International Academy of Cytology Yokohama System for reporting Breast Fine Needle Aspiration Biopsy (FNAB) cytology: A Retrospective Study in a Single South African Tertiary Institution.

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DECLARATION:

I, *Patricia Pamacheche nee Pariza* hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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DEDICATION:

First and foremost I would like to thank my husband Togara, my children; Rudado, Mazvita and Kudzanai and my parents Gladys and Shadreck for without their unwavering support, this dissertation would not have been completed.

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ABSTRACT:

Introduction:

Breast carcinoma is the most common malignancy amongst women in South Africa. Triple assessment has been pivotal in the work up and management of breast carcinoma. Breast cytology has been used as a component of the triple assessment. Although core needle biopsy (CNB) is the gold standard and the preferred diagnostic modality, there is still a role for fine needle aspirate cytology (FNAC) in resource limited settings. The present study was conducted at Groote Schuur Hospital in Cape Town, South Africa.

Aims:

1. To assess the utility of the International Academy of Cytology (IAC) Yokohama System for Reporting Breast FNAC five category stratifications in our institution.
2. To assess the respective risk of malignancy (ROM) for each category.
3. To assess the diagnostic yield of the breast FNAB at our institution by comparing it to the matched histopathology over a 12-month period.

Methodology:

A retrospective longitudinal descriptive study was done. A computerized search on TrakCare NHLS for the year 2019, identified 884 patients who had breast cytology and corresponding histology specimens. The cytology categories(C1-C5) were first reclassified according to the IAC Yokohama system. The new cytology category was then compared to the histological diagnosis for each patient. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and risk of malignancy (ROM) were calculated.

Results:

The sensitivity, specificity, PPV, and NPV were 83.10%, 93.01%, 88.86% and 89.13% respectively. The Cohen's kappa coefficient was 0.659 and percentage agreement was 80.85%. The ROM was calculated; insufficient (9.09%), benign (4.46%), atypia (45.28%), suspicious for malignancy (72.5%) and malignant (91,09%).

Conclusion:

Breast aspiration cytology performed at GSH has shown good correlation with histopathology as well a high sensitivity and specificity comparable to international standards. The ROM is comparable to previous similar studies. Overall, our results show that breast aspiration cytology is a rapid, accurate and cost-effective diagnostic procedure in our institution that is very useful in the diagnosis of benign and malignant breast lesions.

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LIST OF ABBREVATIONS

CNB	Core needle biopsy
FNAB	Fine needle aspiration biopsy (used interchangeably with FNAC).
FNAC	Fine needle aspirate cytology.
GSH	Groote Schuur Hospital.
NHLS	National Health Laboratory Service
ROSE	Rapid Onsite Evaluation.
Trakcare	National Health Laboratory Services computer software
US-FNAB	Ultrasound guided fine needle aspirate biopsy.

CHAPTER 1:

LITERATURE REVIEW:

1.1 Introduction:

Breast cancer is the leading cause of death amongst women with 685 000 related deaths recorded globally in 2020 and 2.3 million newly diagnosed cases (WHO, 2021). South Africa in 2017 had breast cancer as the most histologically diagnosed cancer in women with a total of 9624 out of 41653 cases (NICD, 2020).

Breast pathology is common amongst women. Breast lesions can be classified as benign, borderline, or malignant. Benign breast lesions are the most common pathology with malignant cases forming a smaller proportion of the total cases. Women commonly present with a myriad of symptoms ranging from mastalgia, nipple discharge, skin changes and more commonly breast lumps. Common benign breast lesions include fibrocystic disease, fibroadenomas, breast abscesses and intraductal papillomas.

Breast carcinoma is the most common malignancy of the breast. Risk factors associated with breast carcinoma include old age, family history of breast carcinoma or other carcinomas, early age of menarche, advanced age at first pregnancy and or delivery, and lower number of children. Protective associations include breastfeeding duration, parity, oral contraceptive use, past surgical history of oophorectomy and or hysterectomy (Sufian et al., 2015).

1.2 Triple assessment:

Breast carcinomas usually present as late stage malignancy. Screening is the corner stone in the management of breast carcinoma as it helps in the identification of small and early lesions. Mammography has been used as an ideal tool in the screening of women over 40 years with a sensitivity of 97%, a specificity of 64.5%, a positive predictive value of 89%, and a negative predictive value of 90.9%, with a diagnostic accuracy of 89.3% (Zeeshan et al., 2018). Mammography is a relatively expensive tool. Low to middle income countries are unable to

provide this screening tool for many of their patients due to the high costs, hence the reliance on self-breast examination or breast examination by a trained health worker (Lince-Deroche et al., 2017).

The high incidence and prevalence of breast carcinoma has led to many interventions in the screening and management of breast carcinomas. Triple assessment currently plays a pivotal role in the assessment and management of breast carcinoma. Triple assessment includes breast clinical examination, mammography and/or ultrasonography, and cytology {FNAB/Core needle biopsy (CNB)}. With the advent of triple testing for breast malignancies, fine needle aspirate biopsy (FNAB) has become an integral part of the evaluation of breast lesions.

1.3 Fine needle aspirate biopsy (FNAB).

1.3.1 Advantages of fine needle aspirate biopsy:

FNAB was first introduced in the 1930s (Ellis & Martin, 1934), it has been used as a first line diagnostic procedure over the years for patients with breast lesions. Indications for FNAB of breast lesions include evaluation of cystic lesions, diagnosis of primary, recurrent or metastatic breast cancer and axillary staging of invasive breast cancer (Harigopal & Chhieng, 2010). Currently, the use of breast fine needle aspiration cytology varies greatly between hospitals and cities and between developed and developing countries. It offers many advantages; it is fast, easy, cheap, it shows high accuracy, sensitivity, and specificity. It is minimally invasive, causes minimal physical and psychological discomfort, can be performed with little complications (Mendoza et al., 2011) and is highly acceptable to patients. FNAB also provides material for cell blocks allowing immunohistochemistry to be performed (immunohistochemistry helps in the identification of prognostic indicators), polymerase chain reaction (PCR) and other potential molecular testing (Schmitt & Vielh, 2015).

1.3.2 Disadvantages of fine needle aspirate biopsy:

Specimen inadequacy and lower accuracy when compared to core needle biopsy:

The greatest challenge with FNAB is inadequacy of specimens. Specimen inadequacy can result from poor quality of the FNAB procedure and poor smearing technique. In fact poor performance of FNAB and poor technique in direct smears have been called the elephant in the

room in breast cytology (Field, 2018). Traditionally cytopathologists were responsible for aspirating palpable lesions however with improvement in radiology screening, palpable and non-palpable lesions are increasingly being sampled by radiologists and their trainees, especially in developed countries. Whilst cytopathologists are immediately aware of their sampling techniques because they report on the slides, the same cannot be said for the radiologist who often have minimal contact with the reporting cytopathologists.

In addition, the incidence of inadequate FNA specimens is unacceptably high in many institutions, thus the high suboptimal accuracy has led to criticism of FNAB (Wells et al., 1999) in the management of breast cancers. Some studies have been done to evaluate the efficacy of repeat core biopsy versus repeat FNAB in patients with breast lumps whose initial cytology was insufficient or suboptimal for diagnosis. It was shown that repeat core biopsy was more efficacious in making a diagnosis in comparison to FNAB with the sensitivity for the definitive diagnosis of carcinoma on repeat cytology and core biopsy being 10 and 89 per cent respectively (Carty et al., 1994).

The high inadequacy rates has led to a decrease in the number of FNAB being done in some developed nations resulting in less training opportunities for radiologists and pathologists alike giving rise to inadequate training. This is a challenge because FNAB requires not only good training and ongoing experience but also constant monitoring of the diagnostic yield and adequacy rates.

FNAB is associated with lower accuracy when compared to core needle biopsy. The accuracy of FNA is even lower with non-palpable lesions, however this to some extent depends upon the skill of the aspirators, cyto- screeners and cytopathologists involved in the procedure (Oyama, Koibuci & Mckee, 2004). This disadvantage can be offset by use of ultrasound guided fine needle aspiration. Although ultrasound can be helpful in assessing of both non-palpable and palpable lesions studies have shown that in the case of palpable lesions; an increased in dwell time in the lesion can result in increased incidence of blood contamination and clotting of material in the needle. In addition if aspiration is applied early on without the cutting action of the needle in the lesion then the result can be inadequate , haemodilution and obscured material (Zedie, 2018).

One of the major goals of breast FNAB is to differentiate benign from malignant lesions. However, differentiation is not possible in all cases due to significant overlap of the cytomorphologic features of both benign and malignant breast lesions (Mendoza et al., 2011) leading to false positives and false negatives.

1.4 Quality assurance issues:

Moreover, FNA of the breast requires a level of expertise in cytopathology that is not readily available in some institutions (Oyama, Koibuci & Mckee, 2004). The greatest quality assurance issue in providing a breast FNAB is the quality of the technique of the FNAB procedure and the quality of the technique in the making of direct smears. Best results are achieved when aspiration is done by a trained or training radiologist in the presence of a pathologists specialized in cytopathology (cytopathologists). Due to limited resources; a trained radiologist and cytopathologist may not be available on site in a breast clinic to perform such tests in most developing countries (Kocjan et al., 2008). A study by Berner et al., (2003) compared the utility of FNAB vs CNB and concluded that FNAB is most accurate when experienced cytopathologists are available and a rapid on-site evaluation is done (ROSE) to determine sample adequacy.

1.5 Rapid on-site evaluation (ROSE):

ROSE is service that cytopathologists or cytotechnologists commonly perform to check the adequacy and cellular content of FNAC or touch imprints. When properly done, ROSE informs the operator of the need to obtain additional material for inadequate specimens or in cases of malignancy, more material for cell block and/or immunohistochemistry. A meta-analysis by Schmidt et al (2013) showed an overall 12% increase in the adequacy rates with the introduction of ROSE. The use of ROSE is however operator dependent for example study sites with high adequacy rates showed less improvement with the introduction of ROSE (Tambouret et al., 2014) whilst those with high inadequate rates showed significant improvement in adequacy rates that is, the added value of ROSE is inversely proportional to the skill of the operator.

Whilst ROSE improves efficiency, there has been controversy on who should perform ROSE that is, cytopathologist vs cytotechnologist. Cytotechnologists may not be able to make the final diagnosis but are more efficient in picking adequacy related issues (Burlingame et al., 2012). On the same issue, another challenge is that ROSE is time consuming and not well reimbursed compared to time spent on reading a surgical biopsy, as a result pathologists may choose to opt out of ROSE.

1.6 Sensitivity and specificity of FNAB and CNB:

Over the years, ultrasound guided FNAB cytology and CNB are often used in conjuncture to aid the diagnosis. In developing countries where financial constraints play a major role, FNAB alone still plays a pivotal role in diagnosis and management of breast lesions. There has been a lot of research done to determine the sensitivity and specificity of FNAB vs CNB. There is however controversy on the sensitivity and specificity of FNAB vs CNB in literature. An older study showed that while the specificity of both FNAB and CNB approach 100%, the sensitivity of FNAB was higher (97%) than the sensitivity of CNB (90%) in the diagnosis of palpable breast lesions (Ballo & Sneige, 1996). Another study by Hatada, et al. (2000) showed that ultrasound guided fine needle aspirate (US-FNAB) had a slightly higher sensitivity than CNB (86,9% vs 86.2%) however the diagnostic accuracy and specificity of CNB was higher than that of FNAB.

Most studies on the other hand have shown that CNB is more sensitive and more specific than FNAB leading to some countries abandoning the use of FNAB in favour of CNB (Field et al., 2020). Another study by Frankel et al. (2011), showed that CNB had both higher specificity and sensitivity compared to FNAB.

However, some studies advocate the use of FNAB and CNB in combination in order to increase absolute sensitivity without affecting specificity thereby leading to a decrease in the rate of inadequate diagnosis in the evaluation of breast cancers (Westenend et al., 2001).

1.7 Core needle biopsy (CNB):

CNB has been shown to be superior to FNAB in the diagnosis of breast lesions because of its higher accuracy and correct typing of both benign and malignant lesions as discussed above.

In addition, CNB has a higher utility because the incidence of inadequate specimens is lower than for FNAB. CNB is also a less invasive procedure than open biopsy, and its utility in combination with mammographic or ultrasonographic guidance for non-palpable lesions is especially high. CNB also gives further information of hormone receptor status, tumour grade and presence of lympho-vascular invasion and is therefore more specific and cost effective in giving a definitive histopathological diagnosis, thereby avoiding unnecessary surgical management and can also be used as an alternative to open biopsy(Bhatta et al., 2019).

Despite these advantages of CNB, most participating countries use FNAB as the first-line pathological investigation in both screening and symptomatic populations, except for microcalcifications (Kocjan et al., 2008). FNAB is relatively cost effective for the pre-operative diagnosis of palpable and ultrasound detected impalpable breast lesions. When triple assessment is concordant, final treatment may proceed based on FNAB, without a tissue biopsy.

1.8 Grey areas in diagnosis of breast lesions:

The use of FNAB in the evaluation of breast lesions has changed substantially over a period of 20 years; mainly due to changes in screening programs and available treatments and recent preference for CNB. In 1996 the National Cancer Institute (NCI) proposed five diagnostic categories to allow uniform approach and evaluation of breast lesions by cytopathologists (Abati, 1997). The five categories are listed below:

Table 1.1. Breast cytology categories.

Cytology reporting category	
C1	Inadequate
C2	Benign
C3	Atypia, probably benign
C4	Suspicious of Malignancy
C5	Malignant

An inadequate report was issued when the material aspirated was scanty or acellular or if there was a technical problem making it difficult to make a proper report. A benign diagnosis was made only when the specimen was adequate and had benign cytomorphology. A malignant diagnosis was only made when the specimen was adequate with definite malignant cytomorphology. However, C3 and C4 were borderline categories. These borderline categories not only provided scope for the cytopathologists to make mistakes but spoke volumes on the difficulties experienced and the limitations associated with interpretation of breast smears (Mitra & Dey, 2015). In addition, these grey areas not only confused clinicians but were also surrounded by controversy; they raised questions on the risk of malignancy of each category and the implications on patient management (Bak et al., 2005). The limitations of this classifications system led to its' review and the introduction of the Yokohama international academy of cytology breast reporting system in 2016.

1.9 International Academy of Cytology Yokohama System for reporting Breast Cytopathology (IAC Yokohama system):

In 2016, the International Academy of Cytology (IAC) established a "Breast Group" which included pathologists, radiologists, surgeons, and oncologists mainly to produce comprehensive and standardized guidelines for breast FNAB cytology reporting. The IAC Yokohama System for Reporting Breast Cytopathology incorporates the indications for breast FNAB cytology, FNAB technique, smear making and material handling, a reproducible standardized reporting system, the use of ancillary diagnostic and prognostic tests, and correlation with clinical work-up algorithms. Ultimately, the aim is to facilitate clinician's understanding and use of FNAB cytology in breast pathology (Field, Schmitt & Vielh, 2017).

In the Yokohama System for Reporting Breast Cytopathology, the "Breast Group" has proposed a five-category classification: category 1- insufficient material; category 2- benign; category 3- atypical, probably benign; category 4- suspicious for malignancy, probably in situ or invasive carcinoma; and category 5- malignant (Field, Schmitt & Vielh, 2017) this is summarised in the table below.

Table 1.2. International Academy of Cytology Yokohama System for reporting Breast Cytopathology five category classification system (Field, Schmitt & Vielh, 2017).

Category	ROM[a], %	Management[b]	LMICMX[c]	Comment
Insufficient	2.6–4.8	Review clinical and imaging findings; if imaging indeterminate or suspicious, repeat FNAB or proceed to CNB; if imaging benign consider repeat FNAB	Review clinical findings; if suspicious repeat FNAB	At ROSE, if inadequate due to a technical issue or the material does not explain the clinical or imaging findings, repeat FNAB up to a total of 3 times, ideally using ultrasound guidance; if FNAB still insufficient, proceed to CNB
Benign	1.4–2.3	Review clinical and imaging findings; if "triple test" benign, no further biopsy required, and review depends on the nature of the lesion; if clinical and/or imaging indeterminate or suspicious, repeat FNAB or proceed to CNB	Review clinical findings: if benign, nothing further; if suspicious, repeat FNAB	At ROSE, if the cellular material does not explain the clinical or imaging findings, repeat FNAB, up to a total of 3 times, using ultrasound guidance; follow-up depends on the nature of the lesion, e.g., abscess – 2 weeks after antibiotics, fibroadenoma – 12 months; some centers review in line with screening program policy
Atypical	13–15.7	Review clinical and imaging findings; repeat FNAB if atypia considered likely to be due to a technical issue; if good material available and atypical, repeat FNAB or preferably proceed to CNB[d]	Review clinical findings and repeat FNAB; manage based on FNAB category; if further FNAB atypical, consider excisional biopsy	At ROSE, if atypia is considered due to a technical issue, repeat FNAB; if cellular material adequate and atypical, proceed to CNB
Suspicious	84.6–97.1	Review clinical and imaging findings; CNB is mandatory[e]	IF no CNB available, excision biopsy	At ROSE proceed to CNB
Malignant	99.0–100	Review clinical and imaging findings; CNB if any discrepant findings. If "triple test" is concordant and malignant, proceed to definitive management[f, g]	If no CNB available, excision biopsy	At ROSE may proceed to CNB

A standardised reporting system enables the reproducibility of the results across the institutions and countries and facilitates better communication between the pathologists and the treating surgeon or oncologist.

Some studies have been done to evaluate the efficiency of Yokohama reporting system in different settings. Agarwal, A. et al (2021) looked at the accuracy of using the Yokohama international reporting system in breast cytology and concluded that it was suitable for reporting breast lesions on FNAB. Wong, PY. et al, (2021) investigated the utility of the IAC Yokohama system, and also concluded that the Yokohama system is a reliable, evidence-based, and standardized reporting system that helps to facilitate communication among cytopathologists, radiologists, and surgeons toward individualized patient management.

The Poornima et al. (2019) study calculated the risk of malignancy and compared it with previously published reports; Montezuma et al. (2019) and Wong S et al. (2019). They reported

a similar ROM, in addition the study concluded that the Yokohama reporting system helped in providing diagnostic clarity to the pathologists and helped clinicians better manage patients.

1.10 Situational analysis at Groote Schuur Hospital (GSH), Cape Town, South Africa:

Breast cancer is the most common cancer globally. In South Africa, it has been identified as a national health priority as it is not only the most prevalent cancer, it is the leading cause of death among South African women. In the Western Cape, breast cancer is the most common cancer affecting women and the increasing incidence is a major health concern.

Groote Schuur Hospital (GSH) is one of two tertiary hospitals providing breast cancer care in the city of Cape Town. It services a population of approximately two million and offers the full spectrum of breast cancer care from diagnosis to oncological and palliative care. The first entry point to the breast cancer service is through the Breast Clinic.

The annual number of newly diagnosed breast cancer patients utilising the Groote Schuur Hospital breast cancer service has significantly increased from 320 in 1999 to 608 in 2017.

There is current focus on cancer care by the National Department of Health. This includes strategies such as the National Cancer Campaign and the development of the companion document entitled *Clinical Guidelines for Breast Cancer Control and Management*. This creates the opportunity for multidisciplinary breast teams to optimise coordinated breast cancer care.

The companion document outlines the guidelines for Specialist Breast Units (SBUs) which need to have a multidisciplinary capacity for diagnosis and appropriate management of benign and malignant breast disease.

These units are tasked with running diagnostic Breast Clinics for women who are referred from primary care facilities or health practitioners with breast complaints where patients are able to access same day clinical evaluation, radiological assessment and tissue diagnosis as appropriate to each clinical scenario.

This one-stop diagnostic model implies that after a single visit a patient may be allocated into the relevant referral pathway for malignant disease, benign disease or discharge.

The advantages of these one stop diagnostic clinics are numerous. These include immediate referral to oncology for malignant disease as well as a decrease in multiple clinic visits for investigation and results. There is also an associated decrease in transport costs and loss of income; increased efficiency of evaluation and discharge where applicable. In addition, there is an alleviation of anxiety by eliminating waiting times for a diagnosis and reducing loss to follow up, especially patients with malignant disease.

Patients with breast lesions routinely have both an FNAB and CNB done on a single visit. Discordant diagnoses are not only investigated further but also discussed by a multidisciplinary team.

FNAB of the breast was first introduced at GSH in July 1982. The first study comparing breast cytology and histology was published in 1987 (Learmonth et al., 1987) whereby the first 1500 cases done over a period of 3 years (July 1982 to February 1985) were evaluated. The study reported 358 malignant cases, 150 suspicious, 700 benign and 292 inadequate cases. Of the 358 malignant cases, 349 had a histological diagnosis of malignancy and 9 were benign (false positive). Sensitivity and specificity were unfortunately not calculated in the study. Little similar research has been done over the past 34 years in the form of an audit that compares the breast cytology to histopathology at GSH.

Therefore, there is need for a recent audit to be undertaken in the department in order to identify any deficiencies in the sampling techniques at the breast clinic and in the diagnosis of breast lesions in the division of anatomical pathology. This information can be used in informing decisions on training or retraining of staff in sampling techniques or to decide whether cytological examination of specimens should continue to be offered alongside core needle biopsy or whether FNAB, as a diagnostic tool, should be abandoned all together. To our knowledge, this is the first study of this nature to be done in South Africa to date.

Problem Statement:

Is FNAB still an efficient and acceptable diagnostic tool in the diagnosis of breast cancer in Cape Town, South Africa?

1.11 Aims:

1. To assess the diagnostic yield of the breast FNAB at our institution by comparing it to the matched histopathology over a 12-month period (January 2019-December 2019).
2. To assess the respective risk of malignancy (ROM) for each International Academy of Cytology (IAC) Yokohama System for Reporting Breast Fine Needle Aspiration Biopsy (FNAB) Cytology category.
3. To assess the utility of IAC Yokohama System for Reporting Breast Fine Needle Aspiration Biopsy (FNAB) Cytology five category stratification in our institution.

CHAPTER 2:

MATERIALS AND METHODS

2.1 Ethics approval:

The research protocol was submitted to the Human Ethics Research Committee for review (please see appendix 3). Approval was granted on the 16th of April 2021 with the reference number of HREC REF: 229/2021. Data extraction was only initiated after ethics approval was granted.

2.2 Study design:

The study is a retrospective longitudinal descriptive study that is quantitative in nature. A retrospective study was necessary because the data is readily available on the NHLS website and was therefore cheap and affordable to collect data for the study. In addition the time required to collect the data for a retrospective study was shorter than if a prospective study had been undertaken.

2.3 Sample selection:

The study was done at Groote Schuur hospital, Observatory Cape Town. Participants were selected from the breast clinic which runs once every week. Patients usually have breast lumps on presentation and are referred from the catchment areas. After clinical examination fine needle aspiration for cytology is done if indicated. There is usually a cytology technician on site who reviews the adequacy of the specimens once smearing has been done (a form of rapid onsite evaluation). The FNAB is usually followed by a core needle biopsy for histology. The cytology and histology specimens are reviewed independently by the cytopathologist and histopathologists respectively. In the event that the results are discordant, the patient is usually discussed at the multidisciplinary team where decisions on further management are discussed. Patients with both inadequate cytology and histology are offered repeat procedures, otherwise histology is considered the gold standard when available.

Cohort*:* 884 patients with cytology and corresponding histology were selected from the list of patients seen at Groote Schuur Hospital breast clinic in 2019. The age distribution was 18-95 years.

2.4 Methods:

A research protocol was submitted to the University of Cape Town Human Research Ethics Committee (HREC) for approval of the study. After receiving ethics approval, a computerized search of National Health Laboratory Service (NHLS) TrakCare was performed on all the breast histology specimens from the Division of Anatomical Pathology, Groote Schuur Hospital, National Health Laboratory Service for the year 2019 (1st January – 31st December). An attempt was made to collect all the cytology data first as per research protocol submitted to Human Ethics Research Committee however, the Trakcare research engine was very slow yielding one day's data over a period of two days; making data collection tedious. Modification to the research criteria was made so that histology core needle biopsies were extracted first. The modification was made because the histology research criteria was more efficient than the cytology one in yielding the required data. The integrity of the data collection was maintained during the process as the main aim of the study was to match cytology with histology results; this was still achieved regardless of the starting point.

The Trakcare histology research criteria used was "breast". The search engine yielded research results that included all breast histology specimens (core needle biopsies, lumpectomies, wide local excisions, simple mastectomies and radical mastectomies).

The software system brought up patients names with reference to their respective episode number. The episode number was used to fetch further information of the participant by looking up under cumulative history (all the laboratory investigations ordered under the patients unique hospital number appear under this icon). A scroll down of the cumulative history allowed identification of the previous cytology and/ histology request and results. Only breast core needle biopsies done at Groote Schuur Hospital breast clinic with corresponding cytology from the retrieved data were included in the study.

Since most patients have both FNAB and CNB done on the same day; the date of the CNB was matched to the date of the FNAB. Demographics for each participant were also collected namely, age and sex. The ethnicity of each participant was unfortunately not available on

Trakcare. A total of 3188 cases were found, and of these 884 participants had core needle biopsies with corresponding cytology.

All identified participants were anonymised, and assigned a study number. Laboratory and hospital numbers used for patient identification were removed in the final data, to ensure patient confidentiality.

The following exclusion and inclusion criteria were used for patients who were seen at Groote Schuur Hospital:

Inclusion criteria:

- All patients 18 years of age or older .
- Patients with both breast cytology(FNAB) and corresponding histology specimen(CNB).
- Patients must have been seen at Groote Schuur Hospital breast clinic.

Exclusion criteria:

- Patients under the age of 18 years
- Patients with breast histology specimen(CNB) without corresponding cytology.
- Patients seen at other Cape Town breast clinics such as Mitchell's Plain Hospital and Somerset Hospital.

The data collected was recorded on Excel spread sheet, that is personal descriptors, cytology results and corresponding histology results.

Once all the corresponding cytology data was collected; the primary investigator retrospectively reclassified the specimens according to the newly proposed IAC Yokohama reporting system for breast cytology. The following 5 categories were used: Insufficient (C1), benign (C2), atypical (C3), suspicious for malignancy (C4) and malignant (C5).

Each participant's histology was graded as follows: Suboptimal for diagnosis (B1), benign (B2), atypia of unknown significance (B3), Atypia suspicious for malignancy and malignant (B5).

The populated and coded data was then exported to Stata for analysis. A statistician was consulted to help with analysis.

2.5 Statistical Methods:

All statistical analyses were conducted in Stata version 16.1 which was released in February 2020 (an update of the previous Stata version 16.0 released in 2019). Statistical significance was set at $p<0.05$. A histogram was used to describe the age distribution in participants, as well as mean and standard deviation. A pie chart was used to describe gender; frequencies and percentages were used to describe gender. Frequencies and percentages were used to describe cytology and histology categories. Pearson's chi-squared test was used to compare risk of malignancy across cytology categories. Cohen's Kappa for two unique raters was used to calculate interrater agreement between cytology and histology categories. We calculated sensitivity, specificity, positive predictive value and negative predictive value of FNAB cytology in detecting breast malignancy using histology as the gold standard.

In order to achieve the specific aims the following statistical methods were employed:

Aim 1: To assess the diagnostic yield of the breast FNAB at our institution by comparing it to the matched histopathology over a 12-month period (January 2019-December 2019).

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value(NPV) were calculated from the data collected.

In order to calculate each of the values stated above, C1-C3 categories were given the 0 value (without the disease) whilst C4 and C5 combined were given the 1 value (with the disease). In addition to determine the degree of agreeability between cytology and histology; Cohen's

Kappa was used. Cohen's kappa is a quantitative measure of reliability for two raters that are rating the same thing with the probability of something happening by chance corrected for. The calculations were done in Stata.

Aim 2: To assess the respective risk of malignancy (ROM) for each IAC Yokohama category.

The risk of malignancy(ROM) was determined for each cytology category by calculating the true malignant cases (as picked up by histology) divided by the total number of cases in each cytology category . The results were then tabulated.

Aim 3: To assess the utility of the International Academy of Cytology (IAC) Yokohama System for Reporting Breast Fine Needle Aspiration Biopsy (FNAB) Cytology five category stratification in our institution.

The risk of malignancy was compared to the benchmark (IAC Yokohama reporting system for breast cytopathology).

CHAPTER 3:

RESULTS:

3.1 Descriptive Statistics:

A total of 884 participants were included in the study.

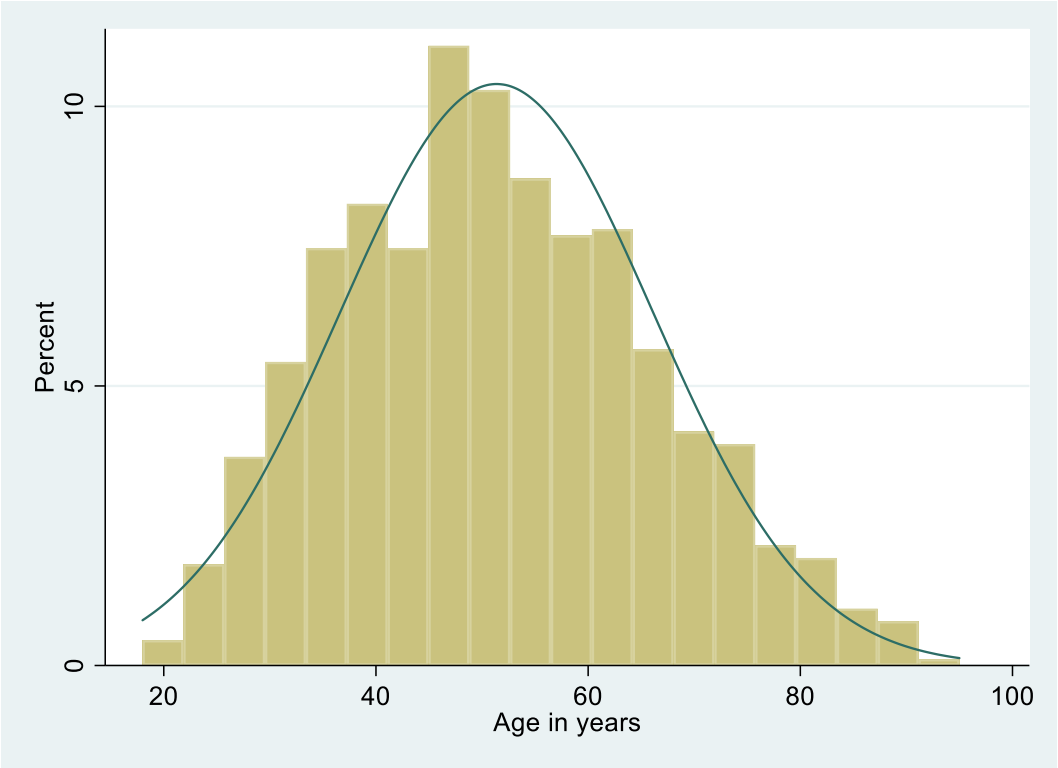

Figure 3.1: Age distribution of participants

The age distribution in participants approximated a normal distribution. Median age was 50 years (Interquartile range 41 – 62), Mean 51.38 (standard deviation 14.77).

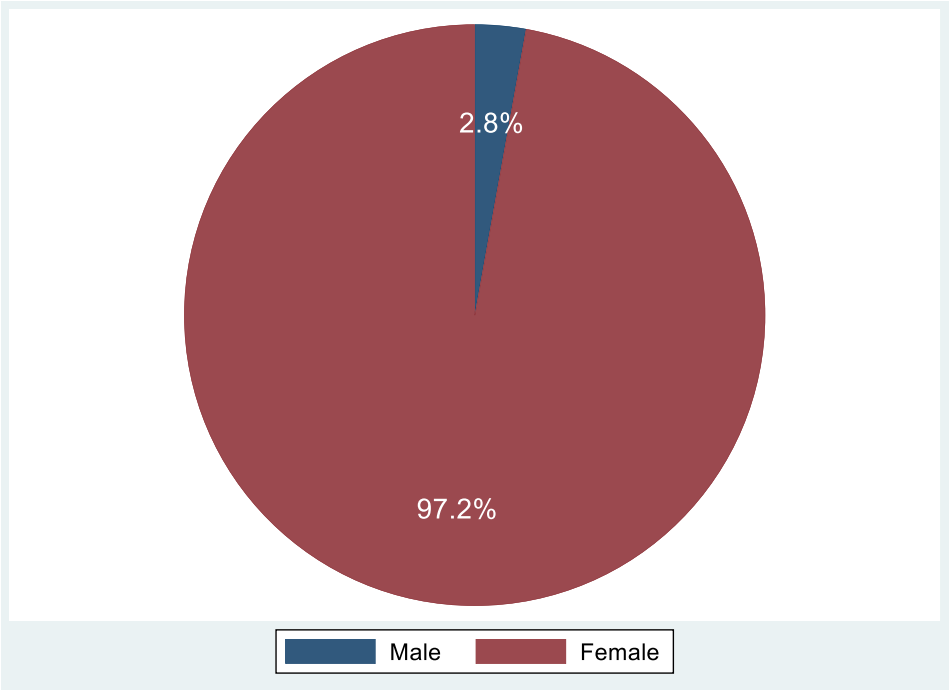

Figure 3.2: Gender

Majority of patients were female (n=859, 97.2%) and males were 25 (2.8%).

Table 3.1: International Academy of Cytology (IAC) Yokohama System for Reporting Breast Fine Needle Aspiration Biopsy (FNAB) Cytology

CYTOLOGY REPORTING CATEGORY	IAC YOKOHAMA REPORTING SYSTEM	N	%
C1	Inadequate	297	33.60
C2	Benign	202	22.85
C3	Atypia	53	6.00
C4	Suspicious of Malignancy	40	4.52
C5	Malignant	292	33.03

The distribution of categories according to the Yokohama IAC were the following: insufficient 297 (33.6%), benign 202 (22.85%), atypia probably benign 53 (6.0%), suspicious of malignancy 40 (4.52%) and malignant 292 (33.03%). The rate of insufficient specimens was quite high, indicative that one in three patients visiting the clinic had a non-diagnostic smear. The number of malignancies diagnosed was higher than diagnosed benign conditions. The cytological categories of atypia probably benign (C3) and atypia suspicious for malignancy (C4) amounted to 10.52% of the diagnoses.

Table 3.2: Histology Classification

HISTOLOGY REPORTING CATEGORY		N	%
B1	Inadequate	170	19.23
B2	Benign	353	39.93
B3	Atypia	6	0.68
B4	Suspicious of Malignancy	3	0.34
B5	Malignant	352	39.82

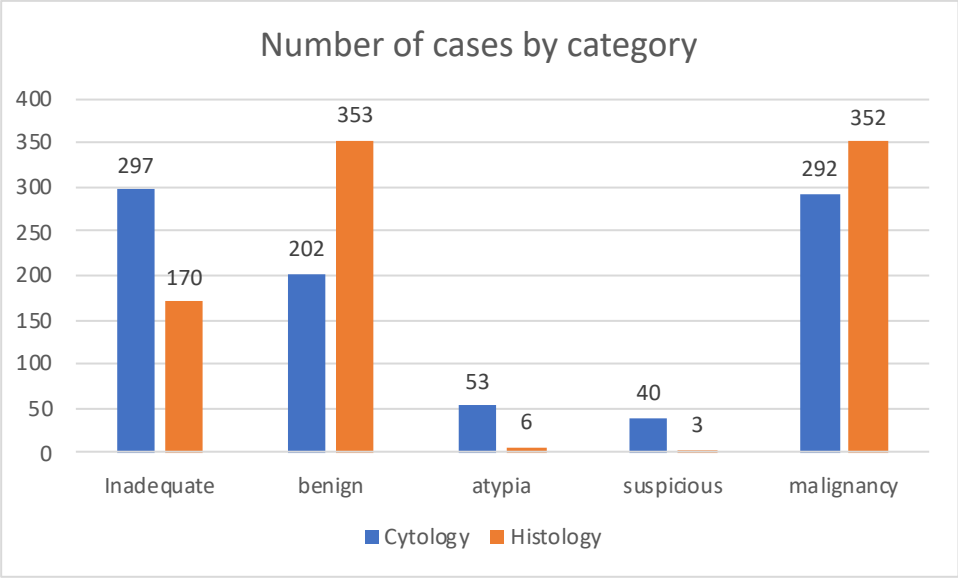

Figure 3.3 Comparison of cytology and histology categories.

The number of inadequate cytological specimens was reduced from 297 to 170 after histological assessment. The number of benign conditions almost equalled the number of malignant cases after histological assessment (353 vs 352 respectively); a stark contrast to cytological assessment whereby the number of malignant cases outnumbered the benign ones. The number of cases in the cytological categories of atypia probably benign (C3) and atypia suspicious for malignancy (C4) were dramatically reduced after histological assessment.

The following images shows some of the different pathologies seen in our cytology sample-benign(Fig 3.4-3.5) and malignant cases (Fig 3.6).

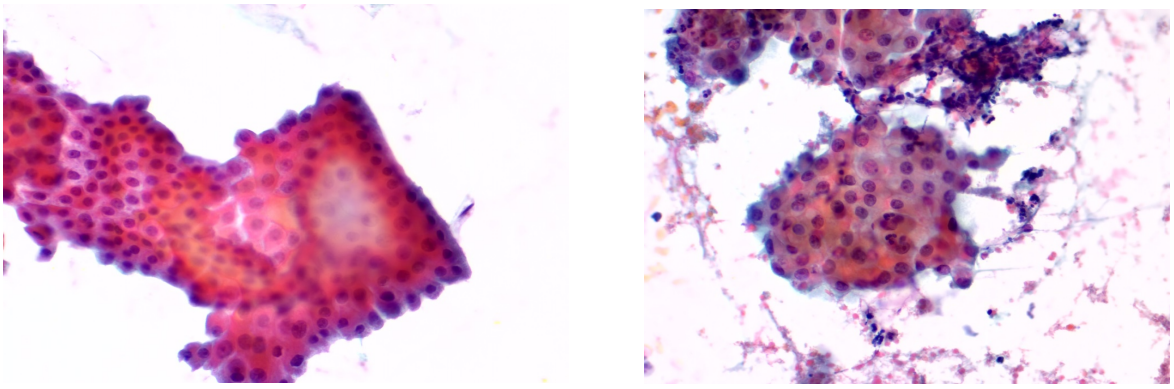

Fig 3.4 Apocrine metaplasia- large flat sheets of apocrine cells that have distinct cell borders, abundant granular cytoplasm and centrally located nuclei (x40 obj magnification).

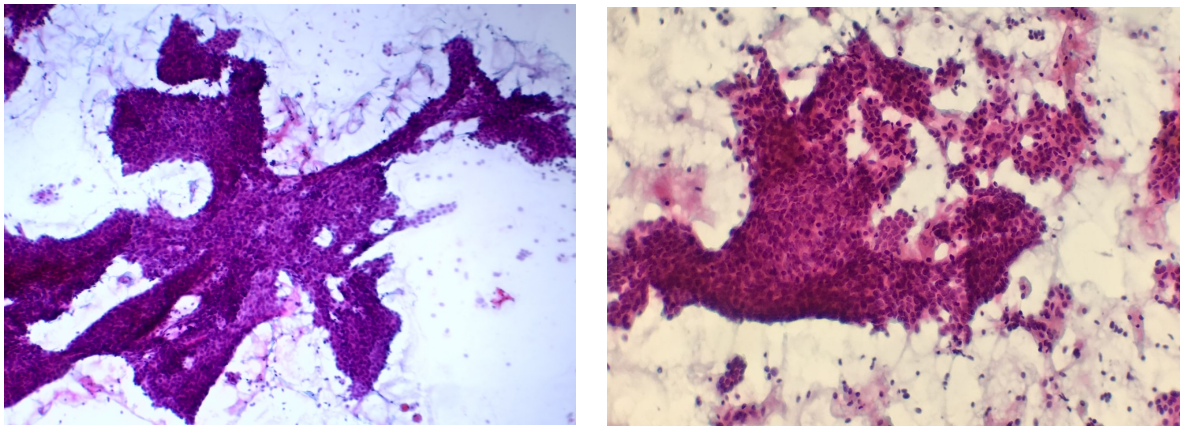

Fig 3.5 Fibroadenoma-hypercellular smear with tightly cohesive cells forming branching antler-horn clusters. Numerous myoepithelial cells are seen in the background (x20 obj magnification). Fibroadenoma confirmed on histology.

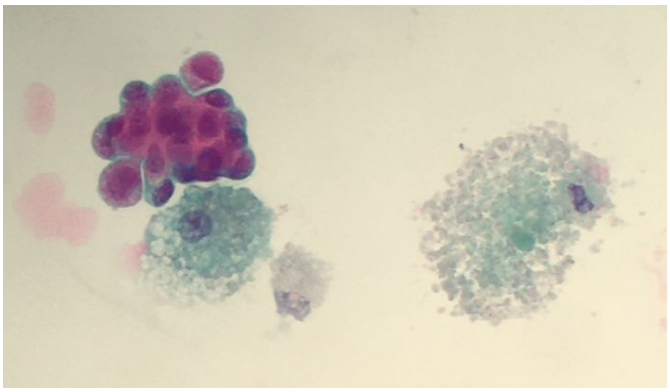

Fig 3.6 Atypia- hypocellular smear shows clusters of moderately pleomorphic cells with mildly increased nuclear to cytoplasmic ratio admixed with macrophages in a blood stained background (x40 obj magnification). The histology confirmed an abscess with numerous histiocytes.

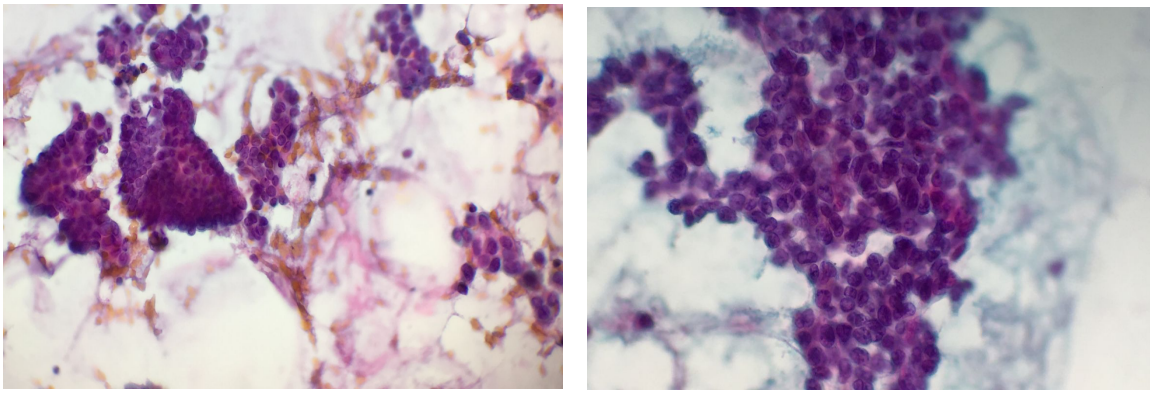

Fig 3.7 Infiltrating ductal carcinoma- shows pleomorphic, single lying and loosely cohesive cells with high nuclear to cytoplasmic ratio in a dirty background (x40 obj magnification). Infiltrating ductal carcinoma confirmed on histology.

3.2 Aim 1:

To assess the diagnostic yield of the breast FNAB at our institution by comparing it to the matched histopathology over a 12-month period.

The extent of agreement between histology and cytology is substantial (80.85%) with a Cohen Kappa of 0.659. The specificity of the study is 83.10%, specificity 93.01%, positive predictive value 88.86% and negative predictive value 89.13%. The results are summarised in the tables below.

Table 3.3 Consensus between cytology and histology categories

		Coefficient	95% CI	P value
FNAB cytology C1-C5 vs histology B1-B5	Percentage agreement	0.6391	0.61 - 0.67	<0.001
	Cohen's Kappa	0.4932	0.45 - 0.53	<0.001
FNAB cytology C2-C5 vs histology B2-B5 (Excluding inadequate samples)	Percentage agreement	0.8085	0.78 - 0.84	<0.001
	Cohen's Kappa	0.6590	0.61 - 0.71	<0.001

Table 3.4 Sensitivity and Specificity of FNAB cytology using histology as the gold standard

Where No malignancy is (C1-C3) and Malignancy is (C4-C5)

Cytology	Histology		
	No Malignancy (B1-B3)	Malignancy (B4-B5)	
No malignancy (C1-C3)	492 (89.13)	60 (10.87)	552
Malignancy (C4-C5)	37 (11.14)	295 (88.86)	332
Total	529	355	884

	Estimate	95% Confidence Interval
Sensitivity	83.10%	80.63 – 85.57
Specificity	93.01%	91.32 – 94.69
Positive predictive value	88.86%	86.78 – 90.93
Negative predictive value	89.13%	87.08 – 91.18

3.3 Aim 2:

To assess the respective risk of malignancy (ROM) for each category.

Table 3.5 Comparison of Yokohama cytology codes with histology codes

Cytology Code	Histology Code					
	B1	B2	B3	B4	B5	Total
C1	126 (42.42)	144 (48.48)	0 (0.00)	0 (0.00)	27 (9.09)	297
C2	21 (10.40)	170 (84.16)	2 (0.99)	1 (0.50)	8 (3.96)	202
C3	4 (7.55)	22 (41.51)	3 (5.66)	0 (0.00)	24 (45.28)	53
C4	7 (17.50)	3 (7.50)	1 (2.50)	1 (2.50)	28 (70.00)	40
C5	12 (4.11)	14 (4.79)	0 (0.00)	1 (0.34)	265 (90.75)	292
Total	170 (19.23)	353 (39.93)	6 (0.68)	3 (0.34)	352 (39.82)	884 (100.00)

The risk of malignancy according to each category were as follows: insufficient 9.09%, benign 3.96%, atypia 45.28%, atypia suspicious for malignancy 70.00% and malignant 90.75%. The risk of malignancy increases with each cytological grade. The results are summarised in the tables below.

Table 3.6 Risk of malignancy by cytology category

Cytology Code	**Histology Code**		**Total**	**P value**
	No malignancy (B1-B3)	**Malignant (B4-B5)**		
C1	270 (90.91)	27 (9.09)	297	
C2	193 (95.54)	9 (4.46)	202	
C3	29 (54.72)	24 (45.28)	53	**<0.001**
C4	11 (27.50)	29 (72.50)	40	
C5	26 (8.90)	266 (91.09)	292	
Total	529 (59.84)	352 (39.82)	884 (100.00)	

ROM was 9.09% in suboptimal/inadequate samples. Where sampling was adequate (C2-C5), ROM increased with cytology grade to 4.46% in C2 category and to 91.09% in C5 category, and these differences were statistically significant (p**<0.001**).

3.4 Aim 3:

To assess the utility of the International Academy of Cytology (IAC) Yokohama System for Reporting Breast Fine Needle Aspiration Biopsy (FNAB) Cytology five category stratification in our institution.

Table 3.7: Risk of malignancy in comparison to IAC Yokohama system:

Category	Yokohama IAC (Field, Schmitt &Vleigh)	Present study
Insufficient	2.6-4.8%	9.09%
Benign	1.4-2.3%	4.46%
Atypia	13-15.7%	45.28%
Suspicious	84.6-97.1%	72.50%
Malignant	99.0-100%	91.09%

The risk of malignancy for the benign, suspicious for malignancy and malignant categories were comparable to the Yokohama IAC study. The insufficient and atypia categories values were substantially higher (2-3 times) than the corresponding categories in the Yokohama IAC system.

CHAPTER 4:

DISCUSSION AND CONCLUSION:

Breast cancer is the leading cause of death amongst women with 685 000 related deaths recorded globally in 2020 and 2.3 million newly diagnosed cases (WHO factsheet, 2021). Disability-adjusted life years (DALYs) are highest in women with breast cancer compared to other types of cancers globally (WHO factsheet, 2021). The cost of treating breast cancer in 2010 was about $16.5 billion in the United States and the costs were estimated to reach $20.5 billion in 2020 (Nelson, 2015). The financial burden is associated with screening, surgical and oncological interventions and the management of side effects arising from treatment. Whilst developed countries can cover most of the care associated costs, developing countries with less medical resources struggle with the burden of disease. South Africa in 2017 had breast cancer as the most histologically diagnosed cancer in women with a total of 9624 out of 41653 cases (NICD, 2020).

Routine screening has been shown to be beneficial in early diagnosis of breast carcinomas. Routine screening for breast carcinoma by use of mammogram is usually done in women over the age of 40 years in most countries whilst younger patients with known risk factors are usually screened by use of ultrasound due to increased breast densities in this young population (Oeffinger et al., 2015). Cytology and/or core needle biopsy are used in the diagnosis of breast carcinoma.

Triple assessment is useful for preoperative diagnosis of breast cancers (Tan et al., 2002). Triple assessment includes clinical breast examination, diagnostic mammography, and fine needle aspirate biopsy cytology (FNAB) of breast lumps (Niaz, Tirmazi & Farooq, 2012). Whilst the efficacy and robustness of triple assessment has been proven (Karim et al., 2020), there has been controversy in the use of FNAB as opposed to use of core needle biopsy in the first line assessment of breast carcinomas. FNAB are associated with sampling issues with a high rate of suboptimal that are unacceptable in some countries. Fine needle aspiration although simple is quite dependent on the technique of the operator. Core needle biopsies are the gold standard in the preoperative diagnosis of breast cancer however this procedure is more

expensive than FNAB of breast lumps. Most health centres in developing countries do not have trained specialists on site that are able to do the CNB procedure.

4.1 Discussion

Groote Schuur Hospital relies on cytology and or histology for diagnosis of breast lesions. An audit was necessary to find out if cytology remains a good and efficient tool in the diagnosis of breast cancer by using the Yokohama IAC reporting system as a bench mark.

4.1.1 Cohort demographics:

Globally women have much higher incidence of breast cancer compared to men. The present study showed similar results with females comprising more than 97% of the total number of patients seen at the clinic. The age distribution of the participants follows a normal bell curve with a median age of 51.38 years with the majority of the participants being older than 40 years. This age distribution is as expected because the incidence of breast cancer has been shown to increase with age, with a median age of 61.8 years (Bidoli et al., 2019).

4.1.2 IAC Yokohama breast cytology reporting system categories:

In all of the previous studies highlighted below, benign lesions form the majority of breast lumps (71-73%). However in the present study malignant cases outnumber the benign cases (293 vs 202). This fact is worrisome as it highlights that a third of patients who are presenting at the breast clinic have malignancy. The results might highlight sampling bias; that is those with worrisome clinical features suggestive of breast cancer are referred to the breast clinic more than those without worrisome features. On the other hand the high rate of malignancy could be a result of the patients presenting late with malignant lesions or the high rate of malignancy could be a function of the high incidence and prevalence of breast cancer in Western Cape province. There is need to investigate further why the patients presenting at Groote Schuur Hospital have a much higher rate of malignancy compared to other countries with their respective studies. Unfortunately further investigation is out of scope of current study.

Table 4.1 Comparison of IAC Yokohama breast reporting system categories.

Category	Montezuma et al.	Wong et al.	Poornima et al.	Present study
Insufficient	209 (5.77%)	301 (11%)	22 (5%)	297 (33.6%)
Benign	2660 (73.38%)	1937 (72%)	332 (71%)	202 (22.85%)
Atypia probably benign	498 (13.74%)	117 (4.3%)	7 (1%)	53 (6.0%)
Suspicious	57 (1.57%)	59 (2.2%)	8 (2%)	40 (4.52%)
Malignant	201 (5.54%)	278 (10%)	101 (21%)	292 (33.03%)
Total	3625	2696	470	884

4.1.3 Inadequate fine needle aspirate biopsy results:

The distribution of cases shows that the number of insufficient cases is quite high, with 1 in 3 patients walking into the Groote Schuur Hospital breast clinic having insufficient cytology results. Most of the studies done in the past had fewer insufficient cases (5-11%) as shown in the table below.

Table 4.2 Comparison of the amount of inadequate FNA cases between different studies.

Authors	Inadequate cases (%)	Total Number of Cases
O-Neil et al.	0.7	697
Nguansangjam et al.	4.2	190
Rosa et al.	8	1583
Day et al.	9	831
Feitcher et al.	16.2	1003
Zarbo et al.	17	13066

Park and Ham	25.3	699
Yamaguchi et al	17.7	5693
Present study	33.6	884

There are numerous reasons for inadequate specimens which can range from hypocellularity, bloody aspiration, smearing and staining errors (Mendoza et al, 2011). The high insufficient rates in our study may highlight problems in sampling and rapid on site evaluation. A low proficiency in sampling and smearing technique of palpable breast lesions by the surgeons in training may also be a reason for the high insufficient results. Whilst from the cytopathology side; there could be inefficiency in reviewing the specimens submitted by the surgeons during the rapid on site evaluation. Staining errors could also result in high inadequate rates.

4.1.4 The risk of malignancy (ROM):

The risk of malignancy (ROM) increases with the category that is after excluding the insufficient category. Although the risk of malignancy in the suspicious and malignant categories is generally lower in the present study compared to previous studies (Table 4.3), the risk of malignancy follows a similar pattern as expected. The comparatively lower risk of malignancy rate in the categories suspicious for malignancy (C4) and malignancy (C5) may highlight some hesitancy in giving a definitive cytological diagnosis on the part of the cytopathologist, even in the presence of overt malignant features. Retraining of the cytopathologist might be necessary in order to the pick-up rates of malignant cases.

The ROM can act as a form of internal audit for quality assurance; low rates may indicate a need to retrain individuals in the cytological evaluation of specimens. In general the ROM has a high utility as it has been shown to provide guidance for the clinical management of patients (Field, Schmitt & Vleigh, 2017).

Table 4.3 Risk of malignancy analysis and its' comparison with previous studies.

Category	Montezuma et al.	Poornima et al.	Field, Schmitt &Vleigh	Hoda & Brachtel	Present study
Insufficient	4.8%	0%	2.6-4.8%	30.3%	9.09%
Benign	1.4%	4%	1.4-2.3%	4.7%	3.96%
Atypia	13%	66%	13-15.7%	51.5%	45.28%
Suspicious	97.1%	83%	84.6-97.1%	85.4%	70%
Malignant	100%	99%	99.0-100%	98.7%	90.75%

4.1.5 Predictive values:

Inadequate specimens were removed from the calculations because they are a function of sampling, their inclusion in the calculations dilute the actual cytological assessment of the specimens. The sensitivity, specificity, positive predictive value and negative predictive values are high and comparable to international studies as shown in the table below. The percentage agreement between histology (gold standard) and cytology is 80.8% which is impressive, this evidence is further supported by the Cohen Kappa which shows substantial agreement between the histology and cytology of 0.659. These figures highlight the high accuracy of the cytological diagnosis at the cytopathology lab at Groote Schuur Hospital.

Table 4.4 Predictive values in comparison with previous studies:

	Mišković et al	Mohanty	Hoda & Brachtel	Oosthuizen et al	Present study
Sensitivity	97.7%	93.42%	96.3%	63%	83.10%
Specificity	89.1%	100%	98.8%	100%	93.01%
Positive predictive value	95.5%	100%	98.7%	100%	88.86%
Negative predictive value	94.2%	91.71%	95.3%	84.6%	89.13%

4.1.6 Delimitations of the study:

The study included only patients with both breast histology and cytology results for comparison. Patients with only cytology results were excluded from the study precluding the calculation of diagnostic utility. In addition the data extraction used episode numbers only, as opposed to hospital numbers meaning that patients with repeat procedures were counted more than once, nonetheless the use of episode numbers allowed each cytology done on a given day to be matched to the histology done on that particular day. It is the concordance of cytology and histology that we are interested in, not the total number of patients seen at the breast clinic.

The ethnic composition of Cape Town is: 42.4% "Coloured", 38.6% "Black African", 15.7% "White", 1.4% "Asian or Indian" and 1.9% other (World population review, 2021). The geographic site of the hospital coupled with South African apartheid history means that the majority of patients seen at the Hospital are white or coloured. Although black patients are seen, there are fewer than the national average: 79.4% “Black African”, 9.2% “White”, 8.8% “Coloured” and 2.6% “Indian or Asian” (World population review, 2021). It is no clear what role the differences in ethnic demographics between Cape Town and the rest of South Africa plays on the generalizability of the results to the broader South African context. A South African study by Singh et al. (2016) showed ethnic differences in breast cancer incidences, however the reasons for the ethnic differences were unclear. Therefore further studies are needed in South Africa to determine the role of ethnic differences on breast cancer incidence. However after highlighting the significance of the ethnicity of the participants; the current

study is limited in this area because the ethnicity of the participants could not be ascertained on Trakcare (the software does not capture ethnicity of patients).

Groote Schuur Hospital provides tertiary health care and is also a training centre for undergraduate and postgraduate medical students, therefore it is expected to have greater human resources capacity compared to smaller hospitals. Therefore, the level of expertise in sampling FNA techniques employed by the stuff might not be generalizable to less resourced hospital settings within South Africa. However, the audit can still provide a benchmark for smaller health systems.

4.2 Conclusion:

This study validates the use of the IAC Yokohama System for reporting breast cytopathology as it allowed ease of comparison of different studies between local and international institutions through ensuring uniformity of reporting systems. Moreover, the comprehensive system allows inefficiencies such as inadequate specimens to be picked up.

The risk of malignancy can be used as form of internal audit assisting in quality assurance of the laboratory. In addition the risk of malignancy can be used by surgeons and oncologists alike as some form of guidance in the clinical management of patients.

Breast aspiration cytology performed at GSH hospital has shown good correlation with histology, in addition to a high sensitivity and specificity comparable to international standards. The ROM is comparable to previous studies. Overall, our results show that breast aspiration cytology is a rapid, accurate and cost-effective diagnostic procedure in our institution that is very useful in the diagnosis of benign and malignant breast lesions.

4.3 Recommendations:

Groote Schuur Hospital cytology department has a cytotechnologist available at each breast clinic to perform rapid on-site evaluation (ROSE). However, the rate of inadequacy is quite high (33.6% of all cases) compared to other studies as discussed above. There is need to for the attending cytotechnologist to receive retraining in reviewing cases for inadequacy so that inadequate specimens are repeated on site rather than the patient coming back in the future for possible repeat procedures. The inadequate cases are also a reflection of the reduced proficiency in sampling. It is possible that the surgeons in training may need retraining on how to perform FNAC and core needle biopsy which also have a high rate of inadequacy (19%). In addition it is possible that the surgeons may need retraining in performing the direct smears, which have a direct effect on the adequacy rates. It is plausible that some of the lesions are small and/or difficult to palpate, in such cases it is recommended that the radiologist gets involved during the breast clinic to provide ultrasound guided FNAC or core needle biopsy. Getting the radiologist to provide on-site intervention will reduce the administrative costs associated with booking for ultrasound guided biopsy in a separate department and the associated repeat visits by the patients. Although potential explanations for the high inadequacy rates have been given in this study; there is still need for further in depth exploration in order to improve future outcomes.

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APPENDICES:

APPENDIX 1.

DEFINITIONS OF STATISTICAL TERMS AND INTERPRETATIONS.

Sensitivity is the percentage of people who test positive for a disease that have that disease in other words a sensitivity measures how often a test correctly generates a positive result for people who have the condition that's being tested for (also known as the "true positive" rate).

Specificity is defined as the percentage of people without the disease who test negative for that disease in other words specificity measures a test's ability to correctly generate a negative result for people who don't have the condition that's being tested for (also known as the "true negative" rate).

Positive predictive value (PPV)is the probability that subjects with a positive screening test truly have the disease whilst negative predictive value (NPV)is the probability that subjects with a negative screening test truly don't have the disease (La Morte, 2020).

How to interpret Cohen's Kappa:

Percentage agreement (prior to correction for chance agreement), and the Cohen's Kappa is the chance-corrected proportional agreement.

Perfect agreement is evident when Cohen's kappa equals 1; a value of Cohen's kappa equal to zero suggests that the agreement is no better than that which would be obtained by chance alone. Although there is no formal scale, the following levels of agreement are often considered appropriate for judging the extent of the agreement. Agreement is

_ Poor if k < 0.00

_ Slight if 0.00 _ k _ 0.20

_ Fair if 0.21 _ k _ 0.40

_ Moderate if 0.41 _ k _ 0.60

_ Substantial if 0.61 _ k _ 0.80

_ Almost perfect if k > 0.80. (Watson & Petrie, 2010)

APPENDIX 2.

RAW CODED DATA, EXPORTED FROM EXCEL.

Table key codes:

B1- Suboptimal for diagnosis

B2- Benign

B3- Atypia, probably benign

B4- Atypia suspicious of malignancy

B5- Malignant

C1- Suboptimal for diagnosis

C2- Benign

C3- Atypia, probably benign

C4- Atypia suspicious of malignancy

C5- Malignant

Table A1: Raw coded data, exported from excel.

Participant number	Age	Sex	Histology	Cytology
1	34	F	B5	C5
2	73	F	B1	C4
3	86	F	B5	C5
4	60	M	B5	C1
5	56	F	B2	C2
6	56	F	B5	C5

7	67	F	B1	C1
8	46	M	B2	C2
9	55	F	B5	C5
10	51	F	B2	C2
11	50	F	B5	C1
12	32	F	B2	C2
13	43	F	B1	C1
14	41	F	B2	C2
15	39	F	B2	C2
16	52	F	B5	C5
17	62	F	B5	C5
18	62	F	B5	C5
19	25	F	B5	C1
20	54	F	B2	C2
21	90	F	B5	C1
22	48	F	B5	C5
23	30	F	B2	C1
24	78	F	B5	C5
25	38	F	B2	C2
26	40	F	B5	C3
27	33	F	B2	C2
28	49	F	B1	C1
29	38	F	B2	C2

30	49	F	B1	C1
31	28	F	B2	C2
32	51	F	B5	C5
33	53	F	B5	C3
34	33	F	B2	C3
35	56	F	B1	C1
36	29	F	B2	C1
37	56	F	B5	C5
38	65	F	B5	C3
39	62	F	B5	C3
40	46	F	B2	C1
41	48	F	B2	C1
42	29	F	B5	C1
43	43	F	B2	C5
44	53	F	B2	C2
45	56	F	B2	C5
46	35	F	B5	C5
47	72	F	B5	C5
48	64	F	B5	C5
49	70	F	B1	C1
50	47	F	B2	C3
51	47	F	B2	C2
52	30	F	B2	C2

53	39	F	B5	C1
54	32	F	B2	C1
55	64	M	B2	C1
56	46	F	B5	C5
57	76	F	B2	C2
58	33	F	B2	C1
59	47	F	B5	C5
60	63	F	B5	C5
61	65	F	B2	C1
62	47	F	B2	C1
63	55	F	B5	C5
64	80	F	B1	C1
65	64	F	B5	C5
66	53	F	B5	C5
67	46	F	B5	C5
68	47	F	B2	C2
69	49	F	B2	C2
70	41	F	B1	C1
71	37	F	B2	C2
72	71	F	B5	C5
73	51	M	B2	C2
74	43	F	B2	C5
75	18	F	B2	C2

76	59	F	B1	C1
77	29	F	B2	C1
78	42	F	B5	C5
79	76	F	B5	C5
80	44	F	B2	C2
81	22	F	B1	C2
82	53	F	B5	C5
83	46	F	B1	C1
84	54	F	B5	C5
85	76	F	B5	C5
86	57	F	B2	C1
87	72	F	B1	C5
88	66	F	B1	C1
89	36	F	B2	C1
90	78	M	B2	C2
91	30	F	B2	C2
92	56	F	B1	C1
93	59	F	B1	C1
94	28	F	B2	C2
95	73	F	B5	C5
96	31	F	B2	C2
97	58	F	B5	C2
98	60	M	B2	C1

99	43	M	B5	C5
100	45	F	B5	C5
101	53	F	B5	C5
102	54	F	B5	C5
103	63	F	B5	C5
104	69	F	B5	C5
105	68	F	B2	C1
106	75	F	B5	C5
107	31	F	B2	C2
108	62	F	B2	C2
109	33	F	B2	C2
110	56	F	B5	C2
111	50	F	B2	C2
112	34	F	B2	C2
113	77	F	B1	C1
114	37	F	B2	C1
115	42	F	B2	C2
116	37	F	B5	C5
117	80	F	B5	C5
118	60	F	B2	C2
119	48	F	B5	C5
120	57	M	B1	C1
121	62	F	B5	C5

122	55	F	B2	C2
123	38	F	B2	C1
124	51	F	B5	C5
125	76	F	B2	C2
126	50	F	B2	C1
127	71	F	B1	C1
128	27	F	B2	C2
129	68	F	B5	C5
130	81	F	B5	C5
131	50	F	B5	C3
132	65	F	B2	C3
133	68	F	B5	C5
134	83	F	B5	C5
135	57	F	B5	C5
136	48	F	B2	C1
137	68	F	B5	C5
138	35	F	B2	C2
139	45	F	B1	C1
140	32	M	B2	C2
141	37	F	B5	C5
142	37	F	B2	C1
143	49	F	B2	C1
144	49	F	B5	C5

145	65	F	B2	C1
146	38	F	B5	C3
147	53	F	B2	C3
148	58	F	B5	C5
149	37	F	B2	C1
150	68	F	B5	C5
151	38	F	B2	C2
152	66	F	B1	C3
153	41	F	B5	C3
154	48	F	B1	C1
155	58	F	B5	C3
156	68	F	B2	C1
157	61	F	B5	C5
158	66	F	B2	C4
159	66	F	B5	C5
160	71	F	B1	C1
161	83	F	B5	C5
162	38	F	B5	C5
163	31	F	B5	C5
164	48	F	B1	C1
165	63	F	B5	C5
166	56	F	B5	C5
167	36	F	B5	C5

168	47	F	B2	C2
179	71	F	B1	C5
170	44	F	B5	C3
171	30	F	B5	C5
172	42	F	B5	C5
173	69	F	B1	C1
174	53	F	B1	C1
175	53	F	B5	C5
176	73	M	B1	C2
177	40	F	B5	C5
178	44	M	B5	C2
179	82	F	B5	C5
180	50	F	B1	C5
181	56	F	B2	C5
182	51	F	B2	C2
183	37	F	B2	C3
184	63	F	B2	C2
185	73	F	B2	C3
186	72	F	B5	C5
187	31	F	B5	C5
188	29	F	B2	C2
189	54	F	B2	C1
190	55	F	B1	C5

191	85	F	B5	C5
192	45	F	B1	C1
193	68	F	B5	C5
194	48	F	B2	C1
195	47	F	B1	C1
196	76	F	B5	C5
197	45	F	B2	C1
198	25	F	B2	C2
199	38	F	B1	C1
200	31	F	B1	C1
201	44	F	B2	C1
202	46	F	B5	C5
203	41	F	B2	C2
204	58	F	B1	C1
205	68	F	B5	C5
206	75	F	B1	C1
207	53	F	B2	C1
208	31	F	B1	C1
209	38	F	B5	C5
210	66	F	B5	C5
211	46	F	B2	C1
212	34	F	B1	C1
213	50	F	B5	C5

214	72	F	B5	C5
215	42	F	B2	C1
216	48	F	B5	C5
217	54	F	B5	C5
218	39	F	B2	C2
219	60	F	B5	C5
220	42	F	B3	C2
221	54	F	B1	C1
222	34	F	B5	C5
223	73	F	B5	C5
224	70	F	B5	C5
225	28	F	B2	C2
226	50	F	B1	C1
227	49	F	B5	C5
228	66	F	B5	C5
229	57	F	B1	C1
230	59	F	B2	C5
231	75	F	B5	C5
232	58	F	B2	C3
233	25	F	B2	C3
234	35	F	B5	C5
235	24	F	B2	C2
236	68	F	B5	C5

237	62	F	B5	C5
238	70	F	B5	C5
239	54	F	B5	C5
240	43	F	B2	C1
241	55	F	B2	C2
242	76	F	B5	C5
243	58	F	B5	C5
244	45	F	B5	C5
245	57	F	B2	C1
246	62	F	B2	C3
247	55	M	B2	C2
248	54	F	B2	C4
249	74	F	B5	C5
250	36	F	B5	C5
251	47	F	B5	C5
252	41	F	B2	C1
253	44	F	B2	C5
254	75	F	B2	C1
255	85	F	B5	C5
256	70	F	B2	C1
257	84	F	B5	C5
258	40	F	B5	C5
259	47	F	B2	C1

260	57	F	B5	C5
261	75	F	B5	C5
262	51	F	B2	C1
263	70	F	B5	C5
264	54	F	B5	C5
265	60	F	B5	C5
266	39	F	B2	C2
267	61	F	B5	C5
268	70	F	B2	C3
269	47	F	B2	C3
270	46	F	B5	C5
271	39	F	B2	C2
272	28	F	B2	C1
273	67	F	B5	C3
274	70	F	B5	C5
275	24	F	B2	C2
276	40	F	B5	C4
277	28	F	B2	C2
278	54	F	B2	C2
279	32	F	B5	C5
280	58	F	B5	C5
281	31	F	B2	C2
282	37	F	B1	C1

283	28	F	B2	C2
284	28	F	B2	C1
285	60	F	B5	C5
286	53	F	B5	C4
287	54	F	B2	C1
288	51	F	B1	C1
289	35	F	B2	C2
290	41	F	B1	C1
291	45	F	B2	C3
292	45	F	B1	C5
293	70	F	B5	C5
294	70	F	B5	C5
295	49	F	B2	C2
296	44	F	B2	C2
297	32	F	B2	C1
298	28	M	B2	C1
299	40	F	B1	C1
300	51	F	B2	C2
301	55	F	B2	C1
302	59	F	B1	C1
303	18	F	B2	C2
304	43	F	B5	C5
305	21	F	B2	C2

306	31	F	B2	C2
307	33	F	B2	C2
308	27	M	B2	C2
309	83	F	B1	C1
310	33	F	B5	C5
311	34	F	B5	C5
312	65	F	B2	C2
313	57	F	B1	C2
314	45	M	B1	C1
315	49	F	B2	C2
316	62	F	B5	C5
317	30	F	B2	C2
318	52	F	B5	C5
319	69	F	B2	C2
320	69	F	B5	C5
321	55	F	B5	C5
322	78	F	B5	C2
323	89	F	B5	C5
324	39	F	B2	C5
325	48	F	B3	C2
326	31	F	B5	C5
327	79	F	B5	C1
328	44	F	B1	C1

329	52	F	B2	C2
330	60	F	B1	C2
331	42	F	B1	C1
332	46	F	B1	C1
333	35	F	B2	C1
334	72	F	B2	C2
335	59	M	B2	C2
336	37	F	B1	C1
337	61	F	B5	C5
338	54	F	B5	C5
339	46	F	B1	C1
340	57	F	B3	C3
341	68	F	B5	C4
342	29	M	B5	C3
343	37	F	B2	C2
344	73	F	B5	C5
345	55	F	B5	C5
346	35	F	B1	C2
347	36	F	B5	C5
348	71	F	B5	C5
349	46	F	B5	C5
350	37	F	B2	C2
351	49	F	B5	C5

352	28	F	B2	C2
353	72	F	B5	C5
354	49	F	B2	C2
355	57	F	B2	C2
356	31	F	B1	C1
357	50	F	B5	C5
358	68	F	B1	C1
359	83	F	B5	C5
360	64	F	B1	C1
361	52	F	B2	C2
362	48	F	B1	C1
363	37	F	B2	C2
364	63	F	B1	C1
365	62	F	B1	C1
366	45	F	B1	C1
367	47	F	B5	C5
368	63	F	B2	C1
369	25	F	B2	C2
370	40	F	B2	C2
371	65	F	B2	C1
372	54	F	B5	C5
373	39	F	B5	C5
374	33	F	B5	C5

375	61	F	B1	C1
376	52	F	B2	C1
377	18	F	B2	C2
378	51	F	B1	C1
379	63	F	B1	C5
380	66	F	B5	C5
381	57	F	B1	C1
382	46	F	B1	C1
383	46	F	B5	C4
384	38	F	B2	C2
385	34	F	B2	C1
386	24	F	B2	C2
387	46	F	B2	C2
388	36	F	B2	C2
389	49	F	B4	C2
390	58	F	B5	C5
391	38	F	B5	C2
392	39	F	B2	C2
393	73	F	B5	C5
394	68	F	B5	C4
395	59	F	B1	C1
396	51	F	B2	C1
397	78	F	B5	C5

398	66	F	B2	C1
399	55	F	B5	C5
400	63	F	B1	C1
401	56	F	B1	C5
402	32	F	B2	C2
403	61	F	B2	C1
404	66	F	B2	C1
405	28	F	B2	C2
406	43	F	B2	C2
407	41	F	B1	C1
408	27	F	B5	C5
409	44	F	B5	C5
410	46	F	B2	C1
411	41	F	B1	C1
412	39	F	B5	C5
413	25	F	B2	C2
414	36	F	B2	C1
415	27	F	B2	C1
416	70	F	B5	C5
417	52	F	B2	C1
418	36	F	B5	C5
419	36	F	B2	C1
420	48	F	B1	C1

421	38	F	B2	C2
422	83	F	B1	C1
423	26	F	B2	C2
424	66	F	B5	C5
425	47	F	B2	C2
426	71	F	B5	C5
427	57	F	B5	C5
428	79	F	B5	C5
429	65	F	B1	C1
430	37	F	B1	C2
431	64	F	B1	C1
432	49	F	B2	C1
433	40	F	B2	C2
434	54	F	B5	C1
435	45	F	B2	C2
436	81	F	B5	C5
437	52	F	B1	C5
438	54	F	B1	C2
439	63	F	B2	C2
440	45	F	B2	C1
441	59	F	B5	C5
442	37	F	B2	C2
443	38	F	B2	C2

444	64	M	B5	C5
445	43	F	B2	C2
446	39	F	B2	C2
447	61	F	B2	C1
448	66	F	B2	C1
449	44	F	B5	C3
450	74	F	B2	C2
451	41	F	B1	C2
452	60	F	B5	C4
453	27	F	B2	C2
454	60	F	B5	C5
455	44	F	B5	C5
456	48	F	B2	C1
457	40	F	B1	C1
458	36	F	B2	C2
459	73	F	B5	C5
460	46	F	B1	C1
461	66	F	B1	C1
462	34	F	B2	C2
463	24	F	B2	C2
464	50	F	B2	C2
465	41	F	B2	C2
466	62	F	B1	C1

467	52	F	B2	C1
468	49	F	B5	C1
469	33	F	B5	C5
470	49	F	B2	C2
471	53	F	B5	C5
472	58	F	B1	C1
473	36	F	B2	C2
474	51	F	B5	C3
475	49	F	B2	C1
476	47	F	B5	C5
477	56	M	B2	C2
478	59	F	B5	C5
479	49	F	B5	C3
480	48	F	B2	C2
481	50	F	B5	C4
482	53	F	B5	C2
483	50	F	B5	C5
484	34	F	B2	C1
485	77	F	B1	C1
486	54	F	B1	C1
487	62	F	B5	C5
488	64	F	B1	C2
489	37	F	B1	C2

490	68	F	B5	C5
491	35	F	B5	C5
492	50	F	B1	C3
493	69	F	B5	C5
494	29	F	B2	C2
495	38	F	B1	C1
496	44	F	B2	C2
497	56	F	B1	C2
498	48	F	B2	C1
499	42	F	B5	C4
500	32	F	B2	C1
501	53	F	B1	C1
502	63	F	B5	C5
503	58	F	B1	C1
504	31	F	B2	C1
505	48	F	B5	C5
506	83	F	B5	C2
507	53	F	B2	C2
508	62	F	B5	C5
509	54	F	B5	C5
510	72	F	B1	C1
511	30	F	B2	C2
512	44	F	B1	C1

513	71	F	B5	C4
514	48	F	B5	C1
515	29	F	B2	C2
516	83	F	B5	C5
517	61	F	B5	C1
518	49	F	B5	C5
519	52	F	B1	C1
520	45	F	B2	C1
521	41	F	B5	C5
522	32	F	B5	C3
523	61	F	B5	C1
524	59	F	B5	C5
525	61	F	B5	C5
526	49	F	B2	C1
527	55	F	B5	C5
528	42	F	B5	C5
529	71	F	B5	C5
530	39	F	B2	C5
531	45	F	B1	C2
532	44	F	B2	C2
533	41	F	B1	C2
534	49	F	B2	C5
535	48	F	B5	C5

536	53	F	B5	C1
537	51	F	B2	C1
538	68	F	B1	C1
539	48	F	B2	C3
540	29	F	B2	C1
541	45	F	B2	C2
542	83	F	B5	C5
543	41	F	B5	C5
544	48	F	B3	C3
545	85	F	B5	C5
546	59	F	B5	C3
547	61	F	B2	C1
548	45	F	B5	C5
549	44	F	B5	C4
550	50	F	B5	C4
551	74	F	B5	C5
552	33	F	B5	C3
553	39	F	B1	C2
554	55	F	B2	C2
555	63	F	B5	C5
556	39	F	B2	C2
557	48	F	B2	C1
558	34	F	B5	C5

559	61	F	B2	C1
560	40	F	B3	C3
561	62	F	B5	C4
562	48	F	B2	C3
563	45	F	B2	C1
564	84	F	B5	C1
565	31	F	B2	C2
566	61	F	B2	C1
567	50	F	B5	C4
568	48	F	B2	C2
569	64	F	B1	C1
570	47	F	B2	C2
571	43	F	B5	C1
572	44	F	B1	C1
573	95	F	B5	C5
574	68	F	B2	C1
575	44	F	B2	C2
576	73	F	B1	C1
577	49	F	B2	C2
578	49	F	B5	C5
579	55	F	B5	C3
580	45	F	B1	C1
581	49	F	B1	C2

582	84	F	B5	C5
583	42	F	B5	C5
584	23	F	B2	C1
585	36	F	B2	C2
586	56	F	B5	C5
587	52	F	B2	C3
588	52	F	B5	C5
589	63	F	B5	C5
590	79	F	B1	C4
591	25	F	B2	C1
592	65	F	B1	C5
593	65	F	B5	C5
594	35	F	B2	C1
595	81	F	B5	C5
596	59	F	B2	C1
597	59	F	B5	C5
598	58	F	B2	C1
599	41	F	B2	C2
600	45	F	B1	C2
601	47	F	B1	C1
602	60	F	B1	C1
603	47	F	B5	C4
604	47	F	B2	C3

605	57	F	B2	C1
606	47	F	B2	C1
607	62	F	B5	C4
608	61	F	B5	C5
609	47	F	B2	C2
610	55	F	B1	C4
611	45	F	B1	C1
612	50	F	B2	C1
613	47	F	B2	C1
614	59	M	B2	C2
615	60	F	B5	C5
616	45	F	B2	C2
617	48	F	B5	C2
618	28	F	B2	C1
619	70	F	B5	C5
620	31	F	B2	C2
621	42	F	B2	C1
622	23	F	B2	C1
623	43	F	B5	C4
624	70	F	B2	C1
625	44	M	B2	C2
626	41	F	B2	C2
627	73	F	B1	C1

628	31	F	B2	C2
629	70	F	B5	C5
630	45	F	B2	C1
631	36	F	B2	C2
632	67	F	B2	C1
633	66	F	B1	C1
634	65	F	B2	C3
635	80	F	B1	C2
636	51	F	B2	C2
637	67	F	B1	C1
638	72	F	B4	C5
639	44	F	B5	C5
640	55	F	B5	C5
641	45	F	B5	C5
642	71	F	B5	C5
643	67	F	B2	C1
644	73	F	B5	C1
645	47	F	B2	C2
646	44	F	B2	C2
647	58	F	B1	C1
648	42	F	B2	C2
649	64	F	B2	C2
650	43	F	B5	C5

651	59	F	B2	C1
652	58	F	B5	C5
653	37	F	B2	C2
654	50	F	B5	C1
655	58	F	B2	C1
656	42	F	B5	C5
657	69	F	B1	C1
658	64	F	B2	C2
659	50	F	B2	C1
660	49	F	B2	C2
661	36	F	B5	C5
662	35	F	B2	C1
663	44	F	B5	C5
664	62	F	B2	C3
665	56	F	B5	C5
666	84	F	B5	C5
667	41	F	B2	C1
668	89	F	B5	C4
669	42	F	B2	C1
670	49	F	B2	C2
671	52	F	B1	C1
672	36	F	B2	C2
673	56	F	B2	C1

674	79	F	B5	C3
675	53	F	B5	C5
676	60	F	B2	C1
677	50	F	B2	C1
678	41	F	B1	C2
679	30	F	B1	C1
680	65	F	B5	C5
681	43	F	B5	C4
682	62	F	B5	C5
683	70	F	B5	C5
684	35	F	B2	C5
685	64	F	B5	C1
686	58	F	B5	C5
687	67	F	B5	C5
688	59	F	B5	C5
689	72	F	B2	C2
690	51	F	B1	C2
691	86	F	B5	C5
692	57	F	B2	C5
693	36	F	B5	C5
694	63	F	B5	C5
695	35	F	B5	C1
696	41	F	B5	C5

697	46	F	B2	C1
698	70	F	B5	C5
699	53	F	B2	C2
700	45	F	B2	C1
701	63	F	B5	C5
702	57	F	B2	C3
703	50	F	B5	C5
704	58	F	B2	C1
705	42	F	B2	C1
706	41	F	B5	C5
707	43	F	B2	C1
708	69	F	B2	C1
709	44	F	B2	C2
710	40	F	B5	C5
711	38	F	B2	C1
712	81	F	B5	C5
713	52	F	B1	C1
714	73	F	B1	C5
715	54	F	B2	C1
716	44	F	B1	C2
717	43	F	B5	C4
718	67	F	B5	C5
719	39	F	B2	C1

720	75	F	B5	C5
721	50	F	B1	C1
722	42	F	B4	C4
723	26	F	B5	C5
724	45	F	B2	C1
725	56	F	B5	C1
726	52	M	B2	C2
727	39	F	B3	C4
728	77	F	B5	C3
729	37	F	B1	C3
730	50	F	B1	C1
731	42	F	B2	C1
732	48	F	B1	C1
733	56	F	B5	C4
734	60	F	B1	C1
735	43	F	B1	C5
736	50	F	B5	C5
737	69	F	B1	C1
738	42	F	B5	C4
739	82	M	B2	C2
740	68	F	B5	C4
741	78	F	B5	C5
742	30	F	B2	C1

743	41	F	B2	C1
744	22	F	B1	C1
745	90	F	B5	C5
746	27	F	B2	C2
747	30	F	B2	C1
748	54	F	B5	C1
749	48	F	B5	C1
750	54	F	B5	C5
751	39	F	B5	C4
752	37	F	B2	C3
753	57	F	B1	C1
754	49	F	B5	C5
755	35	F	B2	C2
756	46	F	B2	C2
757	56	F	B1	C1
758	63	F	B1	C4
759	77	F	B2	C1
760	30	F	B2	C2
761	31	F	B1	C2
762	38	F	B2	C2
763	49	F	B1	C4
764	40	F	B1	C1
765	49	F	B2	C1

766	38	F	B5	C3
767	34	F	B1	C1
768	51	F	B5	C4
769	74	F	B5	C5
770	70	F	B5	C5
771	51	F	B1	C3
772	50	F	B1	C1
773	58	F	B5	C5
774	45	F	B1	C1
775	31	F	B1	C1
776	38	F	B2	C1
777	39	F	B1	C1
778	38	F	B2	C1
779	43	F	B2	C1
780	43	F	B2	C4
781	40	F	B2	C2
782	64	F	B1	C5
783	29	F	B2	C2
784	25	F	B2	C2
785	33	F	B2	C2
786	30	F	B2	C2
787	49	F	B5	C5
788	36	F	B2	C1

789	45	F	B2	C1
790	74	F	B5	C1
791	69	F	B2	C3
792	39	F	B5	C5
793	41	F	B5	C5
794	49	F	B5	C5
795	28	F	B2	C1
796	52	F	B1	C1
797	56	F	B1	C1
798	51	F	B2	C1
799	22	F	B2	C1
800	46	F	B2	C1
801	89	F	B2	C1
802	41	M	B2	C1
803	34	F	B2	C3
804	75	F	B5	C5
805	56	F	B2	C2
806	61	F	B5	C1
807	63	F	B5	C4
808	56	F	B2	C1
809	91	F	B5	C3
810	46	F	B5	C5
811	43	F	B1	C4

812	36	F	B2	C1
813	59	F	B5	C5
814	62	F	B2	C1
815	45	F	B5	C4
816	68	F	B5	C1
817	70	F	B1	C1
818	48	F	B2	C1
819	50	F	B1	C1
820	57	F	B2	C1
821	75	F	B5	C5
822	63	F	B5	C1
823	53	F	B2	C2
824	68	F	B5	C5
825	44	F	B1	C1
826	65	F	B5	C5
827	47	F	B2	C1
828	26	F	B2	C1
829	37	F	B1	C1
830	35	F	B5	C5
831	48	F	B5	C5
832	62	M	B5	C5
833	62	F	B5	C5
834	40	F	B2	C1

835	64	F	B5	C5
836	50	F	B1	C1
837	30	F	B1	C4
838	58	F	B5	C5
839	34	F	B1	C1
840	52	F	B1	C1
841	35	F	B5	C5
842	32	F	B2	C5
843	37	F	B1	C1
844	29	F	B5	C5
845	56	F	B5	C5
846	44	F	B2	C2
847	50	F	B1	C1
848	61	F	B1	C1
849	50	F	B1	C1
850	76	F	B5	C3
851	56	F	B5	C5
852	43	F	B5	C5
853	55	F	B5	C5
854	52	F	B1	C1
855	44	F	B2	C1
856	62	F	B2	C1
857	43	F	B2	C2

858	60	F	B5	C5
859	42	F	B2	C1
860	72	F	B2	C5
861	44	F	B2	C2
862	62	F	B2	C1
863	60	F	B5	C1
864	69	F	B5	C4
865	42	F	B2	C2
866	63	F	B5	C5
867	59	F	B5	C4
868	88	F	B5	C5
869	49	F	B1	C1
870	36	F	B5	C3
871	57	F	B5	C5
872	62	F	B2	C2
873	48	F	B1	C1
874	38	F	B2	C1
875	40	F	B5	C5
876	44	F	B2	C2
877	28	F	B5	C5
878	61	F	B2	C5
879	37	F	B5	C5
880	34	F	B2	C1

881	30	F	B2	C2
882	46	F	B1	C1
883	59	F	B1	C1
884	70	F	B1	C1

Table A2: Total number of cytology and histology cases by category

	Inadequate	Benign	atypia	suspicious	Malignancy
Cytology	297	202	53	40	292
Histology	170	353	6	3	352

APPENDIX 3:

RESEARCH PROTOCOL.

1 RESEARCH PROPOSAL:

Title

International Academy of Cytology Yokohama System for reporting Breast Fine Needle Aspiration Biopsy(FNAB) cytology: A retrospective study in a single South African tertiary institution

Principal Investigator and Supervisor

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2 BACKGROUND:

Breast cancer is the leading cause of mortality globally among women. In 2012 1.67 million were diagnosed with breast cancer and more than half died of the disease (Lince-Deroche et al., 2017). Breast carcinoma is the leading cause of death among females in South Africa, comprising 23.6% (14097) of all newly diagnosed cases in South Africa in 2018 (Globocan, 2018). Screening is the corner stone in the management of breast carcinoma. Mammography is an ideal tool in screening of women over 40 years with a sensitivity of 97%, a specificity of 64.5%, a positive predictive value of 89%, and a negative predictive value of 90.9%, with a diagnostic accuracy of 89.3% (Zeeshan et al., 2018). Low to middle income countries are unable to provide this screening tool for the majority of their patients hence the reliance on self-breast examination or breast examination by a trained health worker (Lince-Deroche et al., 2017).

With the advent of triple testing for breast malignancies, fine needle aspirate biopsy (FNAB) has become an integral part of the evaluation of breast lesions. Triple testing includes breast clinical examination, mammography and/or ultrasonography, and cytology {FNAB/Core needle biopsy (CNB)}.

FNAB is a simple, relatively painless, inexpensive out-patient procedure with speedy results. One of the major goals of breast FNAB is to differentiate benign from malignant lesions. However, differentiation is not possible in all cases due to significant overlap of the cytomorphologic features of both benign and malignant breast lesions.

Over the years, ultrasound guided FNAB cytology and CNB are used often in aiding the diagnosis. In developing countries where financial constraints play a major role, FNAB still plays a pivotal role in diagnosis and management of breast lesions.

Currently, the use of breast fine needle aspiration cytology varies greatly between hospitals and cities and between developed and developing countries. It offers many advantages such as it is fast, easy, cheap, it shows high accuracy, sensitivity, and specificity. It is minimally invasive, causes minimal physical and psychological discomfort, can be performed with little complications (Mendoza et al., 2011) and is highly acceptable to patients. FNAB also provides cell blocks for immunohistochemistry to identify prognostic indicators and smeared cells for polymerase chain reaction (PCR) and other potential molecular testing (Schmitt, F. & Vielh, P., 2015).

Most participating countries use FNAB as the first-line pathological investigation in both screening and symptomatic populations, with the exception of microcalcifications (Kocjan et al., 2008). FNAB is relatively cost effective for the pre-operative diagnosis of palpable and ultrasound detected impalpable breast lesions. When triple assessment is concordant, final treatment may proceed on the basis of FNAB, without a tissue biopsy.

Despite its many benefits like simplicity of the procedure, cost effectiveness, few complications, short turnaround time several factors such as relatively high inadequate rate and suboptimal accuracy in some centres have led to criticism of FNAB (Wells et al., 1999). In addition, the greatest quality assurance issue in providing a breast FNAB is the quality of the technique of the FNAB procedure and the quality of the technique in the making of direct

smears. Best results are achieved when aspiration is done by a trained or training radiologist in the presence of a pathologists specialized in cytopathology (cytopathologists). Cytopathologists are best qualified to collect and interpret FNAB samples, but this is not always possible or practical as most developing countries do not have a trained radiologist and cytopathologist on site in a breast clinic to perform such tests due to limited resources (Kocjan et al., 2008).

Since then use of FNAB in the evaluation of breast lesions has changed substantially over the period of 20 years, mainly due to changes in screening programs and available treatments and recent preference for CNB. In 1996 the National Cancer Institute (NCI) proposed five diagnostic categories (Abati, A., 1997) that are listed below:

Cytology reporting category	
C1	Inadequate
C2	Benign
C3	Atypia, probably benign
C4	Suspicious of Malignancy
C5	Malignant

In 2016, the International Academy of Cytology (IAC) established a “Breast Group” which included pathologists, radiologists, surgeons, and oncologists mainly to produce comprehensive and standardised guidelines for breast FNAB cytology reporting. The IAC Yokohama System for Reporting Breast Cytopathology incorporates the indications for breast FNAB cytology, FNAB technique, smear making and material handling, a reproducible standardised reporting system, the use of ancillary diagnostic and prognostic tests, and correlation with clinical work-up algorithms. Ultimately, this will facilitate clinician’s understanding and use of FNAB cytology in breast pathology (Field, AS, Schmitt, F. & Vielh, P., 2017)

In the Yokohama System for Reporting Breast Cytopathology, the "Breast Group" has proposed a five-category classification: category 1- insufficient material; category 2- benign; category 3- atypical, probably benign; category 4- suspicious for malignancy, probably in situ or invasive carcinoma; and category 5- malignant (Field, AS, Schmitt, F. & Vielh, P., 2015) this is summarised in the table below.

Category	ROM[a], %	Management[b]	LMICMX[c]	Comment
Insufficient	2.6–4.8	Review clinical and imaging findings; if imaging indeterminate or suspicious, repeat FNAB or proceed to CNB; if imaging benign consider repeat FNAB	Review clinical findings; if suspicious repeat FNAB	At ROSE, if inadequate due to a technical issue or the material does not explain the clinical or imaging findings, repeat FNAB up to a total of 3 times, ideally using ultrasound guidance; if FNAB still insufficient, proceed to CNB
Benign	1.4–2.3	Review clinical and imaging findings; if "triple test" benign, no further biopsy required, and review depends on the nature of the lesion; if clinical and/or imaging indeterminate or suspicious, repeat FNAB or proceed to CNB	Review clinical findings: if benign, nothing further; if suspicious, repeat FNAB	At ROSE, if the cellular material does not explain the clinical or imaging findings, repeat FNAB, up to a total of 3 times, using ultrasound guidance; follow-up depends on the nature of the lesion, e.g., abscess – 2 weeks after antibiotics, fibroadenoma – 12 months; some centers review in line with screening program policy
Atypical	13–15.7	Review clinical and imaging findings; repeat FNAB if atypia considered likely to be due to a technical issue; if good material available and atypical, repeat FNAB or preferably proceed to CNB[d]	Review clinical findings and repeat FNAB; manage based on FNAB category; if further FNAB atypical, consider excisional biopsy	At ROSE, if atypia is considered due to a technical issue, repeat FNAB; if cellular material adequate and atypical, proceed to CNB
Suspicious	84.6–97.1	Review clinical and imaging findings; CNB is mandatory[e]	IF no CNB available, excision biopsy	At ROSE proceed to CNB
Malignant	99.0–100	Review clinical and imaging findings; CNB if any discrepant findings. If "triple test" is concordant and malignant, proceed to definitive management[f, g]	If no CNB available, excision biopsy	At ROSE may proceed to CNB

Standardised reporting system enables the reproducibility of the results across the institutions and countries and facilitates better communication between the pathologists and the treating surgeon.

2.1 AIMS:

i. To assess the utility of the International Academy of Cytology (IAC) Yokohama System for Reporting Breast Fine Needle Aspiration Biopsy (FNAB) Cytology five category stratification in our institution.

ii. To assess the respective risk of malignancy(ROM) for each category

iii. To assess the diagnostic yield of the breast FNAB at our institution by comparing it to the matched histopathology over a 12-month period.

3 MATERIAL AND METHODS:

A computerized search of National Health Laboratory Service (NHLS) TrackCare will be performed on all the breast FNAB specimens from the Division of Anatomical Pathology, Groote Schuur Hospital, National Health Laboratory Service for the past year (January 2019 – December 2019). All the reported cytology specimens with corresponding histology biopsy specimens during this period will be considered for the study. A registrar in Anatomical Pathology and consultant Anatomical Pathologist will retrospectively reclassify the specimens according to the newly proposed IAC Yokohama reporting system for breast cytology. These will be compared to histologic biopsy specimens, which are considered the 'gold standard'.

The respective risk of malignancy(ROM) will be determined for each category.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value(NPV) will be calculated. These will be compared to other similar studies.

All cases will be anonymised, and assigned a study number. Laboratory and hospital numbers used for patient identification will be removed, to assure patient confidentiality.

Inclusion criteria:

- All patients 18 years of age or older
- Patients with both breast cytology(FNAB) and histology specimen(CNB)

Exclusion criteria:

- Patients under the age of 18 years

- Patients with breast cytology specimen(FNAB) but no corresponding histology specimen(CNB)

4 ENVISAGED OUTPUTS/OUTCOMES

Data generated from this study will be used:

1. This study will form part of an MMED degree in Anatomical Pathology.
2. To be presented at various national meetings and conferences.
3. To be submitted in part for publication in peer-reviewed journals.
4. The data can be applied for further investigations

5 IMPACT

The main objectives of the study were to categorise the Breast FNAB samples according to this new system of reporting and to assess the ROM for each category as well as the diagnostic yield of the Breast FNAB.

Standardised reporting system enables the reproducibility of the results across institutions and facilitates better communication between the pathologists and the treating oncologists and surgeons.

Uniform reporting system boosts the confidence of signing out pathologist especially with difficult lesions of breast FNAB cytology. This requires uniform system of reporting which is addressed by IAC Yokohama system of breast cytology.

This categorisation of the Breast FNAB cytology according to IAC Yokohama system of reporting will help the pathologist in regards to diagnostic clarity and will guide the clinician in the appropriate patient management.

In addition, the findings of this study will demonstrate that breast FNAB is indeed an accurate test enabling effective diagnosis of breast lesions with practical application to rapid onsite evaluation (ROSE)

If correctly applied at ROSE, this can improve diagnostic yield by decreasing the proportion of “insufficient” and “atypical” and increasing the “suspicious of malignancy” and

“malignant” diagnoses which will further enable immediate triage for further biopsy where necessary.

6 INSTITUTIONAL APPROVAL AND BUDGET

Application for institutional approval by the UCT Human Ethics Committee after review and acceptance by the Departmental Research Committee(DRC) prior to the commencement of the study.

The principal investigator will fund out of pocket as she is not illegible for any research grant offered by the UCT or NHLS.

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16 April 2021

HREC REF: 229/2021

Dr D Chetty
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NHLS, NGSH
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Student: ppamacheche@gmail.com

Dear Dr Chetty

PROJECT TITLE: INTERNATIONAL ACADEMY OF CYTOLOGY YOKOHAMA SYSTEM FOR REPORTING BREAST FINE NEEDLE ASPIRATION BIOPSY(FNAB) CYTOLOGY: A RETROSPECTIVE STUDY IN A SINGLE SOUTH AFRICAN TERTIARY INSTITUTION-MMED CANDIDATE-DR PATRICIA PAMACHECHE

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

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

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & **06 July 2020.**

Approval is granted for one year until the 30 April 2022.

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

The HREC acknowledge that the student: Dr Patricia Pamacheche will also be involved in this study.

Please quote the HREC REF 229/2021 in all your correspondence.

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

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

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON. FACULTY OF HEALTH SCIENCES HUMAN RESEARCH'ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.