Cytological findings of thyroid fine-needle aspirations undertaken at Chris Hani Baragwanath Academic Hospital from January 2016 to December 2019.

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DEDICATION

To my beloved Grandmother

My inspiration and strength

PUBLICATIONS/ PRESENTATIONS ARISING FROM THIS PROJECT:

Poster presentation at the Society of Endocrine, Metabolism, and Diabetes of South Africa (SEMSDA) 2022

Nanabhay S, Goolam Mahyoodeen N, Fatman L, Mohamed NA. Cytological characteristics of thyroid fineneedle aspirations undertaken at Chris Hani Baragwanath Academic Hospital. 55th Society of Endocrine, Metabolism, and Diabetes of South Africa Congress. 8-11 September 2022

AWARDS

Best poster presentation at the Society of Endocrine, Metabolism, and Diabetes of South Africa (SEMSDA) 2022

Nanabhay S, Goolam Mahyoodeen N, Fatman L, Mohamed NA. Cytological characteristics of thyroid fineneedle aspirations undertaken at Chris Hani Baragwanath Academic Hospital. 55th Society of Endocrine, Metabolism, and Diabetes of South Africa Congress. 8-11 September 2022

ABSTRACT

Introduction

Thyroid nodules are commonly encountered in clinical practice, with thyroid cancer being the most frequent endocrine malignancy seen. There is limited data regarding the outcomes of thyroid nodules in a low-resource environment. A reliable preoperative diagnosis will facilitate prompt treatment of malignancy as well as limit the need for unnecessary interventions.

Objectives

To describe the cytological characteristics of thyroid nodules at Chris Hani Baragwanath Academic Hospital (CHBAH) and to compare the outcomes of thyroid fine-needle aspiration (FNA) based on the FNA setting as well as the method of FNA. In addition, to compare the accuracy of preoperative thyroid FNAs and the postoperative histopathological thyroid diagnosis.

Method

A retrospective descriptive study of thyroid nodule FNA results at CHBAH over the period 2016 – 2019. Frequencies and percentages were used to summarise the data.

Results

In our study, 600 cytology specimens were reviewed. The median age of the study population was 52 years (IQR 42 – 62 years), with 516 females and 78 males. There was a higher incidence of female patients, 516 (86%) with thyroid nodules. A higher incidence of malignant nodules was seen in male patients. No correlation was found between thyroid-stimulating hormone (TSH) levels and malignancy. Thyroid nodule FNAs were performed at 3 different sites, with 112 samples (18.7%) being nondiagnostic. Specimens performed at the cytopathology clinic by palpation guidance yielded the most nondiagnostic samples (25.1%), compared to 8.1% at the endocrine clinic and 16.1% at the radiology clinic. From the cytology samples, 105 samples had corresponding histology specimens of which 43 samples (40.9%) were proven to be malignant. There was a statistically significant correlation between the cytological and histopathology samples ($p < 0.05$).

Conclusion

The prevalence of malignancy and gender distribution in our study are largely consistent with those of international studies. It demonstrates that thyroid nodule FNA is an effective tool in the diagnostic algorithm for thyroid nodules. However, nondiagnostic samples pose a diagnostic challenge. Our study demonstrated that ultrasound guided FNA samples are superior to palpation guided FNA samples as they yielded fewer nondiagnostic samples. A subset analysis demonstrated the advantage of a dedicated trained FNA operator over multiple operators. This is a feasible option in a low-resource environment where the availability of a US- machine or specialist may not be available.

ACKNOWLEDGEMENTS

To Dr Luvo Fatman, Dr Nasrin Goolam-Mahyoodeen, and Dr Nazeer Ahmed Mohamed for all their guidance, motivation, and prompt replies to my endless queries.

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ETHICAL CONSIDERATIONS

Permission for this study was obtained by the Medical Advisory Committee (MAC) at Chris Hani Baragwanath Hospital (CHBAH) and Human Research Medical Ethics Committee at the University of the Witwatersrand (clearance certificate number M2011119). In addition, approval to access the National Health Laboratory Service (NHLS) database was obtained (reference number PR2010499).

CONTENTS

LIST OF ABBREVIATIONS

ACR	American College of Radiology
ACR-TIRADS	American College of Radiology Thyroid Imaging Reporting and Data System
ATA	American Thyroid Association
EU-TIRADS	European Thyroid Imaging Reporting And Data System
CT	Computed Tomography
CHBAH	Chris Hani Baragwanath Academic Hospital
FNA	Fine Needle Aspiration
TSH	Thyroid Stimulating Hormone
MRI	Magnetic Resonance Imaging
ROSE	Rapid Onsite Staining and Evaluation
US	Ultrasonography

FIGURES

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PREFACE

Thyroid nodules are discrete lesions within the thyroid gland that are radiologically distinct from surrounding thyroid parenchyma. They are commonly encountered in clinical practice with the risk of a nodule harbouring malignancy being 4% - 8%. However, there is a paucity of local data regarding the cytological characteristics of thyroid FNAs.

The aim of this study was to determine the cytological characteristics of thyroid FNA specific to CHBAH. It aims to assist in determining the optimal setting in which to perform thyroid FNAs in a low-resource environment to minimise the need for repeated diagnostic procedures or unnecessary surgery.

This research report is presented in a format recommended by the Faculty of Health Sciences, University of the Witwatersrand. As such, it is divided as follows:

- Chapter 1 covers the introduction, literature review, and study methodology. These are written in the traditional monograph format.
- Chapter 2 consists of the research report and is presented in a submissible format.
- Chapter 3 comprises the conclusion.

STUDENT CONTRIBUTIONS

I was involved in all stages of research for this study viz study conceptualisation, study design, ethics approval, data collection, data analysis and write-up. The data was verified by one of my supervisors, Dr Luvo Fatman, a consultant cytopathologist. I performed the statistical analyses with the assistance of Dr Tendesai Kufta. I was primarily responsible for each of the steps outlined above and all aspects of the research overseen by my supervisors.

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

Background

1.1 Introduction

The thyroid gland is a butterfly-shaped gland situated on the anterior aspect of the neck that secretes several hormones, collectively referred to as thyroid hormones(1). They act throughout the body influencing metabolism, growth, development, and body temperature(1). A thyroid nodule is an abnormal growth of thyroid cells that forms a lump within the thyroid gland(2). Most thyroid nodules do not cause symptoms and are often found incidentally during routine physical evaluation or imaging tests(1). Occasionally, an abnormal thyroid function test is the reason the nodule is detected(1).

Historically, detecting a thyroid nodule would subject a patient to surgical removal of the nodule to evaluate its contents. The introduction of fine-needle aspiration in the 1930s, although more widely used within the 1960s, allowed nodules to be analysed prior to subjecting patients to surgery(3). Initially, thyroid nodules were detected upon palpation. However, the introduction of ultrasound analysis of the thyroid gland has allowed the workup of thyroid nodules to become far more nuanced(4). Furthermore, the introduction of the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) in 2007 has allowed for a standardised reporting system for the evaluation of thyroid nodules(5).

The evaluation of a thyroid nodule involves a stepwise approach, as illustrated in Figure 1.1(6). Firstly, a thorough physical examination of the thyroid gland is performed to differentiate between a single nodule versus multiple nodules, as well as a diffusely enlarged gland(6). The next step would include laboratory evaluation of thyroid hormones(6). Most thyroid nodules are nonfunctioning, however, occasionally nodules may produce excess amounts of thyroid hormone(6). Thirdly, imaging of the nodule is performed, with ultrasonography(US) becoming the first-choice modality in the evaluation of a thyroid nodule(6). Thereafter, a tissue sample is sought with the use of fine-needle aspiration(FNA) of the nodule, with the gold standard being ultrasound guided FNA(1). Nodules that are noted to contain malignancy or are highly suspicious for malignancy should be removed whereas nodules that are benign or too small to biopsy should be monitored by ultrasound examination(5). In a low resource environment with

a high patient load, the evaluation algorithm of a thyroid nodule is often altered to suit the resources available. In this context, most patients in our setting with palpable nodules do not receive ultrasound evaluation prior to FNA; with the majority of FNAs performed palpation guided. Patients will be referred for a thyroid ultrasound if at FNA the nodule is not palpable, a difficult to access lesion is found or with repeated nondiagnostic samples.

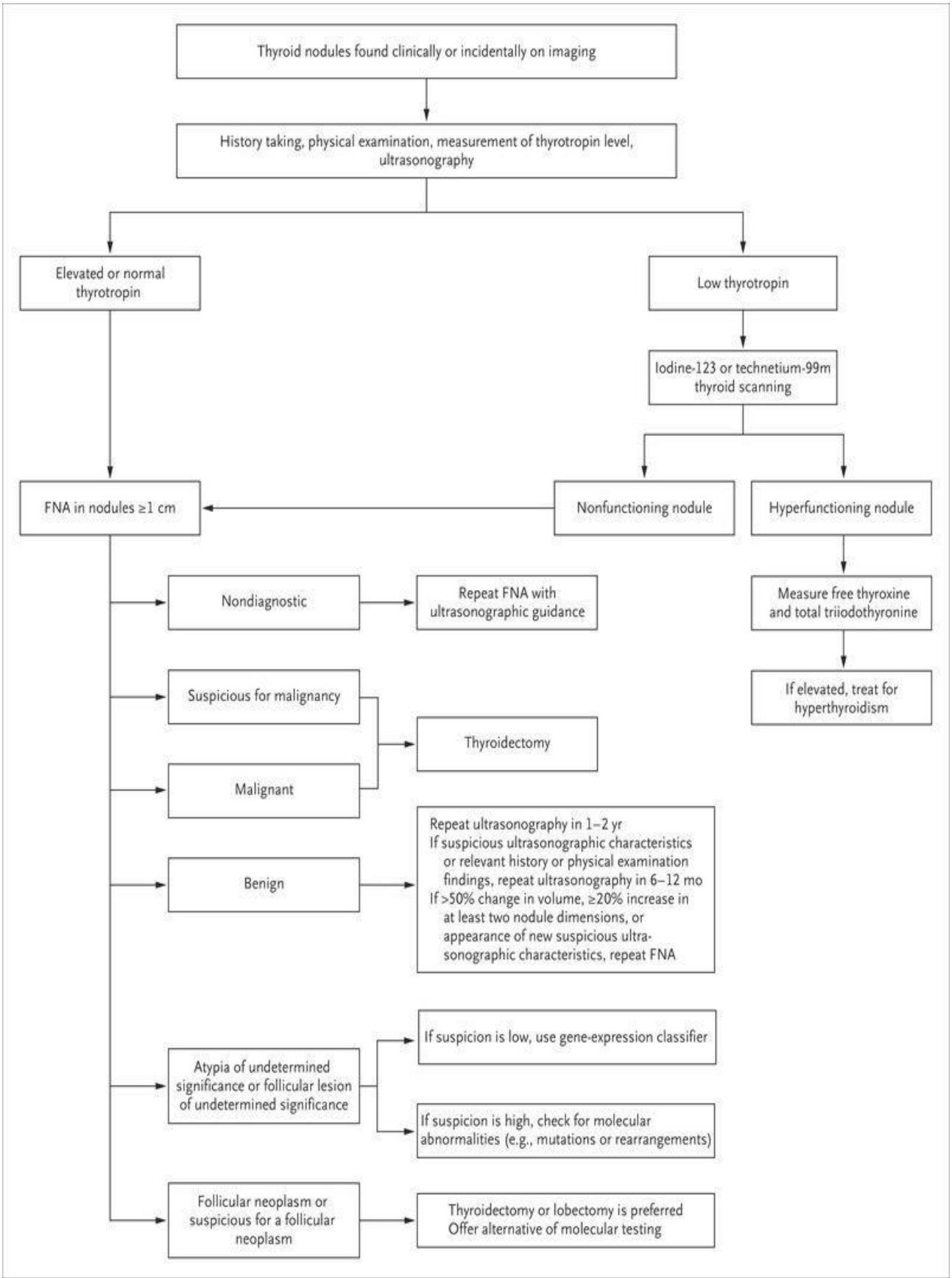


Figure 1.1 Thyroid Nodule Algorithm (*Wartofsky, L. Burman, KD. Thyroid Nodules. N Engl J Med. 2015; 373:2347-56.)*

1.2 Epidemiology

Thyroid nodules are commonly encountered in clinical practice. Approximately 4% up to 7% of adults have palpable thyroid nodules and 19% to 67% have thyroid nodules visible on US(7). There is a 4% to 8% risk of malignancy within these nodules(8). Thyroid cancer is the most frequent endocrine malignancy encountered worldwide with an incidence of 7.3% – 15% in a surgical series in Africa(9). Thus, a confident preoperative diagnosis will facilitate prompt treatment of malignancy whilst minimising the need for unnecessary surgical procedures and interventions.

The prevalence of thyroid nodule disease as well as the incidence of multinodularity increases with advancing age(10). With each successive age group the relative risk of multinodularity increases by 1.6%(10). The incidence of malignancy is increased after the age of 50 years in both men and women(8). Age is an independent prognostic factor for differentiated thyroid cancer with a diagnosis between the ages of 20 and 55 years of age inferring excellent survival(11). A significant inverse relationship is observed between the risk of papillary thyroid cancer and age(12). Younger patients are more likely to develop well-differentiated malignancies compared to older patients who are more likely to have a higher risk of papillary thyroid carcinoma variants, poorly differentiated cancers or anaplastic carcinoma(10).

Thyroid nodules are observed predominantly in females compared to males with a ratio of 5:1(8). However, the incidence of thyroid cancer in patients with thyroid nodules is higher in males than females(13). The gender disparity in thyroid cancer is also specific to the histological subtypes with differentiated thyroid cancers, follicular thyroid cancer and papillary thyroid cancer being more common amongst women (14). However, the more aggressive types of thyroid cancer such as anaplastic and medullary thyroid cancer have similar rates of incidence between males and females(14). The difference between males and females is in sex hormones and their influences on various systems in the body(14). Estrogen receptors are expressed in papillary thyroid cancer(14). Inoue and colleagues demonstrated that estrogen can dramatically increase the rate of cell proliferation in thyroid cancer cell lines compared with male sex hormones(14). The increase in serum estrogen has been associated with an increased size of pre-existing thyroid nodules and the possible development of new benign thyroid nodules(14). Estrogen treatment promoted the growth of papillary thyroid cancer cells in culture but inhibited growth in anaplastic thyroid cancer(14). While reproductive factors would

seem a logical hypothesis to account for the gender disparity, several studies show no conclusive effect of sex on the risk of developing thyroid cancer.

1.3 The role of Thyroid-stimulating hormone (TSH)

Recent practice guidelines in the management of thyroid nodules include the American Thyroid Association(ATA) guidelines as well as the American College of Radiology Thyroid Imaging Reporting And Data System(ACR-TIRADS) score(1). The ATA guidelines recommend initial biochemical evaluation by measuring the TSH(1). TSH is a well-established growth factor for thyroid nodules(15). Benign and malignant thyroid tumours express functional TSH receptors on the plasma membrane(15). TSH increases adenylate cyclase activity leading to cAMP production and cell growth through stimulation of these receptors(15). Studies have shown that higher preoperative serum TSH concentrations, even within the normal range, are associated with increased incidence of differentiated thyroid cancer and advanced cancer stage at diagnosis(15). In patients undergoing TSH suppression, there was a reduction in the rate of growth and prevention of new molecule formation(15). Thus, these findings suggest that TSH may play a central role in the development of thyroid carcinoma(15).

1.4 The diagnostic utility of ultrasonography

Once the thyroid nodule is found to be euthyroid, the next step would involve sonographic analysis of the nodule(1). Ultrasound has become the first-choice modality in screening and detection of thyroid nodules(16). It has superior spatial resolution compared to computed tomography(CT) and magnetic resonance imaging(MRI)(16). The ATA guidelines combine thyroid nodule ultrasound findings and give an estimated risk of malignancy(1). They utilize the following ultrasound features of the thyroid nodule; the echogenicity of the nodule, the sharpness of the border/margin of the nodule, shape of the nodule, presence/absence of halo around the nodule, microcalcifications, internal architecture or composition of the nodule (spongiform, cystic or solid) and the vascularity of the nodule (peripheral or central vascularity)(1). Features that are suspicious for malignancy include marked hypoechogenicity, the presence of microcalcifications and micro lobulated margins(17). The American College of Radiology(ACR) developed a reporting system for thyroid nodules, the ACR-Thyroid Imaging Reporting And Data System(ACR-TIRADS) score, which uses a standardized scoring system for reports providing users with recommendations regarding when to utilize US follow up versus when to proceed to FNA for suspicious nodules(18). The scoring system is determined by 5 categories of US findings: composition/ echogenicity/ shape/ margin and

echogenic foci(18). Nodules that have features suspicious of malignancy require cytological evaluation by FNA(18). In a study assessing the diagnostic value of the EU-TIRADS score in Congolese Hospitals, the EU-TIRDS score had a sensitivity of 96.6% and a specificity of 56.3%. Thus, in a low-income country, thyroid ultrasound, using the EU-TIRADS score, is an important tool in selecting thyroid nodules suspected of malignancy(1)

Table 1.1 European Thyroid Imaging Reporting And Data System(18)

Category		Ultrasound features	Malignancy Risk (%)
EU-TIRADS 1	Normal	• No nodules	None
EU-TIRADS 2	Benign	• Pure cysts • Entirely spongiform	0
EU-TIRADS 3	Low risk	• Ovoid, smooth, isoechoic/hyperechoic • No features of high suspicion	2-4
EU-TIRADS 4	Intermediate risk	• Ovoid, smooth, mildly hypoechoic • No features of high suspicion	6-17
EU-TIRADS 5	High risk	At least 1 of the following features of high suspicion • irregular shape • irregular margin • microcalcification • marked hypoechogenicity	26-87

A

B

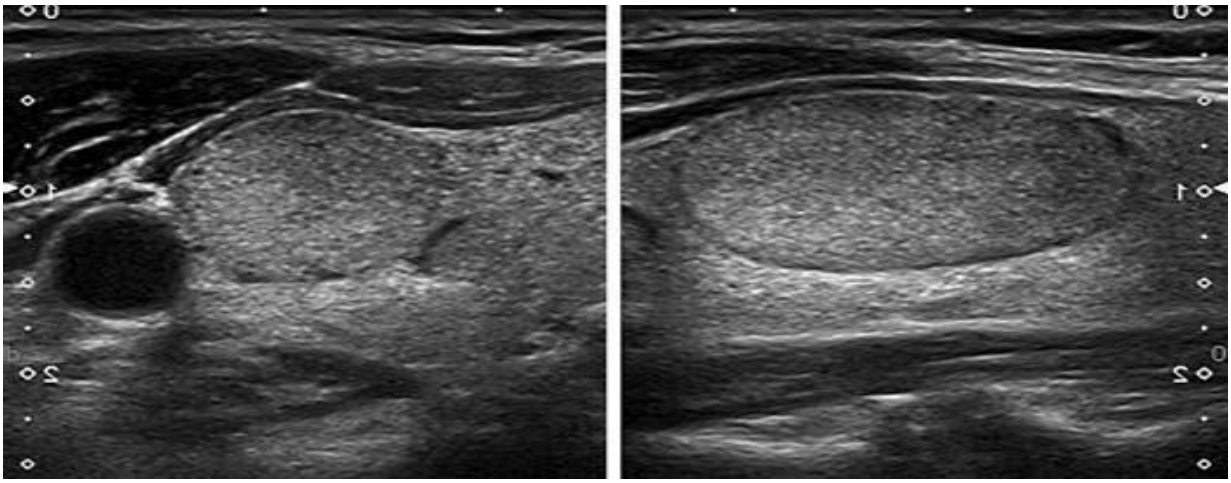


Figure 1.2 European Thyroid Imaging Reporting And Data System 3(18)

Low risk – Isoechoic nodule with an oval shape and smooth margins without any high-risk features(18).

A: Longitudinal view

B: Transverse (right) planes

A

B

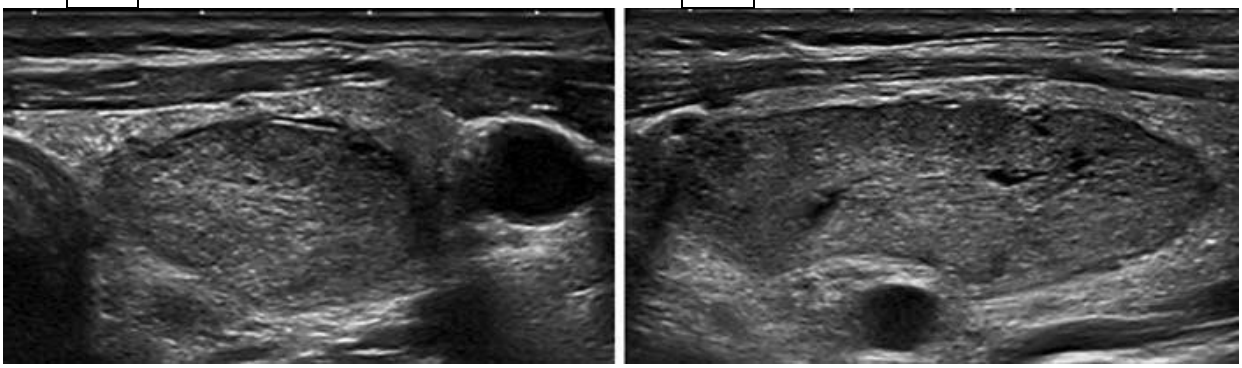


Figure 1.3 European Thyroid Imaging Reporting And Data System 4(18)

Intermediate risk – Mildly hypoechoic nodule with an oval shape and smooth margins without any high-risk features(18).

A: Longitudinal view

B: Transverse (right) planes

A

B

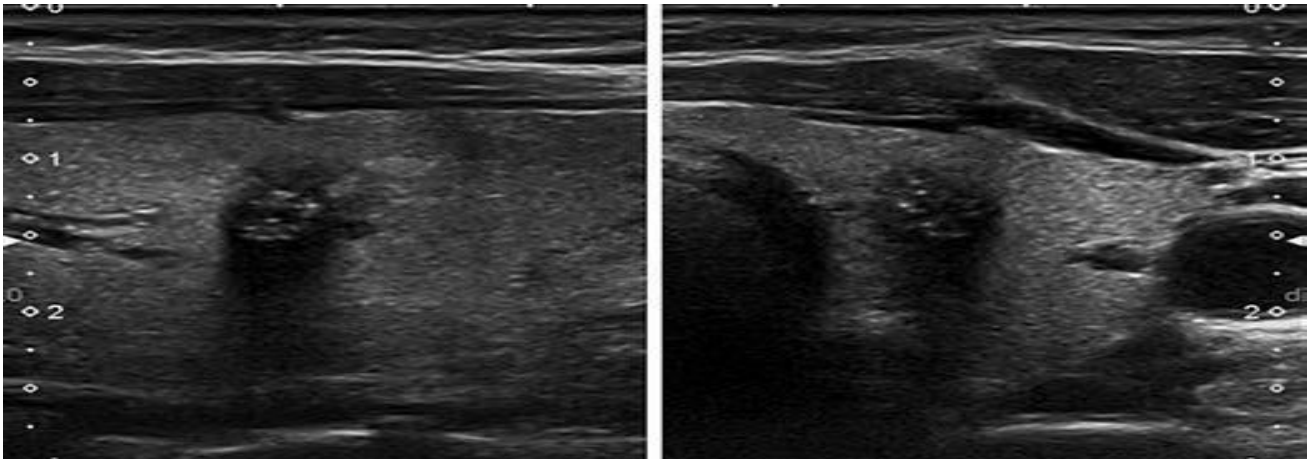


Figure 1.4 European Thyroid Imaging Reporting And Data System 5(18)

High risk – Nodule with a non-oval shape, spiculated margins, microcalcifications and marked hypoechogenicity(18).

A: *Longitudinal view*

B*: Transverse (right) planes*

1.5 The role of fine needle aspiration

Thyroid FNA can be used to triage patients effectively based on the cytopathological results(19). Thyroid FNA is considered an effective procedure that is cost-effective, minimally invasive, has good patient tolerance, easy to perform and is highly sensitive(13). An accurate FNA cytology diagnosis depends upon several factors including a skilled operator, the FNA technique and specimen preparation as well as the cytological interpretation(19). Before the routine use of FNA in the workup of thyroid nodules, the malignancy rate of resected nodules was approximately 15% however with current FNA practice these rates have increased to over 50%(19). Thyroid FNAs have a sensitivity and specificity of 94% to 98.5% of diagnosing malignancy respectively(13). The FNA utility has increased in recent years with the availability of US guided techniques, illustrated in figure 1.5, that help improve the diagnostic accuracy of the sample(13).

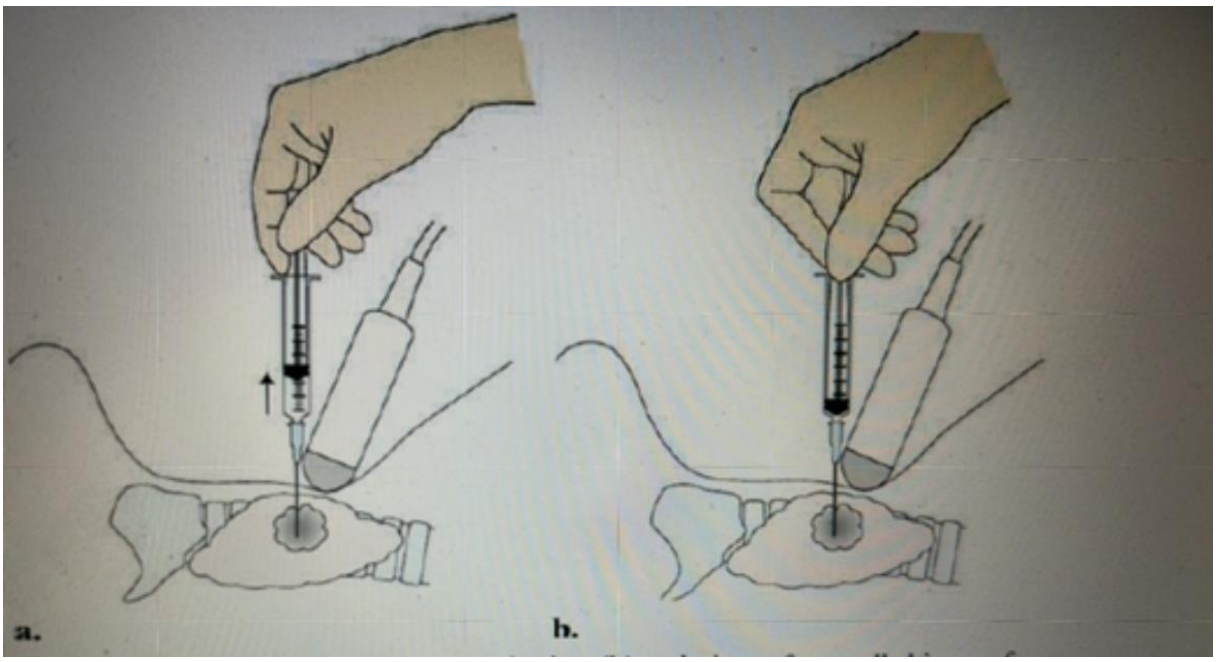


Figure 1.5 Demonstration of US guided fine-needle aspiration.
The nodule is identified with the US probe, and a small gauge needle attached to a syringe passes through the skin and enters the nodule. As soon as aspirate appears, suction is released and the needle is withdrawn.
(Kim MJ, Kim EK, Park SI, Kim BM, Kwak JY, Kim SJ, et al. US-guided Fine-Needle Aspiration of Thyroid Nodules: Indications, Techniques, Results. RadioGraphics. 2008 Nov;28(7):1869–86.)

1.6 Cytological evaluation

Thyroid nodule FNA cytology should be reported using the diagnostic groups outlined in TBSRTC(5). The Bethesda System was developed in 2007 by the National Cancer Institute to address the significant variability in reporting cytological findings(5). The third edition of the Bethesda System for reporting thyroid cytopathology was published in 2023(2). The current research was undertaken prior to 2023 and hence the second edition of the Bethesda System for reporting thyroid cytopathology has been utilised. Histological diagnosis mandates a binary endpoint such as benign or malignant whereas the cytological interpretation categorizes the sample along a spectrum of cancer risk using the Bethesda system(20). The classification includes a standardized, category based reporting system with the estimation of cancer risk within each category(5). This includes 6 diagnostic criteria(5)

Table 1.2: The Bethesda System of reporting thyroid cytopathology

Diagnostic category	Description	Risk of malignancy (%)
I	Non-diagnostic/unsatisfactory	1-4
II	Benign	0-3
III	Atypia or follicular lesion of undetermined significance	10-30
IV	Follicular neoplasm or suspicious for follicular neoplasm	25-40
V	Suspicious malignancy	50-75
VI	Malignant	75-99

The use of this classification system can help facilitate effective communication among the pathologist, clinician, and surgeon(5). The implementation of the Bethesda System has improved the yield rate for malignancy from diagnostic thyroid surgery from 15% to 50% significantly reducing unnecessary operations(20).

1.7 The challenges involving nondiagnostic samples

Although the majority of FNAs are adequate for cytological diagnosis, 5% to 20% will be nondiagnostic(Bethesda Class I)(21). A nondiagnostic sample fails to meet the established qualitative or quantitative criteria required for cytological adequacy(22). The presence of at least six groups of well-visualised follicular cells in each group containing at least ten well preserved epithelial cells deems a sample adequate(1). A low rate of nondiagnostic specimens is inherent to the procedure itself,

however, nodules with greater cystic content often yield higher nondiagnostic samples(23). Alexander et al. confirm that 5% of nondiagnostic specimens were ultimately malignant(23). Thus, the current opinion suggests that nondiagnostic aspirates should be repeated(23). There are several factors that can be considered to try and reduce the frequency of nondiagnostic samples such as the use of US guided FNA, rapid onsite staining and evaluation(ROSE) as well as the use of core needle biopsies.

Palpable thyroid nodules can be aspirated without the use of US guidance. However, palpation guided thyroid FNAs are less accurate for determining the access to the lesion, as it is not possible to distinguish between parts of the lesion that are solid or fluid filled(21). Nonpalpable nodules or complex nodules are preferably aspirated under sonar guidance to help increase the diagnostic accuracy of the sample(24). The AACE guideline recommends the use of US guided FNA for all thyroid nodules >1cm whereas the ATA guideline recommends either palpation or US guided FNA(1). Ultrasound guided FNA offers the advantage of accessing posterior nodules, detecting nonpalpable nodules as well as choosing the thyroid nodule with the most suspicious features on US(25). One of the advances of US guided FNA is the reduction of nondiagnostic samples(21). Carmeci et al. reported a significant reduction in inadequate specimen rate from 16% with the use of palpation guided FNA to 7% with US guided FNA(26). The use of FNA in conjunction with ultrasonography achieved 74.8% sensitivity, 97% specificity and 91.9% accuracy rate in the diagnosis of malignancy(8).

Rapid onsite staining and evaluation(ROSE) is an additional step that can be implemented to reduce the rate of nondiagnostic FNA samples. This is a service offered by cytopathologists that involves checking for specimen adequacy onsite at the time of specimen collection(27). The slides are stained with either a rapid Papanicolaou stain or Romanowsky stain and assessed onsite for specimen adequacy as well as triaging in case ancillary tests are needed(27). Rapid onsite specimen evaluation allows for analysis of specimen adequacy at the time of the procedure so

that if the sample is inadequate the procedure can be repeated in the same setting(27). This aims to decrease the incidence of nondiagnostic samples as a nondiagnostic sample results in a delay in obtaining a diagnosis as well as additional costs involved in repeating the procedure later(27). Ghofrani et al reported that on-site adequacy assessment reduced the rate of inadequate smears for palpation guided samples by 12% to 7% and for ultrasound guided samples from 7% to 5%(24). Studies have demonstrated that ROSE can allow a reduction in complication rates, decrease procedure time and costs and most importantly improve diagnostic yield rates(27). ROSE should be limited to cases where it is technically difficult and should be mandatory in cases where the procedure is being repeated(27). However, ROSE is often underutilized, as the availability of a cytopathologist onsite may not always be feasible.

Thyroid nodule core biopsy offers an alternative to FNA. It is a rapid, inexpensive, and reliable procedure with lower rates of complications(21). The most frequent complication noted for core needle biopsies include haematoma formation as well as bleeding(28). Core needle biopsy complication rates have been reported between 0.2% and 1%(29). Pinnar and Renshaw demonstrate that the adequacy rate with core needle biopsy (82.2%) was significantly higher than FNA (70.3%) but combined adequacy was significantly higher than either test alone (88.9%)(28). The Task Force Committee of Korean Society of thyroid radiology developed the first guidelines on core needle biopsy containing evidence-based recommendations. It suggests the use of core needle biopsies in lesions with undetermined cytology(30).

1.8 Factors affecting thyroid malignancy

Well-differentiated thyroid carcinomas, which include papillary carcinomas and follicular carcinomas, remain the most common histological subtype(1). Other undifferentiated thyroid cancers include anaplastic and medullary subtypes(1). Papillary cancer accounts for 80% of all thyroid cancers in the developed world(31). Follicular thyroid cancers predominate in iodine deficient populations(31). Bombil et al (2019) illustrated that follicular morphology predominates in black residents in

rural regions of the former Transvaal while papillary histology predominated in urban areas, irrespective of race(11). This histological incidence is strongly influenced by the nutritional iodine status of the population(32). The introduction of iodine prophylaxis has changed the incidence of histological cancer types towards the less aggressive papillary form(32).

The incidence of thyroid cancer has been increasing in several high-income countries as well as in urban areas in several low-middle-income countries (LMIC)(3). A study looking at the incidence and mortality of thyroid cancer from 1990 – 2019 suggested that overdiagnosis may be associated with elevated thyroid cancer risk due to progress in diagnostic imaging, thyroid surgery and national screening programs(4). In contrast however, two LMICs; Vietnam and India; also saw increasing rates of incidence and mortality rates for thyroid cancer over the past 30 years(3). More data regarding thyroid cancer in LMIC is required to assess trends in thyroid cancer incidence in these areas adequately.

Papillary thyroid cancer has a good prognosis with a 5 -year survival rate of up to 98%(11). Follicular thyroid cancer, on the other hand, accounts for 15% of thyroid cancers globally(11). It is more aggressive with a less favourable prognosis than papillary thyroid cancer with a 5- year survival rate of 71%(11). Anaplastic thyroid cancer is an invasive and aggressive cancer with a 5 -year survival of 5-14%(17). Patients with disease confined to the thyroid or with local/regional metastasis survive longer than those with distant metastasis(17).

1.9 Conclusion

Thyroid nodules are commonly encountered in clinical practice with factors such as gender and TSH influencing their development. Even though the incidence of malignancy in thyroid lesions is low, this supports the importance of using FNA as an effective screening and triage tool. The diagnosis of nondiagnostic samples poses a significant clinical dilemma in the workup of thyroid nodules as not only does it delay reaching a diagnosis, there are additional costs incurred as well as increased

patient stress. Ultrasound guided FNA should be considered as a first choice modality when feasible, in order to decrease the percentage of nondiagnostic samples as well as increase the diagnostic accuracy of the sample.

Justification of the study

There is a paucity of local data regarding the cytological characteristics of thyroid nodule fine needle aspirations (FNA) in low resource settings. The study evaluated outcomes between dedicated FNA operators and non-dedicated FNA operators. In addition, the use of ultrasound guided versus palpation guided FNA in our setting was analysed. This aided in determining the optimal setting in which to perform thyroid FNAs in a low resource environment, in order to minimize the need for repeated diagnostic procedures or unnecessary surgery.

Aim

To determine the cytological characteristics and outcomes of thyroid FNAs specific to Chris Hani Baragwanath Academic Hospital (CHBAH).

Objectives

Primary Objectives

4.1 To describe the cytological characteristics of thyroid nodules at CHBAH from 1 January 2016 to 31 December 2019.

4.2 To compare the percentage of nondiagnostic thyroid FNAs based on the FNA setting. The percentage of nondiagnostic thyroid FNAs will be compared between the National Health Laboratory Service (NHLS) nursing staff, endocrine clinic and radiology department.

4.3 To compare the accuracy of preoperative thyroid FNAs and the postoperative histopathological thyroid diagnoses.

Secondary Objectives

4.4 To analyse whether palpation guided FNA versus ultrasound guided FNA yields superior results.

Methods

5.1 Study Design

A retrospective descriptive study

5.2 Study Period

1 January 2016 to 31 December 2019

5.3 Study Population

Patients at CHBAH that underwent thyroid nodule FNAs that were analysed by the NHLS between 1 January 2016 to 31 December 2019.

i) Inclusion criteria

All patients who had thyroid nodule FNAs reported by the NHLS at CHBAH

ii) Exclusion criteria

- Patients for whom necessary information cannot be found on the NHLS database
- Thyroid FNAs performed in an alternative setting other than the FNA settings being analysed eg. in another hospital or ward/ clinic not stated above.

5.4 Study Setting

The study was conducted using the cytology unit, NHLS, computerized database for all thyroid FNAs performed at CHBAH between 1 January 2016 and 31 December 2019.

5.5 Measurement Tool

The measurement tool for data collection was data capture sheets (Appendix A)

5.6 Data Collection

Data was obtained from the NHLS database for all thyroid FNAs performed at CHBAH between 1 January 2016 and 31 December 2019. No patient identification was used; rather patients were allocated a specific study number. Data was extrapolated from the NHLS reports.

Data included:

- Patient demographics such as age and sex
- Date of FNA procedure
- Site of FNA: cytopathology clinic, endocrine clinic or radiology department. Within the radiology department, whether the FNA was performed with/without the use of rapid onset specimen evaluation (ROSE) will be specified.
- Method of FNA: ultrasound guided FNA versus palpation guided FNA
- TSH and T4 level
- Bethesda classification

Data was captured on an Excel spreadsheet and then analysed.

For patients who underwent thyroid surgery, the postoperative histopathological diagnosis, where available, was compared to the preoperative thyroid FNA.

5.7 Study Definitions

Nondiagnostic sample (Bethesda Class I)– inadequate samples. These include specimens with obscuring blood, poor cell preservations and an insufficient sample of follicular cells(2).

Adequate FNA sample – the presence of at least six groups of well visualized follicular cells each group containing at least ten well preserved epithelial cells(2).

FNA site – site at which the FNA procedure took place.

- Cytopathology clinic – FNAs in this setting are performed by two dedicated cytology nursing personnel trained in the FNA technique. The FNAs are performed under palpation guidance.
- Endocrine clinic – FNAs are performed under ultrasound guidance by a single trained endocrinologist.
- Radiology department – FNAs are performed using ultrasound guidance by rotating radiology registrars and consultants.

Rapid onset staining evaluation (ROSE) – a service performed by the cytotechnologist and anatomical pathology registrars (in addition to qualified pathologists)in order to check the cellular content and adequacy of the FNA smear. The slide is stained with a rapid Papanicolau stain or Romanowsky stain on-site to assess sample adequacy.

5.8 Data Analysis

Each study participant was assigned a unique study number and anonymised data. It was entered into an Excel spreadsheet. The data was analysed using standard statistical methods. Data was presented as a mean and standard deviation if normally distributed, or median and interquartile range if skewed. For continuous variables a T-test was used if normally distributed and a Mann-U-Whitney test if skewed. For categorical data, a Chi-square test was used. Statistical significance was measured using a 95% confidence interval with $p<0.05$. Results across the 3 clinical settings was compared by ANOVA followed by a Tukey post hoc test if the ANOVA is significant.

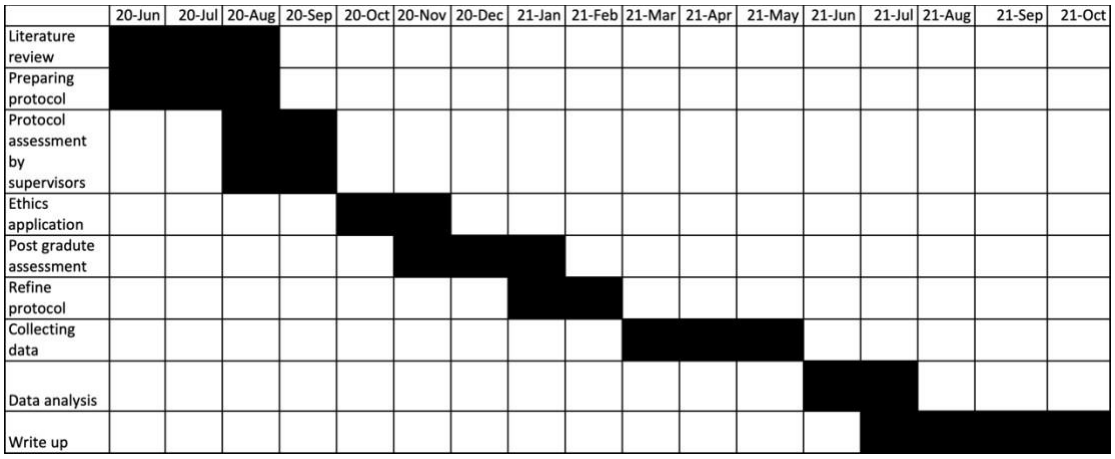
5.9 Limitation and bias of the study

- Retrospective, cross-sectional study.
- All information required may not be documented adequately on the NHLS report
- The ability to compare study participants between different FNA sites may be limited by smaller numbers between the sub-groups.
- A small number of patients with a postoperative histopathological diagnosis to allow for adequate comparative analysis.

Ethics

- Consent was obtained from the National Health Laboratory Service in order to access their database (reference number PR2010499).
- Data was anonymised.
- The study proposal was submitted to the Postgraduate Committee of the University of Witwatersrand and the Humans Research Ethics committee of the University of the Witwatersrand in order to get approval for the study National Health Laboratory Service reports.

Timeline



Funding

This study was self- funded. No extra cost was imposed on the hospital or the patient.

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CHAPTER 2: SUBMISSIBLE ARTICLE

Cytological Findings of Thyroid Fine Needle Aspirations at Chris Hani Baragwanath Academic Hospital from January 2016 to December 2019

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Abstract

Introduction

Thyroid nodules are commonly encountered in clinical practice with thyroid cancer being the most frequent endocrine malignancy seen. There is limited data regarding the outcomes of thyroid nodules in a low resource environment. A reliable preoperative diagnosis will facilitate prompt treatment of malignancy as well as limit the need for unnecessary interventions.

Objective

To describe the cytological characteristics of thyroid nodules at Chris Hani Baragwanath
Academic Hospital (CHBAH), Johannesburg, South Africa, and to compare the outcomes of thyroid fine-needle aspiration (FNA) based on the FNA setting as well as the method of FNA. In addition to compare the accuracy of preoperative thyroid FNAs and the postoperative histopathological thyroid diagnoses.

Method

A retrospective descriptive study of thyroid nodule FNA results at CHBAH over the period 2016 – 2019. Frequencies and percentages were used to summarize the data.

Results

This study reviewed 600 cytology specimens. The median age of the study population was 52 years (IQR 42 – 62 years) with 516 females and 78 males. There was a higher incidence of female patients, 516 (86%) with thyroid nodules. A higher incidence of malignant nodules was seen in male patients. No correlation was found between (TSH) levels and malignancy. Thyroid nodule FNAs were performed at 3 different sites with 112 samples (18.7%) being nondiagnostic. Specimens performed at the cytopathology clinic by palpation guidance yielded the most nondiagnostic samples (25.1%), compared to 8.1% at the endocrine clinic and 16.1% at the radiology clinic. One hundred and five samples had corresponding histology specimens of which 43

samples (40.9%) were proven to be malignant. There was a statistically significant correlation between the cytological and histopathology samples ($p < 0.05$).

Conclusion

The prevalence of malignancy and gender distribution in our study that was undertaken in a middle income country are largely consistent with those of international studies. It demonstrates that thyroid nodule FNA is an effective tool in the diagnostic algorithm for thyroid nodules; however, nondiagnostic samples pose a diagnostic challenge. Our study demonstrated that ultrasound guided FNA samples are superior to palpation guided FNA samples as they yielded fewer nondiagnostic samples. A subset analysis demonstrated the advantage of a dedicated trained FNA operator over multiple operators. This is a feasible option in a low-resource environment where the availability of a US- machine or specialist may not be available.

Introduction

Thyroid nodules are discrete lesions within the thyroid gland that are radiologically distinct from surrounding thyroid parenchyma(1). They are commonly encountered in clinical practice with at least 4 - 7% of adults having palpable thyroid nodules and 19 - 67% having thyroid nodules visible on ultrasonography (US)(2). The risk of a nodule harbouring malignancy is 4 - 8%(3).

The use of thyroid fine-needle aspiration (FNA) is effective in stratifying patients based on the cytopathology results(4). Thyroid FNA has a high sensitivity and specificity ranging from 94 - 98.5%(5). Its utility has increased in recent years with the availability of ultrasound guided techniques that help improve detection rates as well as the diagnostic accuracy of the sample(6). Thyroid nodule FNA cytology is reported using the diagnostic groups outlined in The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)(7). The classification system aims to standardize reporting terminology and achieve greater understanding between pathologists, clinicians, and surgeons(8).

At Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg, South Africa, thyroid FNAs are performed in three different clinical settings viz. the cytopathology, radiology, and endocrine clinics. At the cytopathology clinic, thyroid FNAs are performed via palpation guidance by trained nursing personnel. This is unique to this low-resource environment in which the availability of specialists and ultrasound imaging are often scarce. At the radiology clinic FNAs are performed via ultrasound guidance by radiology registrars on a rotational basis and at the endocrine clinic under ultrasound guidance by endocrinologists trained in thyroid ultrasound.

There is paucity of local data regarding the cytological characteristics of thyroid FNAs. The aim of this study is, therefore, to determine the cytological characteristics of thyroid FNA specific to CHBAH. It aims to assist in determining the optimal

setting in which to perform thyroid FNAs in a low resource environment to minimize the need for repeated diagnostic procedures or unnecessary surgery.

Study Methods

This retrospective descriptive study reviewed the records of patients seen between 1 January 2016 to 31 December 2019 at CHBAH, a tertiary hospital in the Gauteng province of South Africa. The data was collected using the National Health Laboratory Service (NHLS) computerized database for all thyroid FNAs performed during the study period. The NHLS is the public sector laboratory in South Africa. If available, the corresponding histology results were obtained and compared with the original cytology results.

Adult patients who had thyroid nodule FNAs reported by the NHLS at CHBAH were included in our study. Patients were excluded from the study if the cytology specimens were inconsistent with thyroid tissue or if the thyroid FNAs were performed in an alternative setting other than the FNA settings being analysed. FNAs in our setting were performed palpation guided by cytology nursing personnel trained in the FNA technique at the cytopathology clinic as well as under ultrasound guidance by endocrinologists and radiologists. The FNAs were reported using the Bethesda System for reporting thyroid cytopathology(8).

The Bethesda System for reporting thyroid cytopathology include 6 diagnostic categories (5):

I – Non-diagnostic/unsatisfactory (Risk of malignancy 1-4%)

II – Benign (Risk of malignancy 0-3%)

III – Atypia or follicular lesion of undetermined significance (Risk of malignancy 10-30%)

IV – Follicular neoplasm or suspicious for follicular neoplasm (Risk of malignancy 25-40%)

V- Suspicious for malignancy (Risk of malignancy 50-75%)

VI – Malignant (Risk of malignancy 75-99%)

Statistical Analysis

The data were analysed using standard statistical methods. Data was presented as a mean and standard deviation if normally distributed, or median and interquartile range if skewed. Data were analysed as follows: Student's t-test (for continuous variables if normally distributed), Mann-U-Whitney test (for continuous variables with a skewed distribution), and a chi-squared test (for categorical data). Statistical significance was measured using a 95% confidence interval with $p<0.05$. Results across the 3 clinical settings were compared by ANOVA followed by a Tukey *post hoc* test if significant.

Study Definitions

Nondiagnostic sample (Bethesda Class I)– inadequate samples. These include specimens with obscuring blood, poor cell preservations and an insufficient sample of follicular cells(9)

Adequate FNA sample – the presence of at least six groups of well visualized follicular cells each group containing at least ten well preserved epithelial cells(9).

FNA site – site at which the FNA procedure took place.

- Cytopathology clinic – FNAs in this setting are performed by two dedicated nursing personnel trained in the FNA technique. The FNAs are performed under palpation guidance
- Endocrine clinic – FNAs are performed under ultrasound guidance by a single trained endocrinologist
- Radiology department – FNAs are performed using ultrasound guidance by rotating radiology registrars and consultants

Rapid onset staining evaluation (ROSE) – a service performed by the cytotechnologist and anatomical pathology registrars (in addition to qualified pathologists) in order to check the cellular content and adequacy of the FNA smear. The slide is stained with a rapid Papanicolau stain or Romanowsky stain on-site to assess sample adequacy.

Results

Descriptive data

A total of 600 samples were included in the analysis as illustrated in table 2.1. The median (IQR) age of the study population was 52 (42-62) years with no statistical difference noted between males and females. More than half of the samples obtained, 315 (52.5%), were performed at the cytopathology clinic whilst the remaining 161 (26.8%) and 124 (20.7%) were performed at the endocrine and radiology clinic respectively. A minority of samples, 54 (9.0%), included ROSE. The median TSH level of our population was 1.2mmol/l. There was no correlation between the TSH value and malignancy with 351 (58.5%) samples being <4mmol/l, 16 (2.7%) between 4 – 10mmol/l, and 8 (1.3%) >10mmol/l.

Table 2.1 Characteristics of study population (N=600)

Variable	Female (N=516) N(%)	Male (N=78) N(%)	All (N=600)* N(%)
Age in years (IQR)	52 (42- 62)	52 (40- 65)	52 (42- 62)
Site of FNA			
Cytopathology Clinic	277 (53.7)	37 (47.7)	315 (52.5)
Endocrine Clinic	135 (26.2)	22 (28.2)	161 (26.8)
Radiology Clinic	104 (20.2)	19 (24.4)	124 (20.7)
Method of FNA			
Palpation guided	278 (53.9)	37 (47.4)	316 (52.7)
US guided	237 (45.9)	41 (52.6)	283 (47.2)
Missing	1 (0.2)	0 (0)	1 (0.2)
ROSE done			
No	467 (90.5)	74 (94.9)	546 (91.0)
Yes	49 (9.5)	4 (5.1)	54 (9.0)
TSH level (µIU/L)			
(IQR)	1.1 (0.7- 2.0)	1.3 (0.9- 2.6)	1.2 (0.7- 2.0)
FT4 level(pmol/L)			
(IQR)	14.5 (12.3- 16.8)	15.2 (12.9- 17.3)	14.5 (12.3- 16.8)
Year			
2016	137 (26.6)	14 (18.0)	153 (25.5)
2017	126 (24.4)	23 (29.5)	150 (25.0)
2018	114 (22.1)	23 (29.5)	137 (22.8)
2019	139 (26.9)	17 (21.8)	159 (26.5)
Missing	0 (0)	1 (1.3)	1 (0.2)

*sex missing for six individuals

FNA (Fine needle aspirate), IQR (Interquartile range),ROSE (Rapid onsite staining and evaluation), TSH (Thyroid stimulating hormone), T4 (Thyroxine), US (ultrasound).

Classification of thyroid nodules

The cytological classification of thyroid nodules in terms of TBSRTC is illustrated in figure 2.1. From 600 thyroid samples analyzed, 112 samples (18.7%) were classified as nondiagnostic samples.

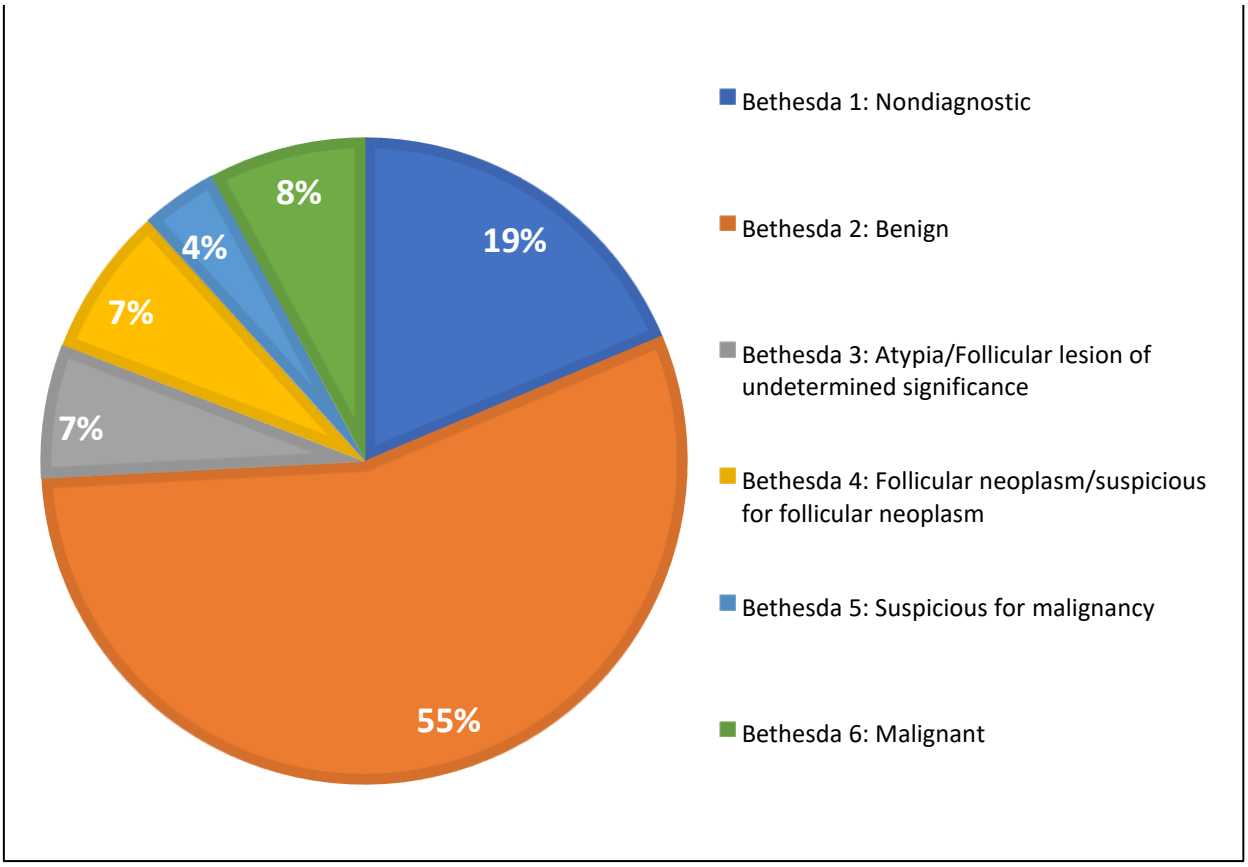

Figure 2.1 Distribution of thyroid nodules according to the Bethesda classification

Gender differences

Females had a higher prevalence of benign nodules (297 out of 516), thus a prevalence of 57.56%; while the prevalence was 41.03% in males (32 out of 78). Taking the gender distribution into account, 90% of the total benign nodules occurred in females, and 10% in males. Among female patients, the prevalence of atypia/FLUS was 32/516 = 6.20% versus 8/78 =10.26% in males. Of the total population, 80% of atypia/FLUS occurred in females, and 20% in males. The prevalence of follicular neoplasms was 39/516 = 7.56% in females, versus 6/78 = 7.69% in males. Of the total population, 87% of the follicular neoplasm occurred in females, and 13% in males.

Although malignancy on histopathological diagnosis was more common in males than females, 7/13(53.8%) among males vs 35/88 (39.8%) among females, this difference was not statistically significant (p=0.307)

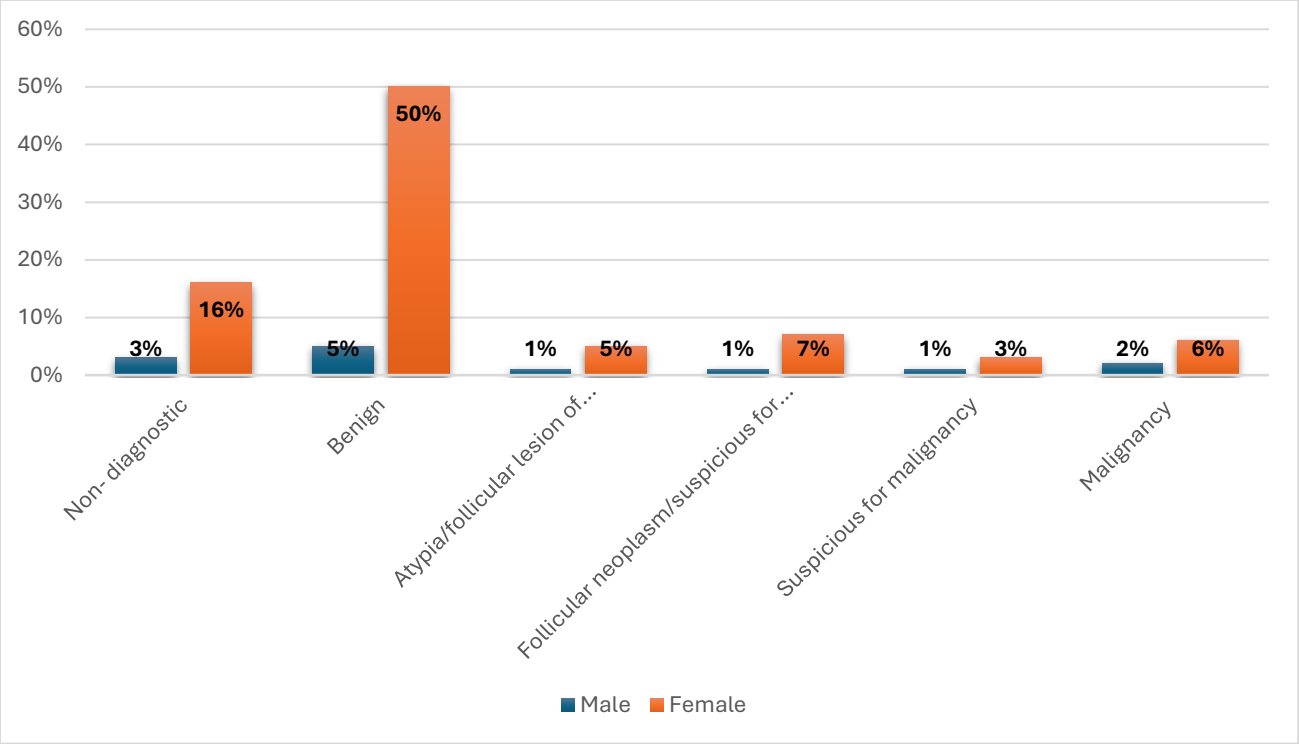

Figure 2.2 Cytological characteristics of thyroid nodules

Method of FNA

From 600 cytological samples, 316 (52.7%) FNAs were performed palpation guidance and 284 (47.2%) FNAs were performed using an US guided technique. Palpation guided FNAs yielded more nondiagnostic samples, 79 (25%), in comparison to US guided FNAs, 33 (11.6%) (p <0.001). In addition, US guided FNA samples detected a higher percentage of nodules suspicious for malignancy compared to the palpation guided FNAs (5.6% vs 2.2%) (p<0.001). Specimens performed at the radiology department with the aid of ROSE demonstrated a reduction in the number of nondiagnostic samples, however this reduction was not statistically significant (p=0.173).

Table 2.2 Cytological characteristics of thyroid nodules by method of FNA

	Palpation guided	**US guided**	**US guided**	
Cytological characteristics	**Cytopathology clinic (N=315) N(%)**	**Endocrine clinic (N=151) N(%)**	**Radiology clinic (N=124) N(%)**	**All (N=600) N(%)**
Non- diagnostic	79 (25.1)	13 (8.1)	20 (16.1)	112 (18.7)
Benign	163 (51.8)	95 (59.0)	75 (60.5)	333 (55.5)
Atypia of undetermined significance / follicular lesion of undetermined significance	22 (7.0)	13 (8.1)	5 (4.0)	40 (6.7)
Follicular neoplasm or suspicious for follicular neoplasm	21 (6.7)	19 (11.8)	5 (4.0)	45 (7.5)
Suspicious for malignancy	7 (2.2)	5 (3.1)	11 (8.9)	23 (3.8)
Malignancy	23 (7.3)	16 (9.9)	8 (6.5)	47 (7.8)

Site of FNA

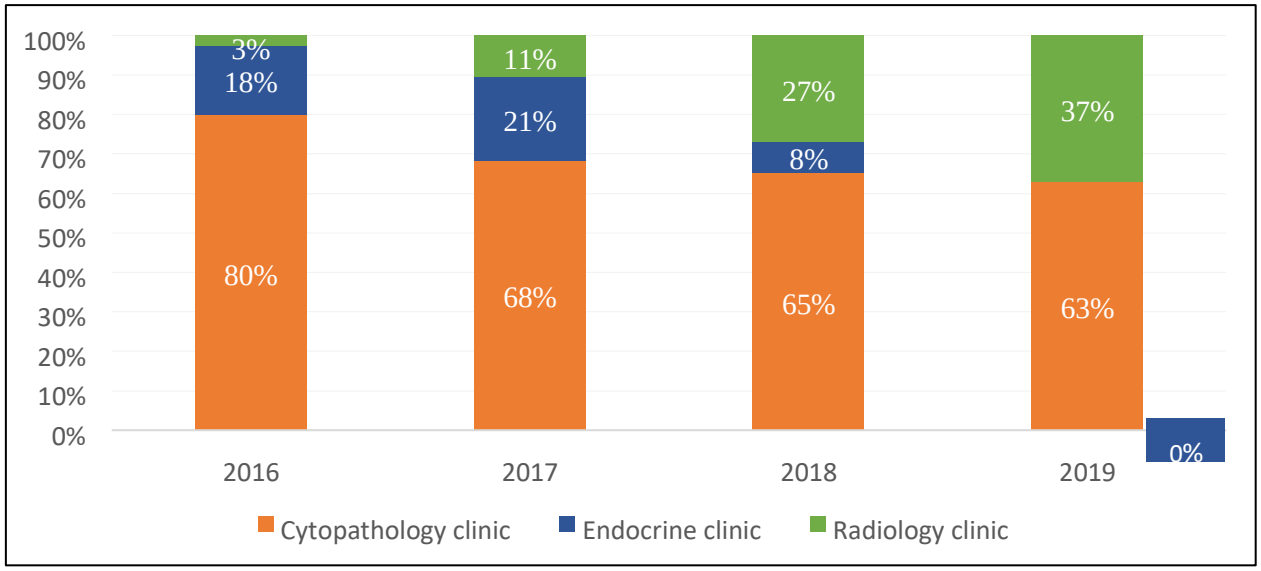

Figure 2.3 The distribution of nondiagnostic samples by site and year at CHBAH

*Radiology clinic p=0.044

Thyroid nodule FNAs were performed at three different sites, with 315 (52.5%) performed at the cytopathology clinic, 151 (25.1%) performed at the endocrine clinic, and 124 (20.6%) performed at the radiology clinic. As demonstrated in figure 2.3, nondiagnostic FNA samples, showed a numerical decline at the cytopathology clinic from 2016 - 2017; after that, no significant reduction was noted between 2017 - 2019 (p=0.221). The endocrine clinic reported a decline in nondiagnostic samples yearly from 2016 - to 2018 (p=0.464). Conversely, the radiology clinic demonstrated a statistically significant increase in the number of nondiagnostic samples from 2016 - to 2019 (p=0.044). Overall, there was a significant decline in nondiagnostic samples from 2016 to 2019 (p=0.023).

Correlation between cytology and histology results

Table 2.3 The correlation between cytology results in terms of the Bethesda System of reporting cytopathology and the histology result

Histology / Cytology	Benign	Follicular/ Hurthle thyroid carcinoma	Papillary thyroid carcinoma	Medullary thyroid carcinoma	Spindle cell carcinoma	Total
Non- diagnostic	14	1	2			17
Benign	34	1	6		1	42
Atypia/follicular lesion of undetermined significance	8		4			12
Follicular neoplasm/suspicious for follicular neoplasm	5	6	2			13
Suspicious for malignancy	1		4			5
Malignancy			13	3		16
TOTAL	62	8	31	3	1	105

Table 2.3 illustrates the correlation between cytology and histology results. There was a statistically significant correlation between the cytological and histological samples with a p-value <0.05. From 105 histological samples, 43 samples (40.9%) had proven malignancy. At the cytopathology clinic 25% (2/8) of the samples performed were malignant and 50% (1/2) of samples performed at the endocrine clinic were malignant. One sample done at the radiology clinic was benign. In addition, missing data regarding the site of FNA and the method of FNA for 1 sample was malignant. For patients who had AUS/FLUS who were referred for surgery, 66.7% (8/12) were benign. Of note, 19% (8/42) nodules reported as benign were found to be malignant on histology. From the nondiagnostic FNA samples, 17,6% (3/17) were malignant.

Discussion

This retrospective study conducted at CHBAH analysed thyroid cytology reports on 600 samples evaluating cytology results conducted in three different operator settings. There was a predominance of thyroid nodules in female patients. The difference in FNA technique significantly affected the FNA result, with US guided FNA proving superior to palpation guided FNA as it yielded significantly fewer nondiagnostic results. Our study therefore demonstrated that US is an important diagnostic tool in the evaluation of thyroid nodules.

This study demonstrated a higher prevalence of females with thyroid nodules and a higher prevalence of malignant nodules observed in males; this is in keeping with global reviews(3). However, a detection bias may account for a higher thyroid nodule incidence in women as they reportedly have greater health-seeking behaviour. In addition, the cosmetic effects of thyroid enlargement may influence women to seek help earlier than men(10).

Thyroid stimulating hormone level is a well-established growth factor for thyroid nodules, with higher preoperative serum TSH concentrations associated with an increased risk of differentiated thyroid cancer(11). However, our review found no correlation between TSH levels and malignancy. Sixty percent of samples performed at the cytopathology clinic had missing TSH levels illustrating that patients referred to the cytopathology clinic are not always adequately worked up or monitored before FNA.

Papillary thyroid carcinoma was the commonest histological subtype in this cohort compromised, 29.5% of histological samples. This is consistent with reports in the literature(12). The increase in papillary thyroid cancer incidence yearly from 20.8% in 2016 to 35.5% in 2019, mirrors that seen in developed countries(12). In addition, the increased incidence of malignancy from 2016 to 2019 may be attributed to more frequent diagnostic imaging leading to the incidental discovery of malignancy at an

earlier stage and increased discernment with regards to more high-risk nodules being aspirated.

As demonstrated in our study, the cytopathology clinic in which FNAs are performed via palpation guidance by dedicated FNA trained nursing staff resulted in the most nondiagnostic samples(25%). On the other hand, ultrasound guided samples yielded fewer nondiagnostic samples and detected a higher percentage of malignant nodules. This reflects the ability of ultrasound imaging to detect the most suspicious nodule and direct the needle to the solid portion of mixed cystic nodules(13). These results are in keeping with international literature(14). Whilst the cost of performing FNA samples with ultrasound guidance may initially be higher, the decreased number of nondiagnostic samples will limit the need for repeat FNA samples(15), thus being cost-effective in the long run. The use of ultrasound guidance and ROSE further reduced the number of nondiagnostic samples obtained. The use of ROSE can be used to prevent inadequate samples and thus prevent repeated procedures and a delay in diagnosis(16). However, in our resource-constrained setting, the availability of a cytopathologist for onsite evaluation is not feasible for every radiologically guided FNA.

The cytopathology clinic saw a decline in the number of nondiagnostic samples from 2016 – to 2017 reflecting improvement in the FNA technique through continuous practice. Whilst both the endocrine clinic and radiology department perform US guided FNA samples, it was interesting to note the trend of nondiagnostic samples yearly. The endocrine department reported a decrease in nondiagnostic samples annually, whilst the radiology department noted an increase. This may be attributed to a single-user versus multi-user variability. The endocrine department has a single dedicated, thyroid FNA trained operator, whereas in the radiology department, thyroid FNAs are performed by registrars rotating through the department for only a short time. These individuals may not have been adequately trained or may not have had the time to develop expertise in the procedure.

There was a high agreement between the cytopathology results and the histology results. This is in keeping with Nicolaou et al., 2019 study that found 98.8% sample agreement. In addition, a retrospective observational study performed at Helen Joseph Hospital between 2016 – 2019 demonstrated good correlation between cytology and histology for thyroid nodules, $p<0.001$(17) . A study conducted in Congo between 2005- 2019 demonstrated that in a low-income country, a well performed thyroid US using the EU-TIRADS score is an important tool in the selection of thyroid nodules suspected of malignancy with a sensitivity of 96.6% and specificity of 59.3%(18).

Despite this significant correlation, 19% of cytologically benign nodules were malignant. It is noteworthy that these patients were referred for surgical resection, thus implying that the evaluation of a patient with a thyroid nodule should not be completed in isolation. Clinical, radiological, and cytological parameters should guide the final assessments.

Limitations

The main limitation of this study was its retrospective cross-sectional design. Smaller numbers between the subgroups may have limited the ability to compare study participants between different FNA sites. The study was undertaken at one site, an urban hospital. Inclusion of samples from other health facilities would improve study generalisability.

Conclusion

The findings of this study are in keeping with the literature and emphasize that the quality of FNA samples is operator-dependent. It highlights the optimal evaluation of a thyroid nodule would include a US guided FNA sample by a dedicated operator. However, in a resource constrained environment where the availability of a US is not freely available, the importance of a trained, dedicated FNA operator should not be

overlooked. In addition, there was a good correlation between the cytopathology results and the histology results.

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CHAPTER 3 CONCLUSION

Our study illustrated the prevalence of thyroid nodule incidence and malignancy at CHBAH between 2016 - 2019. It illustrated the female predominance of thyroid nodules as well as benign thyroid nodules. It highlighted that whilst men are less likely to develop thyroid nodules, once detected they have a higher likelihood of the nodule being malignant.

It demonstrated that thyroid FNA is an effective tool in the diagnostic algorithm for thyroid nodules as depicted by a significant correlation between cytology and histology results. However, nondiagnostic samples pose a diagnostic challenge for clinicians. Ultrasound guided FNA samples are superior to palpation guided FNA samples, yielding fewer nondiagnostic samples as well as detecting more nodules suspicious of malignancy. In a low-resource setting the additional cost of the former method is offset by savings to, both the hospital and the patient, related to avoiding a second procedure. Further analysis demonstrated the advantage of a dedicated trained FNA operator over multiple operators as illustrated by a decline in nondiagnostic samples at the cytopathology and endocrine clinic. This demonstrates that in resource constrained environment, importance should be placed on training a dedicated thyroid FNA operator. The study also highlights the role a trained clinician operator may play in areas where radiologists are not available.

APPENDICES

Appendix A Supplementary Data

Classification of histology samples

Histology	Number of specimens
Hyperplasia	4
Follicular adenoma	6
Benign colloid nodule	2
Hurthle cell adenoma	2
Multinodular goitre	46
Hurthle cell carcinoma	4
Papillary thyroid carcinoma	30
Thyroglossal duct cyst	2
Follicular thyroid cancer	5
Spindle cell carcinoma	1
Medullary thyroid carcinoma	3

Appendix B Data Collection Sheet

Data Collection Sheet

Study Number

1 Demographics

1.1 Age

1.2 Sex

i) Male ii) Female

Date of FNA 2

Procedure

3 Site of FNA

3.1 Cytopathoogy clinic

3.2 Endocrine Clinic

3.3 Radiology department

i) With ROSE ii) Without ROSE

4 TSH Level

5 T4 Level

6 Bethesda Classification

6.1	Non- diagnostic	
6.2	Benign	
6.3	Atypia of undetermined significance	
6.4	Follicular neoplasm/suspicious for follicular neoplasm	
6.5	Suspicious for malignancy	
6.6	Malignant	

7 Method of FNA

7.1	Palpation-guided FNA	
7.2	Ultrasound-guided FNA	

8. Histopathological diagnosis

Appendix C Ethic Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr S Nanabhay

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M2011119

NAME: (Principal Investigator)	Dr S Nanabhay
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Medical School University
PROJECT TITLE:	*Cytological findings of thyroid fine needle aspirations undertaken at Chris Hani Baragwanath Academic Hospital from January 2016 to December 2019*
DATE CONSIDERED:	2020/11/27
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs NA Mohamed, N Goolam-Mahyoodeen & L Fatman
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/02/19

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **«Missing mail merge field»** and therefore reports and re-certification will be due in the month of **«Missing mail merge field»** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

Date