Diagnostic accuracy of fine needle aspiration cytology in patients undergoing thyroidectomy in Uganda: tertiary hospital experience.

Robert Masereka[1], Paul K. Okeny[2], Jane .O. Fualal[3], Dan Wamala[4]

1. Department of Surgery, Makerere University College of Health Sciences (MakCHS), P.O Box 7062 Kampala – Uganda
2. Department of Surgery, Gulu Regional Referral and Teaching Hospital, P.O Box 160 Gulu – Uganda
3. Department of Surgery, Mulago National Referral Hospital
4. Department of Pathology, Mulago NationalReferral Hospital

Abstract

Background: Thyroid disease affects about 5% of the World's population. Fine Needle Aspiration Cytology (FNAC) helps in planning extent of surgery. In some studies, FNAC has been found to have a low accuracy for malignancy.

Objective: To estimate the sensitivity and specificity of FNAC in detecting malignancy for thyroid disease using histopathology as the gold standard.

Methods: Patients who underwent clinical and laboratory evaluation and thyroidectomy at Mulago National Referral hospital and the Pathology department of Makerere University College of Health Sciences were consecutively recruited over a four months period. Analysis using STATA version 10 focused on sensitivity, specificity and accuracy of FNAC in detecting malignancy.

Results: In total, 99 patients were recruited, the 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 proportion of patients with 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 61.5% and specificity 89.5% .

Conclusion: This study revealed high specificity and low sensitivity of Fine Needle Aspiration Cytology (FNAC) at detecting malignancy in thyroid nodules

Keywords: Diagnostic accuracy, fine needle aspiration, cytology, thyroidectomy, tertiary hospital.

DOI: http://dx.doi.org/10.4314/ahs.v16i4.32

Cite as: *Masereka R, OkenyPK, Fualal JO, Wamala D. Diagnostic accuracy of fine needle aspiration cytology in patients undergoing thyroidectomy in Uganda: a tertiary hospital experience. Afri Health Sci.2016;16(4): 1143-1150. http://dx.doi.org/10.4314/ahs.v16i4.32*

Introduction

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% and annual incidence of 0.1% in some adult populations[1-2]. Nodules are more frequent in females and are mostly benign. Fine Needle Aspiration Cytology (FNAC) has been in use since the 1950s and is a safe, cost effective method of diagnosing thyroid nodules[3].

Despite several studies showing a high accuracy with FNAC, emerging studies especially in tropical Africa and other developing countries with a high prevalence of nodular thyroid disease, have shown the accuracy of FNAC to be lower than previously reported[4-5] and its diagnostic performance has been shown to vary across different studies[6]

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 an annual increase of about 350-370 new patients with thyroid disease has been reported over the last five years (Mulago hospital records).

Corresponding author:
Paul K. Okeny,
Department of Surgery,
Gulu Regional Referral and
Teaching Hospital,
P.O Box 160 Gulu – Uganda
Email: okenykpaul@yahoo.ca

In this hospital, nodular goiter was found to constitute about 82%[7].

The diagnostic performance of FNAC in Mulago hospital is not known. The purpose of this study was to estimate the sensitivity and specificity of FNAC in detecting malignancy for thyroid disease using histopathology of excised specimen as a gold standard and to describe histopathological diagnoses of thyroid disease in patients following thyroidectomy.

Materials and methods

Study design

This was a cross sectional study with both prospective and retrospective arms carried out from January 2014 to April 2014. The retrospective arm involved retrieving patients' records (cytological and histopathological reports) from the pathology department of Makerere University College of Health Sciences (MakCHS) that had undergone thyroidectomy from January 2008 to December 2013 and the other arm involved prospective recruitment of patients from January to April 2014. Consecutive sampling was used.

Sample size was estimated using the formula for single proportions[8]. Using sensitivity and specificity proportions of 90% initially found by Nyawawa et al[9] in Tanzania and a significance level of 0.05, we estimated the sample size to be 175 participants (75 prospective and 100 retropective arm). This division is because we expected to perform 20 thyroid surgeries per month for the study period of 4 months in the prospective arm.

Study setting

In the FNAC technique, equipment involved glass slides, cover slips, antiseptics, disposable gloves, fixative (absolute ethyl alcohol),swabs, 23 French (Fr) gauge hypodermic needles (23Fr, 24Fr, 25 Fr is recommended) and 10 ml syringes.

The patient was made to lie supine on an examination couch with slight neck extension and 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 immobilised and stabilised between the index finger and the thumb of the left hand.

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 maneouvre 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. At least 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.

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.

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.

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.

Histopathology

During histoprocessing of biopsy specimens after thyroidectomy, fixation was done with 10% formalin immediately after surgery whose main objective was to preserve protoplasm with minimal alteration from the living state of the cell.

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.

The paraffin wax embedded tisssue specimens were sliced into very thin sections of 3-10 microns thick.
The section was then put on a clean glass microscope slide and warmed to let the specimen settle on the slide.

Staining was done with Eosin and Haematoxylin. The slide was then placed in a solution of paraffin solvent (xylol or tolunol) to remove the paraffin.
Excess dye was washed away with water. The section was dehydrated by 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.

Data collection, quality assurance and quality control

Interviews were conducted with all fully consenting patients using a standard pretested questionnaire aimed at capturing patients' history, examination and investigation findings.
For the retrospective arm, enough information was extracted as much as possible from the cytology and histopathology reports.
Standard Operating Procedures (SOPs)for both FNAC and histopathology and Standards for Reporting of Diagnostic accuracy studies (STARD) were followed till this study was completed.
Quality control was assured by maintaining that FNB procurement, processing and reporting was done by experienced cytopathologists (using the Bethesda system for reporting thyroid cytopathology), the histopathologist examining excised thyroid specimens was blinded to preoperative diagnosis with FNAC and 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.

Data analysis

Patients' data was entered into EPIDATA 3.1 and exported to STATA Version 10 for analysis. Using the NCI (Bethesda) FNAC reporting system[10], only individulas with a "benign" report were considered benign cases on FNAC, where cases with "follicular neoplasm", "suspicious for malignancy" or "malignancy" reports consitituted malignant cases on FNAC. All patients enrolled in the study were included in the analysis to determine the sensitivity and specificty of FNAC for malignant conditions using a 2 X 2 table.

Ethical consideration

Before the start of this study, ethical clearance was obtained from the Institutional Review Board of Makerere University College of Health Sciences. Written informed consent was obtained from patients both for the surgery and for inclusion in the study. Waiver of consent was obtained for the retrospective arm of the study.

Results

A total of 99 patients were enrolled (45 prospective and 54 retrospective).
Overall, median age (IQR) was 42 years (34-50), 92 females and 7 males with a female to male ratio of 15.5:1 [Table 1].

Table 1. Social demographic characteristics of patients who underwent thyroidectomy at Mulago Hospital during the study period (prospective arm).

Characteristics	Prospective arm (N=45)
Gender, n (%)	
Female	41 (91.1)
Tribe, n (%)	
Ganda	11 (24.4)
Nkole/Kiiga	6 (13.3)
Soga	3 (6.7)
Others*	25 (55.6)
Marital status, n (%)	
Married	28 (62.2)
Not married	17(37.8)
Address, n (%)	
Central	17 (37.8)
Western	7 (15.6)
Eastern	16 (35.6)
Northern	5 (11.1)
Education, n (%)	
Formal education	42(93.3%)
No formal education	3(6.7%)
Occupation, n (%)	
Peasant	19 (42.2)
Salaried	14 (31.1)
Self-employed/business	9 (20.0)
Others#	3 (6.7)

refers to students, unemployed.
* refers to Banyoro, Iteso, Batoro, Bagisu, Karamojong

Of the five solitary nodules, two (40%) were malignant and of the 40 multinodular goiter, two (5%) were malignant (p value=0.055) [Table 2 and Table 3]

Table 2. Baseline clinical characteristics of patients who underwent thyroidectomy at Mulago Hospital during the study period (prospective arm).

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)
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)
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)

Table 3. Distribution of histopathological diagnoses among patients who underwent thyroidectomy in Mulago Hospital by method of participant enrollment

Diagnosis	Overall, N=99, n (%)	Prospective, N=45, n (%)	Retrospective, N=54, n (%)
Colloid goitre	66(66.7)	35(77.8)	31(57.4)
Nodular goitre	16 (16.2)	4(8.9)	12(22.2)
Papillary carcinoma	11 (11.1)	3(6.7)	8(14.7)
Follicular carcinoma	2 (2.0)	1(2.2)	1(1.9)
Chronic thyroiditis	2 (2.0)	1(2.2)	1(1.9)
Follicular adenoma	1 (1.0)	0(0.0)	1(1.9)
Inflammatory cyst	1 (1.0)	1(2.2)	0(0.0)

Malignant nodules tended to be bigger with median size of 50 mm (IQR 39.5-76.5) compared to benign nodules with median size of 37 mm (IQR 27-51) but this was not statistically significant (p value of 0.055). Sensitivity and specificity were 61.5% (CI 35.5 – 69.0) and 89.5% (CI 81.3 – 94.4) respectively. [Table 4].

Table 4. 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)	85.8 (77.7-91.4)

Discussion

The aim of this study was to estimate the sensitivity and specificity of FNAC in detecting malignancy for thyroid disease using histopathology as the gold standard. We found a sensitivity of 61.5% and specificity of 89.5%. [Table 4].

The median age of patients was 42 years, the youngest was 16 years and the oldest was 78 years. In a related study in Uganda the median age was 43.2 years[7], in Tanzania it was 42.7 years[4], in Egypt it was 44 years[11]. The female to male (F:M) ratio was 15.5:1 meaning that this is predominantly a disease of women. This was observed in related studies within the East African region[7,12].

In all patients the main presenting complaint was an anterior neck swelling with median time interval to presentation of 364 weeks (7 years) [Table 2]. The long time interval to presentation could probably explain the fact that all patients had either grade 3 or grade 4 goitre [Table 2].

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 emphasizes the fact that iodine deficiency still remains top most cause of thyroid disorders on the African continent[13-14].

The sensitivity and specificity for detecting malignancy on FNAC was 61.5% and 89.5% respectively and the 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[4,15]. For most studies, the diagnostic accuracy of more than 90% is seen in malignant disease and about 77.8% in benign disease[16].

For a rare disease (thyroid cancer is relatively uncommon), specificity is the most desirable so that when the test result is negative then chances are very high that the individual has no disease. 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.

Majority of the goiters were benign (86.9%). The proportion of patients with malignancy in this study was 13.1%. Kobusingye found malignancy rate of 19.6% in Uganda[17] whereas in Tanzania it was 18.6%[4]. This contrasts with what is reported in Europe and North America were incidence of malignancy in thyroid nodules is about 5%6. The difference could probably be attributed to the fact that a significant proportion of long standing multinodular goiter in areas endemic for iodine deficiency tend to undergo malignant transformation[18].

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%[17] and in Tanzania, FTC predominated at 72.2%[4]. 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[14]

Study limitations

For the retrospective arm, blinding of the histopathologist to the corresponding cytological diagnosis with FNAC may not have been observed. The many pathologists involved in reporting histopathology could have over-estimated or under-estimated malignancy rate (random error).

We were unable to achieve the estimated sample size within the study period. The prospective arm was dependent on availability of theatre space whereas the retrospective arm was limited by poor and to a large extent non computerized record keeping.

The findings of this study may not be generalizable because of the relatively small numbers used in analysis compared to the relatively big number of patients with nodular thyroid disease.

Conclusion

This study reveals high specificity and a low sensitivity for FNAC at detecting malignancy in thyroid nodules. These findings give good preliminary data on performance of FNAC in thyroid disease in our setting.

There appears to be a changing trend towards the frequent occurrence of papillary thyroid carcinoma (PTC) compared to follicular thyroid carcinoma (FTC).

Acknowledgement

The authors appreciate the co-operation of patients who participated in this study, the staff from the records section of Pathology Department for retrieving patients' data and Dr. Innocent Mutyaba for helping with the statistical analysis.

Author contributions

RM developed the concept, participated in data collection and manuscript writing, PKO participated in data collection, analysis, manuscript writing, JOF and DW reviewed the concept, data analysis and manuscript. All the authors contributed equally and agreed to the final manuscript.

Funding

This study received no external funding.

Conflict of interests

The authors declare no conflict of interests

References

1. De Groot L, Hennemann G. Thyroid disease manager. Thyroid disease manager. 2003.

2. Nguyen G-K, Lee MW, Ginsberg J, Wragg T, Bilodeau D. Fine-needle aspiration of the thyroid: an overview. *Cytojournal*. 2005;2(1):12 PubMed.

3. Solderstrom N. Puncture of Goitres for aspiration biopsy. *Acta Med Scand*. 1952;144:237 - 44 PubMed.

4. Nyawawa E, Yongolo S, Tupa J. Radionuclide Scan and Other Diagnostic Studies in Goitre Patients in Tanzania. *East and Central African Journal of Surgery*. 2006;11(2):15-20.

5. CostamagnaD, Pagano L, Caputo M, Leutner M, Mercalli F, Alonzo A. Incidental cancer in patients surgically treated for benign thyroid disease. Our experience at a single institution. *Il Giornale di chirurgia*. 2013;34(1-2):21-6.

6. Wang C-CC, Friedman L, Kennedy GC, Wang H, Kebebew E, Steward DL, et al. A large multicenter correlation study of thyroid nodule cytopathology and histopathology. *Thyroid*. 2011;21(3):243 -51 PubMed.

7. Nyonyintono J, Fualal J, Wamala D, Galukande M. Comparing Aspiration and Non-aspiration Fine Needle Techniques in Cytodiagnosis of Thyroid Nodules. *East and Central African Journal of Surgery*. 2011;16(2):46-54.

8. Kelsey JL. Methods in observational epidemiology: Oxford University Press; 1996.

9. Nyawawa E, Yongolo S, Tupa J. Radionuclide Scan and Other Diagnostic Studies in Goitre Patients in Tanzania. *East and Central African Journal of Surgery* 2006;11(2):15-20.

10. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. *American Journal of Clinical Pathology*. 2009;132(5):658-65.

11. Sinna EA, Ezzat N. Diagnostic accuracy of fine needle aspiration cytology in thyroid nodules. *Journal of the Egyptian National Cancer Institute*. 2012.

12. Sang CK, Sekadde-Kigondu C, Muchiri L. Fine needle aspiration cytology of thyroid nodules at Kenyatta National Hospital, Nairobi. *East African Medical Journal*. 2007;84(3).

13. Bimenya GS, Kaviri D, Mbona N, Byarugaba W. Monitoring the severity of iodine deficiency disorders in Uganda. *African Health Sciences*. 2002;2(2):63-8.

14. Ogbera AO, Kuku SF. Epidemiology of thyroid diseases in Africa. *Indian journal of endocrinology and metabolism*. 2011;15(Suppl2):S82.

15. Ch, Maharajan r, Rao H. Correlation of fine needle aspiration and final histopathology in thyroid disease: a series of 702 patients managed in an endocrine surgical unit. *Online J Otolaryngol*. 2012;2(3):85-95.

16. Likhar K, Hazari R, Gupta S, Shukla U. Diagnostic accuracy of fine needle aspiration cytology in thyroid

lesions: A hospital-based study. Thyroid Research and Practice. 2013;10(2):68.
17. Kobusingye OC. Thyroid disease in Mulago hospital: Clinical and histopathological patterns. . Dissertation submitted in partial fulfillment for the award of degree of master of medicine in surgery of Makerere University. 1993.
18. Fualal J, Moses W, Jayaraman S, Nalugo M, Ozgediz D, Duh Q-Y, et al. Characterizing thyroid disease and identifying barriers to care and treatment in Uganda. *World J Endoc Surg*. 2012;4(2):47-53 PubMed.