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Comparison of Cytological and Histopathological Findings of Thyroid Lesions at Muhimbili National Hospital, Tanzania

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Abstract

Background

Thyroid lesions are endemic in Tanzania but poorly documented. Fine needle aspiration cytology (FNAC) is a reliable, cheaper, quicker and easier diagnostic test compared to histopathology but a representative specimen and experience are pre-requisites. Histopathology is available at only a few tertiary health-care centres in Tanzania. Comparable thyroid cytological findings can obviate the need for histopathology where this is not available.

Methods

This hospital-based retrospective descriptive cross-sectional study was carried out to compare cytology and histopathology in thyroid lesions diagnosis. It included surgical in-patients while pre-operative FNAC was done prior at surgical outpatient (SOPD) clinics between May-2012 and February-2014. Convenience sampling of all patients who underwent FNAC and thyroidectomies with subsequent histopathological evaluation and the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC-2017/18) were used.

Results

A total of 124 patients were enrolled and age ranged from 12-77 years, mean 40.5±11.66 years, peak-age 31-40 years, and male:female (M:F) ratio=1:7.3. Cytologically, the vast majority (80.6%, n=100/124) were benign, 11.3% (n=14/124) malignant and 8.1% (n=10/124) indeterminate. Comparatively, histopathology showed a similar (82.3%, n=102/124) proportion of benign lesions and a higher (17.7%, n=22/124) proportion of cancers. Furthermore, histopathologically, the commonest (38.1%, n=48/124) benign lesions were colloid goitre and follicular adenoma (19.4%, n=24/124). Nine cases negative for malignancy cytologically, were histologically confirmed as papillary (44.4%, n=4) and follicular carcinoma (55.6%, n=5). Most (92.9%, n=13/14) cases diagnosed as malignancies cytologically, were so confirmed histologically. One patient had papillary carcinoma by FNAC but histologically follicular adenoma. The sensitivity of FNAC was 59.1%, specificity 98.9%, positive predictive value (PPV) 92.9%, negative predictive value (NPV) 91% and accuracy was 91.2%.

Conclusion

Thyroid lesions at Muhimbili National Hospital (MNH) are comparable to elsewhere. Although FNAC shows low sensitivity it is specific, and accurate as an initial diagnostic test for these lesions which is useful where histopathology is not available.

Keywords: *Thyroid Lesions, Cytology, Histology, Cancer, Diagnosis, Accuracy.*

Introduction

Histopathological diagnosis of thyroid lesions is the gold standard although fine needle aspiration cytology (FNAC) of the thyroid gland is now a well-established, cost-effective, first-line diagnostic test for the evaluation of diffuse thyroid lesions aiming at confirming benign ones and reducing unnecessary surgery. However, FNAC use in developing countries including Tanzania is limited to very few specialized centres, partly due to scarce competent human resources, awareness and data. Although there is a large body of literature in the world claiming high accuracy and usefulness of thyroid cytology; concurrent evidence shows possible limitations and including inadequate sampling, cyto-histological discrepancy, dual pathology as well as errors in interpretation (2-5). The research question thus was to investigate whether FNAC is reliable in comparison with the gold standard histopathological findings of thyroid lesions at MNH.

The initial assessment of a patient with thyroid nodule(s) includes triple modalities of clinical examination, cytology and imaging. However, indeterminate FNAC results and cytodiagnostic errors are unavoidable due to overlapping cytological features particularly among hyperplastic adenomatoid nodules, follicular neoplasms and follicular variants of papillary carcinomas. The corroboration of cytology findings with histology is an important quality assurance (QA) measure as it allows laboratories to calculate their false positive and false negative rates (6).

Thyroid FNAC alone generates much higher non-diagnostic (ND) or indeterminate (ID) rate and thus routine use of USS-guided Aspiration Cytology as well as the ***r***apid ***o***n-***s***ite ***e***valuation (ROSE)/adequacy assessment of cytopathologic specimens should dramatically reduce the ND/ID rate and thus, the cost of a true diagnosis (7).

Thus, the mainstay of definitive anatomical diagnosis for thyroid lesions in Tanzania is still open surgical biopsy of the primary site or the lymph node for histopathology. The reasons for this include the almost complete lack of cytology services in the country alongside very low awareness of cyto-diagnosis even among the medical professionals; scarce cytologically competent pathologists in the country and lack of career Cytopathology training in the country. These facts together with the availability of histopathological diagnosis at only few centres in the country, results in considerable under-diagnosis of thyroid lesions. This study evaluated the utility of FNA Cytology in comparison to the gold-standard histopathology in order to promote the use of this cheaper, quicker and less labour-intensive method in attaining definitive anatomical diagnosis which will benefit the patients' treatment as well as the country generally. Our current study also elucidated the pattern of thyroid lesions encountered at MNH.

Methods

Study design and area

This was a hospital-based retrospective descriptive cross-sectional study done between May 2012 and February 2014 at the Muhimbili National Hospital (MNH), Dar es Salaam, Tanzania which is the National referral hospital but also the regional and zonal referral hospital for nearby eastern and southern zones. The hospital has a bed capacity of 1,500 of which 120 beds are set apart for adult general surgery services.

Study population

All Patients with a diagnosed thyroid lesion who underwent FNAC and surgical biopsy at MNH for the period of twenty months of the study.

Sampling procedure and inclusion criteria

Convenience sampling method was used and the Inclusion Criteria included all patients with thyroid lesions who underwent FNAC and thyroidectomies (total, subtotal, lobectomy or nodulectomy) with subsequent histopathological evaluation during the study period. The exclusion criteria included lack of retrievable clinical records, tissue blocks or slides/smears.

Data collection

Archived pathology reports from patients with thyroid lesions who had been attended in the department of surgery at MNH and had FNAC, surgery and histopathological evaluation during the study period were retrieved. Corresponding case notes were also retrieved from the medical records department. All the information was filled in a questionnaire. Furthermore, patients who were either being admitted to general surgery wards or attending the surgical outpatient clinics (SOPD) and underwent thyroid FNAC, thyroid surgery and histopathological evaluation were recruited and entered in questionnaires.

Cytological Biopsy Collection

Fine Needle Aspiration Biopsy (FNAB) for Cytology was performed and reported by Anatomical Pathologists. A palpable mass was aspirated using a 22 or 23G needle attached to a 10cc syringe held in a holder (gun). The smears were made on three glass slides, immediately fixed in 95% ether in alcohol (for 30min). Smears were Papanicolau stained, mounted and cover-slipped for reporting.

Surgical Biopsies Collection and Processing

This was done as previously described (8,9). Briefly, post-surgery (either thyroidectomy or lobectomy) the specimen was immediately put in a container with 10% neutral and well-

buffered formalin for at least 24hrs and a form properly filled requesting histopathological evaluation. However, before surgery at MNH some patients undergo physical examination of the lesions as well as thyroid ultrasonography (USS) or isotopic thyroid scan (ITS) to guide the operation and/or biopsy sampling although this practice is not yet routine and we do not yet have an algorithm for thyroid lesions management in Tanzania.

The tissues were cut into appropriate sizes during grossing, run in a tissue processing machine with graded alcohol containers 70%, 80%, 95%, 95% for proper dehydration. Then the tissues were passed through three jars containing xylene to cleanse off the alcohol and run in a jar containing molten wax and then blocked, sectioned (five microns) by microtome and stretched in warm water and mounted on glass slides and stained by haematoxylin and eosin (H & E), mounted with DPX and cover-slipped.

Microscopic evaluation

Histopathological and cytopathological review of reported biopsies and smears as well as photomicrography was performed by one Senior Anatomical Pathologist and first author (ARM) using an Olympus (CX31RBSF Model) light microscope equipped with a digital camera (Olympus Corporation, Tokyo, Japan). The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) of 2017 which was also modified in 2018 was used to categorize cytological findings. This offers a six-tiered diagnostic scheme for thyroid Fine Needle Aspiration (FNA): Benign, Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS), Suspicious for Follicular Neoplasm, Suspicious for Malignancy, Malignant, and Unsatisfactory/Non-diagnostic with an aim to standardize diagnostic criteria (2).

Data analysis

Data was analysed using Statistical Package of Social Sciences (SPSS) version 20.0. Statistical tests to assess the validity of association were *Chi*-square test (χ^2) or Fisher's Exact test for subgroups wherever appropriate. The significance of association was determined by calculations of *P- value* and 95% confidence interval. The two-sided *p*-values ≤0.05 were considered statistically significant. Diagnostic value of the FNAC was checked by calculating the sensitivity, specificity, positive predictive value, negative predictive value and by calculating the percentage of false positive and false negative results. Histopathological tissue findings were taken as the gold standard. Diagnostic accuracy of FNAC was taken as the proportion of the correct results true positive and true negative in relation to all cases studied. Accuracy $= \frac{(TP + TN) \times 100}{N}$

Ethical considerations

Ethical clearance was sought from the MUHAS ethical committee for and permission to conduct the study was sought from the MNH Management. At all levels the patients' confidentiality was maintained. No risk of harm to subjects and their rights and welfare were expected.

Results

Description of the study population

A total number of 124 patients with thyroid lesions were enrolled in the study. The age of patients studied ranged from 12 to 77 years. The mean age (± standard deviation) of the study participants was 40.5 ±11.66years. The peak age was 31-40 years (33.1%, n=41). The male: female (M: F) ratio was 1:7.3 (Table 1). The commonest (79%, n=98) presenting symptom was a painless neck swelling. However, for the age group 11-20 years none of the patients were found to have malignancy (Table 1).

Table 1: Socio-demographic characteristics vs. broad histopathology of thyroid lesions at MNH during the study period

Characteristics	Categories	Histopathology		Total	*P*-value
		Benign N(%)	Malignant N(%)	N(%)	
Age Group	11- 20	4 (3.9)	0 (0%)	**4 (3.2)**	0.01709 Pearson
	21- 30	15 (14.7)	6 (27.3)	**21(16.9)**	
	31- 40	34 (33.3)	7 (31.8)	**41(33.1)**	
	41- 50	30 (29.5)	5 (22.7)	**35(28.2)**	
	51- 60	15 (14.7)	2 (9.1)	**17(13.7)**	
	61+	4 (3.9)	2 (9.1)	**6(4.8)**	
Age Mean ± SD	**40.5±11.66**	**102 (82.3)**	**22 (17.7)**	**124(100)**	
Sex	Male	14 (93.3)	1 (6.7)	**15(12.1)**	0.01587 Fisher exact
	Female	88 (80.7)	21 (19.3)	**109(87.9)**	
Total		**102 (82.3)**	**22 (17.7)**	**124(100)**	

*****SD= Standard deviation

Comparison of cytological and histological findings of thyroid lesions

Histologically, majority (82.3%, n=102/124) of thyroid lesions were benign the commonest (47.1%, n=48) of which was colloid goitre followed by follicular adenoma (23.5%, n=24); while 17.7% (n=22/124) were malignancies (Tables 2 & 3) including papillary carcinoma [Figures 1 - 3], follicular carcinoma [Figure 4 & 5], Hurtle-cell carcinoma (Figure 6) and others (Table 2). Comparatively, according to TBSRTC, FNAC results showed 80.6% (n=100/124) had benign lesions, 5.65% (n=7/124) suspicious for follicular neoplasm 5.65% (n=7/124) malignant and 8.1% (n=10/124) were indeterminate (ID) lesions (Tables 2 & 3). However, the other two Bethesda categories were not reported during this study period. Cytologically, the most common (51%, n=51) benign thyroid lesion was colloid goitre. Furthermore, cytological, the commonest malignant lesion was papillary carcinoma [Figure 1 - 3] and thyroid malignancy (not otherwise specified) [21.4%, n=3], but as expected, there was no outright follicular carcinoma diagnosed although 7 cases were reported as being suspicious for follicular carcinoma [Figure 4 & 5], and no cases were histopathologically indeterminate (ID) [Tables 2 & 3]. Histopathologically, both papillary (PTC) and follicular (FTC) carcinoma were equally leading in frequency (41%, n=9) while other types were rare.

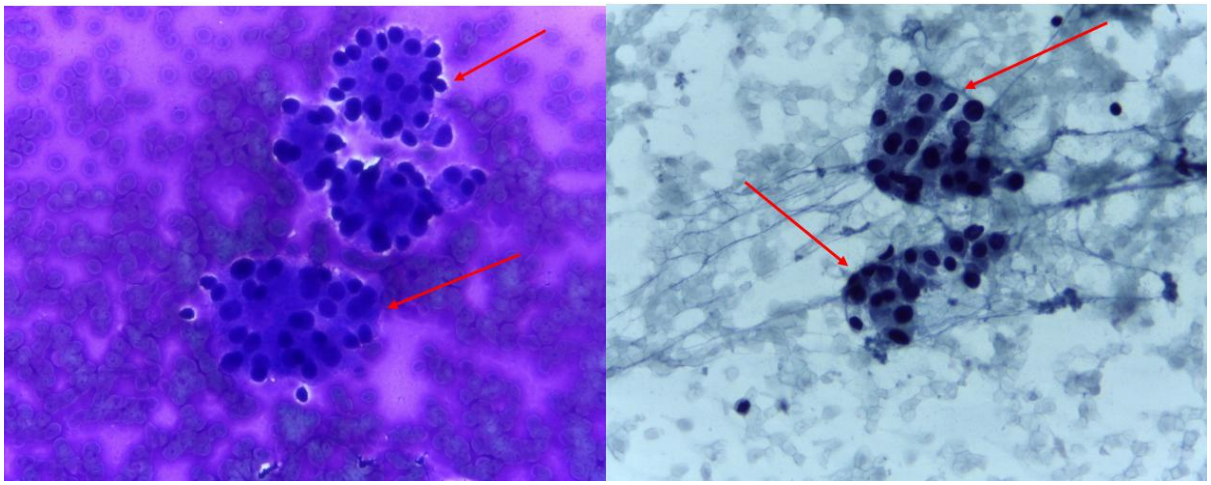

Figure 1. Follicular Thyroid Neoplasm Cytology

Thyroid FNAC Papanicolau stained smears showing microfollicles (red arrows) in Follicular Neoplasms (FN); note it is not easy to specify whether benign or malignant since capsular/vascular invasion can-not be demonstrated cytologically, x40.

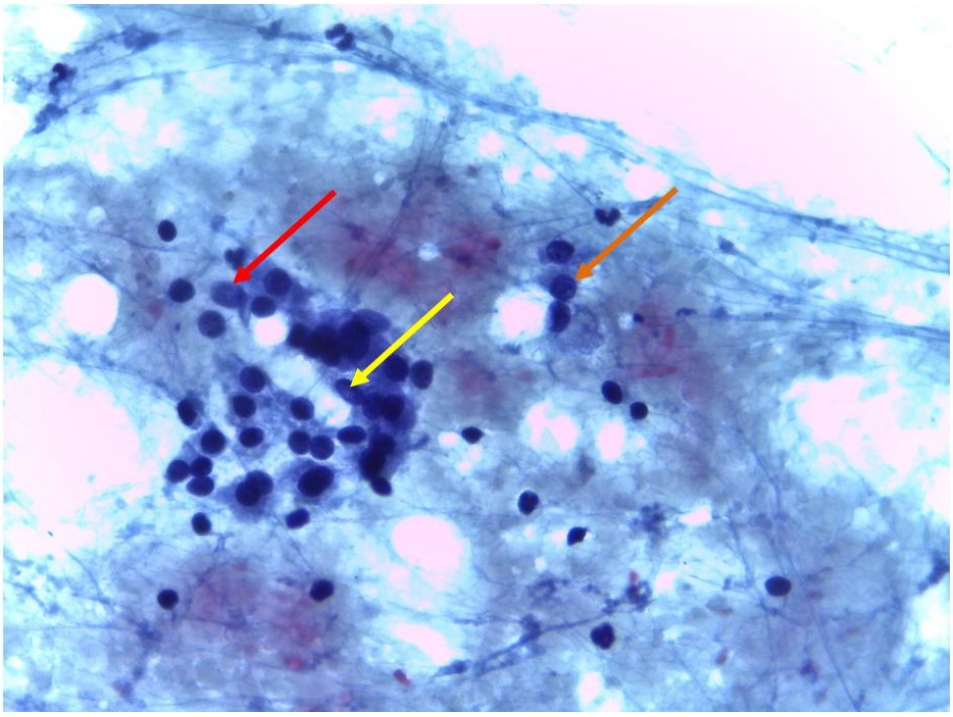

Figure 2(A). Papillary Thyroid Carcinoma (PTC) Cytology

Thyroid FNAC Papanicolau stained smears showing Papillary Thyroid Carcinoma (PTC) of the: note ground glass nuclei (red arrow), pseudo-inclusion (yellow arrow) and a faint nuclear groove (brown arrow), x20.

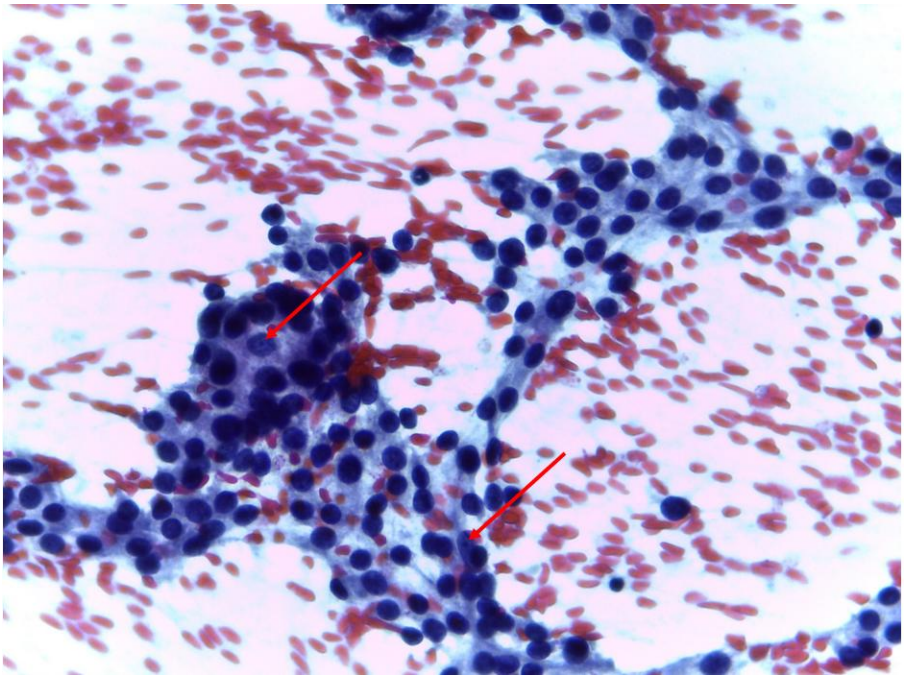

Figure 2(B). A thyroid FNAC smear showing Papillary Thyroid Carcinoma (PTC): note an Orphan Annie Eye (red arrow), x20.

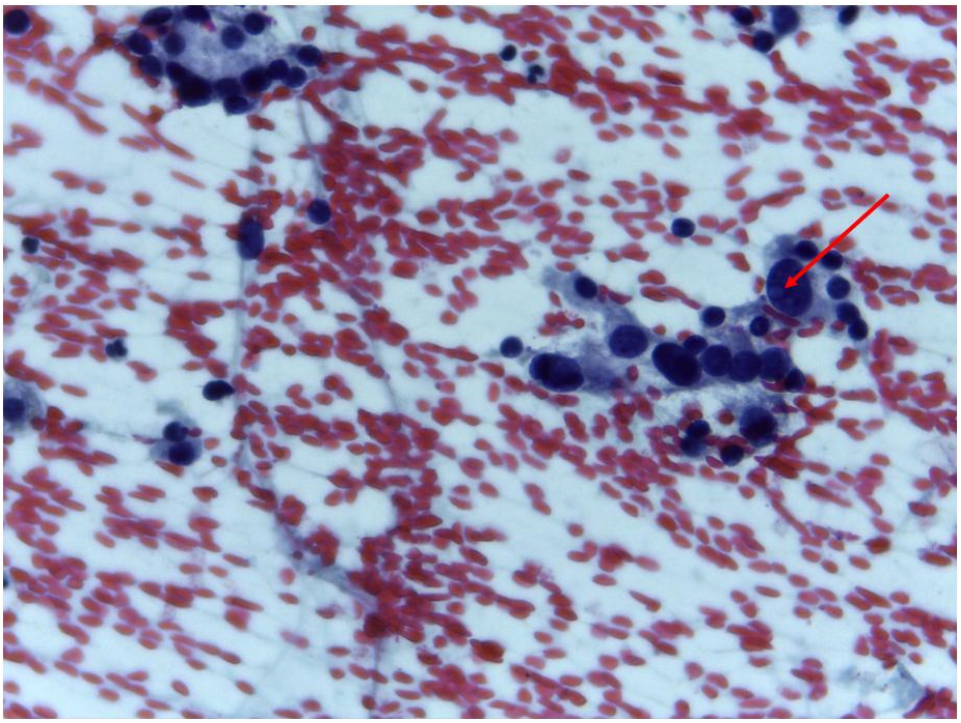

Figure 2(C). A thyroid FNAC smear showing Papillary Thyroid Carcinoma (PTC): note a nuclear pseudo-inclusion (red arrow), notice coincidental findings of anisocytosis and nuclear pleomorphism as well, x40

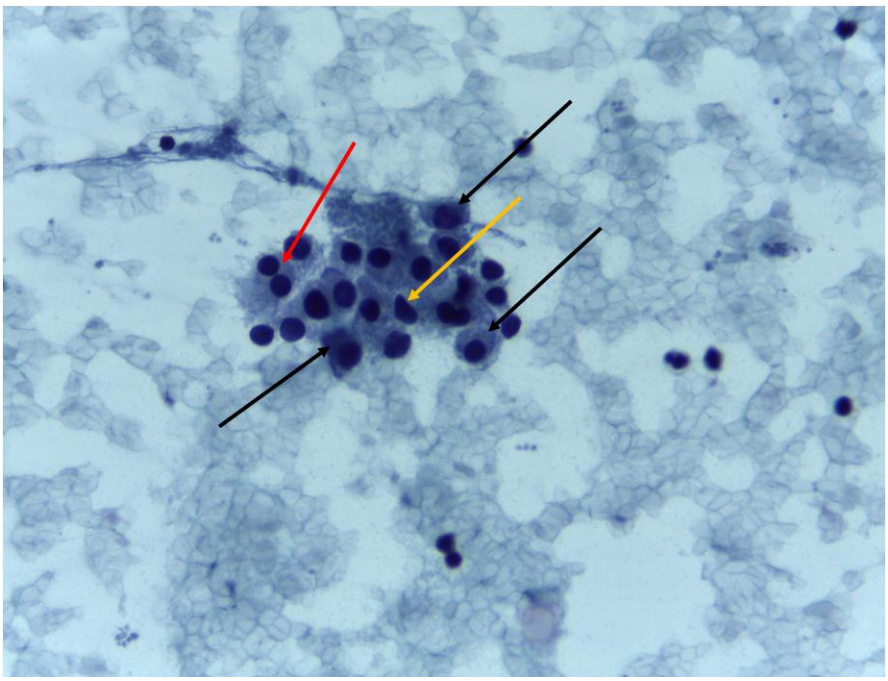

Figure 3. Thyroid Hürthle-cell Carcinoma Cytology

A thyroid FNAC Papanicolau stained smear showing a Hürthle-cell carcinoma: note a microfollicle with plumpy cells with abundant cytoplasm (back arrows) but also showing nuclear pleomorphism (yellow arrow) and a double nucleated cell (red arrow), X40.

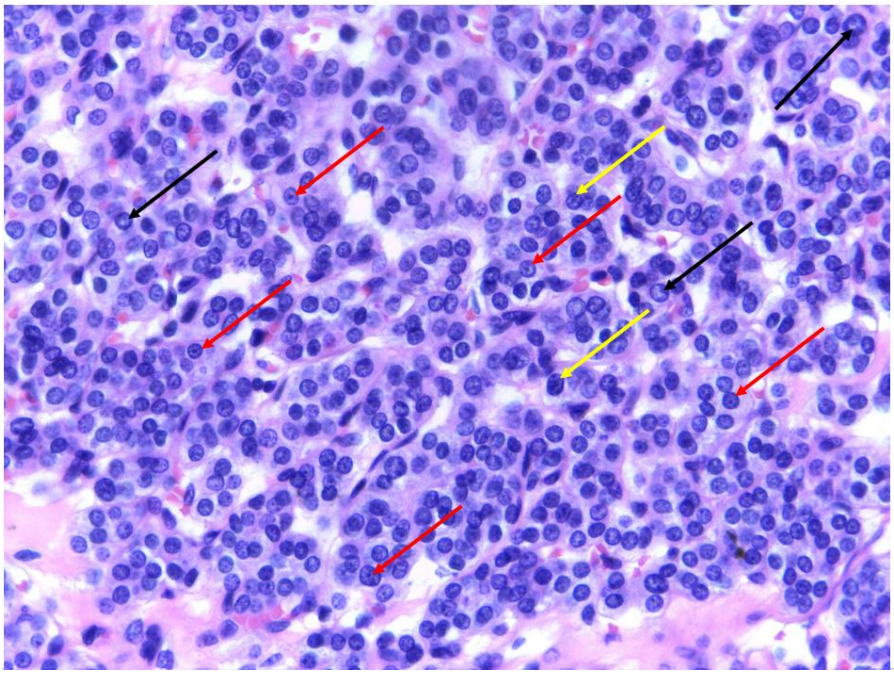

Figure 4(A). Papillary Thyroid Carcinoma (PTC) Histology

A routine (H&E) histological section of Papillary Thyroid Carcinoma (PTC) showing Orphan Annie Eyes (red arrows), and nuclear pseudo-inclusion (black arrows) as well as nuclear grooves (yellow arrows), x40.

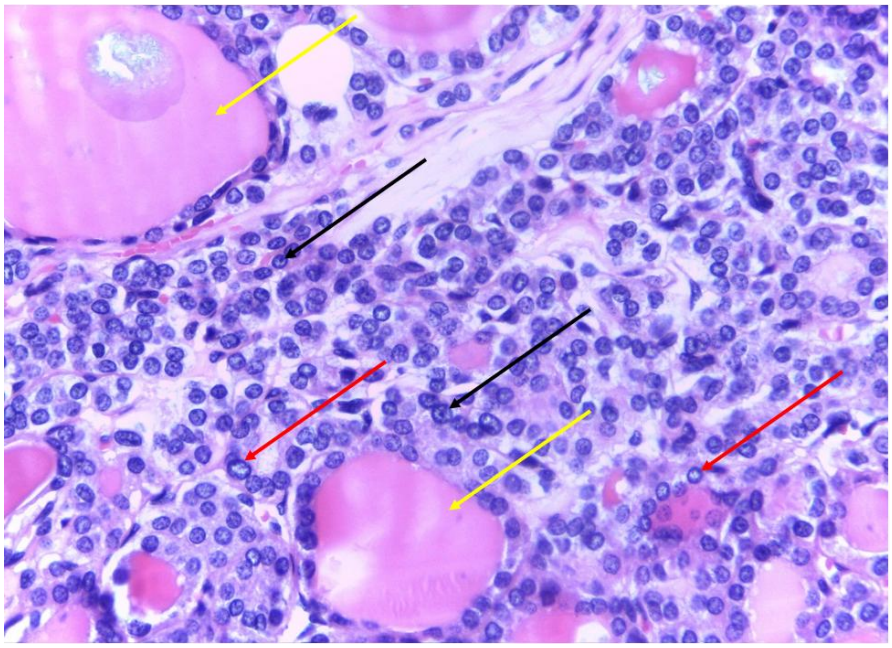

Figure 4(B). Papillary Thyroid Carcinoma (PTC) Histology with Follicular Differentiation

Routine (H&E) histological section of Papillary Thyroid Carcinoma (PTC) with Follicular Differentiation showing Orphan Annie Eyes (black arrows), and nuclear pseudo-inclusions (red arrows) as well as colloid-filled follicles (yellow arrows), x40.

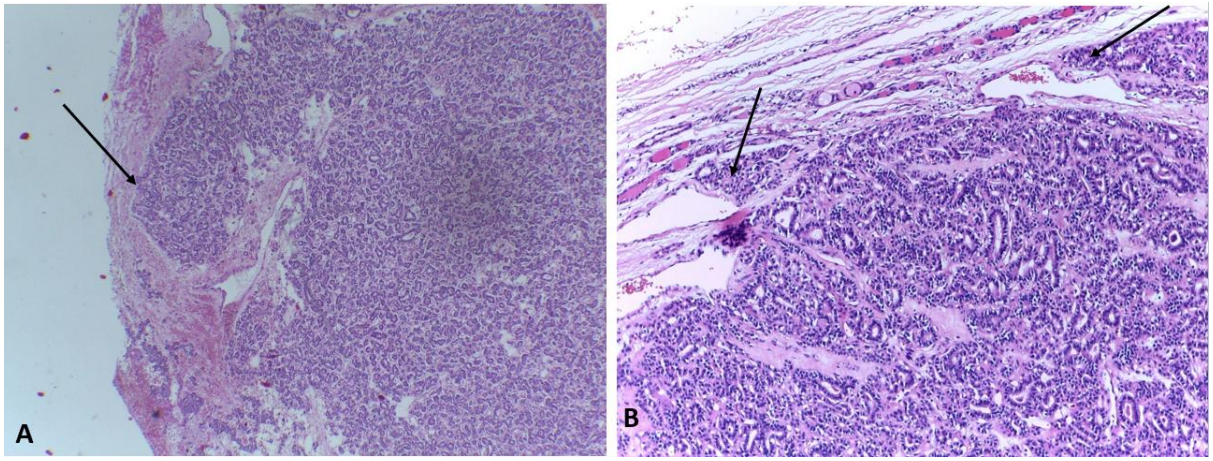

Figure 5. Follicular Thyroid Carcinoma (FTC) Histology

Routine (H&E) histological sections of Follicular Thyroid Carcinoma (FTC) with showing follicular pattern and capsular invasion (black arrows), x20.

Table 2: The patterns of thyroid lesions diagnosed by cytology and histopathology at MNH during the study period

Cytological Diagnosis (TBSRTC)*	FNAC Frequency No (%)	Histopathological Diagnosis	Histopathology Frequency No (%)
Benign	100(100)	Colloid Goiter	48(47.1)
		Follicular Hyperplasia	9(8.8)
		Multinodular Goiter	15(14.7)
		Follicular Adenoma	24(23.5)
		Thyroid Cyst	1(0.98)
		Epidermal Cyst	1(1)
		Haemorrhagic Cyst	0
		Tuberculous Thyroiditis	0
		Apocrine Hidrocystoma + Squamous Metaplasia	1(0.98)
		Hashimoto Thyroiditis	2(2)
		Sub-acute Granulomatous Thyroiditis (Dequervaitis)	1(0.98)
		Total benign histology	**102(100)**
Atypia of undetermined significance or follicular lesion of undetermined significance	0	N/A	N/A

Suspicious for follicular neoplasm	7(50)	N/A	N/A
Suspicious for malignancy	0	N/A	N/A
Malignant	7(50)	Papillary Carcinoma	9(41)
		Follicular Carcinoma	9(41)
		Hurtle Cell Adenocarcinoma	1(4.5)
		Squamous Cell Carcinoma G2	2(9)
		Diffuse Large Cell Lymphoma	1(4.5)
Indeterminate/non-diagnostic cytology	10(100)	**Total malignant histology**	**22 (100)**
Grand Total	**124**	**Grand Total**	**124**

***The Bethesda System for Reporting Thyroid Cytopathology*

Table 3: Distribution of diagnostic groups of thyroid lesions by Cytology and Histopathology at MNH during the study period

Feature	FNAC Diagnosis	Histopathology Diagnosis	P-value
	No (%)	No (%)	
Benign	100 (80.6)	102 (82.3)	**0.00498**
Malignant	14 (11.3)	22 (17.7)	
Indeterminate (ID)	10 (8.1)	0 (0)	
Total	**124 (100)**	**124 (100)**	

Analysis of the sensitivity, specificity, positive predictive value, negative predictive value and to assess the reliability of FNAC in diagnosis of thyroid malignancy

A total of 114 patients were analysed for sensitivity and specificity, as 10 patients which were indeterminate on FNAC were excluded (Tables 2&3). Out of 100 non-malignant lesions on FNAC, 9 aspirates showed non-neoplastic lesions which were then confirmed by histopathology as cancer including papillary carcinoma 4(44.4%) and follicular carcinoma 5(55.6%) [Table 2 – 4].

Out of 14 malignant lesions diagnosed by FNAC, 13(92.9%) were also confirmed by histology to be so. However, 1 patient with papillary carcinoma on FNAC, was confirmed to be a follicular adenoma by histopathology.

Thus, sensitivity of FNAC was 59.1%, specificity 98.9%, positive predictive value 92.9, negative predictive value 91% and diagnostic accuracy was 91.2% (Table 4).

Table 4: Accuracy of FNAC diagnosis of thyroid malignancy vs. histopathological diagnosis at MNH during the study period

FNAC Diagnosis (Screening Test)	Definitive Histopathology Diagnosis		Total
	Malignant No (%)	Non-malignant/ Benign No (%)	
Malignant	13 (59.1) (True Pos)	1 (1.1) (False Pos)	14 (Test Pos)
Non-malignant (Benign)	9 (40.9) (False Neg)	91 (98.9) (True Neg)	100 (Test Neg)
Total	**22 (Disease Pos)**	**92 (Disease Neg)**	**114**

NB: 10 Indeterminate (ID) on FNAC, (P-value <0.001)

Discussion

FNAC continues to play an important role in the management of thyroid lesions. However, its reliability depends on the quality of specimens although it remains the only guiding factor in surgical management decision-making (10). Obtaining histopathological information regarding disease nature, greatly alters treatment options. Furthermore, FNAC as a procedure is cost-effective, less traumatic, less invasive, and more easily performed and useful particularly when cancer is suspected (7,12,13). Important steps in thyroid lesions FNAC include careful sampling, preparation and accurate interpretation. Improper sampling and over-interpretation can lead to discrepant cytologic diagnoses (16). Prudence is recommended to meticulously scrutinize various cytologic features and reduce discrepancy (6,16).

The mean age reported in our index study is very similar to the 42.7 years and age-range of 13-72 years reported previously from Tanzania (17). This apparent similarity is partly due to similarity in the composition of the study population (17). Furthermore, as expected, the age-distribution appeared to be similar to that reported in previous West African and Iranian studies as well (12). The male to female (M:F) ratio in our current study appears to be similar to the 1:6 in a previous Tanzania report, partly again due to similar composition of the study populations (17).

In our current study, a great majority were benign lesions and the rest were either malignant or suspicious lesions according to FNAC. The most common benign thyroid lesion was colloid goitre. Furthermore, malignant lesions included more follicular than papillary carcinomas and those suspicious for follicular neoplasms were similar to the American study reported below. In series of studies done in U.S.A and other parts of the world, benign cytologic diagnosis reportedly ranged from 50-90% average 70% (14,21-24). Moreover, about 10-30% (average 20%) of cytologic specimens may be suspicious for malignancy or indeterminate (14, 24).

In the present study, the frequency of malignant lesions seemed to be higher than in previous Tanzanian thyroid studies which showed the incidence of malignancy to be 6.3% and 18%, respectively (1,17). Possible rise in the frequency over this period could partly be due to increase in use of different diagnostic techniques and rise in iodine deficiency in some regions of the country, despite ionization of table salt. However, our current findings showed considerable false negative cytology results including indeterminate and non-neoplastic lesions which were then confirmed to be thyroid cancer by histopathology is partly contributed by the fact that inherently, thyroid FNAC cannot easily diagnose follicular thyroid carcinoma (FTC) for which histologically, one needs to see evidence of capsular or vascular invasion, and both are not easily picked up cytologically. Other factors contributing to false negative results include pathologist's/cytologist's experience (or lack of), intra-observation errors, sampling bias and sample size, specimen collection/sampling and processing errors.

Majority of patients in developed countries report to hospital early, and management is done accordingly, while patients with goitre in developing countries present late. Nyawawa *et al.*, (2006) showed patients presented on average 4 years from onset, the minimum time to report was 1 year and the maximum was 20 years after onset of symptoms, including pressure, cervical adenopathy and hoarseness of voice (17) and the incidence of malignancy among these patients was found to be high (15%) (25).

One hundred and fourteen patients were analysed for sensitivity and specificity, and 10 patients with suspicious cytologically were excluded. True positives were found to be 13 (92.9%). About 9 out of 100 patients with non-malignant lesions (benign) on FNAC, were confirmed by histopathology to be malignant [papillary carcinoma 4 (44.4%) and follicular carcinoma 5 (55.6%) or false negatives, which could have occurred because of sampling errors or misinterpretation and are of great concern because they represent the potential to miss a malignant lesion (26). Since only a small percentage of patients with benign cytological findings undergo surgery, it is difficult to state the true frequency of false negative results (21). Nevertheless, false negative rates (9.0%) in this index study appears to agree

well with reports that suggest a range from 1 to 16% (21,22,25,27,28). This high rate of failure to diagnose cancer could be partly attributed to blind aspiration instead of using imaging. Furthermore, in the present study, sensitivity of FNAC was 59.1%, specificity 98.9%, positive predictive value 92.9, negative predictive value 91% and accuracy 91.2%. Comparatively, in data previously published, sensitivity, specificity and accuracy of thyroid FNAC in detecting malignancy ranged from 52-86%, 52-87% and 65-80% respectively (29-31). These studies agree well. Furthermore, previous reports show that the accuracy of FNAC is estimated to be between 87% and 95% and varies according to the histological evaluation and this agrees well with the overall accuracy of 91.2% in our present study and also the positive and negative predictive values of 92.9% and 91%, respectively (6, 31-34). Moreover, the application of various techniques like advanced imaging, cell blocks, immunocytochemistry, immunologic analysis, as well as other ancillary studies can result in further reduction of misdiagnosis and considerably increase accuracy.

Conclusions and Recommendations

The frequency and distribution of thyroid lesions at MNH seems to be comparable to elsewhere and occurring more frequently in females and in early adulthood. FNAC is specific and accurate for initial evaluation of thyroid lesions although it shows low sensitivity. Cytodiagnostic errors in some cases can be avoided by careful attention to the clinical context supported by the general and local examination, thyroid imaging (ultrasound as well as thyroid isotope scan), thyroid function tests (TSH, T_3 & T_4) as well as other investigations. Furthermore, a benign diagnosis by FNAC should be viewed with caution, as false negative results occur. However, FNA cytology can be effectively utilized in attaining definitive anatomical diagnosis of various thyroid lesions where histopathology is not available.

Abbreviations

FNAB/FNAC	Fine-needle aspiration biopsy/cytology
FNA	Fine-needle aspiration
FTC	Follicular thyroid carcinoma
ITS	Isotopic thyroid scan
MNH	Muhimbili National Hospital
ND/ID	non-diagnostic/indeterminate
PTC	papillary thyroid carcinoma
SOPD	surgical outpatient clinics
ROSE	***r***apid ***o***n-***s***ite ***e***valuation

TSH	Thyroid Stimulating Hormone
T_3	Tri-iodothyronine
T_4	Tetra- iodothyronine (also Thyroxine)
TBSRTC	The Bethesda System for Reporting Thyroid Cytopathology
USS	Ultrasonography/ultrasound

Declarations

Competing interests

The authors declare that they have no competing financial interests.

Authors' Contributions

H.M.H, A.R.M and C.M designed the research. H.M.H and A.R.M collected clinical and pathological data. H.M.H and C.M analyzed and interpreted the clinical data. A.R.M and H.M.H analyzed and interpreted the histopathological data. H.M.H performed statistical analysis and prepared the initial Bibliography. A.R.M performed statistical analysis, wrote the manuscript, updated and formatted the Bibliography, corrected, reviewed, and submitted the manuscript and did the correspondence. C.M corrected, reviewed and polished the manuscript. A.RM did the digital photomicrography and legends.

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