



MAKERERE UNIVERSITY

**DIAGNOSTIC ACCURACY OF FINE NEEDLE ASPIRATION CYTOLOGY IN
PATIENTS UNDERGOING THYROIDECTOMY IN MULAGO HOSPITAL:
A CROSS SECTIONAL STUDY**

BY

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DECLARATION

I, hereby attest that the work embodied in this dissertation is my original work unless otherwise acknowledged.

This study or part of it has not been submitted for publication anywhere nor has it been submitted for award of a degree or any other qualification in any other University or institution.

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DEDICATION

This book is dedicated to my parents, Denis and Scholastic for they have seen me through thick and thin since my childhood.

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LIST OF ABBREVIATIONS

FNA: Fine needle aspiration

FNB: Fine needle biopsy

FNAB: Fine needle aspiration biopsy

FNAC: Fine needle aspiration cytology

FNS: Fine needle sampling

FNNA: Fine needle non aspiration

Ho: Null hypothesis

Ha: Alternative hypothesis

U/S: Ultrasound scan

CT scan: Computed tomography scan

SOPD: Surgical outpatient department

T3: Tri-iodothyronine

T4: Thyroxine

TSH: Thyroid stimulating hormone

NCI: National Cancer Institute

OPERATIONAL DEFINITIONS

GOITRE: An enlargement of the thyroid gland causing a swelling in the front part of the neck.

MULTINODULAR GOITRE: Goitre with multiple nodules of any size and consistency.

SOLITARY THYROID NODULE: Thyroid with one nodule.

NODULARITY: Solitary thyroid nodule or multinodular goiter.

FNAB: A diagnostic procedure for harvesting cellular material and tissue fragments used for identifying cancer.

FNAC: A technique of biopsy that employs a fine needle French gauge 23 in extracting material for diagnostic cytology.

HISTOPATHOLOGY: Microscopic examination of a biopsy or surgical specimen in order to study manifestations of disease.

SENSITIVITY OF A TEST: Measures proportion of actual positives which are correctly identified as such.

SPECIFICITY OF A TEST: Measures proportion of actual negatives which are correctly identified as such.

ACCURACY OF A MEASUREMENT: The degree of closeness of measurements of a quantity to that quantity's actual (true) value.

POSITIVE PREDICTIVE VALUE: Proportion of positive test results that are truly positive.

NEGATIVE PREDICTIVE VALUE: Proportion of negative test results that are truly negative.

FALSE POSITIVES: Incorrectly identified as having disease.

FALSE NEGATIVES: Incorrectly identified as not having disease.

PRECISION OF A MEASUREMENT: The degree to which repeated measurements under unchanged conditions show same results.

TEST VALIDITY: The extent to which a test accurately measures what it purports to measure.

GOLD STANDARD TEST: Refers to a diagnostic test or bench mark that is the best available under reasonable conditions.

ABSTRACT

Background. Thyroid disease affects about 5% of the general population worldwide. About 82% of patients attending Mulago hospital who present with thyroid disease have nodular thyroid disease. Emerging studies especially in tropical Africa with a high prevalence of nodular thyroid disease show slightly low sensitivity and specificity with FNAC compared to other studies.

The objectives of this study were to estimate the sensitivity and specificity of FNAC for thyroid disease using histopathology of excised specimen as the gold standard and to describe the histopathological diagnoses in patients with thyroid disease that have undergone thyroidectomy.

Methods. A cross sectional study with both prospective and retrospective arms. Patients with goitres underwent clinical evaluation, investigations and surgery. The study was conducted from January 2014 to April 2014. Data were entered into EPIDATA 3.1 and exported to STATA version 10 for statistical analysis.

Results. In total 99 patients were recruited, F: M ratio was 15.5:1 and median age was 42 years (IQR 34-50). The median duration of symptoms was 364 weeks (IQR 104-986). The overall incidence of malignancy was 13.3% with papillary thyroid carcinoma being the most predominant type and colloid goiter was the most predominant benign thyroid disease. The sensitivity was 61.54% and specificity 89.53%.

Conclusions and recommendations. There was a high incidence of malignancy. There was a low sensitivity and high specificity for detecting malignancy by FNAC in our setting. FNAC should be used as part of initial evaluation of thyroid nodules for malignancy before surgery.

CHAPTER ONE

1.0 BACKGROUND

Thyroid disease affects about 5% of the general population worldwide ranging from hypothyroidism, hyperthyroidism, thyroiditis, cancer of the thyroid and nodules. Nodular thyroid disease is a common clinical problem with a prevalence of 4%-7% in the adult population in North America and an annual incidence of 0.1% which translates into approximately 300,000 new nodules in the United States of America (De Groot & Hennemann, 2003; Nguyen, Lee, Ginsberg, Wragg, & Bilodeau, 2005).

Thyroid disorders are the most common endocrine disorders encountered on the African continent with environmental and nutritional factors often implicated in the occurrence of some thyroid disorders. Rates of endemic goitre range from 1% to 90% depending on the area of study with myxedematous cretinism still a prominent feature of iodine deficiency disorders (IDD) in only a few regions of the continent (Ogbera & Kuku, 2011).

The accurate diagnosis of thyroid nodules continues to challenge physicians managing patients with thyroid disease (Wang et al., 2011).

Fine needle aspiration cytology (FNAC) is one of such investigations used in evaluating patients with nodular thyroid disease. The main aim of FNAC is to identify thyroid nodules that are malignant and therefore requiring surgery and those benign nodules that can be observed clinically and decrease the overall thyroidectomy rate in patients with benign thyroid diseases (Nguyen et al., 2005). Utility of FNAC hinges on the fact that high sensitivity and specificity has been reported in several studies though histopathology still remains the gold standard.

Fine needle aspiration (FNA) biopsy is the study of cells obtained by puncturing organs of the human body with the use of small gauge needle. Doctors usually perform the procedure after

detection of a mass lesion through imaging studies such as ultrasound, computerized tomography (CT scan) and magnetic resonance imaging (MRI). The first report on the use of needles for therapeutic purposes can be found in Arab medicine in the writing of Albucasis or Abu al-Qasim Khalaf ibn al-Abbas Al-zahrawi (936-1013 AD) described first therapeutic punctures of the thyroid gland using instruments resembling modern aspiration needles. In the early 20th century, Martin and Ellis are considered to be founders of modern needle aspiration techniques. The German doctor Mannheim was the first to publish reports suggesting the use of fine needles with a small gauge. The establishment and worldwide expansion of FNA should be attributed to the representatives of Swedish school of cytopathology. The school embraced FNA in the 2nd half of the 20th century while serving as training ground for doctors around the world (Diamantis, Magiorkinis, & Koutselini, 2009).

Romanowsky staining method is one of the best available methods in cytology for immediate evaluation of thyroid FNA specimens. This stain can highlight the background watery colloid and cell architecture (papillary, monolayer sheets and macro and micro follicle) and it is able to distinguish between cell types (follicular, Hurthle, lymphocytes and macrophages). Papanicolaou stain is also vital to diagnosis of thyroid lesions for it effectively highlights the nuclear details and alterations (grooves and inclusions) which are crucial in diagnosis of papillary thyroid carcinoma. It also helps in diagnosis of Hurthle cell and C-cell lesion (Suen, 1996).

Histopathological analysis of thyroid tissue is considered gold standard in diagnosis of thyroid disease but unfortunately this is usually after surgery (the cart comes before the horse) and for sure the scope of thyroid surgery (total, near- total, subtotal, partial or lobectomy) is dictated by the form of thyroid disease.

1.2 Problem statement

Knowledge on the burden of thyroid disease in Uganda is still limited. The Mulago hospital endocrine surgical outpatient clinic attends to about 25-30 patients with thyroid disease every week and about 350-370 new patients with thyroid disease predominantly nodular goiter are seen every year (over last five years). In Mulago hospital, nodular goiter was found to constitute about 82% (Nyonyintono, Fualal, Wamala, & Galukande, 2011). About 20 thyroidectomies are done every month (Mulago hospital records).

Despite several studies showing a high accuracy with FNAC, emerging studies especially in tropical Africa and other developing countries where there is a high prevalence of nodular thyroid disease, the accuracy of FNAC has been shown to be lower than previously reported (Costamagna et al., 2013; Nyawawa, Yongolo, & Tupa, 2006) and FNA diagnostic performance has been shown to vary across different studies (Wang et al., 2011)

The diagnostic performance of FNAC in Mulago hospital is not known.

1.3 Justification

By estimating the sensitivity and specificity of FNAC in as far as benign and malignant thyroid disease is concerned, we will enable surgeons to objectively utilize the results of FNAC as they apply them in planning the appropriate surgical scope at the time of operation.

The purpose of this study is to generate preliminary data regarding the performance of FNAC in identifying patients with malignancy in our setting. If we find that a considerable proportion of patients with malignancy are misclassified and therefore initially undertreated, future studies will focus on improving tissue sampling and aspects of histopathology. It will also add to the existing body of knowledge in as far as cytological diagnosis with FNAC is concerned in the endocrine

and breast unit of Mulago hospital and the department of surgery, Makerere University College of Health Sciences (MakCHS) as a whole.

1.4 Research question

What is the diagnostic accuracy of FNAC in patients undergoing thyroidectomy in Mulago hospital?

1.5 Objectives

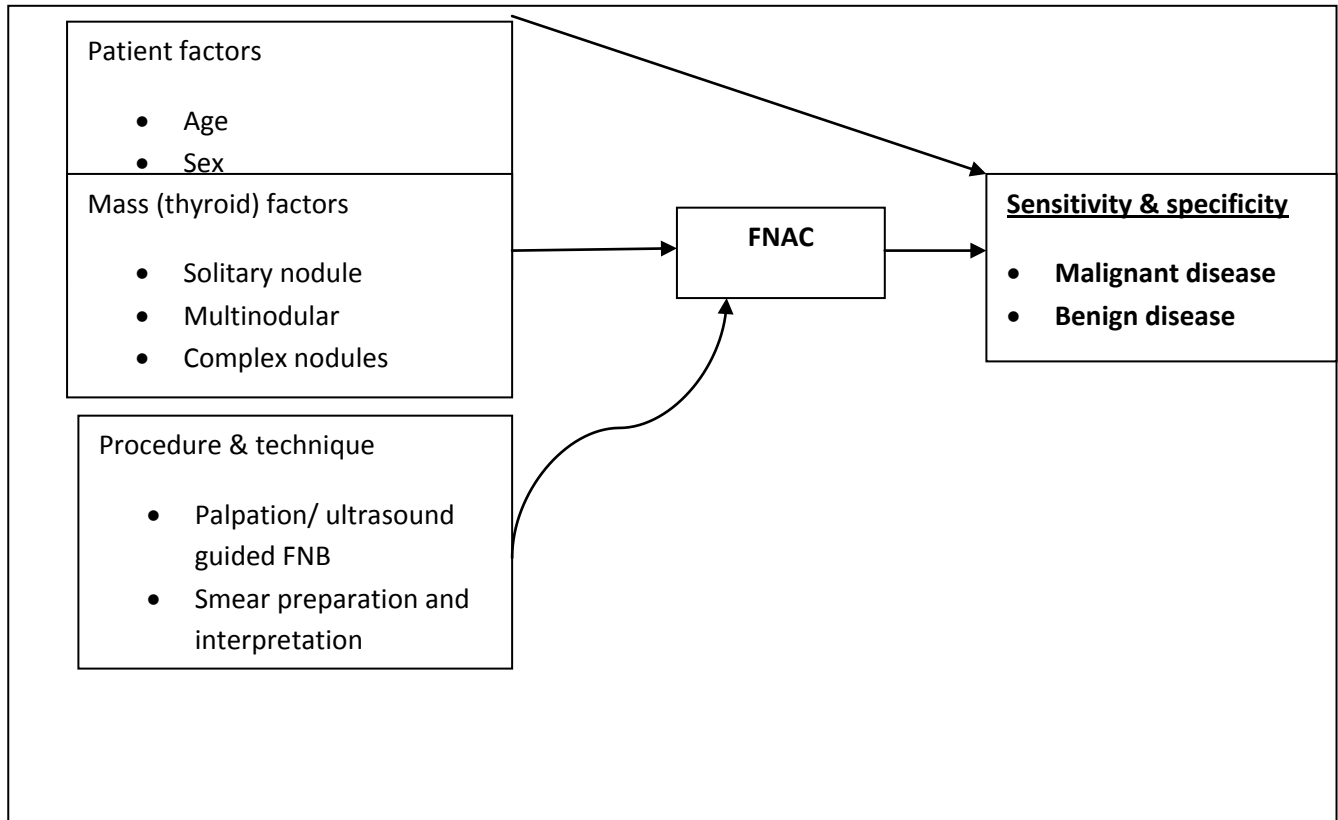
1.5.1 General objective

To determine the diagnostic accuracy of FNAC in patients undergoing thyroidectomy in Mulago hospital.

1.5.2 Specific objectives

- a) To estimate the sensitivity and specificity of FNAC for thyroid disease using histopathology of excised specimen as a gold standard.
- b) To describe histopathological diagnoses of thyroid disease in patients that have undergone thyroidectomy.

1.6 Conceptual framework



CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Role and indication of fine needle aspiration cytology

As part of initial screening for thyroid disease especially enlarged and /or nodular thyroid disease, fine needle aspiration cytology (FNAC) is one of the key investigations done when available for it has been found to be easy, fast and accurate in experienced hands of a cytopathologist (De Groot & Hennemann, 2003).

FNAC is a cost effective method in evaluating thyroid pathology preoperatively and plays a useful role in planning the surgical management of thyroid nodules however results must be interpreted with a clinical picture in mind (Bajaj, De, & Thompson, 2006; Sang, Sekadde-Kigonde, & Muchiri, 2007)FNAC has been observed to be more specific than sensitive in detecting thyroid malignancy (Kumar, Aqil, & Dahar, 2008).

FNAC is able to detect thyroid neoplasms for surgical resection and to identify non-neoplastic lesions that may be managed conservatively. This has reduced the number of diagnostic thyroid surgeries for thyroid nodules by 50-85% (Nguyen et al., 2005).

FNAC is developing into a feasible option in diagnosing Paediatric neck masses with its main advantage being its minimally invasive nature and avoidance of an open surgical procedure, on site rapid interpretation and specimen adequacy and there is good evidence that FNAC is a sensitive test in the Paediatric population and may be useful for excluding malignancy in young patients (Anne, Teot, & Mandell, 2008; Stevens, Lee, Sadatsafavi, & Blair, 2009).

However, other studies have noted low sensitivity of FNAC in thyroid disease like that reported for breast cancer in the same setting (Nyawawa et al., 2006) and in another study, there was a

high percentage of incidental cancer in patients surgically treated for benign thyroid disease (Costamagna et al., 2013).

The reliability of fine needle aspiration (FNA) as a diagnostic test is not affected by the size of the thyroid nodule like previously thought (Albuja-Cruz, Goldfarb, Gondek, Allan, & Lew, 2013; Nyonyintono et al., 2011)

2.2 Fine needle aspiration biopsy (FNAB) versus fine needle sampling (FNS) without aspiration

Fine needle sampling (FNS) without aspiration was found to be superior to fine needle aspiration biopsy (FNAB) in provision of standard follicular cells for cytodiagnosis of thyroid nodules in a study done at Mulago hospital (Nyonyintono et al., 2011).

In a meta-analysis, there is no evidence to suggest superiority of one method over the other save for the fact that FNS may be easier to perform and may produce better samples (Pothier & Narula, 2006) and therefore the method to use while procuring follicular cells should be left to the discretion of the cytopathologist.

2.3 Palpation versus ultrasound guidance in Fine needle aspiration cytology

Thyroid nodules can be aspirated manually (palpation guided) or under ultrasound guidance however ultrasound guidance has several advantages over palpation guidance like real time visualization of the needle in the lesion (Kim et al., 2008). Ultrasound guided FNA has been found to be an excellent modality for evaluation of those nodules with a non-diagnostic result on convention (palpation guided) FNAB (Braga, Cavalcanti, Collaço, & Graf, 2001)

The American Thyroid Association (ATA) recommends ultrasound guided FNAB for evaluating repeat FNA for a non diagnostic result, complex thyroid nodules and not easily palpable thyroid nodules.

2.4 Limitations of fine needle aspiration cytology

Obtaining an adequate cell sample is a pre-requisite to the success of thyroid cytology. The cytological diagnosis of thyroid nodules by FNA is complex for the following reasons: overlap of cytological patterns between neoplastic and non-neoplastic lesions, overlap of cytological features between various neoplasms, co-existence of non-neoplastic and neoplastic processes and multiple malignancies in the same gland (Gharib, 1994; Nguyen et al., 2005).

2.5 The role of surgery in management of thyroid disease

Surgery is the principle treatment for symptomatic goiters and thyroid cancers. Thyroid operations constitute a significant proportion of major elective surgery in the developing countries where endemic goitre is highly prevalent (Fualal et al., 2012). Pressure symptoms were the commonest indication for thyroid surgery at Mulago hospital (Kobusingye, 1993).

Histopathological analysis of thyroid disease in Africa shows a preponderance of nodular colloid goitre which is consistent with dietary iodine deficiency and a much higher incidence of cancer than previously recognized (Kobusingye, 1993; Nggada, Ojo, & Adelusola, 2008; Tsegaye & Ergete, 2004) and it was also noted that follicular carcinoma was more common than papillary carcinoma (Kobusingye, 1993; Nggada et al., 2008) which is clear contrast from the western world where papillary carcinoma is the most common. This underscores the fact that nodular colloid goitre is as a result of dietary iodine deficiency and long standing nodular colloid goitre is a risk factor for developing follicular thyroid carcinoma and therefore follicular carcinoma being the most common in Africa should not be surprising.

CHAPTER THREE

3.0 METHODS AND MATERIALS

3.1 Study design

This was a cross sectional (prospective and retrospective) study.

3.2 Study setting

The study was carried out from the Breast and Endocrine outpatient and inpatient and the Fine needle aspiration clinic of Mulago hospital and the Pathology department of Makerere University College of Health sciences.

Mulago hospital and complex is located on Mulago hill in Kampala, the capital city of Uganda. It is 1500 bed hospital, tertiary and the biggest national referral of Uganda with a population of about 35 million people. It is run under several directorates including Surgical services, Obstetrics and Gynaecology, Paediatrics and Child health, Internal medicine, Orthopaedics, support services, imaging among others.

The Breast and Endocrine unit is under the directorate of surgical services. It runs an outpatient clinic on Wednesday of every week. The clinic attends to about 25-30 endocrine cases predominantly thyroid disease. The unit also runs an inpatient on ward 3C (endocrine, breast and general surgical cases) and about five thyroid surgeries are done in a week.

3.3. Study procedure

Patients with thyroid disease who presented to Breast and Endocrine clinic were seen by the Intern doctors, resident doctors, registrars and consultants where a brief history and physical exam was done. In addition, several investigations were requested including thyroid function tests (TFTs), Ultrasound scan of the thyroid gland and neck, FNAC, thoracic inlet and chest x-ray, fibre optic laryngoscopy (FOL) and if need be a radionuclide scan. Depending on the results

of investigations and availability of space on the ward, patients were then admitted in preparation for surgery.

While on the ward, patients were further evaluated with a number of tests including complete blood count (CBC), renal function tests (RFTs) and electrolytes and liver function tests (LFTs). Other tests were individualized depending on need for example electrocardiography (ECG) and Echocardiography (ECHO) in known hypertensives and those above 40years. The patients also got pre-anaesthetic review to establish fitness for anaesthesia before surgery and whole blood was booked in preparation for surgery. Informed consent was sought prior to surgery.

The surgery was done on any of the three theatre days for elective surgery allotted to the Breast and Endocrine unit. Depending on the indication for surgery, a total, near-total, subtotal, lobectomy or partial thyroidectomy was done under general anaesthesia. The thyroid tissue (specimen) so removed was preserved in 10% formal saline (formalin) before being processed for histopathological examination.

Post operative care of patients was as per the routine protocol on the ward with a fluid balance, analgesia and antibiotics. Discharge of these patients from the ward was on the first or second postoperative day in absence of complications like haematoma formation and difficulty in breathing. Follow up of these patients was in the Outpatient department where their histopathology results were presented to them and a way forward was charted depending on whether results were benign or malignant.

For the retrospective arm of the study, a waiver of consent from the Ethics and Research committee of Makerere University College of Health sciences was sought and obtained. Fine needle aspiration cytology reports and corresponding histopathology reports were retrieved from the Pathology laboratory records.

Patients' information in the Pathology department are filed and bound according to year and kept in shelves in the records section. The records section is under lock and key and only accessed during working hours (8.00 AM to 5.00 PM) in presence of records' staff. Patients' thyroid FNAC reports with corresponding histopathology from January 2008 to December 2013 were manually retrieved. Patients' gender, age, cytological and histopathological diagnoses were abstracted and entered into a standard pre-tested questionnaire.

3.4 Sampling method

Consecutive sampling was used. All accessible patients admitted on the ward or seen in the SOPD with thyroid disease scheduled for surgery were enrolled in the study after fulfilling the inclusion criteria and having freely given written informed consent.

3.5 Target population

All patients with thyroid disease who had indications for thyroidectomy.

3.6 Study population

All patients with thyroid disease admitted to the ward for thyroidectomy having freely consented after meeting the eligibility criteria

3.7 Study period

January 2014 to April 2014 (4 months).

3.8 Eligibility criteria

3.8.1 Inclusion criteria

- Patients scheduled for thyroidectomy.
- Those that had a preoperative diagnosis with FNAC.
- For the retrospective arm, patients with preoperative diagnosis with FNAC with corresponding histopathological diagnosis in the last 5 years.

3.8.2 Exclusion criteria

Patients with non-diagnostic FNAC.

3.9 Study Variables

Interviews were conducted with all fully consenting patients using a standard questionnaire

From the demographics:

- age
- gender
- ethnicity/tribe
- region of residence

From the history:

- time duration and likelihood of malignancy
- head and neck radiation
- Family history of cancer

From the investigations:

- cytological diagnosis
- histopathological diagnosis as benign or malignant.
- Imaging (ultrasound and x-ray) findings

For the retrospective arm, enough information was extracted as much as possible from the cytology and histopathology reports.

3.10 Sample size estimation

Sample size was estimated using the formula for single proportions (Kelsey, 1996)

For Objective 1:

$$n = \frac{Z_{\alpha}^2 * P(1-P)}{D^2} \dots\dots\dots(1)$$

n was (a + c) when sensitivity was used as P and n was (b + d) when specificity was used as P.

$$N = \frac{(a + c)}{\text{Prevalence}} \dots\dots\dots(2)$$

Prevalence

$$N = \frac{(b + d)}{(1 - \text{Prevalence})} \dots\dots\dots(3)$$

Where:

n - proportion sample size, N – total sample size and D –precision.

Z_{α} – significance level was set at 0.05, $Z_{\alpha} = 1.96$ (two sided significance level) and Power of 80%.

From literature, the FNAC sensitivity ranged from 70% - 93.5% and specificity from 75% – 90% (Nyawawa et al., 2006). Based on Mulago hospital records, the prevalence of thyroid disorders range from 4% for malignant conditions and up to 80% for multinodular goiter. For a given test, a high sensitivity is desired if the condition of interest is common, but high specificity is preferred for rare conditions.

When a precision of 5% was used and substituted in formula 1 for a sensitivity and specificity of 90% (upper limit):

$$n = \frac{1.96^2 * 0.9(1-0.9)}{0.05^2} = 138 \text{ (lower limit of specificity/sensitivity used of 70\% , n=323).}$$

When substituted in formular (2): The sample size N used in determining FNAC sensitivity of 90% for common benign conditions with prevalence that ranged from 0.8 was:

$$N = 138/0.8 = 173 \text{ (or } N = 323/0.8 = 403)$$

When substituted in formular (3): The sample size N used in determining FNAC specificity of 90% for uncommon conditions such as malignancy with prevalence ranges of 4 – 10% was

$$N = 138/(1-0.1) \text{ to } 138/(1-0.04) = 144 \text{ to } 153 \text{ (or } N = 343 \text{ to } 359)$$

For this study,a sample size of 175 was preferable to give a precision of less than 5% for both sensitivity and specificity. This sample size was based on the upper limit of sensitivity and specificity, and thought sufficient with a goal to generate preliminary data in regard to the performance of FNAC in identifying patients with malignancy in Mulago hospital.

The prospective arm would have 75 study participants (20 thyroid surgeries per month for the study period of 4 months) where as the retrospective arm would have 100 study participants.

3.11 Specimen procurement and processing

3.11.1 Fine needle biopsy

3.12.2 Technique

Equipment: glass slides, cover slips, antiseptics, disposable gloves, fixative (absolute ethyl alcohol), swabs, 23 French (Fr) gauge hypodermic needles (23Fr, 24Fr, 25 Fr is recommended), 10 ml syringes.

The patient was made to lie supine on an examination couch with slight neck extension with a sand bag underneath the shoulders.

Gloving of hands was done and thereafter the skin was prepped with 70% ethyl alcohol in a swab. The thyroid nodule was mobilised and stabilised between the index finger and the thumb of the left hand. The most dominant nodule was the one sampled in the case of multinodular goitres.

A 23Fr gauge needle attached to a 10 ml syringe was inserted into the nodule. The plunger was retracted to create a vacuum in the needle for suction (in FNA) or without suction (FNNA). Backward and forward movements were used under constant suction with the needle moved at different depths and angles within the confines of the nodule. Biopsy manoeuvre was terminated when fluid appeared in the hub of the needle.

The plunger was released to prevent aspiration of the material into the syringe .

The needle was removed from the nodule and syringe detached. The syringe was reattached after withdrawing the plunger and air was used with the needle tip close to the glass slide, the sample was expressed on the slide. Atleast two passes were made in two different quadrants of the thyroid swelling/nodule.

With a sterile swab, pressure was applied over the biopsy site for about five minutes.

3.11.3 Smear preparation

The aspirated material was smeared on a slide labelled with the patient's laboratory number and another labelled slide was placed on the smear to evenly and thinly spread it between the two slides on pulling them apart, this made two smears per pass and therefore four smears per patient. Two slides were air dried where as the other two were fixed immediately by immersion into absolute ethyl-alcohol.

3.11.4 Staining

The air-dried smears were stained with modified wright stain (Diff-Quick) and the smears fixed with absolute ethyl alcohol were stained with Papanicolaou stain. The attending cytopathologist examined the smears for standard adequate amount of follicular cells for cytodiagnosis.

3.11.5 Reporting of results

Cytology results were categorised into 6 groups according to the Bethesda system for reporting thyroid cytopathology as Non-diagnostic, benign, follicular lesion of undetermined significance, follicular neoplasm, suspicious and malignant.

3.12 Histoprocessing of biopsy specimens after thyroidectomy

3.12.1 Fixation

This was done immediately after surgery while still in the theatre. The fixation was done with 10% formalin.

Its main objective was to preserve protoplasm with minimal alteration from the living state of the cell.

3.12.2 Embedding

The specimen was embedded in paraffin wax. This provided rigid support to tissue blocks so that it was easy to cut them into thin sections.

3.12.3 Sectioning

The paraffin wax embedded tissue specimens were sliced into very thin sections of 3-10 microns thick.

The section was then put on a clean glass microscope slide. It was warmed to let the specimen settle on the slide.

3.12.4 Staining

This was done with Eosin and Haematoxylin.

The slide was placed in a solution of paraffin solvent (xylol or tolunol) to remove the paraffin.

3.12.5 Mounting

Excess dye was washed away with water. The section was dehydrated through increasing concentration of alcohol.

A drop of mounting agent (canadian Balsam) which had the same refractive index similar to that of glass was placed on the section and the preparation covered with a cover slip and allowed to dry.

The slide was read and interpreted by the histopathologist as benign or malignant and report of the results written.

3.13 Data management

3.13.1 Data collection

Data were collected by the principal investigator using a standard pre-tested questionnaire. The following were done:

- Abstraction from cytology and histopathology reports, thyroid function test reports and imaging.
- Interviews (history taking) and physical examination.

- Consent was administered.

3.13.2 Quality assurance

- Questionnaires used were pre-tested before beginning of the actual study.
- Double entry of data
- Standard Operating Procedures for both FNAC and histopathology were followed.
- The Standards for Reporting of Diagnostic accuracy studies (STARD)(Bossuyt et al., 2003) were followed up to when this study was completed.

3.13.3 Quality control

- FNB procurement, processing and reporting was done by experienced Cytopathologists using the Bethesda system for reporting thyroid cytopathology (Cibas & Ali, 2009).
- The histopathologists examining the excised thyroid specimens were blinded to preoperative diagnosis with FNAC.
- The cytopathologists and histopathologists for FNAC and histopathology of excised specimens respectively were generally the same for both the retrospective and prospective arms of the study thus minimizing inter-observer bias.

3.13.4 Data analysis

- The original and duplicate databases entered into EPIDATA 3.1 were compared for consistency and updated using a standardized approach. After cleaning, the datasets were exported to STATA Version 10 for analysis.
- Data were summarized using median and interquartile ranges for continuous variables and proportions for categorical variables.
- Graphical descriptive analyses were presented using box plots and tables.

•Sensitivity and specificity of FNAC was estimated for malignant disease. Using the NCI (Bethesda) FNAC reporting system, only individuals with a “benign” report were considered benign cases on FNAC, where cases with “follicular neoplasm”, “suspicious for malignancy” or “malignancy” reports constituted malignant cases on FNAC. All cases enrolled in the study were included in the analysis to determine the sensitivity and specificity of FNAC for malignant conditions using a 2 X 2 table. Having failed to accrue the anticipated numbers, precision of the results obtained was computed using the enrolled numbers (N=99) which was eight (8%).

3.14 Ethical consideration

- Written informed consent was obtained from all study participants of the prospective arm of the study and a waiver of consent for the retrospective arm of the study was sought and obtained from the School of Medicine Research and Ethics Committee (SoMREC) of Makerere University College of Health sciences.
- Approval of this study was sought from the Department of surgery, MakCHS and final approval was obtained from SoMREC of Makerere University College of Health Sciences.
- Confidentiality of patients’ information and records was observed.

3.15 Role of the principal investigator

- Clinical evaluation of patients and making sure that they were ready/fit for surgery.
- Participated in the thyroid surgeries that were done by a surgeon.
- Participated in patient management on the ward both preoperatively and postoperatively.
- Data collection and proper storage.

CHAPTER FOUR

4.0 RESULTS

This study involved 99 patients, of which 45 were recruited prospectively and 54 were recruited retrospectively by retrieving their records from the Pathology department of MakCHS.

Those recruited retrospectively did not have their demographic and baseline clinical characteristics available for analysis save for age and gender.

Overall:

Age, years (IQR): 42(34-50)

Gender, n (%): Female 92(93.9)

Female: Male =15.5:1

All patients had normal laryngeal anatomy (vocal cords) on fibre optic laryngoscopy.

None of the patients had a family history of thyroid cancer and of the three who had family history of cancer other than thyroid cancer had benign disease on histopathology.

None of the patients had features suggestive of hypothyroidism (e.g cold intolerance, fatigue, poor appetite and weight gain)

Of the five solitary nodules, two (40%) were malignant and of the 40 multinodular goiter, two (5%) were malignant (p value=0.055)

In calculating sensitivity and specificity, the category of benign on FNAC was classified as “benign” and those of follicular neoplasm, suspicious for malignancy and malignancy were classified as “malignant”.

Due to failure of accruing study participants at rate that was previously anticipated, this had an impact on the sample size that was finally analyzed. The precision of these findings are at 8% instead of 5%.

Table 1. Social demographic characteristics of the prospective arm of the study**population**

Characteristics	Prospective arm (N=45)
Age, years (IQR)	46 (34-52)
Gender, n (%)	
Female	41 (91.1)
Tribe, n (%)	
Ganda	11 (24.4)
Nkole/Kiiga	6 (13.3)
Soga	3 (6.7)
Luo	0 (0.0)
Others	25 (55.6)
Marital status, n (%)	
Married/staying together	28 (62.2)
Single	7 (15.6)
Divorced/separated	2 (4.4)
Widowed	8 (17.8)
Address, n (%)	
Central	17 (37.8)
Western	7 (15.6)
Eastern	16 (35.6)
Northern	5 (11.1)
Others	0 (0.0)
Education, n (%)	
No formal education	3 (6.7%)
Primary	17 (37.8)
Secondary	14 (31.1)
Tertiary	11 (24.4)
Occupation, n (%)	
Peasant	19 (42.2)
Salaried	14 (31.1)
Self-employed/business	9 (20.0)
others	3 (6.7)

Table 2. Baseline Clinical Characteristics of the Prospective arm of the Study population

Characteristic	Prospective arm (N=45)
Anterior Neck Swelling, n (%)	45 (100)
Duration of symptoms in weeks, Median (IQR)	364 (104 – 986)
Difficulty in breathing, n (%)	33 (73.3)
Change in Voice, n (%)	16(35.6)
Heat intolerance, n (%)	1(2.2)
Palpitations, n (%)	1(2.2)
Weight gain, n (%)	2(4.4)
Radiation receipt, n (%)	1(2.2)
Family history of thyroid cancer, n (%)	3(6.7)
Goitre grade, n (%)	
Grade 1	0 (0.0)
Grade 2	0 (0.0)
Grade 3	12 (26.7)
Grade 4	33 (73.3)
Systolic BP, Median, mmHg (IQR)	127(120-150)
Diastolic BP, Median, mmHg (IQR)	80(74-90)
Pulse rate, Median, beats/minute (IQR)	80(74-88)
TSH, Median, mU/L (IQR)	0.93(0.45-1.41)
T3, Median, ng/ml (IQR)	2.8(2.2-5.4)
T4, Median, ng/ml (IQR)	21(13-92.3)

Table 3. Clinical Characteristics continued

Biochemical diagnosis, n (%)	
Euthyroid	37(84.1)
Hyperthyroid	5(11.4)
Hypothyroid	2(4.6)
Number of nodules, n (%)	
Solitary	5(11.1)
multinodular	40(88.8)
Size of largest nodule, mm (IQR)	39(29-54)
Site of nodules, n (%)	
Left	10(22.2)
Right	3(6.7)
Bilateral	32(71.1)
Retrosternal extension, n (%)	10(22.2)
Lymphadenopathy, n (%)	1(2.2)
Trachea on x-ray, n (%)	
Normal trachea	15(33.3)
Tracheal compression	10(22.2)
Tracheal deviation	25(55.6)
Thyroid soft tissue shadow calcification	2(4.4)

Table 4. Distribution of histopathological diagnoses overall and by method of participant enrollment

Diagnosis	Overall, N=99, n (%)	Prospective, N=45, n (%)	Retrospective, N=54, n (%)
Colloid goitre	65 (65.7)	34	31
Nodular goitre	16 (16.2)	4(8.9)	12(22.2)
Papillary carcinoma	11 (11.1)	3(6.7)	8(14.8)
Follicular carcinoma	2 (2)	1(1)	1(1)
Chronic thyroiditis	2 (2)	1(1)	1(1)
Follicular adenoma	1 (1)	0(0)	1(1)
Inflammatory cyst	1 (1)	0(0)	1(1)

Table 5. The relations between cytological and histopathological diagnosis

FNAC	Histopathology		Total
	Malignant	Benign	
Benign	5	77	82
Follicular neoplasm	4	4	8
Suspicious	2	3	5
Malignant	2	2	4

Table 6. Summary of results from the 2 x 2 table

Sensitivity, % (CI)	61.5 (35.5-69.0)
Specificity, % (CI)	89.5 (81.3-94.4)
Positive predictive value (PPV), % (CI)	47.1 (26.2-69.0)
Negative predictive value (NPV), % (CI)	93.9 (86.5-97.4)
False positive rate (FPR), % (CI)	10.5 (5.6-18.7)
False negative rate (FNR), % (CI)	38.5 (17.7-64.5)
Accuracy, % (CI)	85.9 (77.7-91.4)

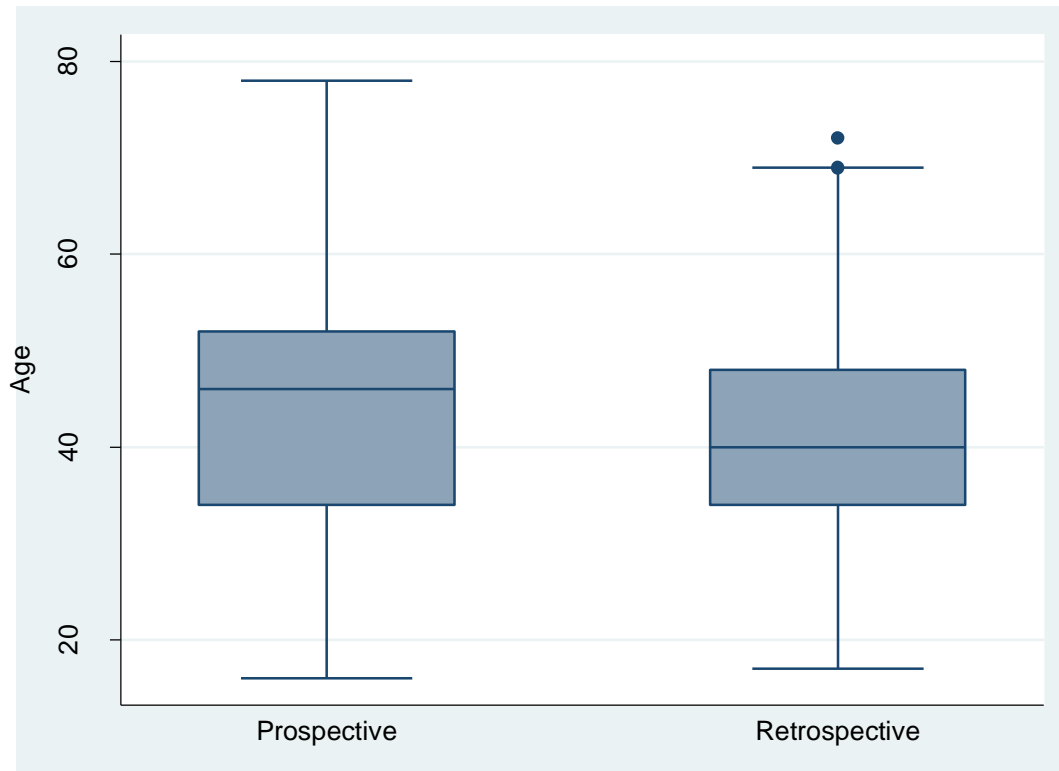


Figure 1. Box plot showing distribution of age (years) within and between the prospective and retrospective arms of the study population.

The two groups are comparable in age distribution and therefore homogenous to a large extent. They were thus analyzed together.

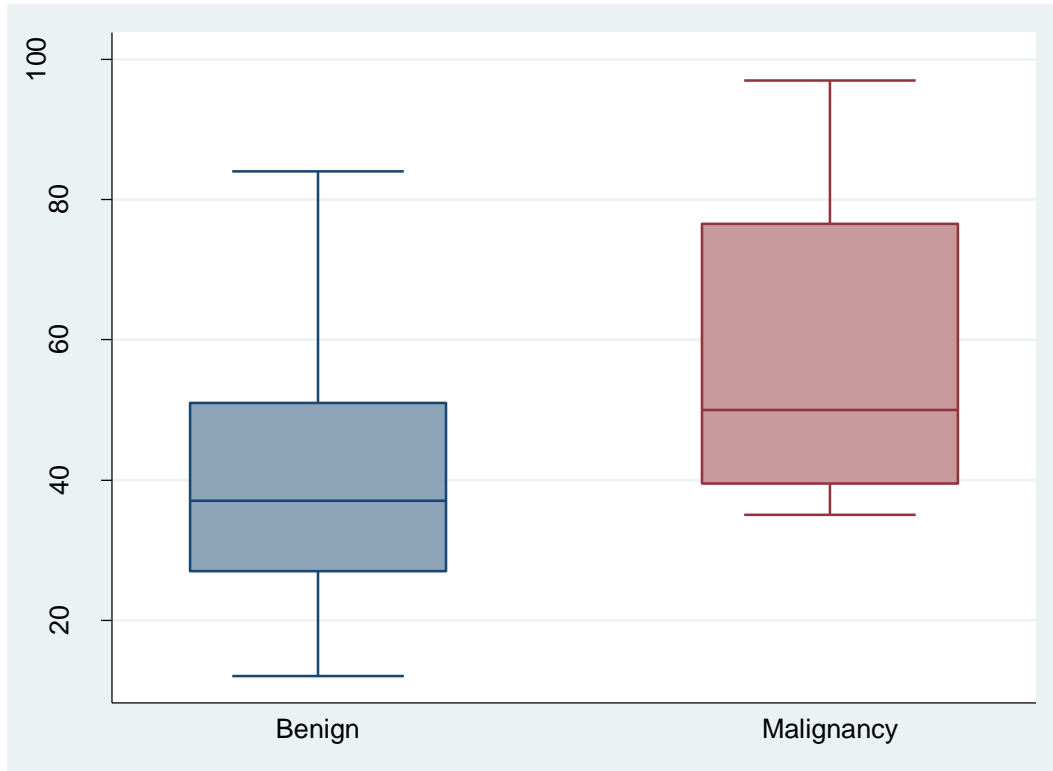


Figure 2. Box plot showing the distribution of nodule size between benign and malignant thyroid nodules.

Malignant nodules tended to be bigger with a median size of 50 mm (IQR 39.5-76.5) compared to benign nodules with a median size of 37 mm (IQR 27-51) although this was not statistically significant (p value of 0.055).

CHAPTER FIVE

5.0 DISCUSSION

5.1 Demographic and clinical characteristics of study participants.

Fine needle aspiration cytology (FNAC) is regarded as the best initial investigation in the diagnosis of thyroid nodules for it has been found to be safe, quick, simple, done as an outpatient procedure, repeated if necessary, good patient compliance and reliable with low complication rates (Bajaj et al., 2006; Likhar, Hazari, Gupta, & Shukla, 2013; Sang et al., 2007; Sinna & Ezzat, 2012). Despite the high sensitivity and specificity for detecting malignancy that is usually reported especially in the Western world (Albuja-Cruz et al., 2013), other studies especially in poor resource settings have noted relatively low sensitivity (Costamagna et al., 2013; Nyawawa et al., 2006; Wang et al., 2011).

This study was undertaken to provide preliminary data about the performance of FNAC in patients undergoing thyroidectomy in order to establish whether a considerable proportion of patients with malignancy are misclassified on FNAC and therefore end up being surgically undertreated.

From January 2014 to April 2014, ninety nine patients with thyroid disease/nodules were recruited from the Breast and Endocrine unit (clinic and ward 3C) of the Directorate of Surgical services at Mulago hospital, of which records of 54 out of 99 were retrieved from the Pathology department laboratory and reviewed.

In this study, the median age of patients was 42 years, the youngest was 16years and the oldest was 78 years. In a related study in Uganda the median age was 43.2 years (Nyonyintono et al., 2011), in Tanzania it was 42.7 years (Nyawawa et al., 2006), in Egypt it was 44years (Sinna & Ezzat, 2012).

The female to male ratio was 15.5:1 meaning that this is predominantly a disease of women. This was observed in a related study in Uganda, F: M was 21:1 (Nyonyintono et al., 2011), in Kenya, F: M was 7:1 (Sang et al., 2007)

The Baganda as a tribe had the single most number of patients at 24.4% (table 1) probably because Mulago hospital is located in Central Uganda which has Baganda as the most predominant tribe.

In all patients the main presenting complaint was an anterior neck swelling with median time interval to presentation of 364 weeks (7 years). The long time interval to presentation could probably explain the fact that all patients had either grade 3 or grade 4 goitre grades.

On Ultrasound scan, majority of patients (88.9%) had multinodular goiter and 71.1% were bilateral. Most goiters in resource poor settings are multinodular and this further emphasizes the fact that iodine deficiency disorders (IDD) is the top most cause of thyroid disorders on the African continent and that this is often affected not only by the iodine status in the region but sometimes also by selenium deficiency and thiocyanate toxicity (Bimenya, Kaviri, Mbona, & Byarugaba, 2002; Ogbera & Kuku, 2011).

The commonest indication for surgery was pressure symptoms (73.3%) especially difficulty in breathing and some patients had more than one indication (table 2). (Kobusingye, 1993) and (Fualal et al., 2012) also reported similar findings. This probably can be attributed to big goiter grades (refer to table 2) that usually compress the surrounding structures in the neck notably the trachea, oesophagus and the recurrent laryngeal nerve.

5.1 Sensitivity and Specificity of fine needle aspiration cytology.

In this study, the sensitivity and specificity for detecting malignancy on FNAC was 61.5% and 89.53% respectively and the overall accuracy was 85.9%. Just like other studies with a high

prevalence of multinodular goiter, the sensitivity for detecting malignancy is relatively low where as specificity is high. (Nyawawa et al., 2006) found 66.7% & 92.5% and (Ch, Maharajan, & Rao, 2012) found 80.2% & 98.9% for sensitivity and specificity respectively. For most studies, the diagnostic accuracy of more than 90% is seen in malignant disease and about 77.8% in benign disease (Likhari et al., 2013).

Despite all said and done, for a rare disease (like in this case where thyroid cancer is relatively uncommon), specificity is the most desirable so that when the test result is negative (Akobeng, 2007) then chances are very high that the individual has no disease and indeed the negative predictive value in this study was 93.9% meaning that when FNAC classifies a patient as having benign disease, then chances of having thyroid cancer are very low.

5.3. Patterns of final histopathological diagnosis

In this study, majority of the goiters were benign (86.9%) and among these were colloid goiter, nodular goiter, chronic thyroiditis, follicular adenoma and inflammatory cyst.

The incidence of malignancy in this study was 13.1%. In a similar study in Uganda, the malignancy rate was 19.6% (Kobusingye, 1993), in Tanzania it was 18.6% (Nyawawa et al., 2006). This contrasts with what is reported in Europe and North America where incidence of malignancy in thyroid nodules is about five percent (Wang et al., 2011). The difference could probably be attributed to the fact that a significant proportion of long standing multinodular goiter in areas endemic with IDD tend to undergo malignant transformation.

Of the malignant histopathology, majority (84.6%) were papillary thyroid carcinoma (PTC) and the rest were follicular thyroid carcinoma (FTC). In a related study in Uganda, FTC predominated at 59.1% (Kobusingye, 1993) and in Tanzania, FTC predominated at 72.2% (Nyawawa et al., 2006). It is now noted that for differentiated thyroid carcinoma (DTC), there is

a changing trend towards the frequent occurrence of PTC compared to FTC and this may be attributable to wide spread iodization programs (Ogbera & Kuku, 2011).

5.4. Study limitations

- For the retrospective arm, blinding of the histopathologist to the corresponding cytological diagnosis with FNAC may not have been observed.
- The number of study participants (patients) did not accrue as fast as previously anticipated during proposal development for both arms of the study. This might have affected the findings of this study though not significantly. The prospective arm was dependent on availability of theatre space which at times was unpredictable because of factors beyond the principal Investigator's control whereas the retrospective arm was limited by poor and to a large extent uncomputerised record keeping.
- The many pathologists who were involved in reporting histopathology could have introduced a random error where the malignancy rate could have been over- or underestimated however the observed average estimate is usually accurate.
- The findings of this study may not be generalized because of the relatively small numbers involved in analysis.

CHAPTER SIX

6.0. CONCLUSIONS

This study at Mulago hospital reveals high specificity and a low sensitivity for Fine needle aspiration cytology (FNAC) at detecting malignancy in thyroid nodules. FNAC should be considered as part of initial evaluation of thyroid nodules for malignancy. These findings are with a precision of eight percent (8%) and this gives good preliminary data in performance of FNAC in thyroid disease in our setting.

6.1. Recommendations

- A large prospective study needs to be undertaken to further evaluate the diagnostic accuracy of fine needle aspiration cytology (FNAC) in thyroid disease in our setting but also to investigate whether the changing trend towards the frequent occurrence of papillary thyroid carcinoma (PTC) compared to follicular thyroid carcinoma (FTC) is indeed true.
- All records including patient information should be computerized so that they are easy to retrieve and in case trends of disease need to be analyzed or research needs to be done for purposes of planning or policy formulation, then it becomes easy just by click of a button.

6.2 Dissemination of results

The findings of this study shall be disseminated and made available to:

- Department of Surgery, MakCHS
- Sir Albert Cook library, MakCHS
- School of Medicine, MakCHS
- Directorate of Research and Graduate Training, Makerere University
- My Supervisors

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APPENDIX I: CONSENT FORM IN ENGLISH

About the principal investigator

Dr. Robert Masereka, a Postgraduate student of Department of Surgery Makerere university College of Health sciences is carrying out a study to determine the diagnostic accuracy of fine needle aspiration cytology in patients undergoing thyroidectomy in Mulago hospital.

This study will help doctors who evaluate patients with thyroid disease how good fine needle aspiration cytology is in distinguishing benign disease from malignant (cancer) disease.

Study procedure

If you qualify for the study and decide to be a participant, you will be expected to do the following:

In the endocrine SOPD or on the ward, you will be interviewed concerning thyroid disease and thereafter a clinical examination will be done by the attending doctor.

Fine needle aspiration cytology (FNAC) will be requested in addition to the routine investigations for thyroid disease.

You will then be admitted to breast and endocrine inpatient (ward 3C) depending on whether you have an indication for surgery (thyroidectomy).

Routine preoperative assessment will be done while on the ward.

On the allocated operation day, an operation will be done to remove part or the whole thyroid gland depending on the reason why you are being operated.

The thyroid tissue removed after operation will be taken for histopathological analysis.

Benefits and risks

You will benefit by having your thyroid disease evaluated for cancer before operation and then confirm after the operation whether you actually have cancer or not and will then be advised accordingly.

No significant complications are expected while doing the FNAC except for slight pain with minor bleeding or swelling at the site and this is irrespective of whether you are a study participant or not.

Operation for thyroid disease is a major operation and therefore carries risks (related to anaesthesia and to the operation) however these risks are in no way increased by this study for they cut across the board for any one undergoing thyroid surgery.

Payment

No payment will be made to you or expected from you as per this study.

Questions

Regarding any concerns, problems or questions that may arise related to this study, you are free to contact **Dr. Robert Masereka**, telephone contact: **+256 779129580**.

If you have queries about your rights as a participant in this study, please contact the Chairman School of Medicine Research and Ethics committee on **0772494120**.

Rights to withdraw from the study.

You are free to withdraw from this study at any time without being denied any medical care.

A consent form will be provided to you if you so wish to participate in the study.

STATEMENT OF CONSENT

I have been fully explained to the nature and purpose of this study, risks and benefits in a language that I understand. I also understand that I can withdraw from the study any time and

this will not affect any medical care that is being rendered and my rights as a patient will not be affected.

I hereby sign below as proof of my consent to participate in the study.

Name.....

.....

Signature/thumbprint.....date.....

I have explained the purpose of this study to the respondent to the best of my knowledge and conviction and he/she has understood the purpose, procedure and benefits/risks to him/her

Sign.....date.....

.....

(PI/research assistant).

APPENDIX II: CONSENT FORM IN LUGANDA

EKITUNDU (i): FOMU EKAKASA OKUKKIRIZA OKWETABAMU, ERI MU LULIMI LUGANDA

OMUTWE: OBWEGENDEREZA OBUKOZESEBWA MU KULONGOOSA AMALOOKOOLI MU BALWADDE ABALI MU DDWALIRO LY'E MULAGO.

Anoonyereza omukulu: Ye musawo Masereka Robert. Ali ku diguli yakubiri mu kitongole ky'abasawo abalongoosa mu ttendekero ly'e Makerere Yunivaasite mu kolegi y'eby'obulam. Anoonyereza ku bwegendereza obukozesebwa ng'abasawo beeyambisa empiso mu kulongoosa amalookooli mu ddwaliro e Mulago. Ali ku ssimu +256-779129580.

Okunoonyereza kuno kwakuyamba nnyo abasawo abakola okunoonyereza kuno mu kunoonyereza obulwadde bw'amalookooli ko n'okubwawula ku ndwadde endala nga kookolo. Era kino kinaalaga obulungi bw'okukola okunoonyereza kuno nga omusawo abadde beeyambisa empiso.

Emitendera gy'okuyitamu: Ng'okkirizza era ng'amateeka gakukkirizza okwetaba mu kunoonyereza kuno, onookola bino wammanga;

Ng'oli ku woodi ekola ku balwadde abalongooseddwa, onoobuuzibwa ebibuuzo ebikwata ku ndwadde y'eddookooli era oluvannyuma omusawo akutwala anaatandikira awo okukujjanjaba. Ng'ojjeeko okunoonyereza ku bulwadde bw'eddookooli, wanaabaawo okuteekateeka omulwadde okumulongoosa ng'omusawo yeeyambisa empiso mu kunoonyereza ku bulwadde bw'eddookooli.

Olwo wano eyeetabye mu kunoonyereza anaaweebwa ekitanda ku woodi 3C okukeberebwa amabeere. Wabula kinaasinziira naddala nga kizuuliddwa nti ddala omulwadde yeetaaga okulongoosebwa eddookooli. Kino kinaddirira okuteekateeka oyo yenna anaaba yeetabye mu kunoonyereza kuno era ku woodi okwo.

Ku lunaku okulongoosa kuno kwe lunaaba lulagiddwa, wanaabaawo okulongoosa okunaagendereranga okujja ekitundu kye kizimba oba ekitundutundu kyakyo era nga kino kinaasinziira ku nsonga lwaki omuntu oyo anaaba alongoosebwa. Ekizimba oba ekitundutundu kyakyo ekinaaba kigyiddwamu kinaatwalibwa okwongerera okunoonyerezebwo mu kasenge omwekenneenyebwa ebitundu nga bino.

Ebirungi ebinaavaamu: Onooganyulwa olw'ensonga nti, obulwadde bw'eddookooli bunaaba bukenenulwa bulungi okuzuula obanga onoobaamu ne kookolo nga tonalongoosebwa. Olwo oluvannyuma lw'okulongoosebwa nga kizuuliddwa nti kookolo mwali, abasawo banaakuwa amagezi.

Obunkenke obunaabaamu: Omulwadde anaafuna obulumi obutonotono naddala ng'afumitibwa akayiso mu bulago, awo awali ekizimba. Era Wanaabaawo okuvaamu otusaayi otutonotono era n'okuzimba okutonotono era kino kyakutwaliramu yenna anaaba yeetabyemu oba nedda.

Okulongoosa amalookooli kulongoosa kwa njawulo era kino kitegeeza nti, kinaaleetawo obunkenke. Naye era, obunkenke buno tebuleetebwa kunoonyereza kuno. Kimanye era nti obunkenke buno butuukirira oyo yenna alongoosebwa eddookooli.

Ensasula y'ebisale: Okukujjanjaba kwonna kunaaba kwa bwereere, kale tewaabe nsimbi yonna eneekugyibwako.

Ebibuuzo oba kale okwemulugunya kwonna: Ensonga yonna kakube kwemulugunya okw'engeri yonna oba na buli kibuuzo kyonna ekikwata ku kunoonyereza kuno, onooba waddembe okubuuza omusawo **Masereka Robert** era ssimuye yiino: **+256 779129580**. Ali ku diguli ya kubiri ku ttendekero ly'e Makerere mu kitongole omuli abasawo abalongoosa. Ekitongole kino kiri mu kolegi yabyabulamu. Ng'oyina ensonga yonna ekwata ku ddemberyo yadde okwemulugunya kwonna, osobola okukubira ssentebe atwala eby'okunoonyereza awamu n'empisa mu kolegi eno ey'eby'obulamu. Essimuye yiino: **0772494120**.

Eddembe ly'obwebange eri eyeetabyemu: Aneetabamu yenna anaasobola okuva mu musomoguno, wonna waanaaba ayagalidde. Wabula tekiitegeze nti kino kinaataataaganya obujjanjabi omulwadde bw'anaaba afuna oba bweyandifunye oluvannyuma. Onooweebwa foomu gy'onojjuzaamu ng'oyagadde okwetaba mu kunoonyerezakuno.

Enkuuma y'ebyama:

Byonna ebinaaba bikukwatako ng'omulwadde binaakuumibwa nga byakyama nnyo era binaakuumibwa butiribiri. Amannyago newoosangibwa tebiiteekebwe ku kyonna ekinaaba bifulumiziddwa. Tewaabe anaasobola kukumanya, kuba mu linnyalyo tunaakozesa nnamba oli aleme kukutegeera. Era zino zezinaatuyamba okukungaanya ebinaaba bivudde mu kunoonyereza. Obukugu n'enkuuma y'ebyama enneekusifu eneeyoleka mu nkola y'omusawo anoonyereza mu balwadde abanaaba bafunye obukosefu obw'amaanyi.

Nga nteeka omukono ku kiwandiiko kino, ke kabonero akalaga nti byonna ebintegeezeddwa mbikkirizza, nti era ngenda kwetaba mu kunoonyereza kuno. Naaba waddembe okuva mu

musomo guno wonna wennaaba njagalidde, so nga kino tekiitaataaganye bujjanjabi bwonna bwennaaba nfuna, kuba bujja kugenda bugenzi mu maaso.

Bwekityo kanteeke omukono ku kiwandiiko kino ng'akabonero akakakasa nti nzikirizza okwetaba mu kunoonyereza kuno.

EKITUNDU B: EKIRAGA OKUKKIRIZA KW'EYEETABYE MU KUNOONYEREZA

Omukono oba ekinkumu ky'omulwadde oba omujjanjabi.....

Ennaku z'omwezi eza leero

Essimu yange

Omukono gw'anoonyereza

Ennaku z'omwezi

Essimu yange

APPENDIX III: ASSENT FORM IN ENGLISH

STUDY TITLE: DIAGNOSTIC ACCURACY OF FINE NEEDLE ASPIRATION CYTOLOGY (FNAC) IN PATIENTS UNDERGOING THYROIDECTOMY IN MULAGO HOSPITAL.

PRINCIPAL INVESTIGATOR

Dr.Robert Masereka (MBChB), Department of Surgery.

Mobile Phone number 0779-129580.

INTRODUCTION

You are requested to participate in a research study about the Diagnostic accuracy of fine needle aspiration cytology in patients undergoing thyroidectomy in Mulago hospital. The study requires that you are a patient with a goiter (thyroid enlargement) which is a swelling in the front part of the neck and that you meet our study criteria. This study shall be carried in the Endocrine and Breast unit of Mulago hospital and Department of Pathology, MakCHS.

PURPOSE OF THE STUDY

The study will help the doctors that evaluate patients with thyroid disease how good fine needle aspiration cytology is in differentiating benign and malignant (cancer) thyroid disease.

PROCEDURE

If you qualify for the study and decide to be a participant, you will be expected to do the following:

In the endocrine SOPD or on the ward, we will seek from you some information concerning your thyroid disease and thereafter a clinical examination will be done by the attending doctor.

Fine needle aspiration cytology (FNAC) will be requested in addition to the routine investigations for thyroid disease. This involves a needle and a syringe which is used to

remove/extract a sample of fluid from your thyroid swelling. This fluid will be analyzed to tell us whether you have cancer or not. Basing on these findings and the rest of the assessment, the type of thyroid surgery will be decided before the actual operation.

You will then be admitted to breast and endocrine inpatient (ward 3C) as you await surgery (thyroidectomy).

Routine preoperative assessment will be done while on the ward.

On the allocated operation day, an operation will be done to remove part or the whole thyroid gland depending on the reason why you are being operated.

The thyroid tissue removed after operation will be taken for histopathological analysis.

CONFIDENTIALITY

All information which is collected about you during the course of the research will be kept strictly confidential. You will not be identified by name in any research reports or publication that may arise from this study. Data will be stored in locked up files and will be available only to the principal investigator and supervisors.

BENEFITS AND RISKS

You will benefit by having your thyroid disease evaluated for cancer before operation and then confirm after the operation whether you actually have cancer or not and will then be advised accordingly.

No significant complications are expected while doing the FNAC except for slight pain with minor bleeding or swelling at the site and this is irrespective of whether you are a study participant or not.

Operation for thyroid disease is a major operation and therefore carries risks (related to anaesthesia and to the operation) however these risks are in no way increased by this study for they cut across the board for any one undergoing thyroid surgery

PAYMENT

No payment will be made to you or expected from you as per this study

RIGHTS TO REFUSE OR WITHDRAW

You may refuse to participate in this study or withdraw your assent at any time and your withdrawal will not affect you in any way.

WHOM TO CONTACT

If at any time you have further questions or concerns you can contact the investigators:

- **Dr. Robert Masereka** (0779129580)
- **Dr. Jane Fualal**, Department of Surgery, Mulago Hospital (0772501662)
- **Dr. Dan Wamala**, Department of Pathology, Mulago Hospital (0752811711)

For ethical consideration please contact the Chairperson, school of medicine Research and Ethics Committee (SOMREC):

Prof. James K. Tumwiine: (Mobile number: 0772494120)

AUTHORISATION TO PARTICIPATE IN THE RESEARCH STUDY

I have read and understood the assent for this study. I have had the opportunity to ask questions which have been answered to my satisfaction. I was also informed that the information I will provide will be kept confidential and that my participation in this study is voluntary and that no consequences will result if I refuse to participate or withdraw from the study.

I hereby give my informed assent to participate in this study

.....

Name of child

Child's signature or thumb print

Date

.....

Name of investigator/Research assistant

Signature

Date

APPENDIX IV: ASSENT FORM IN LUGANDA

EKITUNDU IV: FOOMU EKAKASA OKUKKIRIZA OKWETABAMU , ERI MU

LULIMI LUGANDA

**OMUTWE: OBWEGENDEREZA OBUKOZESEBWA MU KULONGOOSA
AMALOOKOOLI MU BALWADDE ABALI MU DDWALIRO LY'E MULAGO.**

Anoonyereza omukulu: Ye musawo Masereka Robert. Ali ku diguli yakubiri mu kitongole ky'abasawo abalongoosa mu ttendekero ly'e Makerere Yunivaasite mu kolegi y'eby'obulamu. Anoonyereza ku bwegendereza obukozesebwa ng'abasawo beeyambisa empiso mu kulongoosa amalookooli mu ddwaliro e Mulago. Ali ku ssimu +256-779129580.

Ennyanjula: Osabiddwa okwetaba mu kunoonyereza okukwata ku kulongoosa amalookooli mu balwadde abali mu ddwaliro e Mulago. Okwetabamukwo kukwetaagisa okuba ng'olimulwadde wa ddookooli era ng'otuunana n'enteekateeka yaffe. Okunoonyereza kuno kunaakolebwa mu kifo awakeberegwa amabeere awamu n'amalookooli, awamu n'ekitongole omukeberegwa obunyama mu ttendekero ly'e Makerere yunivaasite.

Ekiruubirirwa: Okunoonyereza kuno kwakuyamba nnyo abasawo abakola okunoonyereza kuno mu kunoonyereza obulwadde bw'amalookooli ko n'okubwawula ku ndwadde endala nga kookolo. Era kino kinalaga obulungi bw'okukola okunoonyereza kuno nga omusawo abadde beeyambisa empiso.

Emitendera: Ng'okkirizza era ng'amateeka gakukkirizza okwetaba mu kunoonyereza kuno, onookola bino wammanga;

Ng'oli ku woodi ekola ku balwadde abalongooseddwa, onoobuuzibwa ebibuuzo ebikwata ku ndwadde y'eddookooli era oluvannyuma omusawo akutwala anaatandikira awo okukujjanjaba. Ng'ojjeeko okunoonyereza ku bulwadde bw'eddookooli, wanaabaawo okuteekateeka omulwadde okumulongoosa ng'omusawo yeeyambisa empiso mu kunoonyereza ku bulwadde bw'eddookooli. Kineetaagisa okweyambisa empiso eneeyambisibwa okusika amazzi aganaaba mu ddookooli. Era amazzi gano gaatwalibwa okwekenneenyebwa okuzuula oba eddookoolo eryo lirimu kookolo oba nedda.

Olwo wano eyeetabye mu kunoonyereza anaawebwa ekitanda ku woodi 3C okukeberegwa amabeere. Wabula kinaasinziira naddala nga kizuuliddwa nti ddala omulwadde yeetaaga okulongoosebwa eddookooli. Kino kinaddirira okuteekateeka oyo yenna anaaba yeetabye mu kunoonyereza kuno era ku woodi okwo.

Ku lunaku okulongoosa kuno kwe lunaaba lulagiddwa, wanaabaawo okulongoosa okunaagendereranga okujja ekitundu kye kizimba oba ekitundutundu kyakyo era nga kino kinaasinziira ku nsonga lwaki omuntu oyo anaaba alongoosebwa. Ekizimba oba ekitundutundu kyakyo ekinaaba kigyiddwamu kinaatwalibwa okwongerera okunoonyerezebwo mu kasenge omwekenneenyebwa ebitundu nga bino.

Ebirungi ebinaavaamu: Onooganyulwa olw'ensonga nti, obulwadde bw'eddookooli bunaaba bukenenulwa bulungi okuzuula obanga onoobaamu ne kookolo nga tonalongoosebwa. Olwo oluvannyuma lw'okulongoosebwa nga kizuuliddwa nti kookolo mwali, abasawo banaakuwa amagezi.

Enkuuma y'ebiyama: Ebikukwatako byonna ebinaaba bikugyiddwako mu kunoonyereza kuno binaakuumbwa nga bya kyama nnyo. Tewaabe muntu yenna anaasobola kumanya bikukwatako mu kiwandiiko kyonna. Byonna ebinaaba bikugyiddwako byakuumibwa butiribiri mu fayiro era omusawo yekka gwe kikwatako oba abalondoozi b'omusawo akola okunoonyereza kuno.

Ebirungi n'obunkenke obunaabaamu: Yenna eyeetabyemu anaasobola okukeberegwa oba eddookooliye lirimu obulwadde bwa kookolo oba nedda. Era oluvannyuma lw'okulongoosebwa anaamanya nti ayina kookolo oba nedda. Olwo wano omuntu oyo anaawebwa amagezi okusinziira ku binaaba bifulumiziddwa.

Ku luuyo lw'obunkenke, omulwadde anaafuna obulumi obutonotono naddala ng'afumitibwa akayiso mu bulago, awo awali ekizimba. Era Wanaabaawo okuvaamu otusaayi otutonotono era n'okuzimba okutonotono era kino kyakutwaliramu yenna anaaba yeetabyemu oba nedda.

Okulongoosa amalookooli kulongoosa kwa njawulo era kino kitegeeza nti, kinaaleetawo obunkenke. Naye era, obunkenke buno tebuleetebwa kunoonyereza kuno. Kimanye era nti obunkenke buno butuukirira oyo yenna alongoosebwa eddookooli.

Ensasula y'ebisale: Okukujjanjaba kwonna kunaaba kwa bwereere, kale tewaabe nsimbi yonna eneekugyibwako.

Eddembe ly'obwebange eri eyeetabyemu: Aneetabamu yenna anaasobola okuva mu musomo guno, wonna waanaaba ayagalidde. Wabula tekiitegeeze nti kino kinaataataaganya obujjanjabi

omulwadde bw'anaaba afuna oba bweyandifunye oluvannyuma. Onooweebwa foomu gy'onojjuzaamu ng'oyagadde okwetaba mu kunoonyerezakuno.

Ani ow'okutuukirira? Ng'obadde n'ekibuuzo kyonna ekikwata ku kunoonyereza kuno, osabiddwa okutuukirira abantu bano wammanga:

- Omusawo **Masereka Robert** essimuye: (0779129580)
- Musawo **Jane Fualal**, ali mu kitongole ky'abasawo abalongoosa e Mulago. (0772501662)
- Ne musawo **Dan Wamala** mu kitongole kya pathology mu ddwaliro e Mulago (0752811711).

Ku nsonga eyeekuusa ku neeyisa, osabiddwa okutuukirira Ssentebe atwala akakiiko mu k'ebiyabanoonyereza eby'eddagala n'empisa. (SOMREC), era ye mukenkufu **James K. Tumwine: (0772494120)**

Okukkiriza okwetaba mu kunoonyereza kuno: Nsomye bulungi era nentegeera byonna ebikwata ku kunoonyereza kuno. Ebibuuzo byonna byembuuzizza binziriddwamu bulungi era nembitegeera. Ntegeezeddwa nti ebinaavaamu byonna byakukuumibwa nga bya kyama, nti era n'okwetabamu kwange kunaaba kwa kyeyagalire. Era ntegeezeddwa nti nga nsazeewo okwekutula mu kunoonyereza kuno tekiikose gugenda kwange mu maaso nga nzijanjabwa..

Nga nteeka omukono ku kiwandiiko kino, ke kabonero akalaga nti byonna ebintegeezeddwa mbikkirizza, nti era ngenda kwetaba mu kunoonyereza kuno.

Bwekityo kanteeke omukono ku kiwandiiko kino ng'akabonero akakakasa nti nzikirizza okwetaba mu kunoonyereza kuno.

Amannya g'omwana.....

Omukono oba ekinkumu

Erinnya ly'omusawo anoonyereza oba amuyambako.....

Emukono oba ekinkumukye.....

Ennaku z'omwezi.....

APPENDIX V: QUESTIONNAIRE

DIAGNOSTIC ACCURACY OF FINE NEEDLE ASPIRATION CYTOLOGY (FNAC) IN PATIENTS UNDERGOING THYROIDECTOMY IN MULAGO HOSPITAL: A CROSS SECTIONAL STUDY.

Study number: IPNo/OPNo:.....

SECTION A: IDENTIFICATION/DEMOGRAPHICS.

1. Age (years)
2. Sex :
 - 1) Male
 - 2) Female
3. Tribe :
 - 1) Ganda
 - 2) Nkole/Kiiga
 - 3) Soga
 - 4) Luo
 - 5) Others
4. Address:
 - 1) Central
 - 2) Western
 - 3) Eastern
 - 4) Northern
 - 5) Others
5. Level of education
 - 1) No formal education
 - 2) Primary
 - 3) Secondary
 - 4) Tertiary
6. Marital status
 - 1) Married/staying together
 - 2) Single
 - 3) Separated/divorced
 - 4) Widowed

7. Occupation

- 1) Peasant
- 2) Casual worker
- 3) Salaried
- 4) Self-employed
- 5) Others

SECTION B: CLINICAL PRESENTATION

8. For how long has the patient had symptoms Weeks
9. Anterior neck swelling :
- 1) Yes
 - 2) No
10. Difficulty in breathing:
- 1) Yes
 - 2) No
11. Changes in voice
- 1) Yes
 - 2) No
12. Any history suggestive of hyperthyroidism:
- 1) heat intolerance
 - 2) Palpitations
 - 3) Increased appetite
 - 4) loss of weight
13. Any history suggestive of hypothyroidism:
- 1) Cold intolerance
 - 2) Fatigue
 - 3) Poor appetite
 - 4) Weight gain
14. Head and neck radiation:
- 1) Yes
 - 2) No
15. Family history of cancer :
- 1) Yes
 - 2) No
16. Medications:
- 1) Carbimazole
 - 2) Propylthiouracil
 - 3) Thyroxine
 - 4) Others

On physical examination what is:

17. Goiter grade [1] [2] [3] [4]
18. Systolic BP
19. Diastolic BP

20. Pulse rate

21. Fibre optic laryngoscopy:

- 1) Normal vocal cords
- 2) Abnormal vocal cords: Paralysed

SECTION C: INVESTIGATIONS

22. TSH

23. T3

24. T4

25. Biochemical diagnosis

- 1) Euthyroid
- 2) Hyperthyroid
- 3) Hypothyroid

26. On ultrasound scan of the thyroid gland :

- a. Texture
 - 1) Nodular
 - 2) Diffuse
- b. Number of nodules _____
- c. Site of nodules:
 - 1) left
 - 2) right
 - 3) both
- d. Size of biggest nodule _____
- e. Capsular invasion
 - 1) Yes
 - 2) No
- f. Retrosternal extension
 - 1) Yes
 - 2) No
- g. Regional lymphadenopathy
 - 1) Yes
 - 2) No

27. Thoracic inlet X-ray

- 1) Normal trachea
- 2) Tracheal compression
- 3) Tracheal deviation
- 4) Calcifications
- 5) Retrosternal extension

28. FNAC

- 1) Benign
- 2) Malignant
- 3) Suspicious
- 4) Follicular neoplasm
- 5) Follicular lesion of undetermined significance
- 6) Non-diagnostic

29. Histopathology shows

- 1) Benign disease
- 2) Malignant disease

SECTION D: SURGERY

30. Planned surgery:

- 1) Lobectomy
- 2) Partial thyroidectomy
- 3) Subtotal thyroidectomy
- 4) Near –total thyroidectomy
- 5) Total thyroidectomy

31. Indications: **(circle all that apply)**

- 1) Pressure symptoms
- 2) Cosmesis
- 3) Malignancy
- 4) Graves disease
- 5) Others(specify)

32. Exact operation done:

- 1) Lobectomy
- 2) Partial thyroidectomy
- 3) Subtotal thyroidectomy
- 4) Near-total thyroidectomy
- 5) Total thyroidectomy

33. Exact histopathological diagnosis of excised specimen.....

APPENDIX VI: BUDGET

DIAGNOSTIC ACCURACY OF FINE NEEDLE ASPIRATION CYTOLOGY IN PATIENTS UNDERGOING THYROIDECTOMY IN MULAGO HOSPITAL: A CROSS SECTIONAL STUDY.

Item	Number of items	Unit cost	Total
Stationery		500,000=	500,000=
Histopathology Specimens	45	40,000=	1,800,000=
Computer Back- Up		200,000=	200,000=
Research Assistant	1	500,000=	500,000=
Biostatistician	1	1,000,000=	1,000,000=
Airtime		100,000=	100,000=
Miscellaneous		410,000=	410,000=
GRAND TOTAL			4,510,000=