minimum of 4.5 to maximum 10, via the means procedure.

DISCUSSION:

The yearly trend of increasing subset of referred males, to tertiary institution CMJAH BIU, over the three year period from 1st January 2016 to 31st December 2018, totalled 261 male patients. Although male breast disease follows both the morphology and spectrum of female counterparts, [20] the differing proportionality is that benign Male breast disease (MbD) is preponderant. The spectrum included 223/261 (85.44%) gynaecomastia, 14/261 (5,36%) intramammary breast carcinoma and 2/261 (0,77%) extramammary breast carcinoma of squamous cell origin, one of de novo origin and the other metastatic from laryngeal carcinoma. This audit sample size of 261 is adequate although general conclusions may be skewed. The referral populations are a dynamic one, and therefore may not be representative of the overall population.

Male breast disease is evaluated via a multimodality assessment[26] , as their female counterparts, with clinical, mammographic and breast ultrasound evaluation. With the 'sea' of 93,37% of Mbd benign diseases, one should be ever vigilant for malignant disease, noted to be 15(5.7%).

This study has demonstrated that males only 15 (5.75%) showed as follow up patients and the remainder 246 (94.25%) one time attendees. Males do not attend screening programs for breast pathology and this may be the only time they are evaluated for male breast disease. It is both clinical re-referral or radiological findings play a role in the decision process in which the patients may be followed up for further interval imaging.

The skewed age distribution curve noted for gynaecomastia excludes the neonatal age group and further altered due to HIV and its HAART regimes and other multifactorial etiological factors. This would be an assumption as HIV, CD4 and viral load were not regularly tested for in this population group. Only 155/261(59%) were tested for HIV, of

which only 41/91 (45%) of HIV positive patients had a CD4 test result and a further 22% (20/91) of HIV positive patients had a viral load test done. More regular HIV testing is warranted in large HIV positive population and should become more routine.

Further discussion of the 91/261 (34,87%) HIV positive subset group pathology spectrum is warranted. Although this is a small group sample, the spectrum of disease & percentage distribution appear to mimic that of the HIV negative and non-tested patient majority groups and no extrapolations from being HIV seropositivety can be differentiated. Within the HIV seropositive group, the benign male breast disease 98,90% (90/91) was slightly higher and the malignant disease 2,20%(2/91) was slightly lower than the HIV negative and non-tested patient majority. Concomitant disease and cancers were also noted within this group, correlated with their HIV seropositivity. The singular case of acute pancreatitis was seen as a complication of either HIV or HAART treatment. Multiple myeloma and Kaposi sarcoma, are common extramammary cancers seen in HIV positive patient population. Kaposi sarcoma is also known as AIDS defining illness, which presented in two patients 2,20% (92/91). Interesting that a patient who had presented with cryptococcal antigen positive blood culture (Also a known AIDS defining illness), did not have a HIV test on the NHLS system at the time of data capturing. Thus confirming that as stated earlier, a higher testing percentage is required to evaluate the HIV positive subset of male breast disease in order to draw conclusions of value.

Further serological tests for aetiological factors such as prolactin levels 56/261 (22%) , SHBG 11/261 (4,2%) , abnormal liver function tests (LFT) 34/261 (13%) and diabetics Hb1Ac 14/261 (5,36%) of patients were tested, if clinically indicated. These aetiological factors play a role in disease management and should have a set protocol in place in order to guide the physician, at the imaging and statistician stage this is not apparent. With a median age of 46 years presenting to the CMJAH BIU, a higher volume of standard serological testing percentage should be noted, but is not seen in this study.

The distinct oncogenetics of male breast disease would also have to account for different races, with 224/261 (85,82%) of the male attendees to the CMJAH BIU being of Black African race, 35/261(13.41%) of white race and only 2/261 (0,77%) of mixed race. The genetics of the male breast carcinoma biopsied specimens are not routinely tested for at the NHLS, and hence this aspect is unaccounted for in this audit.

The benign male breast disease spectrum reflects the norm in literature [20]. Infective male breast disease noted to be 6/261 (2,29%) ranging from breast abscess, nipple discharge, mastitis and skin infection not relatively raised for a known HIV preponderant population. The MC&S results for these infective processes showed that the spectrum of inflammatory reactions were a result of gram positive cocci infection, with staphylococcus aureus in 50% of the cases. Only one patient was noted to have a Mycobacterium Tuberculotic lymph node, unusually so for a high TB population.
A total of 2/261 (0,77%) patients with imaging suspicious intramammary and axillary adenopathy was documented histologically, to evaluate malignancy associated adenopathy.

In the non-infective benign extramammary disease group, a typical distribution was noted. However, an unusual occluded verrucous cyst (a rare subset of epidermoid inclusion cysts), TB axillary lymph node and uncommon Poland Syndrome being noted.

An interestingly rare intramammary benign finding was that of benign mammary proliferative disease including epithelial hyperplasia with adenosis and fibroadenomata based on histological biopsy results. These are rare entities, as males embryologically should not have mammary glandular tissue present to develop these pathologies, only mammary ductular tissue in situ. [20] **See figure 1-3**.

Surgical management of the gynaecomastia occurred in 25/223 (11.21%) of the patients, with the majority undergoing mastectomies 19/223 (8,5%) and the minority of 6/223 (2,7%) breast reductions . Gynaecomastia was confirmed histologically on post-surgical specimens.

Extramammary male breast carcinomas showed Kaposi sarcoma, an AIDS defining illness, consistent with high HIV positive population. The squamous cell carcinomas were interesting as one was locally invasive from the skin and the other metastatic in origin from a laryngeal carcinoma. The metastatic squamous carcinoma showed negative hormonal molecular receptors and positivity for CK5/6 receptors, confirming origin from larynx and oral cavity primary origin. [26]. While the locally invasive squamous metaplastic carcinoma showed PAS and DPAS positive receptors.

Of the 13 intramammary male breast carcinoma patients, 12 were black African males and one white male who had a Modified Bloom and Richardson grade 1, consistent with literature demographics for Mbc. The age demographics were preponderantly over the age of 58 up to the age of 74 years old. An outlier of 29 years of age, with Mbc and HIV negative status, was noted. Of the intramammary Mbc patients, only 2 patients were HIV positive, although 3 were not tested and 9 were negative. No direct correlation to HIV positive status and Mbc can be drawn on these statistics. Intramammary breast carcinoma of 5,36% (14/261) is a higher percentage than the commonly stated 1% of the male population with Mbc; this is likely a skewed result as it is an adequate but small sample of male patients audited. [1]

The majority presented with invasive ductal carcinoma of no specific type (now called Invasive carcinoma of no special type). Encapsulated, intraductal and invasive papillary carcinomas as well as adenocarcinoma variants were also documented. These histology findings are similar distribution for Female breast Cancer (FBC). Rarity was noted in that there was an equivalent percentage of both HER2 positive and triple negative molecular receptors in the audited Mbc, both with statistics of 2/14 (14,3 %), both rare with triple negative Mbc being the rarest in literature. [17] HER2 positivity relates with low disease free interval survival in males. [22] Ki-67 values do not correlate with survival in males, although peaks were noted ≤ 20.00 %[22] In Mbc clinical stage is a better prognosticator than histology and tumour markers themselves, contrary to what is used in Fbc. New literature notes that HER2 receptor and p53 genetic markers are better prognosticators than that used for FBC. [22]
Of the two Triple negative Cancers , one was a true intramammary invasive micropapillary carcinoma and the other was an extramammary locally invasive squamous carcinoma from skin.

Other neoplastic disease of interest was the male patient with both a breast adenocarcinoma primary and a simultaneous secondary non breast primary which was invasive laryngeal squamous cell carcinoma. This was most likely progressive age related cancers. [23] as the patient was 60 year old and a known smoker. Both Mbc and Fbc are at

higher risk of acquiring a second non-breast primary carcinoma. [23] Parotid tumours also show progressive age related increase and is noted in 3/261 (1,15%) of our MbD patients. Lymphoproliferative, multiple myeloma, ileocaecal adenocarcinoma and oesophageal carcinomas were also noted concomitantly in the advanced age related male breast disease.

Concomitant co-morbid disease spectrum ranged from those with progressive age related disease, non-age related and HIV related co-morbid disease. Age related co-morbid disease such as hypertension with or without renal dysfunction 3 /261 (1,15%), Diabetes Type1 & 2 10/261 (3,8%), benign prostatic hypertrophy and prostate carcinoma on treatment, 3/261 (1,15%) of each type were documented. Non age related co-morbid disease such as epilepsy and schizophrenia on treatment were present. HIV positively related co-morbid disease, with both low CD4 count and HAART regime side effects such as Kaposi sarcoma , cryptococcal disease, left shoulder abscess and acute pancreatitis was identified . The HIV related co-morbid disease is under reported and not representative, as the patients were not sufficiently serologically tested for in this audit and only 59% of individuals had HIV tests done in this sample group.
The co-morbid disease findings are representative of average population statistics.

Study limitations
This is a small select group of males that were not heterogenous. A larger number may reflect referral populations and broad conclusions may not be reflective of the actual population groups referred to the CMJAH BIU.

CONCLUSIONS

The yearly increasing trend of males referred to and attending the CMJAH BIU (261) shows the normal spectrum and distribution of both benign and malignant male breast disease (MbD). There was a higher incidence of male breast cancer Mbc (5,36%) overall in this study which may be related to the smaller sample size than other studies. The ratio of higher benign MbD to Mbc requires higher vigilance for detecting suspicious pathology.

The Mbc that presented, showed histological and molecular subtypes comparative to literature. [1,24] With exception, there were 2 patients which were histologically molecular receptors HER2 positive, which the new literature supports as a poor prognostic factor in disease free survival. HER2 receptor, along with p53 and clinical staging have shown better management and prognostic values for Mbc than the histopathological staging followed in female breast cancer.

Adolescent gynecomastia is associated with a left varicocele and this should become a routine part of their evaluation. [10].

There is room for improved routine serological testing of the patients attending the Breast imaging unit for both HIV, CD4 and viral load. Only 59% were tested for HIV, and of the seropositive group, only 45% were tested for CD4 count. Viral load followed a low 22%. The small HIV seropositive male subset group benign and malignant pathology mimicked that of the majority non tested and HIV seronegative groups, allowing for little inference of the effects of HIV seropositivity, if any, has on male breast disease presentation. A stronger need for HIV serological testing is warranted as these males referred to CMJAH BIU, originate from a high seropositive population, and hence it should have a stronger reflection in this audit, which it does not.

The multifactorial serological testing of gynaecomastia for prolactin hormone level, Sex hormone binding hormone globulin level and liver function testing was not routinely requested and clinical requests resulted in less than 20% of patients being tested in this sample group. Further protocol establishment may result in more assertive serological testing.

Age-related, age independent and HIV related co-morbid disease was noted, along with a second non-mammary primary in this sample group. The co-morbid diseases and secondary concomitant primary neoplasms warrants further evaluation, as literature states that these Mbd are at higher risk of both. [23]

The sample size only included 14 male diabetics but 9 (64%) of which were well controlled, according to their Hb1Ac, and yet they developed Mbd. Further academic endocrine evaluation is warranted in Type 2 Diabetics.

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Table 1. : Comparative table of Male vs Female Breast Carcinoma spectral percentage of histologic, molecular markers and tumor grade (*Reproduced from article[19]*)

Variable	Male Breast Cancer	Female Breast Cancer
Histologic Type	>90% IDC	< 90% IDC
	<0,5% ILC	10% ILC
Molecular	>90% ER+	75% ER+
Markers	>80% PR+	65% PR+
	<0.5% TN	10-15%TN
Tumour Grade	No correlation with survival	Yes correlation with survival

IDC = Invasive Ductal Carcinoma, ILC = Invasive Lobular Carcinoma,

ER = Oestrogen receptor, PR = Progesterone receptor, TN = triple negative

Table 2. Spectrum of Male Benign Breast Disease presenting to CMJAH BIU:

Male Benign Breast Pathology	Patients presented as either a single diagnosis or a combination diagnosis of GCM with another benign/malignant diagnosis in the total of 261 Male patients that presented to CMJAH BIU.	
GCM :	231	85.44%
Other:	48	14.56%
Other:		
Breast Mass:	18.	6.9%
Breast Abscess:	6.	2.30%
Mastitis:	5.	1.92%
Nipple D/c:	1.	0.38%
Axillary Ln:	2.	0.77%
Intramamary Ln:	1.	0.38%
LPM:	10.	3.83%
Fat necrosis:	2.	0.77%
Lipoma:	2.	0.77%

1 Imaging Dx

Skin Infection:	1.	0.38%
PMA:	1.	0.38%

Table 3: Spectrum Male Breast Disease based on core biopsy histology results.
***No bilateral breast disease documented**

BREAST DISEASE (26):

Mammary disease (19):

Benign:

Benign proliferative disease - Including usual type epithelial hyperplasia & adenosis					**1**
Fibroadenoma (FA)					**2**
Fat necrosis					**1**
Lipoma					**2**

Malignant:

Invasive ductal carcinoma of no specific type	**Modified Bloom & Richardson Grade 1**	**ER +**	**PR +**	**HER2 +**	**1**
Invasive ductal carcinoma of no specific type	**Modified Bloom & Richardson Grade 1**	**ER +**	**PR +**	**HER2 -**	**2**
Invasive ductal carcinoma of no specific type	**Modified Bloom & Richardson Grade 1**	**ER +**	**PR -**	**HER2 +**	**1**
Invasive carcinoma of no special cell type	**Modified Bloom & Richardson Grade 2**	**ER +**	**PR +**	**HER2 -**	**4**
Invasive ductal carcinoma of no specific type	**Modified Bloom & Richardson Grade 2**	**ER +**	**PR +**	**HER2 +**	**1**
Encapsulated papillary carcinoma	**Modified Bloom & Richardson Grade 1**	**ER +**	**PR +**	**HER2 -**	**1**
Intraductal papillary carcinoma	**Modified Bloom & Richardson Grade 2**	**ER +**	**PR +**	**HER2 -**	**1**
Invasive micropapillary carcinoma	**Modified Bloom & Richardson Grade 2**	**ER -**	**PR -**	**HER2 -**	**1**
Invasive breast Adenocarcinoma	**Modified Bloom & Richardson Grade 2**	**ER +**	**PR +**	**HER2 -**	**1**

Total Ki % Values for Fbc

20.00% ≤ 6
20.00% ≥ 7

Extramammary and Metastatic Breast Disease (7):

Benign:

Epidermoid inclusion Cyst	**1**
Occluded Verrucous cyst	**1**
TB Lymph node	**1**

MALIGNANT:

Kaposi Sarcoma	**2**

Invasive squamous carcinoma	**CK5/6 + ER +**	**PR +**	**HER2 -**	**1**
Squamous metaplastic breast carcinoma/adnexal tumour		**PAS +**	**DPAS -**	**1**

There was a total of 26 (10.73%) patients with Male Breast Disease MbD that warranted core biopsy and 6(2,30%) patients underwent Microscopy, culture & sensitivity (MC&S). This excludes histologically confirmed Gynaecomastia from both breast reductions and mastectomies. One fat necrosis diagnosis was based on imaging characteristics alone.

Table 4. Concomitant Disease and Extramammary Cancers noted in Male Breast disease (MbD) - Based and Confirmed on NHLS Laboratory Results:

Concomitant Disease (18) NHLS	18/261
Systemic Hypertension on Treatment	3
Acute Pancreatitis	1
KS	2
Cryptococcal disease	1
Lt shoulder Abscess	1
Juvenile Rheumatoid Arthritis (JRA)	1
Schiziophrenia	2
Epileptic	1
Benign Prostatic disease (BPH)	3
Prostate Cancer on Treatment	3

Concomitant Extramammary Cancers (9)	9/261
Lymphoproliferative Disorder	1
Pleomorphic adenoma parotid gland	2
Mucoepidermoid carcinoma parotid gland	1
AFP Elevated	1
Ileocaecal Adenocarcinoma	1
Laryngeal Squamous Carcinoma (Invasive moderately differentiated)	1
Multiple myeloma	1
Oesophageal Carcinoma(Invasive poorly differentiated squamous carcinoma)	1

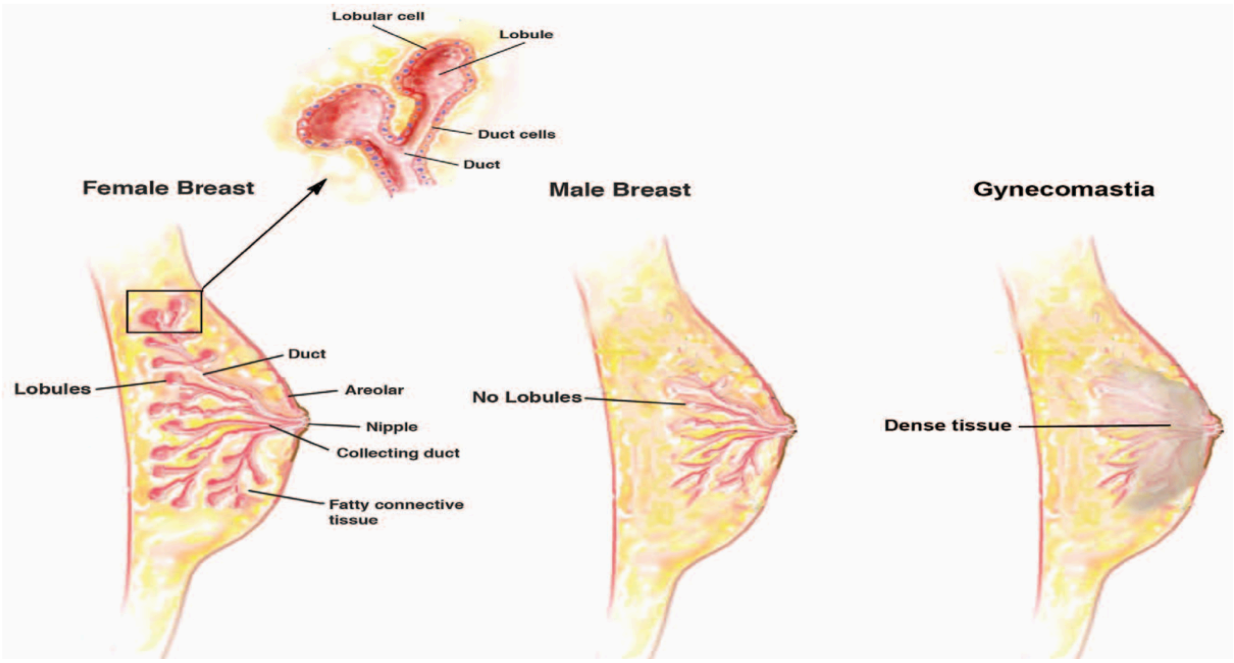

Figure 1. Diagram illustrating the anatomical differences between the male and female breast. The male breast lacks lobules, and the gynecomastia tissue contains dense glandular tissue as shown. Reproduced from open access journal article .See Reference 23.

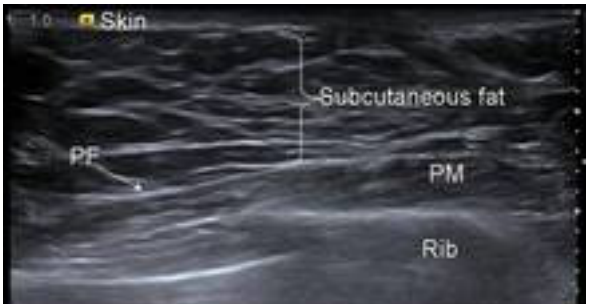

Figure 2: Male Breast Ultrasound

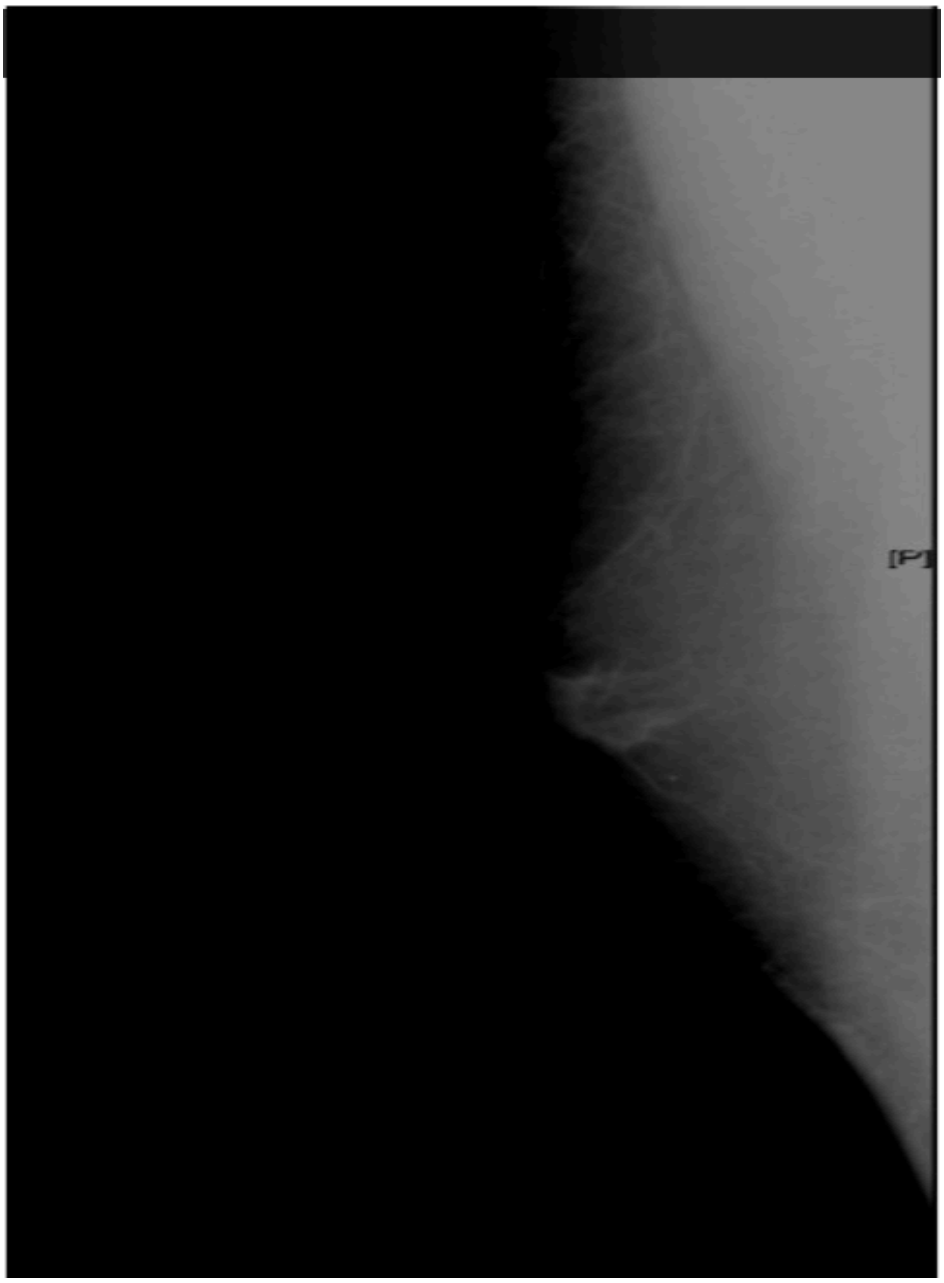

Figure 3. Male Mammogram

EXCEL SPREADSHEET OF DATA COLLECTED: Total of 66 column headings with the following (Cannot be displayed on a single A4 page with reasonable layout & data understanding).

Pt_No Date Month Year AGE F_U Race

GCM Side Other Pathology Breast Mass Side Breast Abscess Side Mastitis Side Nipple D/c Side

Axillary Ln Side LPM Side Fat Necrosis Side Lipoma Side Intrammamary Ln Side Skin Infection Side Pectoralis Assymmetery Biopsy_Done

Histology MC_and_S

HIV_Status HAART_Rx CD4_Count_Available CD4_Count_Original CD4_Count_Value1 CD4_Count_Value2

VL VL_value_Original VL_value1 VL_value2

PRL Sex_Bd_H LFT DM_Hb1Ac_Perc Prostate

Side Mastecomy Side Brst Reduction MC&S: Cells Description MC&S: Culture Decsription

Other_concomittent_Disease/Cancer_Description_ Side

Description of breast mass disease pathology (Non abscess) Grade ER PR HER2 Ki67 % Other Receptors/Subtype Comments_2 C

Appendix:

1.Approved Research Protocol
2.HREC clearance Certificate
3.Turnitin clearance certificate

PROTOCOL

An Audit of the Spectrum of Male Breast Pathology imaged at CMJAH Breast Imaging Department

Dr. T. Murfin
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Table of contents

1. Rationale

Breast pathology awareness, investigation and management, generally pertains to females, due to greater incidence and yet male breast pathology awareness is poorly highlighted [9,10]. There are many causes of male breast disease, and in low-middle income countries (LMIC's) Human Immune deficiency (HIV) disease and its corresponding treatment regime highly active antiretroviral therapy (HAART) are identifiable risk factors [9-11]. Routine mammographic and ultrasonographic review of males with breast pathology requires further evaluation. Both relative frequency and spectrum of male breast disease should be examined, with gynaecomastia and male breast carcinoma representing the different ends of the spectrum [1,2,4,5,10,11].

2. Introduction

2.1. Epidemiology of male breast pathology worldwide

Male Breast cancer and gynaecomastia are the preponderant male breast pathology presenting to breast imaging centres (1). This highlights the epidemiology of these groups.

Male breast cancer (Mbc), follows a similar age standardised incidence for country, both high & low risk countries, to that of their female counterparts, although the reproductive risk factors do not play a role (2). Hence non-reproductive risk factors must play a role in these population groups, such that of environmental, genetic & hyperoestrogenaemia factors (1,9.10,11 & 12). High risk countries have socioeconomic risk factors such as poor diet (obesity), alcohol, occupational exposure & HIV with HAART regime as possible risk factors (1-6,8). Male breast cancer (Mbc) also follows female breast cancer (Fbc) in age distribution with hormone receptor status (2). Mbc correlates with FBC in age groups over 50 years of age, however under 50 years of age, breast cancer incidence peaking later than that of their female counterparts (2). Genetics that play a role in male breast cancer is noted to be in the following regions: the germline BRCA2 androgene receptor gene, PTEN (Cowden syndrome), CHEK2 protein kinase truncation mutation, the oestrogen biosynthesis gene CYP17, the haemachromatosis gene mutation HFE and mismatch repair genes (hMSH2, hMLH1, hPMS1, hPMS2)(12).

Gynecomastia normally has an age related trimodal distribution of neonatal, pubertal & elderly (4,5). The HIV & HAART affected subset of male population, alter this distribution, particularly in low-middle income countries (1,3,5,6,11).

2.2. Epidemiology of Male Breast Pathology in Middle & Low income countries

Low-middle income countries (LMIC's) are at higher risk of obesity (diet), alcohol abuse, occupational exposure hazards, and HIV infection & HAART exposure, than high-income countries as possible aetiological factors (2,4,5,8). HAART role out is more prevalent in middle- income countries than that of low due to financial constraints on public health systems, although high-income countries subsidise HAART regimes (3,6,8). HIV exposure is also due to socioeconomic factors, with imprisonment aggravating HIV exposure in the male population (5,10,11). It is therefore possible to reason that male breast pathology

would be more prevalent in these countries, with male gynaecomastia & male breast cancer, being the most commonly presenting male breast pathology for breast imaging (1).

3. Aim

This research is a formal audit of male attendees of the Breast Imaging unit at CMJAH, whereby possible aetiological proponents such as age, HIV status, HAART exposure, CD4 count & spectrum of disease will be documented for retrospective statistical analysis.

4. Study Objectives

The formal retrospective audit of the Breast Imaging Unit attendance by male patients at CMJAH within January 2016 - December 2018, will aim to record:

4.1 Primary objective is the prevalence of males, presenting with breast pathology to CMJAH breast imaging unit, over the last 3 years.

4.2 Secondary objective is the demographical data of these male patients, in the form of age, race, pathology, histopathology, HIV status, CD4 count and HAART exposure.

5. Methods

5.1. Research paradigm

This research audit is a retrospective cross-sectional study of male breast pathology noted in males attending the Breast Imaging unit at CMJAH from January 2016 – December 2018.

5.2. Sample

The study population reviewed would be males who attended the CMJAH (Charlotte Maxeke Johannesburg Academic Hospital) Breast Imaging Unit from January 2016 to December 2018.

5.2.1. Inclusion criteria

5.2.1.1 All males with clinical breast pathology presenting to the Breast Imaging Unit at CMJAH from January 2016 to December 2018.

5.2.2. Exclusion criteria

5.2.2.1 Female patients.

5.2.2.2 Gender neutral patients.

5.3. Materials and Methods

- Mammograms are routinely performed on a Selenia Dimensions AWS mammographic machine. Routine tomography, with bilateral craniocaudal & mediolateral-oblique views, and 2D C-view reconstructions are performed.

- Breast ultrasounds are routinely performed on a TECMED Xario 100 ultrasound machine, with 18 Mhz ultrasound probe.
- Patient attendance and personal information is documented in handwritten data capture format in date-stratified departmental books at CMJAH, as well as the Picture Archiving and communication system (PACS) and National Health Laboratory Service (NHLS) results, according to patient's hospital number printed sticker.
- The lead researcher will capture the relevant data on a standardized data sheet, which will be transposed onto a Microsoft Excel spread sheet, for further analysis by a statistician.

5.4. Data collection

Data to be collected are as follows:

- Date of attendance, number of males in attendance to CMJAH breast imaging unit from January 2016 to December 2018
- Race, age, confirmation of male gender on all documentation, HIV/HAART status & CD4 count if relevant, male breast pathology presentation (Gynaecomastia/ Breast cancer/other (specifics documented), biopsy required, biopsy results, if cancer: Type, hormone receptor status

5.5. Reliability and validity

This study will be reliable, the data collection sheet can be used by any individual, to repeat the same study, with the same results. The audit is designed to only measure the required variables, by means of a simple tick sheet to collect the data to be audited, with repeatable results each time. The results will be valid, as they only measure the audited variables that they are supposed to measure. Biopsy and lab results are a gold standard for measuring histopathology & HIV related status, which will be accessed in this audit. The audit will cover 3 years of patient attendance to the CMJAH Breast imaging unit, which should supply a sufficient statistical analysis group number to analyse the results.

Poorly documented patients will not be included in my study. Qualified Diagnostic Radiologists will oversee the research to ensure academic accuracy of the results & a medical statistician will review the statistical outcome validity.

5.6. Bias

The bias in this study is the specific hospital based population group that attends CMJAH, a tertiary hospital, with a wide range of referral areas, both provincial, extra provincial and outside South African borders. Referral is not only through the breast clinic surgical department, but other multi-disciplinary departments, with pre-assessment of patients to have pathology prior to referral to the Breast Imaging unit, thus concentrating the number of patients with true pathology & lessen normal or no pathology presentations, in the patients attending the Breast Imaging Unit at CMJAH.
There is no personal bias, as auditing data sheet will be used, as merely as a form of data capturing, with no subjective input.

6. Data analysis and statistics

Data will undergo Descriptive Analysis into two categories:
1 - Categorical variables: summarised as frequency & percentage tabulation, and illustrated by means of bar charts.
2 - Continuous variables (age): summarised by mean, standard deviation, median, interquartile range, and their distribution by means of histograms.

7. Ethics

Patient Identifiers will be random number allocation, with age & not birth date used, in order to ensure patient anonymity.
Human Research Ethics Committee (HREC) clearance application will be applied for, through University of Witwatersrand HREC, prior to data capture & auditing, in 2019.
A permission letter from the CEO of CMJAH & HOD of the Breast ImagIng Unit of CMJAH, have been acquired, prior to start of the data capturing & auditing.

7.1. Consent forms

This is a retrospective study, with review of patient data with anonymity is maintained, no informed consent is required to fulfil the study audit.

7.2. Data safety

Data is collected anonymously, with random number allocation to each patient. Data will be secured on two separate devices, available to the primary investigator & supervisor. Both devices are separate, secure and in two different locations, only known to the primary investigator.

8. Timing

Month of the Year	**1**	**2**	**3**	**4**	**5-7**	**8-10**	**11-15**	**16**	**17,18**
Literature search	NOV 2018	NOV 2018							
Reading literature			NOV 2018						
Summarising literature			NOV 2018						
Preparing Protocol			NOV-DEC 2018						
Protocol Assessment					March 2019				
Ethics application			JAN 2019						
Collecting data					May -July 2019				
Data analysis						AUG – OCT 2019			
Writing up thesis							OCT – DEC 2019		
Submit: marking								DEC 2019	
Writing up paper									JAN – MARCH 2020

9. Budget

Travel	R600
Printing	R600
Stationary	R200
Total	**R1400**

11. References

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UNIVERSITY OF THE
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JOHANNESBURG

R14/49 Dr Tarryn Murfin

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190205

NAME: (Principal Investigator)	Dr Tarryn Murfin
DEPARTMENT:	Diagnostic Radiology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	An audit of the spectrum of male breast pathology presenting at CMJAH mammography department
DATE CONSIDERED:	22/02/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr J Haberfeld and Dr R Minne
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	24/04/2019

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 in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed february and will therefore be due in the month of February 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

9705702a:An_Audit_of_Male_Breast_Pathology_imaged_at_CM.

ORIGINALITY REPORT

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PRIMARY SOURCES

1	Submitted to Napier University Student Paper	1%
2	Fnu Deepinder. "Gynecomastia: incidence, causes and treatment", Expert Review of Endocrinology & Metabolism, 09/2011 Publication	1%
3	Submitted to University of Witwatersrand Student Paper	1%
4	Submitted to CSU, San Jose State University Student Paper	<1%
5	gofishclientcatchers.com Internet Source	<1%
6	Natalie Leon, Catherine Mathews, Simon Lewin, Meg Osler, Andrew Boulle, Carl Lombard. "A comparison of linkage to HIV care after provider-initiated HIV testing and counselling (PITC) versus voluntary HIV counselling and testing (VCT) for patients with sexually transmitted infections in Cape Town, South	<1%