DIAGNOSTIC YIELD OF ULTRASOUND GUIDED FINE NEEDLE ASPIRATIONS OF THYROID NODULES AT CHARLOTTE MAXEKE JOHANNESBURG AND CHRIS HANI BARAGWANATH ACADEMIC HOSPITALS

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Diagnostic Radiology.

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Declaration

I, Elton Ncube, declare that this research report is my own work. It is being submitted for the degree of MMed (Diagnostic Radiology), Faculty of Health Sciences at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

DR E. NCUBE

On this 12th day of August 2019.

I dedicate this to my family, especially my sister, Nqobile Ncube.

Thank you for the encouragement, love and support you have shown me throughout the course of the research.

Publications and presentations

To date, this work has never been published or presented at a congress. However a publication on this work is in draft.

Abstract

INTRODUCTION:

Fine needle aspiration of thyroid nodules is a frequently requested and performed procedure in the Department of Radiology at Charlotte Maxeke Johannesburg Academic and Chris Hani Baragwanath Academic Hospitals. The procedure has to be performed and reported according to acceptable guidelines and the diagnostic yield periodically assessed.

AIM:

To evaluate the diagnostic yield of FNA of thyroid nodules performed at Charlotte Maxeke Johannesburg and Chris Hani Baragwanath Academic Hospitals and to assess for possible pre-analytic variables that affect the quality of cytological specimens obtained.

METHOD:

A retrospective analysis of ultrasound and FNA of thyroid nodule reports and cytology reports was done. The reports were accessed from the Picture Archiving and Communications System and LabTrack (National Health and Laboratory Service) systems respectively. The reports were assessed for completeness and content, results were entered onto a spread sheet. The diagnostic yield was calculated and correlated with factors known to affect it.

RESULTS:

A total of 181 nodules were assessed giving a diagnostic yield of 71.8%. The presence of a cytologist was associated with a higher diagnostic yield with a Fischer's exact p-value of 0.04. Additionally, mixed nodule consistency was associated with a lower non-diagnostic rate.

CONCLUSIONS:

A significant proportion of the FNAs performed were non-diagnostic with just above a quarter of the samples obtained being evaluated as inadequate. Most of the non-diagnostic samples were reported as containing inadequate cells and/or bloody. There were no pre-analytic extrinsic/technical variables identified as a possible cause.

Acknowledgements

I would like to acknowledge the following people - without their support, encouragement and guidance, this study would have never been possible:

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Table of Contents

List of Figures

List of Tables

List of Abbreviations and Terminology

AUS/FLUS	Atypia of Undetermined significance or Follicular lesion of undetermined significance.
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CI	Confidence Interval
FNA	Fine Needle Aspiration
FNAC	Fine Needle Aspiration Cytology
NFITP	Noninvasive follicular thyroid neoplasm with papillary-like nuclear features.
NHLS	National Health and Laboratory Service
Mhz	Megahertz
PACS	Picture Archiving and Communication System
RIS	Radiology Information System
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
TBSRTC	The 2017 Bethesda system for reporting thyroid cytopathology.
USS	Ultrasound

1. Introduction

1.1 Rationale for this study

Thyroid nodules are commonly found incidentally, be it clinically or on ultrasound. However only a small percentage results in thyroid malignancy. To avoid a significant number of unnecessary biopsies and surgeries, an affordable, minimally invasive procedure such as ultrasound guided fine needle aspiration (FNA) is essential to screen for patients with nodules for malignant or suspicious features on ultrasound imaging (1).

The Department of Radiology at the University of Witwatersrand performs approximately 150-200 FNA of thyroid nodules annually across three tertiary hospitals. There is a paucity of documented audits of FNA of thyroid nodules in the South African literature.

The purpose of the study was to assess the diagnostic yield of ultrasound guided FNA of thyroid nodules at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH); and to determine the correlation between diagnostic yield and intrinsic nodule characteristics, including colour Doppler, as well as, difficulty of the procedure as characterised by the number of needle aspiration passes.

The influence of the presence of rapid on-site evaluation by a cytologist and the level of radiology expertise was also assessed.

1.2 Literature review

1.2.1 Thyroid cancer and its incidence

Thyroid cancer arises as a result of thyroid follicular cell mutation (1). With a global incidence of 14.3 per 100,000 cases of women and men combined, it is the most common endocrine cancer. Thyroid cancer incidence has doubled over the last few decades in developed countries, including the United Kingdom, Australia and the United States of America as reported by La Vecchia et al. These countries however did not record corresponding increased mortality from thyroid cancer (2).

A similar trend has been observed in South Africa, according to the national cancer registry (2014), there were 109 new male and 420 new female thyroid cancers recorded in South Africa**.** Thyroid cancer is the 15th most common cancer in women and comes at a low 34 in males.

Thyroid cancer is classified into different histological subtypes ranging from well differentiated to anaplastic tumours. These are constantly reviewed and updated with discovery of new and advanced histological and molecular techniques (3). The differentiated thyroid cancers are classified into medullary thyroid cancer, papillary thyroid cancer, follicular thyroid cancer and anaplastic thyroid cancer (3). Anaplastic thyroid cancer, although relatively rare, is one of the most aggressive cancers with one and 2 year overall survival rates of 48.0% and 26% respectively (4).

Depending on sex, tumour histology and the presence or absence of gross extra thyroid extension, patients are divided into low, intermediate and high risk categories (1). This classification helps to predict prognosis. However compared to other solid cancers, thyroid cancer generally has a better prognosis (1).
A study in three different Thailand regions comparing thyroid cancer prevalence demonstrated that follicular cancer incidence decreases while papillary thyroid cancer increases with decreased population level iodine deficiency levels (5).

1.2.2 Imaging of thyroid gland nodules

A diagnosis of thyroid cancer is usually made after fine needle aspiration of incidentally discovered intra thyroid nodules. Due to the low cancer rates in thyroid nodules, an affordable, minimally invasive screening procedure such as ultrasound guided FNA is important to help identify nodules harbouring malignant or suspicious components (6). Dependent on various factors such as age, sex, a history of neck radiation and family history of thyroid cancer, 7 to 15% of thyroid nodules are known to harbour malignant components (7). FNA will thus assist in avoiding and/or reducing the number of unnecessary surgeries or core biopsies (8).

Thyroid nodules are routinely imaged in the department of radiology at Charlotte Maxeke Johannesburg and Chris Hani Baragwanath Academic Hospitals with most of the

referrals from endocrinologists and neck surgeons. Most of the nodules are discovered incidentally in patients imaged for unrelated clinical indications. Ultrasound evaluation of thyroid nodules is performed using high frequency probes (7.5-10 Mhz). This is recommended for all patients with known or suspected thyroid nodules (7). Ultrasound evaluation should include the assessment of nodule size in three dimensions, thyroid parenchyma (homogeneous/heterogeneous), location (thyroid lobe/ lower or upper part/ anterior or posterior), the margins (regular or irregular), calcifications (the presence or absence thereof and types) and whether taller than wide (7).

A structured reporting tool for reporting of thyroid nodules (see Appendix E) is already present in the department**.** This was used as a guide as to which nodules would undergo FNA**.** Nodules were evaluated for the above-named variables and a decision made, as part of the conclusion whether FNA is recommended or not.

Table 1.1 Factors to consider in ACR TI-RADS thyroid nodule risk stratification

Composition	**Echogenicity**	**Shape**	**Margin**
Cystic or almost completely cystic (0 points)	Anechoic (0 points)	Wider than tall(0 points)	Smooth(0 points)
Spongiform(0 points)	Hyperechoic or isoechoic(1 point)	Taller than wide(3 points)	Ill-defined(0 points)
Mixed cystic and solid(1 point)	Hypoechoic (2points)		Lobulated or irregular(2 points)
Solid or almost completely solid(2 points)			Extra- thyroidal extension (3 points)

This was largely based on the American College of Radiology (ACR) Thyroid Imaging, Reporting and Data System (TI-RADS). According to the ACR TI-RADS lexicon thyroid nodules are classified into five categories based on a number of variables. The variables individually considered and the scores allocated are as shown in the Table 1.1 above**.** The scores are added to give an overall classification of TR1- for a total score of 0, TR2- for 2 points, TR3 –for 3 points, TR4- for 4 to 6 points and TR5 for 7 or more points (9).

1.2.3 The role of FNA in thyroid cancer detection

FNA of thyroid nodules is recommended by most guidelines to exclude nodules with malignant components and plays a vital role in assessment of thyroid nodules due to its accuracy and safety (10).

Agrawal et al demonstrated an FNA accuracy rate of 90.0 % and a specificity of 95.5%. In 69% of patients, FNAC could predict a correct thyroid cancer type (11). Other advantages of FNA are that it is a relatively cheap, technically simply and time efficient when compared to surgical exploration. The average waiting for ultrasound guided FNA at CMJAH and CHBAH is approximately a week to 2 weeks.

1.2.4 Reporting of FNA procedure

It has been proven that completeness of radiology reports and the level of details required are improved by standardized and structured reporting**.** A survey carried out by Swartz et al showed that radiologists achieved greater clarity coupled with better outcomes with structured reporting compared to conventional reports (12)**.** It was also demonstrated in another study that structured reporting allows for standardisation and better transmission of information when compared to free text. Structured reporting also enhances research by making it easier to search and compare information (13).

The adequacy of reporting FNA reports in our institution has never been evaluated and there are no clear guidelines for reporting on the FNA of thyroid in the South African Context.

1.2.5 Reporting of FNA cytology results

Sample inadequacy of FNA described as category 1 by the Bethesda classification remains a major concern as some of these nodules are known to harbour malignancy (14). Different reasons for unsatisfactory samples include specimen with poor cell preservation, obscuring blood and insufficient sample of follicular cells. For adequate cytological evaluation, at least six groups of benign follicular cells are required, with no

less than 10 cells in each group (14). This number of cells is however not necessary in the presence of atypia or inflammation.

Furthermore, samples containing abundant colloid are deemed to be adequate and benign. See Table 1.1 for a complete Bethesda classification (14). The 2017 Bethesda System for Reporting Thyroid cytopathology (TBSRTC) classification system however should be used with caution as some of the categories have different names which can cause confusion between cytologists and surgeons. Having standardised reporting for clear communication and with each category linked to a known cancer risk and management recommendations is advantageous. The reclassification of some thyroid cancers as noninvasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP) has implications for the risk of malignancy (14).

The consequences of an inadequate or non-diagnostic FNA include: the need for a repeat procedure which may contribute to an undiagnostic repeat FNA result, a possible unnecessary surgery, patient inconvenience and wastage of resources (14). The latter is even more relevant in the South African context of an over-burdened public health care system.

Fine needle aspiration of thyroid nodules is one of the most commonly performed procedures in the department of radiology (interventional suite) at CMJAH and CHBAH. Quality assurance is critical as a means of ensuring a high diagnostic yield and there has been no audit in our setting.

A study in Cape Town demonstrated a 100% FNA detection rate for anaplastic and medullary carcinomas, two of the rarer but more aggressive thyroid cancers. In contrast the preoperative FNA demonstrated a lower diagnostic yield for well differentiated follicular tumours (15).

Fine needle aspiration cytology (FNAC) is a minimally invasive procedure which acts as a screening tool in the diagnosis of thyroid cancer. It is an integral part of the preoperative evaluation of patients and results should be audited regularly to ensure expertise is maintained (16).

Table 1.2 The 2017 Bethesda system for reporting thyroid cytopathology (TBSRTC).

DIAGNOSTIC CATEGORY	RISK OF MALIGNANCY IF NIFTP[1] is not equal to CARCINOMA (%)	RISK OF MALIGNANCY IF NIFTP is equal to CARCINOMA (%)	USUAL MANAGEMENT
I : Non-diagnostic or Unsatisfactory	5-10	5-10	Repeat FNA with ultrasound guidance.
II : Benign	0-3	0-3	Clinical and sonographic follow-up.
III : Atypia of Undetermined significance or Follicular lesion of undetermined significance	6-18	10-30	Repeat FNA, molecular testing or lobectomy.
IV: Follicular neoplasm or suspicious for a follicular neoplasm.	10-40	25-40	Molecular testing, lobectomy.
V: Suspicious for malignancy	45-60	50-75	Near total thyroidectomy or lobectomy.
VI : Malignant	94-96	99	Near total thyroidectomy or lobectomy.

[1] NFITP- Noninvasive follicular thyroid neoplasm with papillary-like nuclear features

1.2.6 FNA diagnostic yield in South Africa

In a study of 1,767 cases of FNAs reviewed by the National Health Laboratory Services (in South Africa) over a period of 3 years, Fatman and Michelow demonstrated that 24% (415) of the samples were inadequate. This study included multiple centres, including data from FNAs done under ultrasound guidance, as well as using palpation only (17). This study had limitations in that it included nodules performed by a variety of different clinicians. As such the results cannot be generalised to radiologists performing the procedure under ultrasound guidance. See table 1.3 for comparison with diagnostic yield from other studies.

1.2.7 Factors affecting FNA sensitivity and adequacy rates

In 2017 by Xia et al, in a retrospective study of 412 thyroid nodules in China demonstrated that at a depth more than 15mm, the presence of peripheral rim calcification and a cystic component greater than 50% were independent predictors of non-diagnostic USS guided FNA results (18).

Intrinsic nodule variables affecting the adequacy of thyroid nodule fine aspiration cytology (FNAC) include nodule size, with a size less than 10mm being frequently non-diagnostic (OR of 0.68) in one study. In the same study, mixed lesions were in contrast, frequently more diagnostic with an odds ratio of 0.68 (19). John K et al demonstrated that increasing nodule depth adversely affected FNA thyroid nodule results with an odds ratio of 1.05 per mm (20). The presence of on-site assessment of cytology specimens was demonstrated to be associated with increased adequacy rates of cytology specimens and decreased number of required needle passes, which in turn results in reduced patient discomfort and diagnostic errors (21).

Another study illustrated that cyst dominancy and macro calcifications in thyroid nodules, and operator inexperience were factors associated with a low diagnostic yield of USS guided FNAB in thyroid nodules (22). Table 1.4 illustrates the relationship between diagnostic yield and cystic component (23). In this study it was demonstrated that cystic content is an independent predictor of nondiagnostic FNAs, which increases with nodule cystic component (23).

Features known to have a high suspicion for malignancy include solid hypoechoic nodules or hypoechoic component of a partially cystic nodule and the presence of extra thyroidal extension.

Table 1.3: Summary of background literature analysis and critique.

Author	Year Published	Title of Article	Pertinent Findings	Critique
Xia et al	2017	Non-diagnostic cytological results on USS guided FNA. Does thyroid nodule depth matter?	The aims of the study were to evaluate which factors could predict non-diagnostic cytological results. Nodule depth (>15mm), peripheral rim calcification and cystic content > 50% were independent predictors of non-diagnostic USS guided FNA results. Macro-calcification (5-10mm) was also associated with non-diagnostic results(18).	The sample size was adequate and the study methods matched with the objectives.
Cai XJ et al	2006	Ultrasound (USS) guided fine needle aspiration cytology in the diagnosis and management of thyroid nodules.	The main objective was to examine the accuracy of fine needle aspiration cytology (FNAC) in the diagnosis of thyroid nodules and compare the accuracy rates for USS-guided and free hand FNAC. The results demonstrated that USS-guided FNAC was more accurate than free-hand FNAC. The overall accuracy of FNAC analysis was 97% for predicting malignancy.	

			Nodules with lymphoid infiltrates and degenerative changes proved challenging during analysis (24).	
John K et al	2017	Ultrasound guided fine needle aspiration of thyroid nodules, factors affecting diagnostic outcome and confounding variables.	Factors affecting diagnostic yield negatively included increasing lesion depth (odds ratio of 1,05 per mm) Older patients were more likely to have a non-diagnostic samples (20).	
Redman R et al	2006	The impact of assessing specimen adequacy and number of needle passes for fine needle aspiration biopsy of thyroid nodules.	The analysis of results showed that USS guidance and on-site assessment of cytology specimens increased the adequacy of cytology specimens and decreased the number of required needle passes, which reduced patient discomfort and diagnostic errors (21).	

Choi SH et al	2011	Factors affecting inadequate sampling of ultrasound-guided fine-needle aspiration biopsy of thyroid nodules	Cyst dominancy and macro-calcification in thyroid nodules, inexperience of the performing doctor were factors associated with high inadequate sample rates of ultrasound guided FNAB in thyroid nodules (22).	
Fatman L et al	2015	Thyroid cytopathology with an emphasis on the “atypical cells of uncertain significance” category: a 3-year audit with cytohistologic correlation.	The study of 1767 cases demonstrated that atypia of undetermined significance/follicular cells of undetermined significance was associated with a higher malignant rate than that of the AUS category in TBSRT (17).	
Grani G et al	2013	Intrinsic factors affecting adequacy of thyroid nodule fine-needle aspiration cytology	Nodules diameter of <10mm was found to be more frequently associated with non-diagnostic cytology results. Increased vascularization and the presence of microcalcification/macrocalcification were not associated with increased	

			risk of inadequacy. Mixed lesions were, in contrast associated with a higher diagnostic yield (19).	

Table 1.4 Non-diagnostic yield among solid and cystic thyroid nodules

Cyst content	Number	Non diagnostic yield n (%)
Solid	674	54(8%)
<25% cystic	329	21(6%)
25-50% cystic	142	17(12%)
50-75% cystic	104	26(25%)
>75% cystic	199	71(36%)
Total	1448	189(13%)

2. Aims and Objectives

2.1 Research aim

The study aim was to evaluate the diagnostic yield of FNA of thyroid nodules performed at the tertiary institutions in Johannesburg (CMJAH and CHBAH). This was correlated with factors that possible affected the diagnostic yield of cytological evaluation.

2.2. Study objectives

2.2.1 Primary objective

The study evaluated the diagnostic yield of FNA of thyroid nodules performed at two of the major academic hospitals in Gauteng.

2.2.2 Secondary objectives

- The study audited the success rate of ultrasound guided FNA of thyroid nodules by assessing the percentage of specimens which were adequate and representative for cytological diagnosis.

- Evaluated the reasons for non-diagnostic samples. The variables that were considered are: nodule consistency, the presence of rapid on-site evaluation by a cytologist, the level of experience of radiologist/operator and number of attempts / needle passes. The operators were classified into junior (registrars with <2 years experience), seniors (registrars with >2 years experience), and consultants.

- Determined the percentage distribution of cytology results.

3. Materials and Methods

3.1 Study design and setting

This was a retrospective study of the diagnostic yield of FNA of thyroid nodules. The data was collected from the interventional units of two tertiary hospitals in Johannesburg, South Africa – CMJAH and CHBAH. These public sector hospitals are part of the University of Witwatersrand teaching complex.

Continuous sampling of data from the PACS system and procedure books at the two hospitals was done for the defined study period (01/01/2016 – 31/12/2017).

3.2 Data Acquisition and Analysis

Records were obtained from the booking and procedure books kept in the respective departments of interventional radiology. The hospital numbers and patient were collected and used to extract ultrasound and FNA reports from PACS. A search for FNA reports from the PACS/RIS systems was performed using the key words 'USS thyroid', 'FNA and Thyroid' and 'FNA'. This search was limited to the study period.

The ultrasound and FNA reports were retrieved and patient records (Hospital numbers) obtained for use to access respective NHLS cytology results from the LabTrack system. The data was anonymised and the information was collected using a data collection sheet prepared beforehand. The data collection sheet is attached in Appendix B. The data was then transferred to a spread sheet. Each patient was allocated a patient code and this code was linked to a separate file with patient demographic (pass word protected) and only accessible to the supervisor and primary investigator, sample attached in Appendix C. The patient data was stored on the primary investigator's computer and there was a separate electronic back up.

Descriptive analysis of the data was carried out as follows: categorical variables were summarised by frequency and percentage tabulation, and illustrated by means of bar charts and pie charts.

3.3 Technical Aspects

All ultrasound scan reports that were included in the study were of procedures performed using high frequency probes (7.5 Mhz) to detect the thyroid nodules. Thyroid settings were used during these procedures. All ultrasound guided FNAs were performed according to the standard guidelines and protocols, and a 22G needle was used. The included cytology reports were of specimens sent on slides – one fixed with Cytofix and the other not. A portion of the FNAs had been performed in the presence of on-site cytological analysis**.**

3.4 Inclusion criteria

All patients with available ultrasound, FNA and cytology reports on PACS and NHLS LabTrack, were included in the study. The study period was from 1 January 2016 to 31 December 2017.

Adult patients above the age of 18 were considered for the study. This is because paediatric thyroid FNAs are not routinely performed in the department of interventional radiology at our institutions.

3.5 Exclusion criteria

Ultrasound reports with no corresponding cytology reports on the NHLS LabTrack viewer.

3.6 Ethics

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand, approval number M180260 .This certificate is attached as Appendix A.
Confidentiality was maintained as no demographic identifiers were included in the spread sheet. A link to the data file was created and password protected. This was only accessible to the primary investigator and supervisor. This was a retrospective study and no new radiological procedures were done and patient's safety was thus not compromised.

3.7 Statistical data analysis

Data were analysed using STATA software, version 13.0 (Stata Corp, College Station, Texas).
Quantitative statistical methods were used to analyse the data in a commercially available software package (STATA). The diagnostic yield was calculated using frequency tables and the

proportion of inadequate FNA samples was calculated using percentages. The research data is presented in the form of tabulations, graphs, and diagrams.

The correlation between inadequate samples and presence of on-site evaluation/nodule consistency and operator level is presented using frequencies and cross tables. The association between the above mentioned variables and diagnostic yield was calculated using χ^2 test and the Fisher exact test was used where frequencies were too small.

A representative sample size of 165 patients was obtained using STATA 15 with a minimum statistical power of 80% and alpha (level of significance) $p < 0.05$.

4. Results

One hundred and ninety three patients underwent FNA of thyroid nodules during the study period. Of these, 181 had cytology results and the rest had missing entries in the NHLS LabTrack website.

Descriptive analysis of the data was carried out as follows: Categorical variables were summarised by frequency and percentage tabulation, and illustrated by means of bar charts and pie charts. Continuous variables were summarised by the mean, standard deviation, median and interquartile range, and their distribution illustrated by means of histograms.
Data analysis was carried out using SPSS (Statistical Package for the Social Sciences, Version 13, SPSS, Chicago, IL, USA). A 5% significance level was used throughout. In other words, p-values <0.05 indicate significant results.

4.1 Descriptive analysis of the study group

4.1.2 Study demographics.

The majority of patients in the study cohort were female, constituting 82% of the total. This is illustrated below in Fig 4.1. The proportion of males was less than a 5th of the total. One of the patients preferred not be identified with either sex.

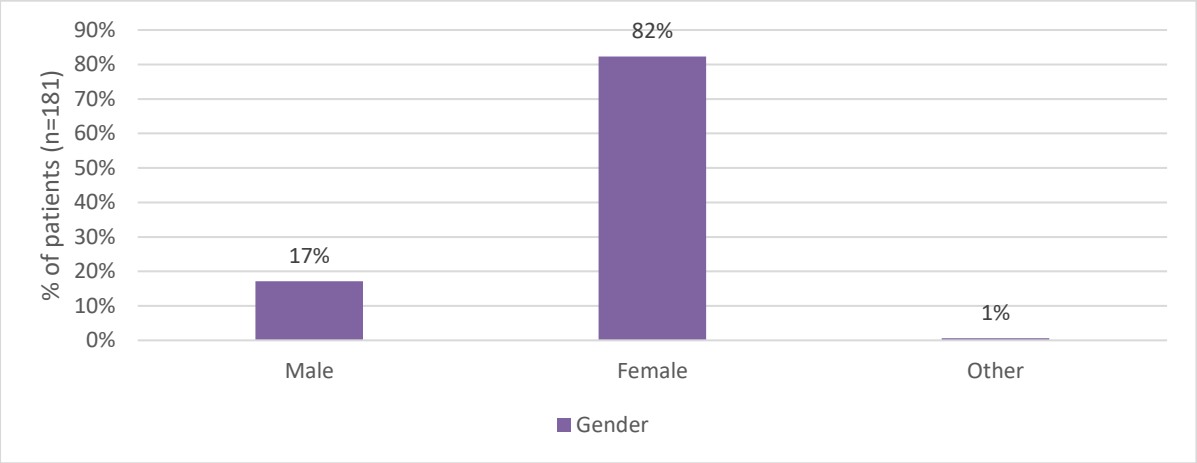


Figure 4.1 Gender distribution of the study cohort

The mean age of patients undergoing FNA thyroid was 52.2 and the median age was 52 .The distribution is as shown in the bar chart in Fig 4.2.

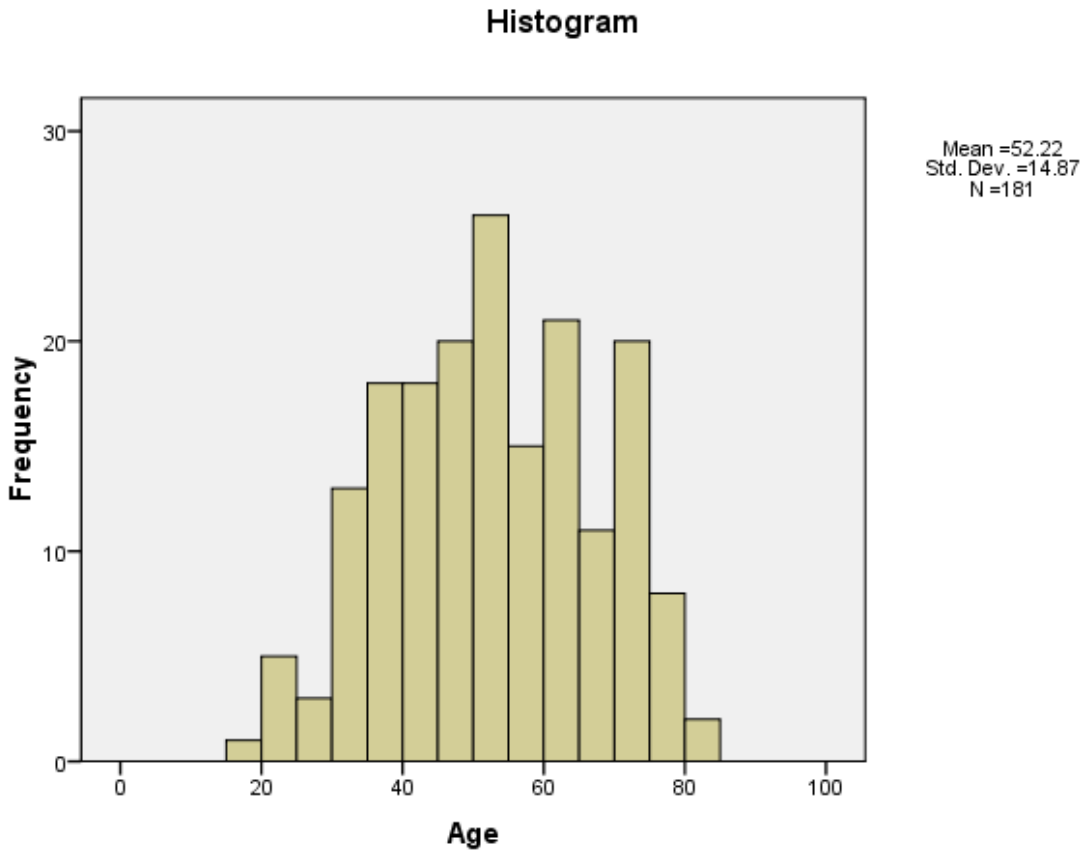


Figure 4.2 Age distribution of patients undergoing FNA of the thyroid

Approximately half of the thyroid nodules sampled were located in the right lobe of the thyroid, at 49.7%. This is followed by the left lobe at 43.1%. A significant proportion of the operators did not document the site of the nodule sampled, with 5% of the reports lacking this information as demonstrated in the bar chart in figure 4.3 below.

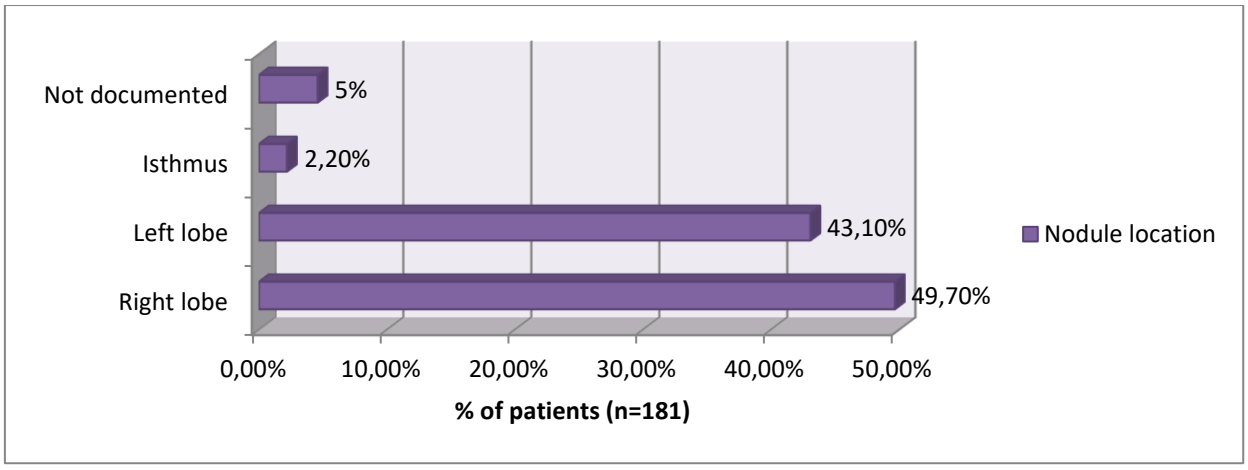


Figure 4.3 Thyroid nodule location per lobe by percentages.

The bar graph in figure 4.4 illustrates the percentage distribution of the number of passes done per each FNA procedure. The majority of operators performed between two and three passes, constituting a combined 82.9%. 12.7% of the operators did not document the number of passes or samples taken.

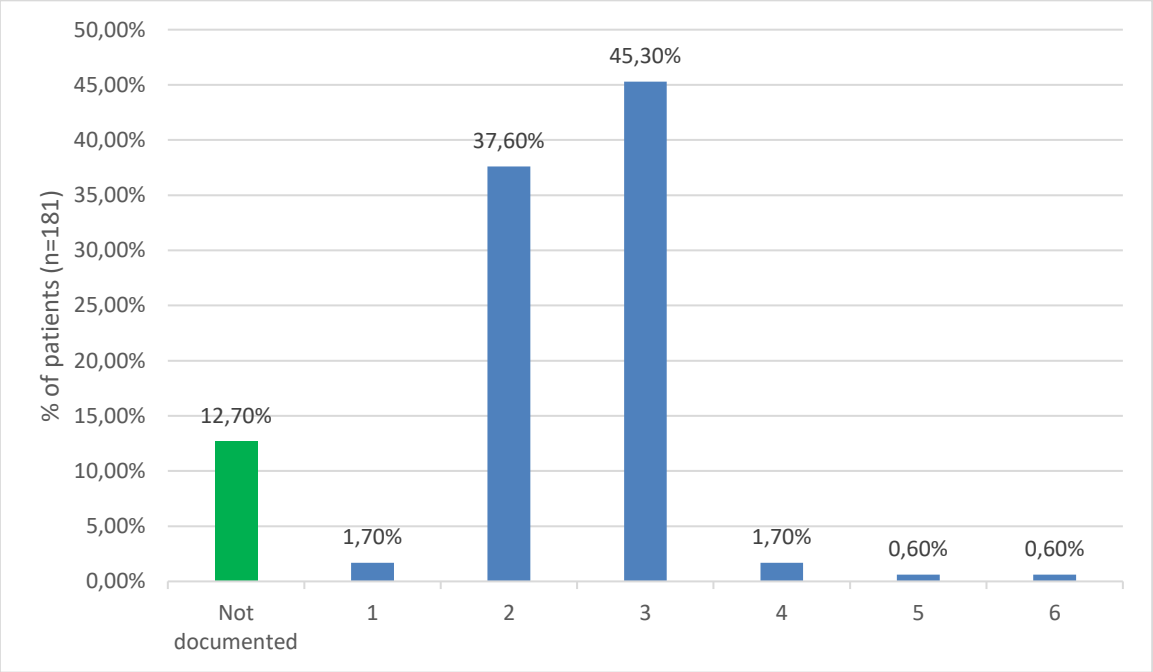


Figure 4.4 Number of passes done by different operators

The majority of operators did not document if rapid on-site evaluation of samples by a cytologist was available during the procedure as illustrated in table 4.1. 102 FNA reports did not have this information, constituting 54% of the total reports. Only 25 (13.8%) of the FNAs were performed in the documented presence of rapid on-site evaluation by a cytologist.

Table 4.1 Number and percentage of studies done with/without rapid on-site evaluation

	Frequency(n)	Percent (%)
Yes	25	13.8
No	54	29.2
Not documented	102	56.4
Total	181	100.0

Approximately seventy two of the FNA samples were considered adequate for cytological evaluation. This means that the calculated non-diagnostic rate was 28.2% as demonstrated in Table 4.2 below.

Table 4.2 Proportion of diagnostic and non-diagnostic FNA samples

	Frequency	Percent
Diagnostic	130	71.8%
Non-diagnostic	51	28.2%
Total	181	100.0%

As shown in Table 4.3 below, the majority of FNA thyroid procedures were performed by consultants at 43.6%. This was closely followed by junior registrars who performed 60 of the total procedures, constituting 33.1% of the total. Senior registrars performed the least number of FNAs.

Table 4.3 Percentage of number of FNAs performed by the different operator levels

	Frequency(n)	Percent
Consultant	79	43.6%
Senior registrar (>2 years)	42	23.2%
Junior registrar (<2 years)	60	33.1%
Total	181	100.0%

The largest proportion of thyroid nodules samples were of mixed consistency, at 42% of the total. In contrast, 14.4 % of the nodules were purely cystic. 12.2% of the reports had no documented nodule consistency as illustrated in Figure 4.5 below.

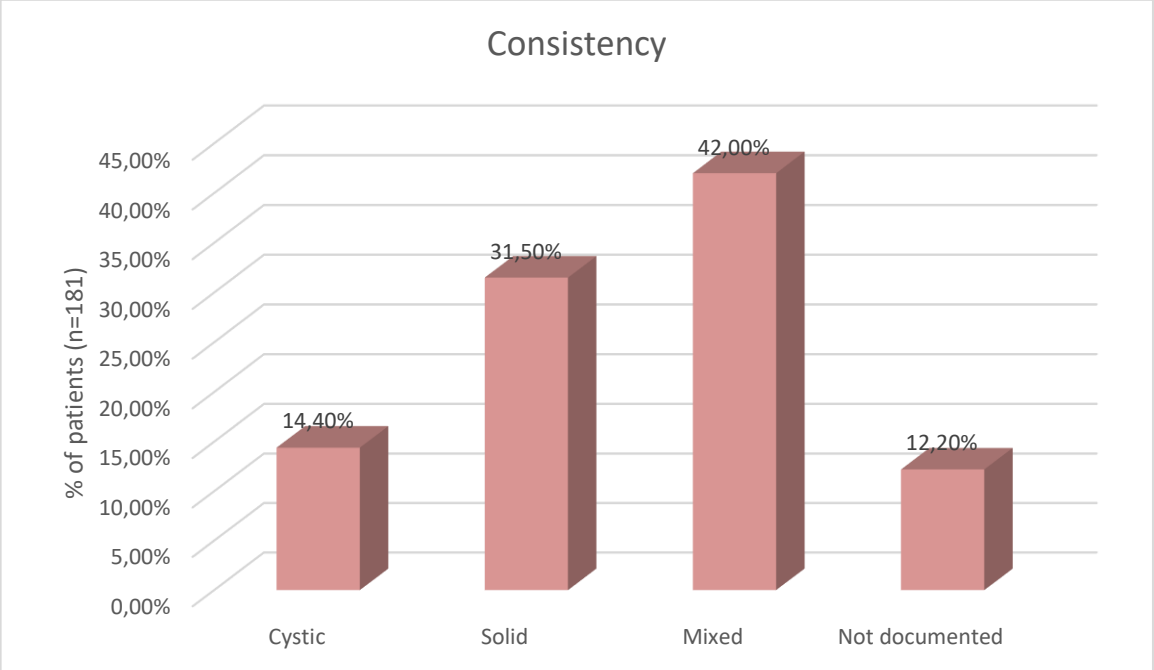


Figure 4.5 Consistency of the thyroid nodules sampled

A review of the cytology reports demonstrated that the majority of the nodules, 53.6% were benign while only 8.3% harboured malignant components. 11% of the nodules had inadequate cells as demonstrated in the bar chart in Figure 4.6.

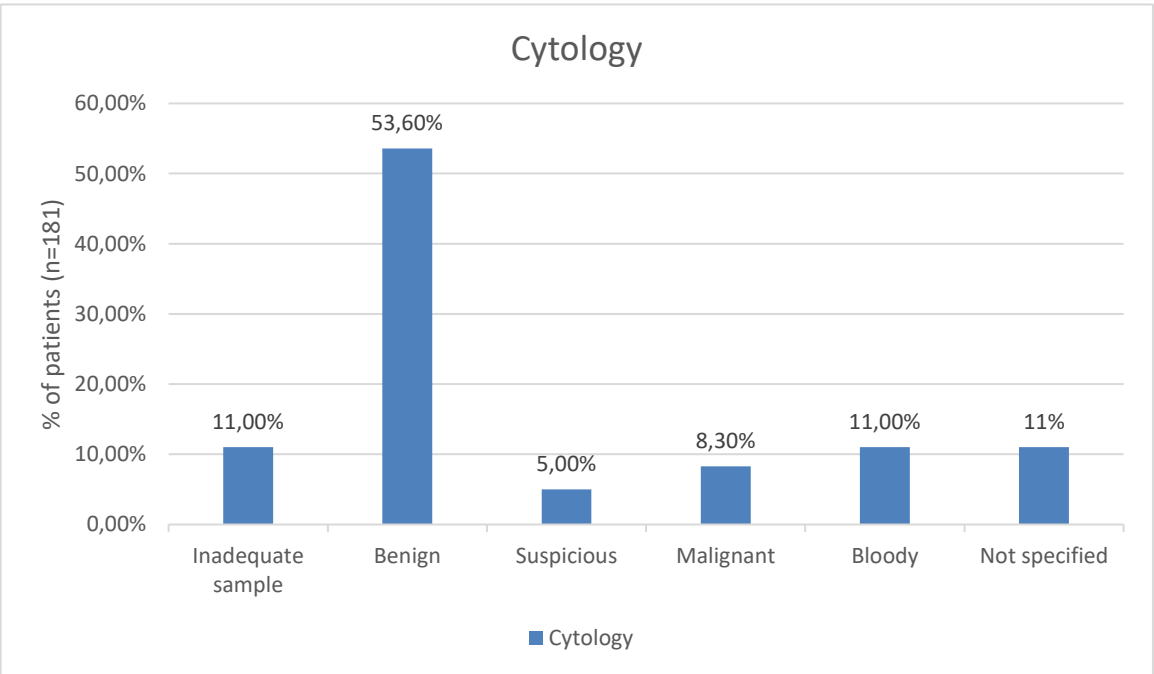


Figure 4.6 Percentage distribution of cytology results

There was no record of skin to nodule depth in all the FNA reports demonstrating a glaring inadequacy of the reports.

There was an association between thyroid nodule consistency and diagnostic yield, with 46% of nodules in the diagnostic group showing a mixed consistency (p-value = 0.033). As shown in Table 4.4 below, only a tenth of the 130 adequate samples were obtained from cystic nodules.

Table 4.4 Determination of association between Consistency and Diagnostic yield

		FNA results		
		Diagnostic(n)/Percentage	Non-diagnostic(n)/Percentage	Total(n)
Consistency	Cystic	13(10%)	13(25%)	26(14.4%)
	Solid	39(30%)	18(35%)	57(31.5%)
	Mixed	60(46%)	16(31%)	76(41.9%)
	Not documented	18(14%)	4(8%)	22(12.2%)
Total		130(100%)	51(100%)	181(100%)

Fisher's exact = 0.033

This study does not demonstrate a statistically significant correlation between the diagnostic yield and operator level (p=0.302).

Senior registrars however demonstrated the highest diagnostic yield of 78% (33/42) as illustrated in Table 4.5 below. Junior operators had a diagnostic yield of approximately 65 %(39/60).

Table 4.5 Association between Operator level and Diagnostic yield

		FNA results		
		Diagnostic	Non-diagnostic	Total
Operator level	Consultant	58 (44.6%)	21(41.2%)	79 (43.6%)
	Senior registrar	33 (25.4%)	9(17.6%)	42 (23.2%)
	Junior registrar	39 (30%)	21(41.2%)	60 (33.2%)
Total		130 (100%)	51 (100%)	181 (100%)

Fisher's exact = 0.302

The highest diagnostic yield was obtained in the presence of rapid on-site evaluation, at just over 88%. This is illustrated in Table 4.6 as 22 of the 25 samples obtained in the presence of onsite cytologist were diagnostic. In contrast the diagnostic yield in the absence of a cytologist was 63%. There is an association between FNA results and Rapid on-site evaluation (p=0.044).

Table 4.6 Association between Rapid on-site evaluation and Diagnostic yield

		FNA results		
		Diagnostic	Non-diagnostic	Total
Rapid on site evaluation	Yes	22(16.9%)	3(5.9%)	25(13.8%)
	No	34(26.1%)	20(39.1%)	54(29.8%)
	Not documented	74(57%)	28(54%)	102(56.4%)
Total		130(100%)	51(100%)	181(100%)

Fisher's exact = 0.044

There is no association between number of passes and diagnostic yield (p=0.2710)

Since the expected frequency in each row was above 5, Mann-Whitney test was used to compare average number of passes between the two groups. This is illustrated in Table 4.7 below.

Table 4.7 Association between number of passes and Diagnostic yield

FNA RESULTS	Obs	Rank sum	Expected
Diagnostic	*113*	*9296*	9040
Non-diagnostic	*46*	*3424*	3680
Combined	159	12720	12720

Unadjusted variance 69306.67

Adjusted for ties -15169.52

Adjusted variance 54137.14

H_o: NoPasses (FNAres~s==Diagnostic) = NoPasses (FNAres~s==Non-diagnostic)

z = 1.100

Prob > |z| = 0.2712

5. Discussion

5.1 Demographic and clinical features

A median age and not the mean age was used as the age of the patients was not normally distributed within this population group based on the Shapiro-Wilk test (p: 0.00457). The majority of patients who underwent thyroid FNA were female, constituting almost two thirds of the total. The mean age for this study was 52.2.

All FNAs performed in the radiology were done under ultrasound guidance. Cytology results were available in the NHLS LabTrack system for all 181 patients included in the study.

5.2 FNA Findings

5.2.1 Non-diagnostic FNA samples

The rate of non-diagnostic samples in the study was 28.2 %. This is relatively high compared to the majority of studies reviewed from the literature, being only lower than two of the 12 papers evaluated.

Of the non-diagnostic samples, 39% were reported as bloody samples and another 39% were simple reported as inadequate for cytological evaluation. The recommended management of non-diagnostic samples is repeat FNA. This can be performed 6-18 months afterwards. If there is a high suspicion for cancer based on ultrasound or clinical features, a shorter repeat interval maybe appropriate (25).

In the current study the rest of the non-diagnostic samples were due to variable combinations of poor cell preservation with degenerate cells, haemorrhagic samples, and /or insufficient cells.

One sample consisted of six air dried slides.

5.2.2 Benign Findings

53.6 % of the FNA thyroid cytology results demonstrated benign results. As per American Thyroid Association guidelines, it is strongly recommended that no further diagnostic studies or treatment done in the immediate future (7).

However, if a benign nodule (per cytology) shows suspicious sonographic findings, repeat FNA cytology is recommended (6). A follow up period of one year is recommended by most series (6). This is because of the presence of a 5% false negative rate associated with a diagnosis of 'benign' nodules (25).

5.2.3 Malignant Findings

If a thyroid cytology result demonstrates a primary thyroid malignancy, surgery is recommended (7). The malignancy rate in our study was 8.3%. This is above the usually reported rate of 2-3% reported by Bongiovanni et al (26). It is recommended that a metastatic work up is performed before surgical excision (25).

5.2.4 Atypia of undetermined significance or Follicular lesion of undetermined significance (AUS/FLUS)

For nodules with AUS/FLUS cytology, the clinical and sonographic features should be re-evaluated and options for further management include active clinical surveillance, molecular testing and ultimately a repeat FNA (7). The American Thyroid association recommends that this rate be in the range of 7%. In our study it was above the acceptable range at 11%.

USS has been demonstrated to be a good diagnostic test for the differentiation of Bethesda class 3 nodules. A nodule with suspicious findings on ultrasound is likely to be malignant (27). Clinical evaluation for a positive history of radiation exposure and family history of thyroid cancer has a role in the triaging of patients with Bethesda category 3 thyroid results (28). Godoi et al reported a malignancy rate of 16% in category 3 cytology results (29).

5.3 Correlation between diagnostic results and investigated variables

Variables investigated as possible factors affecting the diagnostic rates of thyroid FNA were divided into intrinsic thyroid nodule characteristics as determined on ultrasound examination and extrinsic factors.

5.3.1 Extrinsic Factors

Operator experience

In our study there was no association between operator level and the non-diagnostic rate. This could be explained by the fact that most challenging FNAs were reserved for consultants while registrars performed the rest. Of the 60 FNAs performed by junior registrars, 21 were non-diagnostic which represents 35% while 21 of the 79 performed by consultants were non-diagnostic, representing 26.6%. De Fiori et al demonstrated that the rate of non-diagnostic thyroid FNAC was dependent on the operator's level of experience and recommended that at least 200 FNAs need to be performed before one is considered an expert (30).

Gursoy et al concluded that the number of inadequate cytological specimens were inversely proportional to the physician's experience. Of the 1320 nodules assessed, experienced operators had an inadequacy rate of 3.1% versus 16.8% for the inexperienced group (31).

On-site cytological assessment

Our study indicated that there was a correlation between diagnostic results and the presence of rapid on-site evaluation by cytologist, with a Fisher's exact test P-value of 0.044. Of the 25 samples done with on-site cytologist evaluation, only 3 samples were non-diagnostic, compared to 20 non-diagnostic samples out of a total of 54 performed in the absence of a cytologist. This is consistent with findings from previous studies.

56.4% of physicians did not document whether the FNA was done in the presence of a cytologist or not in our study.

Ghofrani et al found that the effect of the presence of cytologist for on-site evaluation depends on the experience of the radiologist. There was no significant difference between the non-diagnostic rate of samples done with cytologist evaluation (4.5%) and without (7.1%) for experienced operators. However it was demonstrated that for the non-experienced group, the non-diagnostic rate was 4.5% in the presence of onsite evaluation compared to 13% in the absence of rapid onsite evaluation (32).

5.3.2 Intrinsic thyroid nodule factors

Consistency of thyroid nodules

There was a positive association between diagnostic cytology results and a mixed consistency of the thyroid nodules on USS evaluation with 46% of total diagnostic nodule being of mixed consistency with a Fisher's exact p-value of 0.033.

In a study of 3279 nodules, Grani demonstrated that cystic nodules with a mixed consistency were more frequently diagnostic (OR 0.68, 95% confidence interval, P<0.001) (19). Of the 26 sampled in our study cystic nodules, half were non-diagnostic. 12% of operators did not document what the nodule sampled consistency was.

Nodule size and skin to nodule depth

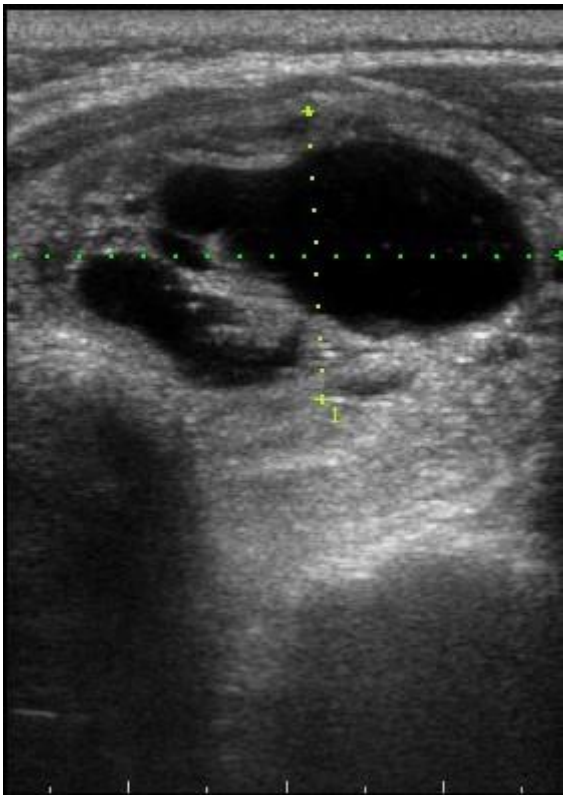
The size of the nodule has been demonstrated in multiple studies to affect the diagnostic yield of FNA thyroid procedures. A size of 5 mm or smaller is associated with an increased chance of a non-diagnostic sample (33).

Grani G et al, in their evaluation of cytology results from FNA of 3279 nodules demonstrated that a nodule size of <10 mm was more frequently associated with non-diagnostic results with an odds ratio of 1.65 (19). The correlation between skin to nodule depth and the diagnostic rate could not be assessed. This was because none of the operators documented this parameter in this study. Examples of typical findings on ultrasound of the thyroid are shown in figure 5.1.

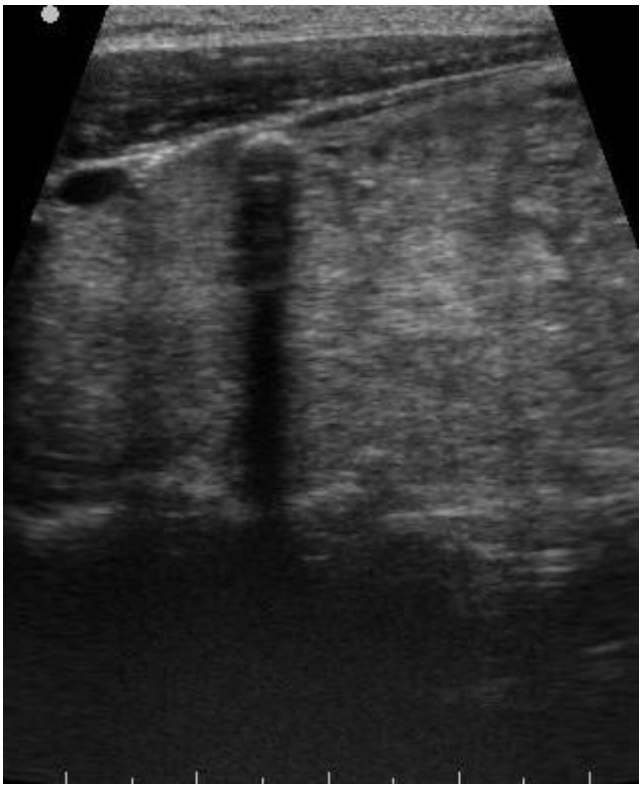
5.4 FNA thyroid report adequacy

Although assessment of thyroid FNA report adequacy was not one of the objectives of this study, there was a glaring inadequacy of information provided in the FNA reports. This presented challenges in accessing information required for a proper and complete audit. For instance, none of the physicians documented the nodule depth. In the presence of multiple nodules, the target nodule was not clearly identified in all the reports. Twenty percent of operators did not document the size of the nodule sampled.

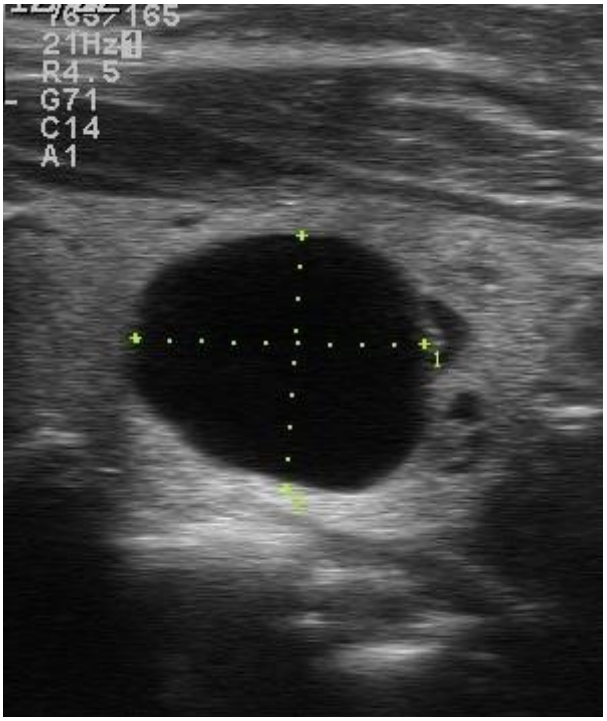
51 year old female with a solid nodule in the left lobe of the thyroid.



46 year old female patient with a complex cystic nodule in the right lobe of the thyroid.



37 year old male with a nodule demonstrating a shadowing calcification.



45 year old female with a cystic nodule in the thyroid gland.

Figure 5.1 Typical findings on ultrasound of the thyroid.

5.5 Results in context

Table 5.1 Comparative analysis of the diagnostic yield of thyroid FNA

Author	Year	No. of Total FNA done	Non-diagnostic rate (%)	Significant	Non-significant
Alexander et al.	2002	1229	13	Cystic change- only significant and independent predictor of non-diagnostic cytology (23).	Size
Ghoframi et al.	2006	981	6.5	Immediate assessment of cytology adequacy (32).	----
Degirmenci et al.	2007	232	33.6	Needle size and capillary sampling (34).	Increasing vascularity, hypo echogenicity.
Sidiropoulus et al.	2009	264	7.2	Standardization of USS-FNA: 25-G, 4 passes and preparation of samples (four total smears: two air dried and two fixed), LBC and personnel involved (35).	----
Baier et al.	2009	944	11.8	Old age>75 years, size >10mm (36).	----
De fiori et al	2010	700	13.7	Experience of operator (30).	----
Gursoy et al.	2010	1320	9.4	Experience of operator (31).	Gender, age, margin and calcification (31).

Author	Year	No. of Total FNA done	Non-diagnostic rate (%)	Significant	Non-significant
Moon et al	2011	1493	10.5	Cytic dominancy, macro calcification, experience of operator (37).	-----
Choi et al.	2011	4077	16.1	Cyst dominancy, macro calcification, experience of operator (22).	------
Moon et al.	2012	1440	17.8	Size<6 mm (38).	------
Wu et al.	2014	710	11.4	Hypo echogenicity with avascularity, hypo echogenicity with hard pattern (33).	------
Grani et al.	2013	1195	36.4	Size <10 mm, hypoechoic, blurred margin (19).	Micro-/macro calcification, increased vascularity.
	Current Study	181	26.4	Mixed nodule consistency associated with higher yield. The presence of rapid on-site cytology evaluation.	Level of operator experience.

5.6. Current applications

There is a need for clearly articulated reports for the FNA thyroid procedure. It is vital that all variables are included in the reports so as to assist in future audits, teaching and research endeavours.

Continuous monitoring of diagnostic rates for each operator is recommended in order to increase or improve diagnostic yield.

Variables to be included:

-Target nodule size, location and skin to nodule depth.

-Target nodule consistency- macro/-micro calcification, echogenicity, extra thyroidal extension.

- Presence or absence of suspicious lymph nodes.

-Presence of and/or reasons for procedure difficulty and complications.

- The presence or absence of a cytologist during the procedure.

-The size of the needles used and number of samples obtained.

Training on how to perform FNA of the thyroid gland should include – the knowledge of US appearance of thyroid nodules and supervised technical work performed in the presence of an expert radiologist. Sidiropoulos N et al demonstrated that standardization of pre-analytic variables was associated with an improvement in the diagnostic yield of thyroid FNAs (35).

5.7 Limitations of the current study

The rate of repeat FNAs of thyroid nodules was not calculated and this could introduce some bias as each nodule may have been sampled at multiple different times. The number of thyroid nodules evaluated is relatively low compared to most papers reviewed in literature.

5.8 Future applications and outcomes of this study

Considering that there were significant deficiencies identified in the reporting of the FNA of thyroid nodule procedures, there is a need to develop standardised reporting guidelines, see Appendix D for proposed reporting template. The skin to nodule depth should be included in all reports and factors that could affect the diagnostic yield, for instance the consistency or presence of calcifications should be documented.

Follow up and regular audits of thyroid FNA procedures and cytology results should become a routine, especially considering that these are teaching hospitals with high staff turnover.

The sensitivity and specificity of FNA of thyroid nodules can be reviewed in a future study. Histology from surgical specimens can be used as a gold standard for assessment.

The impact of having standardised reporting of FNA thyroid nodule can be reviewed at a later stage.

6. Conclusion

Ultrasound guided fine needle aspiration is widely performed as a screening and diagnostic tool for patients with thyroid nodules. The report for the procedure should be clear and contain the entire descriptive thyroid nodule characteristics, the technical aspects of the FNA procedure and the presence of any complications. The overall diagnostic yield of this method is highly variable, as our retrospective study demonstrated an overall diagnostic yield of 71.8% which is comparable to findings from a similar study performed in South Africa which demonstrated a diagnostic yield of 76% (17).

To optimize patient care and the diagnostic yield, radiologists need to have an understanding of technical details, cytological preparation and procedure related complications.

Mixed thyroid nodule consistency and the presence of rapid onsite evaluation by a cytologist were associated with a higher diagnostic yield. There was no correlation between diagnostic yield and level of training/expertise of the operator.

The reports for the thyroid nodule FNA were found to be inadequate with no nodule depth record from all the reports reviewed.

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Appendix A: Ethics Clearance Certificate

R14/49 Dr E Ncube

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180260

NAME: (Principal Investigator)	Dr E Ncube
DEPARTMENT:	School of Clinical Medicine Department of Radiation Sciences Division of Diagnostic Radiology Medical School University
PROJECT TITLE:	Diagnostic yield of fine needle aspirations of the thyroid done at Charlotte Maxeke Johannesburg and Chris Hani Baragwanath Academic Hospitals
DATE CONSIDERED:	23/02/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor N Mahomed
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	23/08/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **February** and will therefore be due in the month of **February** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

25/08/2018
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: Data collection sheet

Diagnostic yield of ultrasound guided fine needle aspiration of thyroid nodules at Charlotte Maxeke Johannesburg and Chris Hani Baragwanath Academic Hospitals.

Data Collection Tool

1. Pseudo no…

2. Ultrasound characteristics of the nodule.

Nodule depth: … mm (from the skin to the nodule)/ 0-if not provided.
Consistency: 1) cystic 2) solid 3) mixed 4) Not documented.
Size...mm x……mm x….mm (volume…..mm3) / 9=Not provided
Nodule location: 1) right lobe 2) left lobe 3) isthmus 4) Not documented.
Additional nodule description ……..

3. Number of passes done during the ultrasound guided FNA…/ 0=not documented

4. Was rapid on-site cytological evaluation by a cytologist performed?
1) Yes 2) No 3) Not documented

5. Was there any documented technical difficulties in accessing the nodule?
1) Yes 2) No
Additional description: ……

6. Level of experience of doctor performing procedure
1. Consultant 2. Junior registrar (< 2 years) 3. Senior registrar (> 2years)

7. What are the FNA results?
1) Diagnostic 2) Non-diagnostic

0 Inadequate sample	1 benign	2 Suspicious	3 Malignant	4. Bloody	5 Not otherwise specified.

Additional description of the cytology

Comments……..

Appendix C: Link file to Data collection sheet

TITLE: Diagnostic yield of ultrasound guided fine needle aspirations of thyroid nodules at CMJAH and CHBAH

Pseudo No/ Patient code	GT No	Age	Gender	Race	Date of Procedure

VERSION 2-27/07/2018

Appendix D: Proposed thyroid FNA reporting template.

FNA Thyroid reporting template

Hospital number:

Date:

Operator level: months/years of radiology.

Operator experience (number of FNA thyroid):

Supervised or Not:

Presence of onsite cytologist: Yes/no

Number of passes/samples:

Target nodule characteristics:

Location (by thyroid lobe). By pole	Right/Left lobe/Isthmus Inferior/mid/lower
Size (Anteroposterior x transverse x craniocaudally)/mm	Include volume calculation.
Depth(Skin to nodule centre)/mm	
Nodule Consistency	Solid/<50 Cystic / 50-75cystic/ >75%cystic
Nodule Calcifications	Present(micro/Macro)/ Absent
Nodule Vascularity	Reduced/Increased/Similar to normal thyroid tissue.
Presence of extra thyroidal extension.	
Associated Cervical Nodes.	If present describe the characteristics.
TIRADS	

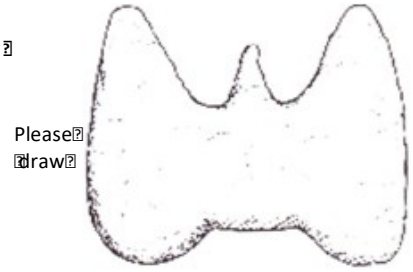
Complications/Difficulties:…….

Appendix E: Reporting template for ultrasound of thyroid nodules.

Patient Name: **Hospital Number:**
Date: **Time:**
Indication:
Examination: Thyroid Ultrasound
Findings:

Size	**Right lobe**	**Left lobe**	**Isthmus (AP)**
AP			
Transverse			
Longitudinal			

Echogenicity: Normal / Increased / Decreased
Homogenous / Inhomogeneous. If inhomogeneous, describe: _____
Lymph nodes: Normal/ Pathological. Description + Zone: _____
Parathyroids visualised: Yes / No. Describe: _____
Nodules: Yes / No



If nodules present, please describe below:

Nodules	**1**	**2**	**3**	**4**
Nodules	**1**	**2**	**3**	**4**
Size				
Site				
Extra-thyroid extension				
Taller than wide				
Echo pattern and consistency				
Margin / Contour				
Halo				

Calcification + type				
Vascularity				
Assessment:				
Benign (B), Intermediate (I), Suspicious (S), Malignant (M)				
FNA Recommended				
FNA Barcode				