THYROIDECTOMIES AT AN ACADEMIC HOSPITAL IN JOHANNESBURG-CORRELATION BETWEEN PRE-OPERATIVE CYTOLOGY FINDINGS AND POST-OPERATIVE HISTOLOGY RESULTS

Dr Lydia Kilani

Student number 78948

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DECLARATION

I, Dr Lydia Kilani, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University. This research report is written in the submissable article format

_____.

(Signature of candidate)

2nd day of May 2023 in Sandton .

DEDICATION

To my son Gabriel, I want you to be proud of me.

ABSTRACT

BACKGROUND- Pre-operative cytological assessments of thyroid nodules have become an inexpensive, uncomplicated and reliable way of making a diagnosis of malignancy, as well as useful in stratifying thyroid nodules according to risk. The Bethesda system for reporting thyroid cytopathology (BSRTC) provides a standardized method for reporting this and more accurately estimating risk. This study examines the correlation between BSRTC and final histology in patients undergoing Thyroidectomies at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)

OBJECTIVES- To determine the accuracy of pre-operative cytological diagnosis in patients undergoing thyroidectomies at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), and also to determine the rate of reporting of each BSRTC category, the rate of malignancy of each category, and the demographics of the study population, which includes age, gender and race.

METHODS- This was a retrospective, observational study, which looked at 113 thyroidectomies performed between July 2013 and December 2016 at CMJAH. Data from each case was captured and analyzed, specifically analyzing pre-operative cytopathological diagnosis which is performed via ultrasound-guided fine needle aspiration FNA, with the post-operative histopathological diagnosis.

RESULTS- A total of 174 patients underwent thyroid procedures during the study period, of which 113 fit the inclusion criteria. The majority of the patients were African (79%) and female (88%). A preoperative diagnosis of indeterminate (BSRTC categories 3 and 4) was made in 30.1% of cases. The most reported BSRTC category was category 2 which made up 42.5% of all pre-operative reports, and all

were confirmed benign on post-operative histology. BSRTC category 3 of “Atypia of unknown significance” (AFLUS) was made in 19 patients of whom 3 had thyroid cancer. BSRTC category 4 describes a “follicular neoplasm”: there were 15 patients in this category of whom 8 were found to be malignant. The diagnosis of BSRTC category 5 or “suspicious of malignancy” and category 6 of “proven malignancy” were made in 14 and 17 times, respectively. Only five of 14 BSRTC category 5 were confirmed cancers. The cancer risk for BSRTC 6 was 82.4% (14 of 17 patients).

CONCLUSION- Pre-operative cytological diagnosis was more accurate in BSRTC categories 2 and 6. A diagnosis of ‘indeterminate’ was made in a significant number of patients (n=19), where more than half of them were found to be malignant. Malignancy risk is lower than expected for BSRTC categories 5 and 6, which may indicate an element of ‘over-diagnosis’ in this institution. Further studies are required.

Word count- 395

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LIST OF ABBREVIATIONS

AFLUS	Atypical follicular lesion of undetermined significance
AUS	Atypia of undetermined significance
BSRTC	The Bethesda System for Reporting Thyroid Cytology
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
FNA	Fine needle aspiration
FN	Follicular neoplasm
NDT	Multidisciplinary team
PNET	Primitive neuroectodermal tumor
SFN	Suspicious for follicular neoplasm
SM	Suspicious for malignancy
TBSRTC	The Bethesda system for reporting thyroid cytopathology
TSH	Thyroid stimulating hormone

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1 INTRODUCTION

1.1 BACKGROUND

Thyroidectomies and thyroid lobectomies have increased in incidence within the last few years, mainly due to an increase in pre-operative investigation of thyroid nodules, incidentalomas during carotid artery imaging and improved diagnostic and referral protocols (1).

The Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is an established academic center for endocrine surgery. Thyroid and parathyroid surgery predominates the procedures performed.

The management of patients with thyroid pathology at CMJAH is conducted within a multi-disciplinary team (MDT), which includes Endocrinologists, Radiologists, Nuclear Medicine physicians and pathologists. If surgery is indicated the team decides on the most appropriate procedure.

Each discipline contributes to the pre- and post-operative management, allowing decisions to be made that reflects the patient's best interest and in accordance with international standards.

The Bethesda system for reporting thyroid cytopathology (BSRTC) was developed in 2007 in Maryland USA (2) as a standardized system of reporting thyroid cytopathology and thereby improving communication between disciplines and international centers, aiding in thyroid malignancy risk stratification and improving the correlation between pre-operative cytological findings and the final post-operative diagnosis (2). The report guides the clinicians in the MDT towards the appropriate management of thyroid

nodules with or without suspicion of malignancy. This system of reporting is widely accepted and utilized internationally and consists of six cytological categories, each with a corresponding percentage risk of malignancy and suggested management protocol (Appendix 1). Specifically, the diagnostic categories cover 1) non diagnostic/unsatisfactory findings, 2) benign, 3) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), 4) follicular neoplasm (FN) or suspicious for FN (SFN), 5) suspicious for malignancy (SFM), and 6) malignant. As a result, the BSRTC has aided substantially in appropriate surgical decision making and in the management of thyroid nodules.

Studies done after the introduction of the BSRTC demonstrated that pre-operative fine needle aspiration (FNA) is an inexpensive and technically uncomplicated investigation that shows “superior diagnostic reliability over thyroid ultrasound and scintigraphy” (3). In 2008, Bukhari *et al* demonstrated that the use of pre-operative thyroid nodule assessment with FNA is an accurate and valuable tool also in developing countries (4). This latter study was conducted in Lahore, Pakistan, and achieved similar results as other international studies (5), showing the overall accuracy of FNA findings to be as high as 87%, thus mirroring similar study outcomes in first world countries. Moreover, Bukhari’s group reported the sensitivity and specificity of FNA results as 90% and 87.5% respectively.

The “pre-Bethesda era” studies also support the use of FNA as a first line investigation. A study conducted in 2000 (6) looking at 239 post-operative histology reports and comparing them with corresponding pre-operative cytology, showed FNA assessment as a useful diagnostic tool with sensitivities of 86% and 88% for predicting neoplasia and malignancies respectively, despite there not being a standardized cytological

reporting protocol. This study demonstrated that there was a lack of formalized risk stratification and incongruence in thyroid cytopathological reporting, hence necessitating the development of the BSRTC. Having said that, as the BSRTC is widely utilized, continuous audits of its efficiency and post-operative congruency in multiple unique clinical environments is important. Since the implementation of the BSRTC, many institutions have reported a higher rate of detection of malignancy, and a decreased rate of unnecessary thyroidectomies (7).

There are various indications for thyroidectomy or thyroid lobectomy: benign conditions, thyroid nodules with atypical cells, and confirmed or suspected thyroid malignancies need to be evaluated from a clinical, radiological and cytological point of view. Indication for surgery depends on an accurate FNA result, which guides the type and extent of surgery, as well as the need to a lymph node dissection. Currently FNA findings that reveal specific pathological types of thyroid malignancies are also playing a role in the decision to perform associated lymph node dissections of the neck during thyroid surgery. It is thus imperative to have a high quality system of cytopathological evaluation and an accepted standardized reporting system with established management protocols for a well-functioning MDT.

Multiple international correlation studies have been conducted over the years looking at pre-operative cytological versus histological findings on thyroidectomy specimens. Regular auditing and comparisons between pre-procedural cytopathological assessments and post-operative histological diagnoses is imperative. Accurate pre-operative assessments of patients with thyroid nodules directly affects the surgical

management plan. Both the endocrine surgery and cytopathology departments benefit greatly from such an audit, as it allows us to improve the quality of health care provided while maintaining high standards of academic excellence. A recent study looked at 1021 FNA samples submitted in a large Turkish hospital over a two-year period and assessed the correlation between the cytological and histological findings on 219 patients who had undergone thyroidectomies (8). Their findings demonstrated a 100% cyto-histological correlation in the lesions reported as benign and malignant, making up 63% and 2.4% of the samples, respectively. Even though the rates of malignancy for the indeterminate classification groups BSRTC 3, BSRTC 4 and BSRTC 5 (12.7%, 35.0% and 91.4% of samples, respectively) were not significantly different to the corresponding BSRTC risk of malignancy values, the lack of a strong cyto-histological correlation highlights the importance of clinical and radiological pre-operative considerations as part of a robust thyroid work-up (8).

In 2014, Naz *et al* (9) investigated the diagnostic accuracy of the BSRTC at their Pakistani hospital. Based on their findings they recommended the continued use of FNA, whilst adopting the BSRTC as a first line assessment of thyroid nodules. They reported a good correlation between pre-operative cytological diagnoses and postoperative histological findings, with 100% accuracy in BSRTC 5 and 6 categories, while findings for categories 2-4 were similar as other studies and correlated with the percentage malignancy risk documented by the BSRTC. However, they noted that further clinical and radiological considerations were required when analyzing indeterminate BSRTC categories as their incidence of malignancy alarmingly tended to be higher, indicating that these indeterminate categories represent weak areas in previous, non-standardized reporting systems, potentially resulting in under-diagnosing and thus inappropriate management of the patient. This latter finding is

common in multiple studies that also assessed cyto-histological congruency (7, 10, 11).

A local study by the Department of Pathology at the University of the Witwatersrand retrospectively investigated three years of thyroidectomy samples and the incidence of pre-operative AUS FNA diagnoses when compared to the final histological findings (12). The study reported a higher rate of malignancy in the final histological diagnosis for AUS, than that predicted by the BSRTC. This result may suggest an under-reporting of this particular category. The likelihood of this, and the possible causal factors, need to be investigated. Furthermore, the diagnostic accuracy of the other BSRTC categories, especially category 4, also have to be determined, as these have repeatedly been identified as areas of concern in other cyto-histological thyroidectomy correlation studies as mentioned above.

Each BSRTC category has a recommended reporting rate (13). This may vary according to specific population demographics and the quality of cytopathological assessment. Of note an inadequate cytology report (BSRTC category 1) should not be more than 30% of all thyroid cytological assessments (ideal rate is 2-20%), this would indicate poor FNA technique. The majority of cytology reports are expected to invariably be benign (60-70%) in most laboratories. If the indeterminate categories (3 and 4) are reported too often this may indicate the hesitancy of the cytopathologist to make a definitive diagnosis. The recommendation is that the use of these indeterminate categories is limited to less than 7%. The rate of definitive or suspicious for malignancy reporting (BSRTC 5 and 6) will be higher in regions where thyroid cancer is endemic, this ranges from 3-7% in most centers (13).

The BSRTC system for reporting thyroid cytopathology has since been revised in 2017 after extensive review of post-2010 international thyroid data. The nomenclature of the six BSRTC categories remain unchanged, although some of the categories have been sub-categorized for clarity, for example- the benign category can be sub classified into either benign follicular nodule, lymphocytic thyroiditis (Hashimoto), granulomatous thyroiditis or 'other'. The introduction of molecular testing has been widely accepted and now recommended to further characterize the indeterminate BSRTC cytopathological categories (14).

The 2017 updated BSRTC system for reporting thyroid cytopathology further established the importance of a standardized, cohesive approach to reporting for cytopathologists. Studies performed a few years after the implementation of the updated system in 2017 continues to demonstrate congruency in results among pathologists, which further ensures diagnostic accuracy. One specific study in 2020 reported a 100% congruency amongst its 3 pathologists, their rate of malignancy and diagnostic accuracy were in line with pre-2017 studies (15).

Another contemporary study, which aimed to prove the diagnostic accuracy and reproducibility of results when utilizing the updated BSRTC in their institution was conducted in 2020 by Anand et al (16). The study confirms that the updates made to the second offering of TBSRTC is contributing to accuracy, congruency and risk of malignancy rates in the area of thyroid cytological assessment in various clinical settings.

The issue of standardization and reproducibility of results and has been addressed in a few studies performed pre and post the update of TBSRTC in 2017. The cornerstone of its worldwide adaptation is the fact that it ensures these two key advantages within

the thyroid cytopathology field. A study in rural southeastern Ohio in 2017 demonstrates this within their findings. Their accuracy specificity rates were comparable to results from other larger centers in the United States of America. It is now widely accepted that the adoption of TBSRTC ensures reproducible results despite variations in setting, facility capabilities and level of institution (17).

We have a unique setting at the CMJAH in that it is a relatively young, but rapidly growing multi-disciplinary endocrine surgery center. The number of thyroid procedures performed has increased exponentially over the last 10 years, with strengthening collaborations between the relevant disciplines of general surgery, pathology, radiology, nuclear medicine and the medical endocrine unit. This robust partnership approach ultimately results in high quality, sound patient care, which is comparable with international standards despite an overwhelming patient burden and limited resources.

1.2 AIM

This study aims to add to the already growing body of work on the accuracy of the BSRTC by assessing pre-operative cytological diagnosis and post-operative histological findings in our local setting. This research will determine the accuracy of the BSRTC in our institution and could highlight potential pitfalls in our system. The resulting information from this study may aid in establishing diagnostic and management protocols for thyroid nodules that are specific to and appropriate in CMJAH.

1.3 OBJECTIVES

The primary objectives of this study were:

- To determine the accuracy of pre-operative cytological diagnosis of patients presenting with a thyroid swelling in CMJAH, by assessing the degree of congruency between pre-operative cytology and post-operative histology diagnosis.
- To determine the rate of reporting of each (BSRTC) cytological category.
- To determine the malignancy rates of each (BSRTC) pre-operative category.

A secondary objective was to describe the epidemiology of surgically managed thyroid disease at CMJAH.

2 METHODS

2.1 STUDY DESIGN

This was a retrospective, observational, longitudinal study.

2.2 STUDY SITE & SAMPLING

The study was conducted at the Department of Endocrine Surgery at the Charlotte Maxeke Johannesburg Academic Hospital.

2.3 STUDY SAMPLING

Thyroid cytopathological reports performed at CMJAH from July 2013 to December 2016 were drawn from National Health Laboratory System (NHLS) records. Of those patients who had an ultrasound-guided thyroid FNA within the study period, we reviewed the files of those who underwent a thyroidectomy or thyroid lobectomy.

Post operative histological reports of these patients were also drawn from NHLS records. For each patient we recorded the following data on a data capturing sheet: age, gender, race, pre-operative diagnosis and BSRTC category from cytology, as well as the post-operative diagnosis following histological investigations.

***Inclusion criteria*:** Patients who presented to the CMJAH Department of Endocrine Surgery, had an FNA of a Thyroid nodule/lesion and subsequently proceeded to have a total thyroidectomy or a thyroid lobectomy between the period of July 2013 to December 2016.

Exclusion criteria: Patients who underwent parathyroidectomies; patients who did not have pre-operative cytological assessments performed at CMJAH; patients who

were admitted for re-excision or completion thyroidectomies; and/or patients with inadequate FNA specimens.

2.4 ETHICAL APPROVAL

Ethics approval was granted by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand. Ethics clearance certificate number- M170613.

2.5 STATISTICAL ANALYSIS

The study data were entered in a MS Excel spreadsheet without any patient identifiers and imported into the suites of analytics software STATA Version 16.0 and SAS version 9. The Shapiro-Wilk W test was performed to determine the normality of data distribution. Descriptive statistics were performed for all study participants and reported as mean and standard deviation (SD) or frequencies and percentages, as appropriate. Comparisons between the type of procedure performed, age, race and gender were conducted using the Two-sample t-test or Chi-squared test, as appropriate. Analysis of the grouping variable on final histological diagnosis of benign, indeterminate or malignant outcome, was conducted using One-way ANOVA or Chi-squared tests. For paired data comparisons between pre-operative cytology diagnosis versus post-operative histology findings, a test of Symmetry/Agreement and the Kappa statistics were applied. A 5% level of significance was considered statistically significant.

3 RESULTS

A total of 174 patients underwent thyroid procedures between July 2013 and December 2016 of whom 113 patients met the inclusion criteria. Of the 61 patients that were excluded from the study, 38 patients did not have pre-operative cytology results on the hospital's laboratory system, a further 16 patients underwent completion thyroidectomy and some patients either had their procedures performed at another institution or were completely untraceable, and five of the excluded patients had inadequate cytology samples (BSRTC 1) of whom 3/5 patients had multiple repeated FNA's, all of which remained unsatisfactory. These patients went on to have thyroidectomies for various clinical indications, post op histology revealed multinodular goiters in 4 of the 5 patients, the 5th post- op histology showed a follicular thyroid carcinoma. There is a 3% reporting rate for BSRTC category 1 in this study sample which is acceptable according to the stipulate recommended reporting rate (2). Additionally, patients were excluded if they underwent combined para-thyroidectomies and thyroidectomies, as was the cases with two patients during the study period. Their primary pathology was parathyroid disease and therefore pre-operative work up focused on investigation of the parathyroid pathology alone, no pre-op thyroid cytology was available to assess.

3.1 DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

The demographic characteristics of the study population are summarized by final diagnosis as determined by histopathology outcome in Table 1. Overall, the mean (±SD) age of the patients was 47.0 (±14.4) years and ranged from 12 to 80 years old, with 19.5% (n=22) of patients above 60 years old, 77.9% (n=88) between 20 and 60

years and only 2.7% (n=3) below 20 years old (data not shown). Of the three young patients, two were confirmed thyroid malignancy. The majority of thyroidectomy patients in this study population were females (87.6%) and patients from Black African origin (78.8%). Even though the malignant patients presented younger, there were no significant differences between age, gender or race according to the final histopathological diagnoses. There were also no differences between age according to gender (p=0.31), race (p=0.18) or procedure performed (p=0.19) (data not shown).

Table 1. Demographic characteristics of the study patients according to histological diagnoses

Parameter	All patients (n=113)	Histological diagnosis, n (%)		P-value
		Benign (n=83)	Malignant (n=30)	
Age in years, mean (±SD)	47.0 (±14.4)	47.7 (±14.0)	44.9 (±15.3)	0.37
Gender, n (%)				
Female	99 (87.6)	74 (74.7)	25(25.3)	0.52
Male	14 (12.4)	9 (64.3)	5(35.7)	
Race, n (%)				
Black	89 (78.8)	66 (74.2)	23 (24.8)	0.74*
Caucasian	11 (9.7)	8 (72.7)	3 (27.3)	*Black vs all other
Indian	10 (8.9)	8 (80.0)	2 (20.0)	
Coloured	3 (2.7)	1 (33.3)	2 (66.7)	

3.2 PRE-OPERATIVE CYTOLOGY RATE OF REPORTING

Table 2 shows the frequency in which pre-operative cytology categorized patients according to each of the BSRTC categories. Out of the 113 pre-operative cytology reports, the majority (42.5%) were reported as benign, and 15.0% of FNAs had a definitive diagnosis of thyroid malignancy pre-operatively.

An ‘indeterminate’ cytological diagnosis of BSRTC 3 and 4 was made 30.1% of the time. This is a large percentage of patients where a definitive diagnosis is not made on pre-operative cytopathological assessment, but this frequency of patients in BSRTC categories 3 and 4 is not dissimilar from that seen in other units worldwide.

Table 2. Frequency of each pre-operative Bethesda (BSRTC) category

BSRTC category	Number of times reported, n(%)
2	48 (42.5%)
3	19 (16.8%)
4	15 (13.3%)
5	14 (12.4%)
6	17 (15.0%)
TOTAL	**113 (100.0%)**

3.3 RATE OF CYTOLOGICAL ACCURACY

Table 3 shows the cytohistological agreement, malignancy rates and BSRTC expected malignancy rates. A pre-operative diagnosis of benign disease was correct 100% of the time. A pre-operative diagnosis of BSRTC 4 carries a 53.3% malignancy risk. If a patient’s cytology was highly suspicious of thyroid malignancy (BSRTC 5) it was confirmed as malignancy 35.7% of the time. A definitive pre-operative diagnosis of malignancy was confirmed on post-operative histology 82.4% of the time.

Table 3. Cytohistological agreement, malignancy rates and BSRTC expected malignancy rates

Cytological category	Histological diagnosis, n (%)		BSRTC expected malignancy rate (2)
	Benign	Malignant (Malignancy rate)	
BSRTC 2 – Benign (n = 48)	48 (100%)	0 (0%)	0 – 3%
BSRTC 3 – AUS/FLUS (n = 19)	16 (84.2%)	3 (15.8%)	5 – 15%
BSRTC 4 – FN/SFN (n = 15)	7 (46.7%)	8 (53.3%)	15 – 30%
BSRTC 5 – SM (n = 14)	9 (64.3%)	5 (35.7%)	60 – 75%
BSRTC 6 – Malignant (n = 17)	3 (17.6%)	14 (82.4%)	97 – 99%
Total (n = 113)	83 (73.4%)	30 (26.6%)	

Figure 1 shows the agreement between the pre-operative cytology diagnosis and post-operative histology diagnosis with a borderline significant weighted kappa-statistic of 0.87 (95% CI: 0.73-1.00), p-value <0.08. From Figure 1, the exact agreement between post-operative benign diagnosis and pre-operative BSRTC 1 is evident, as it is for the diagnosis of malignant between post-operative histology and BSRTC 6 results. Importantly, this figure has not included 42% of the patients who had pre-operative BSRTC categories 3-5 and hence this becomes then a sensitivity analysis on only a smaller group of patients with preliminary findings only.

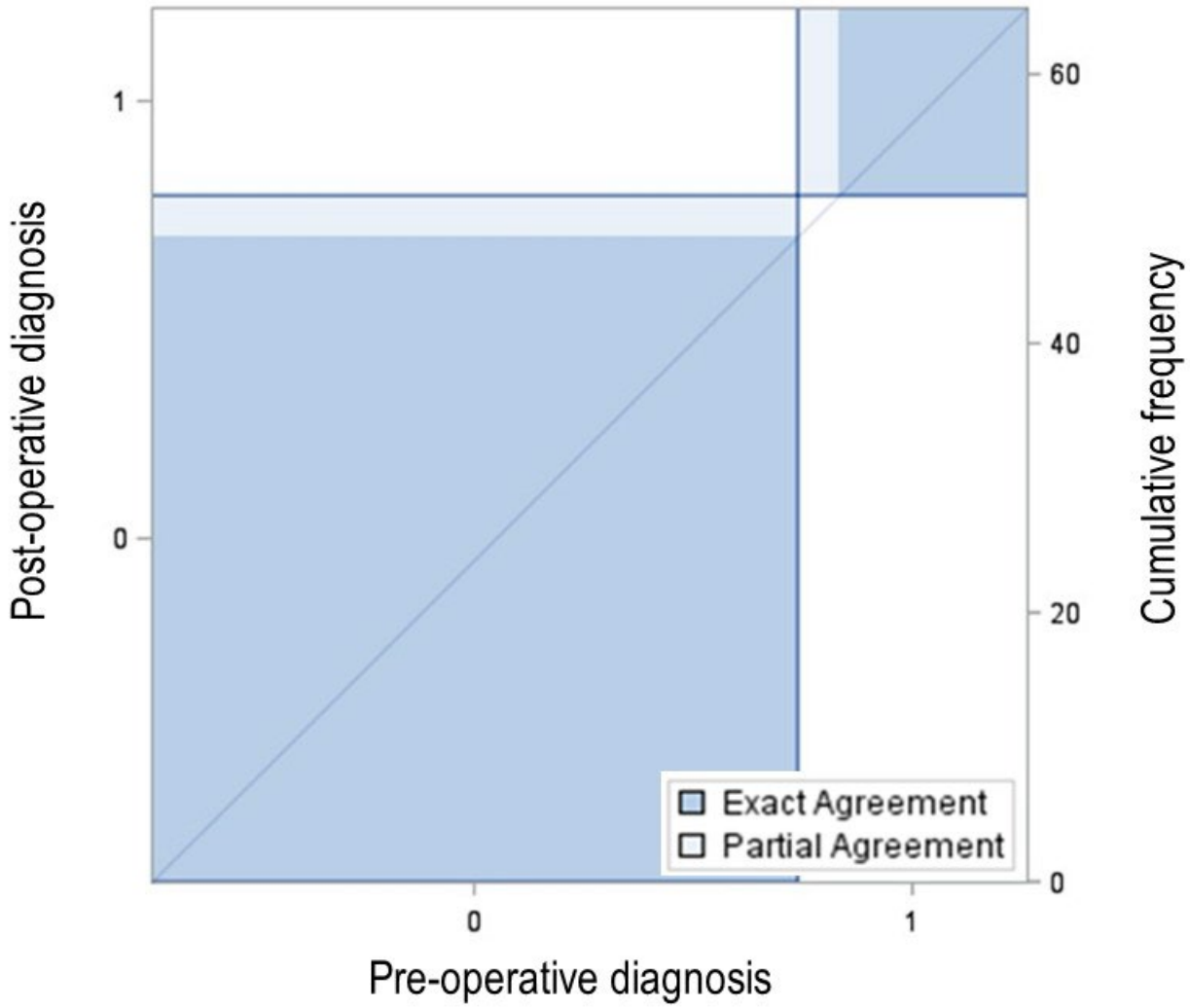

Figure 1. Kappa agreement between post-operative histology diagnosis versus pre-operative cytology diagnosis.

Key: Post-operative diagnosis: 0, benign; 1, malignant. Pre-operative diagnosis: 0, BSRTC 2; 1, BSRTC 6.

The next section describes the results according to the individual BSRTC categories.

BSRTC category 2

Of the benign pre-operative cytology group (48 patients), all 48 were confirmed benign on postoperative histology, with one being a benign follicular adenoma. No diagnosis

of thyroid malignancy was seen in the BSRTC category 2, benign group. This correlates with the proposed percentage risk of malignancy as stipulated on the BSRTC system (Table 3).

Indeterminate categories BSRTC 3 and 4

The controversial indeterminate BSRTC pre-op cytological diagnosis of AUS/FLUS (BSRTC category 3) was made 19 times out of the 113 cytological reports (16.8%). Out of these 19 patients, 16 were benign (84.2%) on post-operative histological diagnosis. The remaining three patients (15.8%) had a diagnosis of thyroid malignancy, one was a follicular thyroid carcinoma and two were papillary thyroid cancers. The BSRTC system purports that this AUS/FLUS group carries a 5-15% risk of malignancy. We demonstrated a rate within the upper limit of this frequency rate.

The BSRTC category 4 was identified in 15 out of the 113 cases (13.3%), of whom 7 patients were benign on post-operative histology (46.7%) and 8 were malignant, a 53.3% malignancy rate in this category. The malignant risk in this group is much higher than expected as the Bethesda system reflects a 15-30% risk. This high rate of malignancy could reflect the difficulty and hence hesitancy of cytopathologists to make a pre-operative diagnosis of follicular thyroid carcinoma. Another explanation for the increased rate of malignancy is that our sample population is known to historically have a higher incidence of follicular thyroid carcinoma (18) than compared to other centers where similar studies have been conducted. Recently, Chagi et al. reported that papillary to follicular cancer ratio is now 4:1 in this population (19).

BSRTC category 5

Pre-operative cytology that was suspicious for thyroid malignancy (BSRTC category 5) was diagnosed in 14 patients (12.4%), of whom 9 were benign (64.3%), and only five were confirmed as malignant (35.7%), as opposed to the BSRTC rate of malignancy risk of 60-75%. This could possibly mean that pre-operative cytopathology is “over-calling” the suspicious features of thyroid malignancy. This overdiagnosis could also to be due to subclinical hyperthyroidism, unfortunately TSH values for these subjects are missing.

BSRTC category 6

Out of the 113 patients in the study, 17 were diagnosed definitively as thyroid malignancy on pre-operative histology (15.0%), of whom 14 had a confirmatory post-operative histological report of thyroid malignancy (82.4%). The diagnosis of cancer was incorrect in 3 patients (17.6%). The 82.4% risk of malignancy in this group versus the 97-99% seen on the BSRTC system is of concern, and could also suggest over-diagnosis of malignant features on pre-operative cytological assessment. A diagnosis of malignancy has implications on the extent and type of thyroid surgery offered to the patient.

3.4 MALIGNANCY RISK

Out of the 113 patients enrolled in this study, 30 had a final diagnosis of thyroid malignancy (26.6%). The majority of patients were papillary thyroid cancer and follicular thyroid cancer, three patients had medullary thyroid cancer, one had a primitive neuroectodermal tumor (PNET)/sarcoma (as stated on report) and another patient had squamous cell carcinoma which could possibly be metastatic disease from an unknown primary tumor.

Out of these 113 patients who underwent thyroid surgery, 73.4% (n=83) had benign disease. Our rate of diagnosis of malignancy is lower than the BSRTC reported risk of malignancy in the last two BSRTC categories. BSRTC category 5 is especially low, which would suggest that our institution is overly-suspicious of thyroid malignancy in the pre-operative setting. In this study, the indeterminate group of BSRTC category 4 carries a higher than expected rate of malignancy in the post-operative histology. Further analysis on possible explanations for the deviation in the risk of malignancy seen in this particular BSRTC category is required, especially because the implications of overdiagnosing and missing a malignancy can be dire. This can lead to unnecessary thyroid surgery, multiple surgical procedures, complications of surgery, recurrent cancers and delayed intervention.

Further studies in this institution utilizing the newly adopted, widely accepted updated adjuncts to cytopathological assessment as recommended in the 2017 BSRTC guidelines will be of benefit to assess if this malignancy rate can be lowered. BSRTC categories 2 and 3 have similar, and expected post-operative rates of malignancy as compared to the reported standard risk for their groups.

4 DISCUSSION

The demographic profile of the study population seems to be in keeping with a typical South African academic and government-funded referral health care center (19). The rate of malignancy correlates with international trends in age distribution.

The overall accuracy rates in this study were significantly higher in certain categories (namely BSRTC 2 and 6) which is in keeping with international standards and similar to previous studies conducted on thyroid FNA accuracy. The indeterminate groups however revealed unexpected malignancy rates as compared to similar studies. These categories have long been a controversial and difficult pre-operative diagnosis to make. The use of molecular testing, sound clinical and radiological assessment has never been more imperative than in the work up of patients in these indeterminate categories. These have been stressed as important adjunctive diagnostic tools in the 2017 updated BSRTC recommendations.

The malignancy rates in our study become discordant with the reported malignancy rates put forward by the BSRTC, with categories 4, 5, and 6 being the most removed from the official purported values. In the case of BSRTC 4, this disagreement can be explained by the well accepted fact that it is difficult to differentiate between a follicular invasive carcinoma and benign disease on cytology. Notably, the category of concern is BSRTC 5 for which the diagnosis of malignancy was almost half of what is expected according to BSRTC. Other studies do not report such a wide discrepancy. Further analysis of this sub-group is required.

In terms of rate of reporting of each category, the indeterminate BSRTC categories 3 and 4 are reported too often in this study as compared to what is recommended. This could be addressed by analyzing the cytopathologists' review process.

The rate of reporting of BSRTC 5 and 6 is higher than recommended, but conversely the rate of malignancy is lower than BSRTC standards.

Limitations of the study

This study relies heavily on accurate and meticulous record-keeping in theatre archives, thus with many record reviews any errors could affect the outcomes. The study was only able to review patients who agreed to surgical procedures after a cytological diagnosis. We acknowledge that there may be a few patients (albeit a very minimal number) who refused thyroid surgery and therefore do not have post-operative histology to analyze.

In patients with multiple nodules on thyroid sonar, a significant limitation to the study was that we are unable to correlate the pre-operative cytology with the specific pathological nodule in the post-operative specimen.

TSH levels for patients in category 5 would have been helpful in proving the hypothesis that subclinical hyperthyroidism could be a cause for the overdiagnosis of follicular cancer, unfortunately these values were not obtained.

5 CONCLUSION

The rate of accuracy of this institution's pre-operative thyroid cytopathology is higher in the definitive BSRTC categories of benign (BSRTC 2) and malignant (BSRTC 6). Diagnoses made on pre-operative cytology in these two categories are very likely to

be confirmed on post-operative histology. In this study, many cases assessed as BSRTC category 3 and 4 were incorrectly categorized.

The risk of malignancy in BSRTC cytological categories 2 and 3 are similar to international standards. BSRTC categories 5 and 6 have a significantly lower rate of post-operative diagnosis of malignancy, this seems to suggest that our institution is “over-prognosing” malignancy in thyroid patients. We recommend that where an FNA is reported as “indeterminate” or category 5, a repeat image-guided FNA is advised to avoid the consequences of an overdiagnosis of cancer.

A continued audit of pre-operative thyroid cytopathology and post-operative thyroid histopathology at this institution is encouraged and required to better to validate these findings.

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APPENDICES

APPENDIX A – Approved protocol

(not to be examined)

THYROIDECTOMIES AT AN ACADEMIC HOSPITAL IN JOHANNESBURG- CORRELATION BETWEEN PRE-OPERATIVE CYTOLOGY FINDINGS AND POST-OPERATIVE HISTOLOGY RESULTS

MMED PROTOCOL

DEPARTMENT OF SURGERY, UNIVERSITY OF WITSWATERSRAND

STUDENT-DR LYDIA KILANI

STUDENT NUMBER 789488

PRIMARY SUPERVISOR- DR MARCUS SCHAMM

SECONDARY SUPERVISOR- DR DEIRDRE KRUGER

SUMMARY

Pre-operative cytological assessments of thyroid swelling have become an inexpensive, technically easy and reliable way of making a diagnosis of malignancy, as well as stratifying thyroid nodules according to risk. Since the adoption of the Bethesda system for reporting thyroid cytopathology globally we now have a standardized approach to the report of thyroid cytology. This has greatly improved decision making and aided the appropriate management of thyroid nodules. The incidence of thyroidectomies (and thyroid lobectomies) worldwide has steadily increased in recent years. The correlation between pre-operative cytological

diagnoses and post-operative histological findings provides an important tool in auditing a centre's standard and appropriateness of care. This retrospective study looks at approximately 200 thyroidectomies performed at Charlotte Maxeke Johannesburg academic Hospital from July 2013 to December 2016 and compares the pre-operative cytopathological diagnosis with the post-operative histopathological diagnosis. We expect this correlation to be similar to other large centres and mirror predicted malignancy rates stipulated by the Bethesda system for reporting thyroid cytopathology (BSRTC). Variations to the standard in our findings would indicate over or under- reporting of particular cytopathological categories and may reveal potential pitfalls in pre-operative diagnostic cytological evaluation unique to our setting.

BACKGROUND

Thyroidectomies (and thyroid lobectomies) have increased in incidence within the last few years, mainly due to an increase in pre-operative investigation of thyroid nodules and improved diagnostic and referral protocols (1). The Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is an established teaching and academic centre for endocrine surgery, mainly thyroid surgery and our knowledge, training capacity and number of complex thyroid procedures has steadily increased in the recent years. This sophisticated endocrine surgical service works as a part of a multi-disciplinary team which includes endocrinologists, radiologists and specifically cytopathologists. All facets offer valuable peri-operative work-up of patients presenting with thyroid masses. There is great effort in insuring that management protocols within the various disciplines at CMJAH are in accordance with international standard of care.

The Bethesda system for reporting thyroid cytopathology (BSRTC) was developed in 2007 in Maryland USA, (2) as a standardized system of reporting thyroid cytopathology and thereby improving communication between disciplines and international centres, aiding in thyroid malignancy risk stratification and improving the correlation between pre-operative cytological findings and post op histolopathological confirmation (2). This would subsequently lead to appropriate management of thyroid malignancies or suspected malignancies. This system of reporting is widely accepted and utilised internationally, it consists of six cytological categories, each with a corresponding percentage risk of malignancy and suggested management protocol

(Table 1). Studies done after the introduction of the BSRTC demonstrated that pre-operative fine needle aspiration (FNA) is an inexpensive and technically easy investigation that shows “superior diagnostic reliability over thyroid ultrasound and scintigraphy” (3). In 2008 Bukhari et al also demonstrated that the use of pre-operative thyroid nodule assessment with FNA is an accurate and valuable tool also in developing countries(4). This latter study was conducted in Lahore, Pakistan, and achieved similar results as other international studies (5), showing the overall accuracy of FNA findings to be as high a 87% (mirroring similar study outcomes in first world countries).Moreover sensitivity and specificity of their FNA results was reported as 90% and 87.5% respectively. We anticipate similarly high accuracy rates of our pre-operative FNA diagnostic reports.

The “pre-Bethesda era” studies also support the use of FNA as a first line investigation. A study conducted in 2000 (6) looking at 239 post-operative histology reports and comparing them with corresponding pre-operative cytology, showed FNA assessment as a useful diagnostic tool with sensitivities of 86 and 88% for predicting neoplasia and malignancies respectively, despite there not being a standardized cytological reporting protocol. This study demonstrated was a lack of formalized risk stratification and incongruence in thyroid cytopathological reporting, hence necessitating the need for the development of the BSRT. Having said that, as the BSRTC is widely utilized, continuous audits of its efficiency and post-operative congruency in multiple unique clinical environments is important. Since the implementation of the BSRTC, many institutions have reported a higher rate of malignancy detection, and a decreased rate of unnecessary thyroidectomies (7).

There are various indications for thyroidectiomy or thyroid lobectomy; benign disease, thyroid nodules with atypical cells and confirmed or suspected thyroid malignancies need to be evaluated from a clinical, radiological and cytological point of view. Indication for surgery is highly dependent on an accurate pre-operative cytopathological diagnosis, especially when malignancy is suspected. Not only does it (in conjunction with clinical and radiological assessment) dictate the need for surgery but also the type/extent of surgery that is required. Currently FNA findings (revealing

specific pathological types of thyroid malignancies) are also playing a role in the decision to perform associated lymph node dissections of the neck during thyroid surgery. Thus it is imperative to have a high quality system of cytopathological evaluation and a well accepted standardized reporting system with established management protocols that is adhered to by a functioning multi-disciplinary team in our institutions.

Our setting at Charlotte Maxeke Johannesburg Academic Hospital is unique in that it is a relatively young, but rapidly growing multi-disciplinary endocrine surgery centre. The number of thyroid surgical procedures performed has increased exponentially over the last 10 years, with strengthening collaboration between the relevant disciplines; General surgery, pathology, radiology, nuclear medicine and the medical endocrine unit. This robust partnership approach ultimately results in high quality, sound patient care, comparable with international standards despite our overwhelming patient burden and limited resources. As general surgeons, we appreciate the importance of high quality, accurate pre-operative assessments of patients with thyroid swellings as this directly impacts our surgical management plan. Therefore regular auditing and comparisons between pre-procedural cytopathological assessments and post-operative histological diagnoses is imperative. Both the endocrine surgery and the cytopathology unit benefit greatly from such invaluable information, it allows us to improve our standards of health care delivery while becoming a center of academic excellence.

Multiple international correlation studies have been conducted over the years looking at cytological versus histological findings on thyroidectomy specimens. A recent study looked at 1021 FNA samples submitted in a large Turkish hospital over a 2 year period and assessed the correlation between the cytological and histological findings on 219 of the subjects which had undergone thyroidectomies. Their findings demonstrated a 100% cytohistological correlation of lesions that were reported as benign (63% of the specimens) and the lesions that were reported as malignant (2.4%). The rates of malignancy for the indeterminate classification groups (AUS/FLUS- 12.7%; FN/SFN-35.0%; SM-91.4%) were not dissimilar to the BSRTC risk of malignancy values but

rather highlight the importance of clinical and radiological pre-operative considerations as part of a robust thyroid work-up(8).

Naz et al (9)recently looked into the diagnostic accuracy of the BSRTC at their Pakistani hospital. Based on their findings they recommended the continued use of FNA adopting the BSRTC as a first line assessment of thyroid nodules. They reported a good correlation between pre-operative cytological diagnoses and postoperative histological findings, with 100% accuracy in BSRTC 5 and 6 categories, while findings for categories 2-4 were similar as other studies and correlated with the percentage malignancy risk documented by the BSRTC. However, they noted that further clinical and radiological considerations were required when analyzing indeterminate BSRTC categories as their risk of malignancy tended to be alarmingly higher, indicating that these indeterminate categories represent weak areas in previous, non-standardized reporting systems, potentially resulting in under-diagnosing or inappropriate management of the patient. This latter finding is common in multiple studies that also assessed cytohistological congruency(7, 10, 11).

The University of Witswatersrand's Department of Pathology recently published an article on how well our local cytohistological laboratories faired in obtaining accurate malignancy rates of the BSRTC category 2 of 'atypical cells of unknown significance (AUS)" (12). The study retrospectively looked at 3 years of thyroidectomy samples and the incidence of pre-operative AUS FNA diagnosis as compared to the final histological findings. The study reported that our local laboratory has a higher malignancy rate for AUS than that predicted by the BSRTC. These results may suggest an under-reporting of this particular category. The likelihood of this and the possible causal factors needs to be investigated. Furthermore, the diagnostic accuracy of the other BSRTC categories, especially the indeterminate categories 2-4, also have to be determined as this has repeatedly been identified as an area of concern in other cytohistological thyroid correlation studies as mentioned above.

Our study proposes to add to the already growing body of work on the accuracy of the BSRTC by assessing pre-operative cytological diagnosis and post-operative histological findings in our local, resource restricted, setting. This research will determine the accuracy of the BSRTC in our setting and could highlight potential

pitfalls in our system. In addition this study could aid in building diagnostic and management protocols for thyroid nodules that are unique and appropriate in our setting.

STUDY OBJECTIVES

- To determine the accuracy of pre-operative cytological diagnosis of patients presenting with a thyroid swelling in CMJAH. This will be done by comparing their pre-operative cytopathological reports to post-thyroidectomy/lobectomy histology and assessing the congruency of the 2 reports.
- To compare FNA sensitivity and specificity rates of this institution with that of international standards.
- A secondary objective will be to describe the epidemiology of surgically managed thyroid disease in CMJAH

STUDY METHOD

- STUDY DESIGN- This will be a retrospective, observational, longitudinal study
- SITE OF STUDY- Department of Endocrine surgery at the Charlotte Maxeke Johannesburg Academic Hospital
- STUDY POPULATION- All patients who had a pre-operative thyroid FNA and underwent thyroidectomies or thyroid lobectomies at CMJAH department of Endocrine surgery from July 2013 to December 2016.
- SAMPLING-
    - Thyroid cytopathological reports performed at CMJAH from July 2013 to Dec 2016 will be pulled from NHLS records.
    - Of those that had a thyroid FNA within this period, we will only review those that underwent a thyroidectomy or thyroid lobectomy
    - Post operative histological reports of these patients will also be pulled from NHLS
    - For each patient we will record the following data- age, gender, race, pre-op diagnosis and Bathesda category, and post op diagnosis.

- All these variables will be inserted onto a spreadsheet and statistically analysed, with the aim of determining the degree of correlation between pre and post procedural diagnoses.

- INCLUSION CRITERIA- any patient who underwent a total thyroidectomy or a thyroid lobectomy at CMJAH over the period of 2011 to May 2015.
- EXCLUSION CRITERIA- patients outside of this period, patients who underwent parathyroidectomies, patients who did not have pre-operative cytological assessments performed at CMJAH, patients who are for re-excision or completion thyroidectomies.
- A pilot study is not required

EXAMPLE OF DATA CAPTURING SHEET

STUDY NUMBER

DEMOGRAPHICS

AGE

GENDER

ETHNICITY

PRE-OPERATIVE DIAGNOSIS

DATE OF OPERATION

NATURE OF OPERATION

POST-OPERATIVE DIAGNOSIS

CORRELATION YES NO

DATA ANALYSIS

This will be a quantitative research project, with analysis performed on existing institutional data.

By making use of correlational statistics, we aim to measure relationships between nominal variables, and possibly, prove a degree of multiple regression.

The specific test of statistical significance that will best suit our study is the Chi-square test.

STRATA, the biostatistics program was utilized to analyze the collected data

ETHICAL CONSIDERATIONS

Application for ethics approval will be submitted via HREC

FUNDING

This is a relatively inexpensive study to conduct, a budget of approximately R50 will be required for photocopying and other administrative costs.

PROBLEMS

This study relies heavily on accurate and meticulous record-keeping in theatre archives, any errors could affect the outcomes.

We are only looking at patients who agreed to surgical procedures after a cytological diagnosis.

TABLE 1 The Bethesda system for reporting thyroid cytopathology

Recommended Diagnostic Categories	Findings and disease	Risk of Malignancy
Nondiagnostic or Unsatisfactory	Cyst fluid only Virtually acellular specimen Other	1-4%
Benign	Consistent with lymphocytic thyroiditis Consistent with granulomatous thyroiditis Other	0-3%
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance		~5-15%
Follicular Neoplasm or Suspicious for a Follicular Neoplasm	Specify if Hurthle cell (oncocytic) type	15-30%
Suspicious for Malignancy	Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma Other	60-75%
Malignant	Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features (specify) Metastatic carcinoma Non-Hodgkin lymphoma Other	97-99%

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APPENDIX B – Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Dr L Kilani
School of Clinical Medicine
Department of Surgery
Medical School
University

E-mail: 78948@students.wits.ac.za

CC: Supervisor: Drs M Schamm and Professor D Kruger
<Deirdre.Kruger@wits.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2022/11/28

REF: R14/49

PROTOCOL NO: **M2211115** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Thyroidectomies at an academic hospital in Johannesburg - correlation between pre-operative cytology findings and post-operative histology results*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr L Kilani

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M2211115

NAME: (Principal Investigator)	Dr L Kilani
DEPARTMENT:	School of Clinical Medicine Department of Surgery Medical School University
PROJECT TITLE:	*Thyroidectomies at an academic hospital in Johannesburg - correlation between pre-operative cytology findings and post-operative histology results*
DATE CONSIDERED:	Ad hoc
DECISION:	Approved unconditionally
CONDITIONS:	Renewal of M17/06/13 - expired on 2022/08/17
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs M Schamm and Professor D Kruger
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/11/28

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 **November** and therefore reports and re-certification will be due in the month of **November** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

29/11/2022
Date

APPENDIX C – Turnitin report

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by Deirdre Kruger

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