DIAGNOSTIC ACCURACY OF ULTRASOUND-GUIDED FINE NEEDLE ASPIRATION CYTOLOGY OF THYROID NODULES AT UNIVERSITAS ACADEMIC HOSPITAL, BLOEMFONTEIN

by

DR. FAYYAZ AHMAD

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Supervisor:

Prof. Anandan Moodley

Declaration of authorship:

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Fayyaz Ahmad (candidate) Date

__9 /9/2020____

Anandan Moodley (supervisor) Date

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Table of contents:

Title page	i
Declaration	ii
Acknowledgements	iii
Table of Contents	iv
Abstract	v
Keywords	v
List of abbreviations	vi
List of appendices	vii
Chapter 1 Literature review	1
1.1 Introduction	1
1.2 Clinical assessment	2
1.3 Laboratory studies	3
1.4 Ultrasonography	3
1.5 Radioisotope studies	5
1.6 CT and MRI	5
1.7 FDG PET/CT	5
1.8 Fine needle aspiration cytology	6
1.9 Technical aspects of FNA	7
Aims and objectives	12
References	14
Chapter 2 Publishable article	23
Appendices	42

Abstract

Background: Fine Needle Aspiration Cytology (FNAC), is safe, reliable and minimally invasive first-line investigation used to evaluate thyroid nodules.

Aim: To determine the diagnostic accuracy of FNAC performed at our institution by correlating its results with histopathological diagnoses.

Methods: A retrospective analysis was conducted of cytology and histopathology results of patients who underwent both FNAC and thyroidectomy at Universitas Hospital, Bloemfontein, over a 5-year period (2014–2018). Cytological findings were classified into six Bethesda categories while histological results were categorised as benign or malignant. Adult patients (≥ 18 years) who underwent both thyroidectomy and FNAC for nodular thyroid disease were included.

Results: Sixty-one cases fulfilled the inclusion criteria. On cytological examination, 28/61 (45.9%) were reported as benign, 11/61(18.0%) as malignant and 10/61(16.4%) as suspicious. On histopathological reports, 29 cases were confirmed as benign and 10 as malignant. Among 10 suspicious cases, four were malignant on histopathology. False positive and false negative rates were 15.3% and 12.8%, respectively. The sensitivity and specificity were 50.0% and 79.3%, respectively. The positive and negative predictive values were 45.5% and 82.1%, respectively. The diagnostic accuracy of FNAC was 71.8%.

Conclusions: FNAC at our institution has not performed as good as most similar studies published previously.

Keywords: thyroid nodules, fine needle aspiration cytology, FNAC, thyroidectomy, diagnostic accuracy

List of abbreviations:

18 FDG-PET/CT: 18 F-fluorodeoxyglucose Positron Emission Tomography-Computed Tomography

AUS/FLUS: Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance

BSRTC: Bethesda System for Reporting Thyroid Cytopathology

CI: Confidence Interval

CT: Computed Tomography

FN/SFN: Follicular Neoplasm or Suspicious for a Follicular Neoplasm

FNAB: Fine Needle Aspiration Biopsy

FNAC: Fine Needle Aspiration Cytology

FTC: Follicular Thyroid Cancer

HSREC: Health Sciences Research Ethics Committee

LBC: Liquid Based Cytology

MNGs: Multi Nodular Goiters

MRI: Magnetic Resonance Imaging

NHRD: National Health Research Database

PTC: Papillary Thyroid Cancer

SD: Standard Deviation

SUSP: Suspicious for malignancy

T3: Triiodothyronine

T4: Thyroxin

Tg: Thyroglobulin

TSH: Thyrotropin Secretory Hormone

US: Ultrasound

List of Appendices:

Appendix A: Letter of approval from Health Sciences Research Ethics Committee

Appendix B: Permission from department of health

Appendix C: Permission letter from HOD

Appendix D: Copy of protocol approved by HSREC

Appendix E: Data collection sheet

Appendix F: Turnitin plagiarism summary report

Appendix G: Author guidelines for JEMDSA

CHAPTER 1

LITERATURE REVIEW

1.1 Introduction

Thyroid nodules are lesions occurring in the thyroid gland that can be distinguished from the normal thyroid parenchyma on radiographic imaging.[1,2] Asymptomatic nodules that are clinically non-palpable and only incidentally discovered on imaging studies performed for the work-up of other conditions, are called "thyroid incidentalomas".[3,4] Globally, nodular thyroid disease is a common condition with an increasing incidence.[5] Thyroid nodules are more common in women and older individuals, those living in iodine-deficient areas, in patients diagnosed with Hashimoto's thyroiditis and in people who had been exposed to external irradiation.[6]

Several epidemiological studies have found that around 5% of females and 1% of males residing in iodine-sufficient areas have goiters with palpable nodules. However, imaging investigations such as neck ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) performed for an indication other than thyroid diseases, can detect thyroid incidentalomas in up to 70% of people.[1,7,8] It has also been found that an estimated 50% of the general population by the age of 60 years have at least one thyroid nodule.[1,3,4]

Nodules are more frequent in females, although malignant nodules are more common in males. The male-to-female ratio of thyroid nodules is 1.2 to 4.3.[9] Benign thyroid nodules, which are most commonly seen, include adenoma, multinodular goiters (MNGs), localised thyroiditis associated with autoimmune disease and cysts. Malignant nodules include papillary adenocarcinoma, follicular adenocarcinoma, medullary carcinoma, undifferentiated carcinoma or lymphoma. Approximately 10–15% of thyroid nodules are malignant and require surgical intervention.[10] Overall, nodules that are more than 1 cm in size pose significant potential of being malignant.[7,8] Table I summarises the causes of benign and malignant thyroid nodules.[11]

Table I. Categories and causes of thyroid nodules.[11]

Benign (85–93%)	Malignant (7–15%)
• Focal thyroiditis (mainly autoimmune) • Dominant nodule(s) in multinodular goiter • Follicular adenoma • Hürthle cell adenoma • Parathyroid adenoma • Cyst (thyroid, parathyroid, thyroglossal) • Thyroid lobe agenesis • Post-surgical hyperplasia of remnant thyroid tissue • Post-radioactive iodine hyperplasia of remnant thyroid tissue ***Very rarely*** • Teratoma • Lipoma • Hemangioma • Infiltrative disease	• Papillary carcinoma • Follicular carcinoma • Medullary carcinoma ***Very rarely*** • Anaplastic carcinoma • Parathyroid carcinoma • Lymphoma • Fibrosarcoma • Metastases

The primary purpose of evaluating thyroid nodules is to identify potentially malignant nodules. Evaluation consists of detailed clinical assessment and various investigations including blood tests, thyroid ultrasound, radiological scans and fine needle aspiration cytology (FNAC). A detailed history, including family history, and a thorough examination are important assessment tools in the initial evaluation of the patient.[11]

1.2 Clinical assessment

Patients usually present to the clinician after noticing a palpable nodule in the neck, or when they are referred after an incidental nodule has been detected on sonar or other imaging studies of the head and neck performed for unrelated indications.[12] Significant aspects in the patient's history that increase the possibility of malignancy include age of presentation (below 20 years or above 70 years of age), male sex, previous head and neck irradiation, history of rapid increase in nodule size, dysphagia, dysphonia, Horner syndrome, and a family history of thyroid carcinoma, especially medullary thyroid carcinoma or multiple endocrine neoplasia.[7,11–14]

On physical examination the signs that increase the likelihood of malignancy include nodules more than 4 cm in size, firm in consistency, adhered to adjacent tissues, enlarged cervical lymph nodes and vocal cord immobility. Although all these clinical findings may be suggestive of a malignant a thyroid nodule, none is absolutely specific for the detection of malignancy.[7,11,13–14] A nodule that is associated with cervical lymphadenopathy of more than 1 cm and vocal cord paralysis is 100% predictive of thyroid malignancy.[15] On the contrary, a family history of goiter and residency in an iodine-deficient area are more indicative of a benign lesion.[1,7]

1.3 Laboratory studies

To establish functional status, laboratory tests are required and include thyroid function tests such as serum thyrotropin secretory hormone (TSH) level, total or free thyroxin (T4), and total triiodothyronine (T3). Most thyroid nodules are euthyroid, although approximately 10% of solitary thyroid nodules are benign hyper-functioning adenomas.[16] Serum calcitonin and calcium levels should be determined in patients with a positive family history of pheochromocytoma, medullary thyroid carcinoma, multiple endocrine neoplasia types 2a or b, or hyperparathyroidism.[17]

Serum thyroglobulin (Tg) levels are not performed as in most of the thyroid diseases Tg concentrations are elevated, and Tg levels are therefore regarded as non-specific with regard to evaluating the risk of malignancy in a thyroid nodule.[1,18,19]

1.4 Ultrasonography

Thyroid ultrasound (thyroid US) is the most significant initial imaging method of choice. It evaluates thyroid gland size, thyroid parenchyma (homogeneous or heterogeneous), the number of nodules present and their location within the thyroid gland, their dimensions, shape (taller vs wider) and margins (smooth, infiltrative or microlobulated). Additional characteristics of the nodule, such as echogenicity, composition (solid or cystic), presence of calcifications and vascularity, can also be evaluated by means of thyroid US. The ultrasound examination is often extended to include cervical lymph node evaluation.[1,18,20,21]

The sonar characteristics suspicious of malignancy include nodule size more than 1 cm, the presence of microcalcifications, irregular margins, and a vertical orientation of the nodule (taller rather than wider).[21–28] Vascularity of the nodule on its own does not predict malignancy risk.[25,26] An increase in peripheral vascularity may occur in the nodules associated with papillary thyroid carcinomas (PTC), compared to nodules of follicular thyroid cancers (FTC) that are characterized by intra-nodular or mixed increased vascularity.[25,29]

Overall, the suspicious characteristics of nodules observed on ultrasound should not be taken as absolutely diagnostic of malignancy, but should be viewed in total and not as single unrelated features.

The malignancy risk for each nodule type is calculated by determining the nodule's category on a continuum that is graded 1–5, (benign to high suspicion for malignancy) as shown in Table II.[11] Each of the five categories has its own defined risk ranges for malignancy dependent on the nodule's sonar characteristics, but not collectively covering the 0–100% risk range altogether.[1,13,21–30] While these sonar features do not eliminate the necessity of performing a biopsy, they are particularly valuable to select the specific position within a nodule for fine needle aspirate biopsy (FNAB).Furthermore, these sonar characteristics also help in the selection of the most suitable nodule for aspiration within a multinodular goiter to maximize the diagnostic yield.[26]

Table II. Thyroid nodule malignancy risk continuum.[11]

Category	Type	Nodular characteristics	Malignancy risk
1	Benign	Purely cystic	<1%
2	Very low suspicion	Partially cystic with no characteristics of categories 3–5 or spongiform	<3%
3	Low suspicion	Partially cystic with eccentric uniformly solid areas with no characteristics of categories 4–5 or isoechoic or hyperechoic solid	5–10%
4	Intermediate suspicion	Hypoechoic solid with no characteristics of category 5	10–20%
5	High suspicion	Hypoechoic solid or partially cystic,	>70–90%

	presenting at least one of the following characteristics: micro-calcifications, irregular margins, orientation "taller than wide", disrupted rim calcifications or extra-thyroidal extension

1.5 Radioisotope studies

The primary role of radioisotope scanning is to determine whether a nodule is hyperfunctioning (hot nodule), hypofunctioning (cold nodule) or normal functioning (warm nodules), but it does not accurately estimate the nodule's size. Radioisotopes that have been utilised are technetium (^{99}Tc) and iodine (both ^{123}I and ^{131}I). All of these scans have similar radiation exposure. ^{123}I is the isotope of choice for functional evaluation and ^{99}Tc for anatomic evaluation.[31] Approximately 80–85% of thyroid nodules are cold, of which around 10% exhibit malignancy. Warm nodules account for 10–15% of the nodules, with a risk of malignancy of less than 10%. Around 5% of all the nodules are hot nodules; however, the risk of malignancy in hot nodules is less than 1%.[31] If warm and cold nodules are combined into one group because of their similar malignancy risk, the sensitivity of nuclear scans for the diagnosis of thyroid malignancy is between 89% and 93%, its specificity is 5% and the positive predictive value is 10%. Therefore, the radionuclide scan does not play role in the initial work-up of a thyroid nodule, except to identify a hyperfunctioning nodule so as to avoid biopsy of such nodule.[31]

1.6 Computed tomography (CT) and magnetic resonance imaging (MRI)

CT and MRI do not play a contributory role in the initial work-up of nodular thyroid disease. However, these imaging modalities are indicated to evaluate the extent of sub-sternal goiter and are used in the work-up for staging of malignant nodules.[32]

1.7 ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}FDG-PET/CT)

Malignant cells in thyroid nodules have a higher uptake of ^{18}FDG because of the high

metabolic demands of malignant cells. Therefore, ^{18}FDG-PET/CT is used in oncology for the purpose of staging, detecting recurrence and assessing the response to therapy.[33] It has been suggested that because of its high negative predictive value of 95–100%, ^{18}FDG-PET/CT can be of value in decreasing the need for diagnostic thyroid lobectomy in patients with indeterminate lesions on FNAC. However, no universal consensus has yet been reached on this matter.[34,35]

1.8 Fine Needle Aspiration Cytology (FNAC)

Fine Needle Aspiration Cytology (FNAC) is the most important first-line investigation when working up a thyroid nodule, because treatment protocols depend on the cytology results. It is a safe and cost-effective approach for the work up of thyroid nodules. Furthermore, FNAC has significantly declined the number of thyroidectomies performed for benign lesions, and simultaneously an increase in cancer yields identified in thyroidectomy specimens. The percentage of surgeries for non-malignant nodules can be reduced from 40% to 3% by means of FNAC.[36–38]

Although it can be performed without ultrasound, FNAC is usually performed under ultrasound guidance, which greatly improves the diagnostic yield, resulting in a reduction of inadequate samples and false negative results.[39] The two main parameters that determine the indications for FNAC are (i) the category (1-5) of the thyroid nodule on the malignancy risk continuum (as shown in Table II); and (ii) the size of the nodule in its greatest dimension (see Table III).[11]

Table III. Indications for FNAC.[11]

Category*	Type	Malignancy risk	Indication of FNAC
1	Benign	<1%	Not recommended for diagnostic purposes.
2	Very low suspicion	<3%	Recommended for nodules >2 cm in greatest dimension.
3	Low suspicion	5–10%	Recommended for nodules >1.5 cm in greatest dimension.
4	Intermediate suspicion	10–20%	Recommended for nodules >1 cm in greatest dimension.
5	High	>70–90%	Recommended for nodules 0.5 to 1 cm in

suspicion	greatest dimension.

*Position on malignancy risk continuum (see Table II).

Nodules of which the greatest dimension is less than 0.5 cm pose a very low risk of malignancy, therefore FNAC is not recommended for such nodules, regardless of its characteristics found on sonographic investigation.[1,18,22-30] Similarly hyperfunctioning (hot) nodules are also not considered for FNAC. With regard to multiple nodules, the criteria to select the suitable nodule for biopsy is the same as for single nodules, and each nodule selected for FNAC must be chosen on its own merit.[1,18,40]

The thyroid malignancy that can reliably be diagnosed by means of fine needle aspiration is the papillary carcinoma. Cytological features of papillary carcinoma, such as Orphan Annie nuclei, nuclear grooves, intra-nuclear inclusions and psammoma bodies, are sufficient to make the diagnosis. Nevertheless, other types of thyroid malignancies, such as medullary carcinoma, anaplastic carcinoma, poorly differentiated carcinoma, metastatic carcinoma or lymphoma, have also been diagnosed on the basis of FNAC.[41]

1.9 Technical aspects of FNA

1.9.1 Consent

Informed consent should always be obtained prior to perform FNA. The procedure should be discussed with the patient in detail in a language the patient can understand. The complications, such as haematomas that can compress the airway, and the possibility of obtaining inadequate samples that may necessitate repeating the procedure, must also be explained.[42–49]

1.9.2 Local anaesthesia

Local anaesthesia is not routinely used because when performed by an experienced person. The procedure usually involves only one needle puncture that is not associated with significant pain.[43,48–50] However, local anesthesia can be administered when it is expected that the patient will not tolerate the procedure well without local

anesthesia, or when performing FNA of deep, non-palpable nodules where more than one needle puncture is anticipated. When local anaesthesia is justified, the subcutaneous tissue overlying the thyroid capsule is infiltrated with 1–2 ml of 1–2% lidocaine hydrochloride solution.[43,48,51]

The patient lies in a supine position having a pillow under the shoulders to extend the neck for better visualisation of the area. The nodules with at least one of the US features suggestive of malignancy, namely micro- or macrocalcification, taller than wider orientation, marked hypo-echogenicity, irregular margins and/or extra-thyroidal extension, should be selected for aspiration.[9,52]

For adequate aspiration, a 2–10 ml plastic syringe attached to a 23–25 gauge needle is used.[42,43,48–50] The needle is inserted into the target nodule and the sample is collected with 6–7 to-and-fro needle movements for approximately 5–10 seconds, while applying 2–3 ml suction.[53] However, the suction pressure may cause microscopic haemorrhage which can affect the sample quality. Therefore, an alternative method of obtaining an adequate sample is "capillary sampling" where the needle is moved back and forth without applying suction to eliminate the risk of blood contamination.[48,50,54,55] Concern has been raised, however, by some authors regarding the sample adequacy by means of this method, while other studies indicated that both methods do not differ with regard to sample adequacy.[54,56–58] The best approach therefore is to use both methods to obtain appropriate sample where capillary sampling should precede the suction aspiration.[53] After an adequate amount of tissue has been collected in the needle hub, the suction should be released and the needle withdrawn, which will prevent seeding of the needle tract with potentially malignant cells.[42,43,50,51]

1.9.3 Processing of FNA samples for cytological diagnosis

Proper methods of smearing, fixation and staining of the sample slides should be followed to increase diagnostic yield.[42] In the traditional ways of smear preparation, the syringe is detached from the needle, filled with air and reattached to the needle, after which the contents are expelled onto the glass slide. The smear is then fixed with 95% ethyl alcohol for a Papanicolaou stain and the slide can be used immediately for

cytological evaluation.[42,59]

Another method of sample preparation is liquid-based cytology (LBC), which is primarily used for gynecologic cervical smear preparation. However, LBC has also recently been introduced for thyroid nodule aspiration cytology. The conventional method as described above, is fast, assesses sample adequacy in real time and ensure more accurate evaluation of cell architecture and colloids than LBC. The advantage of LBC includes achieving a clear background, a monolayer cell preparation, better sample handling and a low non-diagnostic rate. However, its drawbacks include loss of cell architecture, cytomorphologic changes of colloid, and decreased inflammatory cells.[42,59,60] Therefore, a well-structured, standardised training program for cytopathologists must be ensured to maintain high standards of diagnostic accuracy of FNAC.[42,60]

1.9.4 FNAC reporting and management of the nodules based on FNAC category

With regard to the cytology reporting of FNAC, a number of standard international classifications systems are available and include the Italian Consensus,[61] the Bethesda System for Reporting Thyroid Cytopathology,[62] and the UK Royal College of Pathologists classification system.[63] Among these cytology reporting methods, the Bethesda System for Reporting Thyroid Cytopathology (BSRTC)[62] is the most common system that is used globally, and is also used at our institution to report the findings of thyroid cytology samples.

The cytology results are reported under six categories recognised by the BSRTC, as summarised in Table IV. The section following Table IV contains a more detailed description of these categories and their management protocols.

Table IV. The Bethesda System for Reporting Thyroid Cytopathology (BSRTC).[62]

Category	Type	Malignancy risk
1	Non-diagnostic or unsatisfactory	1–4%*
2	Benign	0–3%

3	Atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS)	5–15%
4	Follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN)	15–30%
5	Suspicious for malignancy (SUSP)	60–75%
6	Malignant	97–99%

*The actual risk of malignancy in nodules from this category surgically excised is higher (median 20%)

1. Non-diagnostic or unsatisfactory (malignancy risk 1–4%)

In this category, the tissue sample does not fulfill the criteria of adequacy. An adequate sample must contain a minimum of six groups of well visualised follicular cells, where each must group bear at least 10 well-preserved epithelial cells, preferably present on a single slide.[62,64,65]

The 1–4% risk of malignancy in this category is much lower than the actual malignancy risk of 20% when nodules in this category are surgically excised.[66] In the event where the sample is inadequate but cytologically in keeping with a benign cystic lesion, the laboratory report should mention this clearly.

With regard to the management of category 1, if the cytology is reported as non-diagnostic or unsatisfactory, fine needle aspiration should be repeated under sonar guidance. Should the repeat cytology results still fall under category 1, a decision regarding surgical excision or close observation would depend on the nodule's ultrasound characteristics and the individual features of each patient.[1,18]

2. Benign (malignancy risk 0–3%)

Generally, no further investigation or treatment is required for lesions cytologically reported as benign. However, when the nodule's size is more than 4 cm, zero malignancy risk cannot be assured. In addition, there is no consensus whether the larger size nodules in this category should be managed differently. The decision to treat such nodules therefore will again depend on the ultrasound features of the nodule and the individual patient's characteristics, such as age, other comorbidities, and the

patient's own preferences.[1,18] Follow-up Thyroid US should be performed in 12–-24 months and FNA should be repeated in the event of identifying a >20% increase in two dimensions or >50% in total volume. No further observation of such a nodule is recommended if the cytology results show a benign lesion on the second FNAC.[67–69]

3. *Atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS) (malignancy risk 5–15%)*

The highest discordant rates have been reported for this category. Some studies have further sub-classified this category into AUS with nuclear atypia (high malignancy risk) and FLUS with architectural atypia (low malignancy risk).[62,64,70]

With respect to the management of category 3, the clinicians have the choice to either repeat FNAC or opt for surgical excision. The choice depends on US features of the nodule and the patient's characteristics, such as general health and age.[1,18] When available, molecular testing may also contribute to the diagnosis.[71,72] Should the decision be made to repeat FNAC and the results are inconclusive, surgical excision or the active surveillance are the next appropriate steps in management, but still taking the US features of the nodule and patient's clinical features into consideration.[1,18] In general, cytology reported as AUS with nuclear atypia poses a greater risk of malignancy than FLUS with architectural atypia.[62,64,70]

4. *Follicular neoplasm or suspicious of a follicular neoplasm (FN/SFN) (malignancy risk 15–30%)*

This category also accommodates the diagnosis of Hürthle cell neoplasm/suspicious of Hürthle cell neoplasm.[62,64] Surgical excision is the preferred for such nodules, and molecular testing may also be considered if available.[1,18,71–74]

5. *Suspicious for malignancy (SUSP) (malignancy risk 60–75%)*

Where possible, the precise histological type of the malignancy needs be mentioned in the description.[62] The management approach in this category is surgical excision. However, molecular testing can be considered before surgery if it is expected that the

molecular testing may alter the decision for surgery.[1,18,71–76]

6. Malignant (malignancy risk 97–99%)

The FNAC results in this category are conclusive for malignancy, but the exact type of malignancy (for example, papillary thyroid carcinoma, medullary thyroid carcinoma) should be described in the report.[63] The management protocols are the same as for category 5. However, in patients with very low risk tumors (small papillary carcinoma < 1 cm in size), patients who are at very high risk for a major surgery (concurrent illnesses or comorbidities, and patients with reduced life expectancy, may be candidates for active surveillance instead of surgery.[1,18,77]

2. Aim and objectives of the study

Although many research studies have described a high accuracy of FNAC, the growing literature especially from tropical region of Africa and some other developing countries has shown a reduced accuracy of FNAC. Moreover, its diagnostic performance also differs among various studies. [78–80]

Many studies conducted to determine the diagnostic accuracy of FNAC have been reported in the literature. The performance of FNAC in different studies varies significantly. According to the literature, the sensitivity of thyroid FNA ranges from as low as 38% to as high as 98%, and the specificity from 72% to 99%.[81–84] Similarly, the positive and negative predictive values among different studies also vary considerably. The range for the positive predictive value of FNAC is between 66.7% and 98.7%,[83,85] whereas its negative predictive values range between 64% and 96.5%.[81,87] The diagnostic accuracy in various studies included in this literature review ranged from 69% to 94.58%.

The diagnostic performance of thyroid FNAC at Universitas Academic Hospital is unknown. The aim of this study was to determine the diagnostic accuracy of FNAC by estimating its sensitivity, specificity, positive and negative predictive value in detecting malignancy for thyroid nodules, using histopathology of thyroid specimens as the gold standard. The authors is of the opinion that the diagnostic performance of

FNAC at our institution would be in keeping with the majority of studies conducted previously in different parts of the world.

The study was conducted at Universitas Academic Hospital in Bloemfontein. The researcher could not find any similar study done before at our institution or even in South Africa. Therefore, knowing the local statistics about the performance of FNAC and their comparison with international figures is worthwhile and beneficial for our institution and will open the doors for further research on this topic.

References

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016; 26(1): 1–133.
2. Marqusee E, Benson CB, Frates MC, Doubilet PM, Larsen PR, Cibas ES, Mandel SJ. Usefulness of ultrasonography in the management of nodular thyroid disease. Ann Intern Med 2000; 133(9): 696–700.
3. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to non-palpable nodules discovered incidentally on thyroid imaging. Ann Intern Med 1997; 126(3): 226–231.
4. Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. Eur J Clin Invest 2009; 39(8): 699–706.
5. Pang H-N, Chen C-M. The incidence of cancer in nodular goiters. Ann Acad Med Singapore 2007; 36(4): 241–243.
6. Rojeski MT, Gharib H. Nodular thyroid disease. Evaluation and management. N Engl J Med 1985; 313(7): 428–436.
7. Hegedüs L. The thyroid nodule. N Engl J Med 2004; 351(17); 1764–1771.
8. Burman KD, Wartofsky L. Thyroid nodules. N Engl J Med 2015; 373(24): 2347–2356.
9. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009; 19(11): 1167–1214.
10. Luo J, Zhang C, Huang F, Chen J, Sun Y, Xu K, Huang P. Risk of malignancy in thyroid nodules: predictive value of puncture feeling of grittiness in the process of fine-needle aspiration. Sci Rep 2017; 7(1): 13109.

11. Paschou SA, Vryonidou A, Goulis DG. Thyroid nodules: a guide to assessment, treatment and follow-up. Maturitas 2017; 96: 1–9.
12. Bomeli SR, LeBeau SO, Ferris RL. Evaluation of a thyroid nodule. Otolaryngol Clin North Am 2010; 43(2): 229–238.
13. Ferrone S, Marincola FM. Loss of HLA class I antigens by melanoma cells: molecular mechanisms, functional significance and clinical relevance. Immunol Today 1995; 16(10): 487–494.
14. McCoy KL, Jabbour N, Ogilvie JB, Ohori NP, Carty SE, Yim JH. The incidence of cancer and rate of false-negative cytology in thyroid nodules greater than or equal to 4 cm in size. Surgery 2007; 142(6): 837–844.
15. Raza SN, Shah MD, Palme CE, Hall FT, Eski S, Freeman JL. Risk factors for well-differentiated thyroid carcinoma in patients with thyroid nodular disease. Otolaryngol Head Neck Surg 2008; 139(1): 21–26.
16. Wong CK, Wheeler MH. Thyroid nodules: rational management. World J Surg 2000; 24(8): 934–941.
17. Elisei R, Bottici V, Luchetti F, Di Coscio G, Romei C, Grasso L, Miccoli P, Iacconi P, Basolo F, Pinchera A, Pacini F. Impact of routine measurement of serum calcitonin on the diagnosis and outcome of medullary thyroid cancer: experience in 10,864 patients with nodular thyroid disorders. J Clin Endocrinol Metab 2004; 89(1): 163–168.
18. Gharib H, Papini E, Jarber GR, Duick DS, Harrell RM, Hegedüs L, Paschke R, Valcavi R, Vitti P. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules – 2016 update. Endocrinol Pract 2016; 22(5): 622–639.
19. Suh I, Vriens MR, Guerrero MA, Griffin A, Shen WT, Duh QY, Clark OH, Kebebew E. Serum thyroglobulin is a poor diagnostic biomarker of malignancy in follicular and Hurthle-cell neoplasms of the thyroid. Am J Surg 2010; 200(1): 41–46.
20. Smith-Bindman R, Lebda P, Feldstein VA, Sellami D, Goldstein RB, Brasic N, Jin C, Kornak J. Risk of thyroid cancer based on thyroid ultrasound imaging characteristics: results of a population-based study. JAMA Intern Med 2013; 173(19): 1788–1796.

21. Kwak JY, Han KH, Yoon JH, Moon HJ, Son EJ, Park SH, Jung HK, Choi JS, Kim BM, Kim EK. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. Radiology 2011; 260(3): 892–899.
22. Moon WJ, Jung SL, Lee JH, Na DG, Baek JH, Lee YH, Kim J, Kim HS, Byun JS, Lee DH. Benign and malignant thyroid nodules: US differentiation – multicenter retrospective study. Radiology 2008; 247(3): 762–770.
23. Salmaslioğlu A, Erbil Y, Dural C, Işsever H, Kapran Y, Ozarmağan S, Tezelman S. Predictive value of sonographic features in preoperative evaluation of malignant thyroid nodules in a multinodular goiter. World J Surg 2008; 32(9): 1948–1954.
24. Cappelli C, Pirola I, Cumetti D, Micheletti L, Tironi A, Gandossi E, Martino E, Cherubini L, Agosti B, Castellano M, Mattanza C, Rosei EA. Is the anteroposterior and transverse diameter ratio of nonpalpable thyroid nodules a sonographic criteria for recommending fine-needle aspiration cytology? Clin Endocrinol (Oxf) 2005; 63(6): 689–693.
25. Moon HJ, Kwak JY, Kim MJ, Son EJ, Kim EK. Can vascularity at power Doppler US help predict thyroid malignancy? Radiology 2010; 255(1): 260–269.
26. Papini E, Guglielmi R, Bianchini A, Crescenzi A, Taccogna S, Nardi F, Panunzi C, Rinaldi R, Toscano V, Pacella CM. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. J Clin Endocrinol Metab 2002; 87(5): 1941–1946.
27. Gul K, Ersoy R, Dirikoc A, Korukluoglu B, Ersoy PE, Aydin R, Ugras SN, Belenli OK, Cakir B. Ultrasonographic evaluation of thyroid nodules: comparison of ultrasonographic, cytological, and histopathological findings. Endocrine 2009; 36(3): 464–472.
28. Frates MC, Benson CB, Doubilet PM, Kunreuther E, Contreras M, Cibas ES, Orcutt J, Moore FD Jr, Larsen PR, Marqusee E, Alexander EK. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J Clin Endocrinol Metab 2006; 91(9): 3411–3417.
29. Jeh SK, Jung SL, Kim BS, Lee YS. Evaluating the degree of conformity of papillary carcinoma and follicular carcinoma to the reported ultrasonographic findings of malignant thyroid tumor. Korean J Radiol 2007; 8(3): 192–197.

30. Kim SH, Kim BS, Jung SL, Lee JW, Yang PS, Kang BJ, Lim HW,Kim JY, Whang IY, Kwon HS, Jung CK. Ultrasonographic findings of medullary thyroid carcinoma: a comparison with papillary thyroid carcinoma. Korean J Radiol 2009; 10(2): 101–105.
31. Cases JA, Surks MI. The changing role of scintigraphy in the evaluation of thyroid nodules. Semin Nucl Med 2000; 30(2): 81–87.
32. Mazzaferri EL. Management of a solitary thyroid nodule. N Engl J Med 1993; 328(8): 553–559.
33. Rohren EM, Turkington TG, Coleman RE. Clinical applications of PET in oncology. Radiology 2004; 231(2): 305–332.
34. Mitchell JC, Grant F, Evenson AR, Parker JA, Hasselgren PO, Parangi S. Preoperative evaluation of thyroid nodules with 18FDG-PET/CT. Surgery 2005; 138(6): 1166–1175.
35. de Geus-Oei LF, Pieters GF, Bonenkamp JJ, Mudde AH, Bleeker-Rovers CP, Corstens FH, Oyen WJG. ^{18}F-FDG PET reduces unnecessary hemithyroidectomies for thyroid nodules with inconclusive cytologic results. J Nucl Med 2006; 47(5): 770–775.
36. Soderstrom N. Puncture of goitres for aspiration biopsy. Acta Med Scand 1952; 144(3): 237–244.
37. Gharib H. Fine-needle aspiration biopsy of thyroid nodules: advantages, limitations, and effect. Mayo Clin Proc 1994; 69(1): 44–49.
38. Kendall CH. Fine needle aspiration of thyroid nodules: three years' experience. J Clin Pathol 1989; 42(1): 23–27.
39. Danese D, Sciacchitano S, Farsetti A, Andreoli M, Pontecorvi A. Diagnostic accuracy of conventional versus sonography-guided fine-needle aspiration biopsy of thyroid nodules. Thyroid 1998; 8(1): 15–21.
40. Langer JE, Agarwal R, Zhuang H, Huang SS, Mandel SJ. Correlation of findings from iodine 123 scan and ultrasonography in the recommendation for thyroid fine-needle aspiration biopsy. Endocr Pract 2011; 17(5): 699–706.
41. Baloch ZW, LiVolsi VA, Asa SL, Rosai J, Merino MJ, Randolph G, Viehl P, DeMay RM, Sidaway MK, Frable WJ. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagn Cytopathol 2008; 36(6): 425–437.

42. Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedüs L, Vitti P. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. Endocr Pract 2010; 16(3): 468–475.
43. Baloch ZW, Cibas ES, Clark DP, Layfield LJ, Ljung BM, Pitman MB, Abati A. The National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference: a summation. Cytojournal 2008; 5: 6.
44. Cibas ES, Alexander EK, Benson CB, de Agustín PP, Doherty GM, Faquin WC, Middelton WD, Miller T, Raab SS, White ML, Mandel SJ. Indications for thyroid FNA and pre-FNA requirements: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagn Cytopathol 2008; 36(6): 390–399.
45. Polyzos SA, Anastasilakis AD. Clinical complications following thyroid fine-needle biopsy: a systematic review. Clin Endocrinol (Oxf) 2009; 71(2): 157–165.
46. Hor T, Lahiri SW. Bilateral thyroid hematomas after fine-needle aspiration causing acute airway obstruction. Thyroid 2008; 18(5): 567–569.
47. Tsilchorozidou T, Vagropoulos I, Karagianidou C, Grigoriadis N. Huge intrathyroidal hematoma causing airway obstruction: a multidisciplinary challenge. Thyroid 2006; 16(8): 795–799.
48. Pitman MB, Abele J, Ali SZ, Duick D, Elsheikh TM, Jeffrey RB, Powers CN, Randolph G, Renshaw A, Scoutt L. Techniques for thyroid FNA: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagn Cytopathol 2008; 36(6): 407–424.
49. Crockett JC. The thyroid nodule: fine-needle aspiration biopsy technique. J Ultrasound Med 2011; 30(5): 685–694.
50. Kim MJ, Kim EK, Park SI, Kim BM, Kwak JY, Kim SJ, Yoyk JH, Park SH. US-guided fine-needle aspiration of thyroid nodules: indications, techniques, results. Radiographics 2008; 28(7): 1869–1887.
51. Kim DW, Choo HJ, Park JS, Lee EJ, Kim SH, Jung SJ, Ryu JH. Ultrasonography-guided fine-needle aspiration cytology for thyroid nodules: an emphasis on one-sampling and biopsy techniques. Diagn Cytopathol 2012; 40(Suppl 1): E48–E54.

52. Moon WJ, Baek JH, Jung SL, Kim DW, Kim EK, Kim JY, Kwak JY, Lee JH, Lee JH, Lee YK, Na DG, Park JS, Park SW. Ultrasonography and the ultrasound-based management of thyroid nodules: consensus statement and recommendations. Korean J Radiol 2011; 12(1): 1–14.
53. Rausch P, Nowels K, Jeffrey RB Jr. Ultrasonographically guided thyroid biopsy: a review with emphasis on technique. J Ultrasound Med 2001; 20(1): 79–85.
54. Degirmenci B, Haktanir A, Albayrak R, Acar M, Sahin DA, Sahin O, Yucel A, Galiskan G. Sonographically guided fine-needle biopsy of thyroid nodules: the effects of nodule characteristics, sampling technique, and needle size on the adequacy of cytological material. Clin Radiol 2007; 62(8): 798–803.
55. Mahony GT, Mahony BS. Low nondiagnostic rate for fine-needle capillary sampling biopsy of thyroid nodules: a singular experience. J Ultrasound Med 2013; 32(12): 2155–2161.
56. Romitelli F, Di Stasio E, Santoro C, Iozzino M, Orsini A, Cesareo R. A comparative study of fine needle aspiration and fine needle non-aspiration biopsy on suspected thyroid nodules. Endocr Pathol 2009; 20(2): 108–113.
57. Haddadi-Nezhad S, Larijani B, Tavangar SM, Nouraei SM. Comparison of fine-needle-nonaspiration with fine-needle-aspiration technique in the cytologic studies of thyroid nodules. Endocr Pathol 2003; 14(4): 369–373.
58. Tublin ME, Martin JA, Rollin LJ, Pealer K, Kurs-Lasky M, Ohori NP. Ultrasound-guided fine-needle aspiration versus fine-needle capillary sampling biopsy of thyroid nodules: does technique matter? J Ultrasound Med 2007; 26(12): 1697–1701.
59. Fadda G, Rossi ED. Liquid-based cytology in fine-needle aspiration biopsies of the thyroid gland. Acta Cytol 2011; 55(5): 389–400.
60. Saleh H, Bassily N, Hammoud MJ. Utility of a liquid-based, monolayer preparation in the evaluation of thyroid lesions by fine needle aspiration biopsy: comparison with the conventional smear method. Acta Cytol 2009; 53(2): 130–136.
61. Nardi F, Basolo F, Crescenzi A, Fadda G, Frasoldati A, Orlandi F, Palombini L, Papini E, Zini M, Pontecorvi A, Vitti A. Italian consensus for the classification and reporting of thyroid cytology. J. Endocrinol Invest 2014; 37(6); 593–599.
62. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Am J Clin Pathol 2009; 132(5): 658–665.

63. Cross P, Chandra A, Giles T, Johnson S, Kocjan G, Poller D, Stephenson T. Guidance on the reporting of thyroid cytology specimens. London: The Royal College of Pathologists; 2016. Available at https://www.rcpath.org/uploads/assets/7d693ce4-0091-4621-97f79e2a0d1034d6/g089_guidance_on_reporting_of_thyroid_cytology_specimens.pdf (accessed 22 May 2020).
64. Crippa S, Mazzucchelli L, Cibas ES, Ali SZ. The Bethesda System for reporting thyroid fine-needle aspiration specimens. Am J Clin Pathol 2010; 134(2): 343–344.
65. Crothers BA, Henry PM, Firat P Hamper UM. Nondiagnostic/unsatisfactory. In: Ali SZ, Cibas ES (eds.). The Bethesda System for Reporting Thyroid Cytopathology. New York: Springer; 2010, pp. 5–14.
66. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda System for Reporting Thyroid Cytopathology: a meta-analysis. Acta Cytol 2012; 56(4): 333–339.
67. Nou E, Kwong N, Alexander LK, Cibas ES, Marqusee E, Alexander EK. Determination of the optimal time interval for repeat evaluation after a benign thyroid nodule aspiration. J Clin Endocrinol Metab 2014; 99(2): 510–516.
68. Oertel YC, Miyahara-Felipe L, Mendoza MG, Yu K. Value of repeated fine needle aspirations of the thyroid: an analysis of over ten thousand FNAs. Thyroid 2007; 17(11); 1061–1066.
69. Illouz F, Rodien P, Saint-André JP, Triau S, Laboureau-Soares S, Dubois S, Vielle B, Hamy A, Rohmer V. Usefulness of repeated fine-needle cytology in the follow-up of non-operated thyroid nodules. Eur J Endocrinol 2007; 156(3): 303–308.
70. Nishino M, Wang HH. Should the thyroid AUS/FLUS category be further stratified by malignancy risk? Cancer Cytopathol 2014; 122(7): 481–483.
71. Eszlinger M, Hegedüs L, Paschke R. Ruling in or ruling out thyroid malignancy by molecular diagnostics of thyroid nodules. Best Pract Res Clin Endocrinol Metab 2014; 28(4): 545–557.
72. Wylie D, Beaudenon-Huibregtse S, Haynes BC, Giordano TJ, Labourier E. Molecular classification of thyroid lesions by combined testing for miRNA gene expression and somatic gene alterations. J Pathol Clin Res 2016; 2(2): 93–103.

73. Nikiforov YE, Ohori NP, Hodak SP, Carty SE, LeBeau SO, Ferris RL, Yip L, Seethala RR, Tublin ME, Stang MT, Coyne C, Johnson JT, Stewart AF, Nikiforova MN. Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. J Clin Endocrinol Metab 2011; 96(11): 3390–3397.
74. Ferris RL, Baloch Z, Bernet V, Chen A, Fahey TJ 3rd, Ganly I, Hodak SP, Kebebew E, Patel KN, Shaha A, Steward DL, Tufano RP, Wiseman SM, Carty SE. American Thyroid Association statement on surgical application of molecular profiling for thyroid nodules: current impact on perioperative decision making. Thyroid 2015; 25(7): 760–768.
75. Kuo LE, Kelz RR. Management of thyroid nodular disease: current cytopathology classifications and genetic testing. Surg Oncol Clin N Am 2016; 25(1): 1–16.
76. Hyeon J, Ahn S, Shin JH, Oh YL. The prediction of malignant risk in the category "atypia of undetermined significance/follicular lesion of undetermined significance" of the Bethesda System for Reporting Thyroid Cytopathology using subcategorization and BRAF mutation results. Cancer Cytopathol 2014; 122(5): 368–376.
77. Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, Tomoda C, Takamura Y, Kobayashi K, Miya A. An observational trial for papillary thyroid microcarcinoma in Japanese patients. World J Surg 2010; 34(1): 28–35.
78. Nyawawa E, Yongolo S, Tupa J. Radionuclide scan and other diagnostic studies in goitre patients in Tanzania. East Centr Afr J Surg 2006; 11(2): 15–20.
79. Costamagna D, 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. G Chir 2013; 34(1–2): 21–26.
80. Wang CC, Friedman L, Kennedy GC, Wang H, Kebebew E, Steward DL, Zeiger MA, Westra WH, Wang Y, Khanafshar E, Fellegara G, Rosai J, Livolsi V, Lanman RB. A large multicenter correlation study of thyroid nodule cytopathology and histopathology. Thyroid 2011; 21(3): 243–251.
81. Cusick EL, MacIntosh CA, Krukowski ZH, Williams VM, Ewen SW, Matheson NA. Management of isolated thyroid swellings: a prospective six year study of fine needle aspiration cytology in diagnosis. BMJ 1990; 301(6747): 318–321.

82. Afroze N, Kayani N, Hasan SH. (2002). Role of fine needle aspiration cytology in diagnosis of palpable thyroid lesions. Indian J Pathol Microbiol 2002; 45(3): 241–246.
83. Al-Hureibi KA, Al-Hureibi AA, Abdulmughni YA, Aulaqi SM, Salman MS, Al-Zooba EM. The diagnostic value of fine needle aspiration cytology in thyroid swellings in a university hospital, Yemen. Saudi Med J 2003; 24(5): 499–503.
84. Mahar SA, Husain A, Islam N. Fine needle aspiration cytology of thyroid nodule: diagnostic accuracy and pitfalls. J Ayub Med Coll Abbottabad 2006; 18(4): 26–29.
85. Kessler A, Gavriel H, Zahav S, Vaiman M, Shlamkovitch N, Segal S, Eviatar E. Accuracy and consistency of fine-needle aspiration biopsy in the diagnosis and management of solitary thyroid nodules. Isr Med Assoc J 2005; 7(6): 371–373.
86. Haberal AN, Toru S, Ozen O, Arat Z, Bilezikçi B. Diagnostic pitfalls in the evaluation of fine needle aspiration cytology of the thyroid: correlation with histopathology in 260 cases. Cytopathology 2009; 20(2): 103–108.

CHAPTER 2

PUBLISHABLE ARTICLE

Title

Diagnostic accuracy of ultrasound guided Fine Needle Aspiration Cytology of thyroid nodules at Universitas Academic Hospital Bloemfontein

Authors

Dr. Ahmad F, MBBS, MRCP (UK), MFAMMED (UFS)
Department of Internal Medicine, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa

Email address: fayyaz307@hotmail.com
Postal Address: Department of Internal Medicine, University of the Free State, 205 Nelson Mandela Drive, Bloemfontein, 9301
Telephone: 051 405 3154
Cell: 083 453 5975

Prof. Moodley AA, MBCHB, FCP (Neurology), FEBN, PhD
Department of Neurology, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa

Email address: moodleyAA@ufs.ac.za
Postal Address: Department of Neurology, University of the Free State, 205 Nelson Mandela Drive, Bloemfontein, 9301
Telephone: 051 405 3550
Cell: 084 595 5077

Abstract

Background: Fine Needle Aspiration Cytology (FNAC), is safe, reliable and minimally invasive first-line investigation used to evaluate thyroid nodules.

Aim: To determine the diagnostic accuracy of FNAC performed at our institution by correlating its results with histopathological diagnoses.

Methods: A retrospective analysis was conducted of cytology and histopathology results of patients who underwent both FNAC and thyroidectomy at Universitas Hospital, Bloemfontein, over a 5-year period (2014–2018). Cytological findings were classified into six Bethesda categories while histological results were categorised as benign or malignant. Adult patients (≥ 18 years) who underwent both thyroidectomy and FNAC for nodular thyroid disease were included.

Results: Sixty-one cases fulfilled the inclusion criteria. On cytological examination, 28/61 (45.9%) were reported as benign, 11/61(18.0%) as malignant and 10/61(16.4%) as suspicious. On histopathological reports, 29 cases were confirmed as benign and 10 as malignant. Among 10 suspicious cases, four were malignant on histopathology. False positive and false negative rates were 15.3% and 12.8%, respectively. The sensitivity and specificity were 50.0% and 79.3%, respectively. The positive and negative predictive values were 45.5% and 82.1%, respectively. The diagnostic accuracy of FNAC was 71.8%.

Conclusions: FNAC at our institution has not performed as good as most similar studies published previously.

Keywords: thyroid nodules, fine needle aspiration cytology, FNAC, thyroidectomy, diagnostic accuracy

Conflict of interest: None

Introduction

Globally, nodular thyroid disease is a common condition with an increasing incidence.[1] Worldwide, the prevalence of the thyroid nodules ranges between 4–7% on neck palpation which significantly increases to 30-50% when investigated by ultrasound.[1,2] Nodules are more frequent in females, with a male-to-female ratio of 1.2 to 3.4; however, malignant nodules more commonly occur in the male patients.[3] Most nodules are benign, with approximately 10–15% of the thyroid nodules being malignant and requiring surgical intervention.[4] The primary purpose of evaluating the thyroid nodules is to identify the potentially malignant nodules.

Fine Needle Aspiration Cytology (FNAC) has been in use since the 1950s for the pre-operative diagnosis of thyroid nodules, and is a safe, cost-effective method of diagnosing thyroid nodules.[5] The primary objective of FNAC is to recognise the nodules that need surgery, so as to avoid thyroidectomy for the benign nodules. Due to the use of FNAC, a significant decrease in the number of thyroidectomies performed for benign disease has been observed, and simultaneously an increase in cancer yields found in surgically excised specimens.[6] The percentage of surgeries for non-malignant nodules can be reduced from 40% to 3% by means of FNAC.[7]

Despite the advantages of FNAC, the technique has some drawbacks. The two main shortcomings of the technique are false-negative cytology and the inability to detect microcarcinomas, which could be attributed either to an interpretation error or inadequate sampling.[8] Furthermore, FNAC is "un-interpretable" in 10–20% of cases or "suspicious" in 9–38% of the cases, which eventually requires histological assessment of the nodule to confirm the diagnosis.[9–11] In addition, the FNAC technique is operator-dependent and the operator's experience and skills contribute substantially to the accuracy of the results.

Although various research studies have reported a high accuracy of FNAC, growing literature, especially from tropical regions of Africa and other developing countries having high numbers of nodular thyroid disease, have shown a lower accuracy of FNAC compared to what was reported previously. Moreover, its diagnostic performance also varies among different studies.[12–14]

The aim of our study was to evaluate the correlation between cytological and histopathological findings of thyroid nodules, since treatment protocols are greatly influenced by the FNAC results. FNACs are usually mandatory before major thyroid surgical intervention.

Methods

We performed a retrospective analysis of cytology and histopathology results of patients who underwent both FNAC and thyroidectomy procedures at Universitas Academic Hospital in Bloemfontein, South Africa over the 5-year period from 1st January 2014 to 31 December 2018.

Histopathological and cytology reports of all thyroidectomies performed for the diagnosis and/or treatment of nodular thyroid diseases during the study period were retrieved from medical records. Data regarding the age and sex of the patients were also collected. Cytological results were classified into six categories proposed by the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) (see Table 1),[15] while histology results were categorised as benign or malignant. Adult patients only (≥ 18 years of age) who underwent both FNAC and thyroidectomy were included in the study. Thyroidectomies performed primarily for nodular thyroid diseases were included. We excluded thyroidectomies performed for reasons other than nodular thyroid disease, such as Grave's disease and hyperthyroidism.

Data was collected from the patients' National Health Laboratory Service (NHLS) records and captured in a Microsoft Excel spreadsheet and included each patient's age, sex, Bethesda category (Table I) of cytological findings and histological category (benign or malignant).

Table I. The Bethesda System for Reporting Thyroid Cytopathology (BSRTC).[15]

Category	Type/description
I	Non-diagnostic or unsatisfactory
II	Benign
III	Atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS)
IV	Follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN)
V	Suspicious for malignancy (SUSP)
VI	Malignant

The data was analysed by the Department of Biostatistics at University of the Free State (UFS). The statistical analysis included true positive rate, true negative rate, false positive rate, false negative rate, sensitivity, specificity, positive predictive value, negative predictive value and accuracy.

Approval to conduct the study was obtained from the Health Sciences Research Ethics Committee (HSREC) of the University of the Free State, with ethical clearance number UFS-HSD2019/0738/3007. Approval was also obtained from the Free State Province Department of Health via the National Health Research Database (NHRD), with reference number FS 201907 001.

Results

In total, 128 patients had thyroidectomies during the study period of 5 years. Sixty-seven patients were excluded from the study because among them, 56 patients had no FNAC performed prior to thyroidectomy, and in 11 cases, thyroidectomies were performed for Graves's disease, which was an exclusion criterion in the study protocol. The remaining 61 patients who had undergone both FNAC and thyroidectomy procedures were included in the study.

The majority of patients were female (n=57; 93.4%), giving a male-to-female ratio of 1:15. The patients' age ranged between 20 and 90 years, with a mean age of 53.37 (±

15.93 SD) years. The highest number of cases was seen in the age group 51–60 years (n=18; 29.5%), followed by patients 41–50 years of age (n=15; 24.6%). The age and the sex distribution of the patients included in the study are shown in Figures 1 and 2 respectively.

Figure 1. Age distribution of patients with thyroid nodules

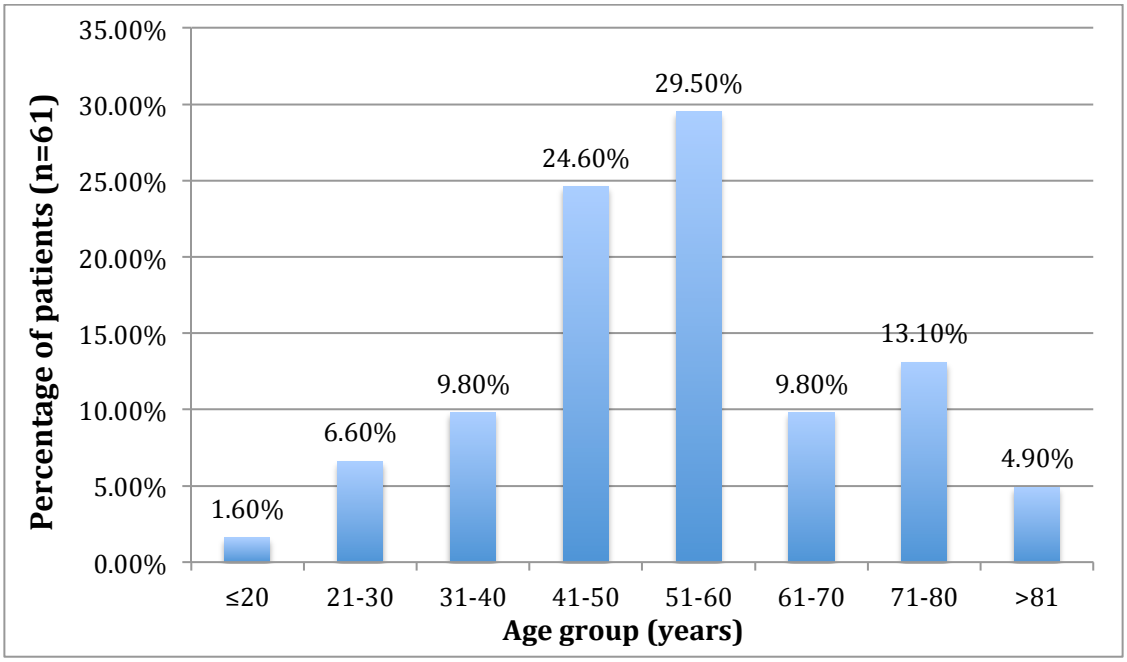
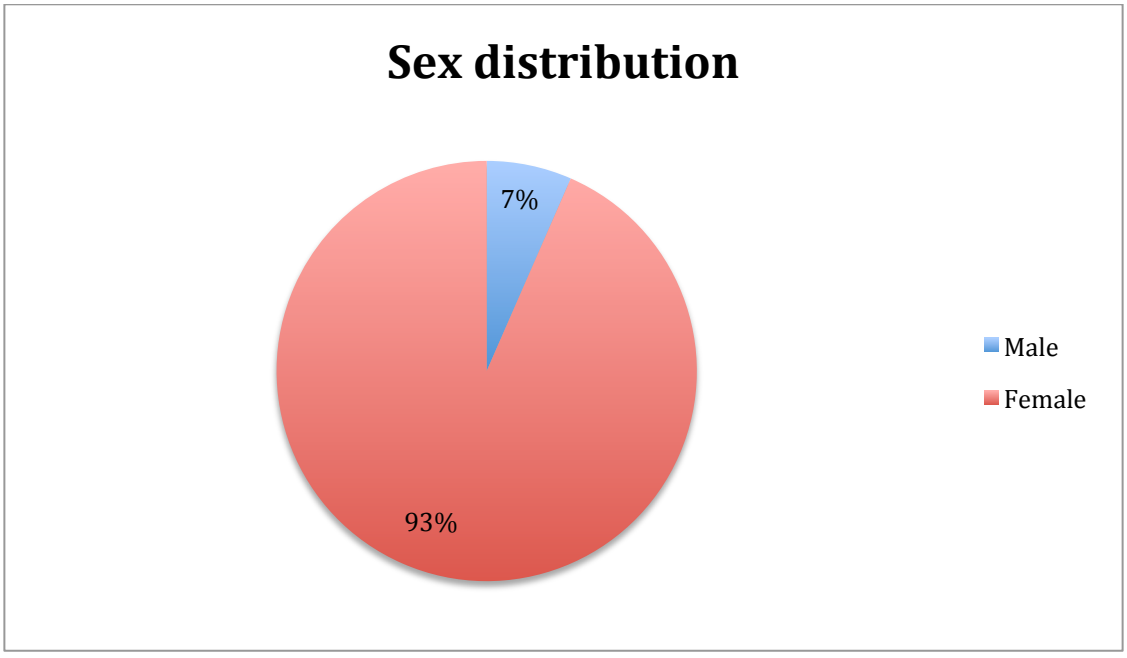
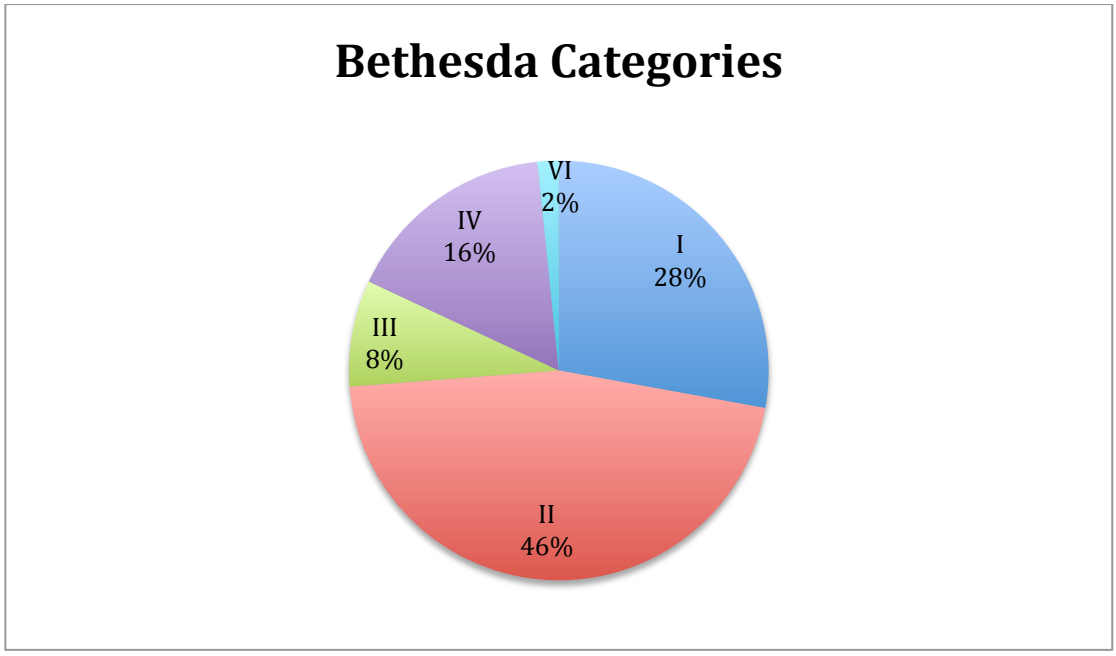


Figure 2: Sex distribution of study population



Among 61 specimens of FNAC, 17 (28%) were reported as Category I (Unsatisfactory), 28 (46%), as category II (benign), 5 (8%) as category III (atypia or follicular lesions of undetermined significance-AUS), 10 (16%) as category IV (follicular neoplasm or lesions suspicious for follicular neoplasm-FN), 0(0%) as category V (suspected malignant) and 1(2%) as category VI (malignant). This distribution is illustrated in Figure 3.

Figure 3: Distribution of FNAC diagnosis



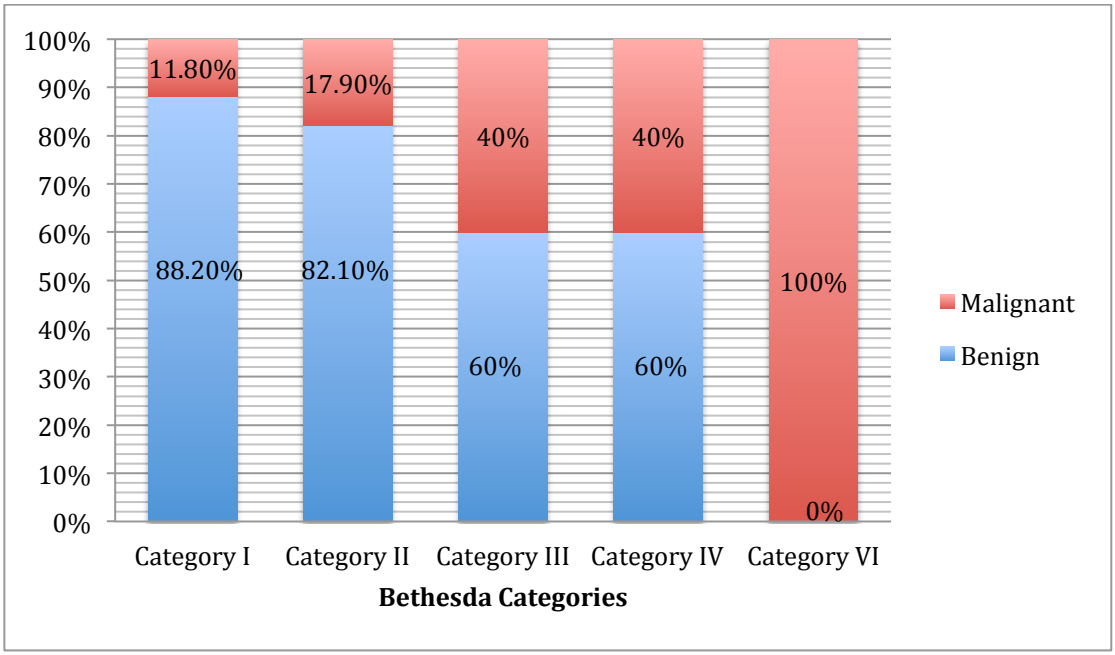
Findings of the histopathological analysis of 61 thyroidectomy specimens showing malignancy rates per BSRTC category are summarised in Table II and figure 4. The majority of cases (n=47; 77.0%) were classified as benign. With the exception of category VI (n=1; 100% malignancy rate), the malignancy rate was the highest in BSRTC categories III and IV (n=2 of 5; 40.0% and n=3 of 10; 40.0%, respectively).

Table II. Correlation of cytological and histological findings of thyroid nodules

Cytology (BSRTC category)	Frequency (%) (N=61)	Histopathology	
		Benign	Malignant
	n (%)	n (%)	n (%)
I	17 (27.9)	15 (88.2)	2 (11.8)

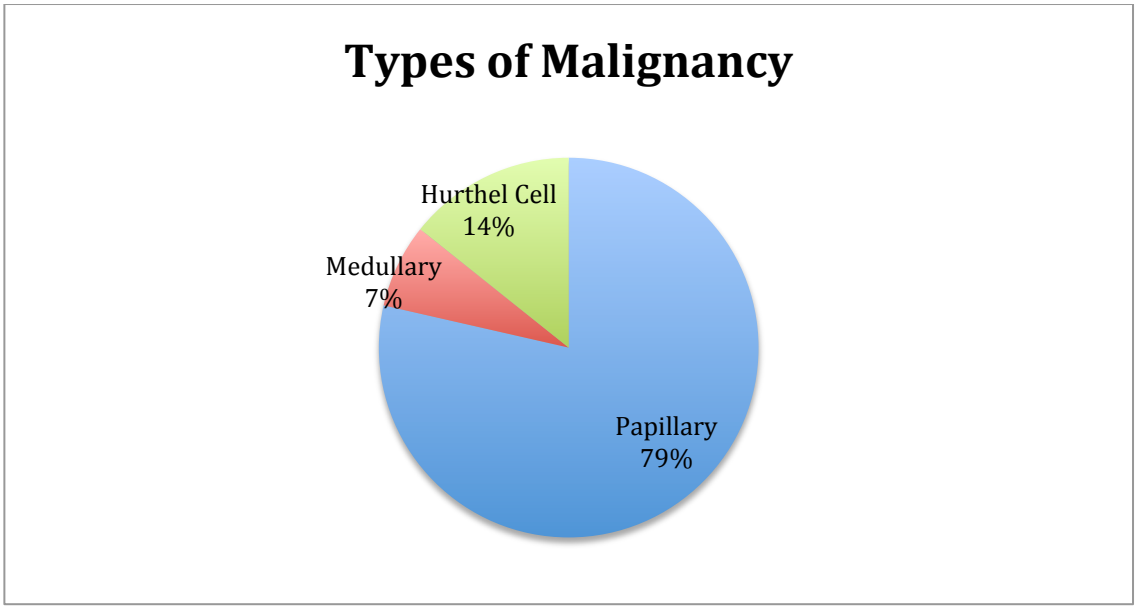
II	28 (45.9)	23 (82.1)	5 (17.9)
III	5 (8.2)	3 (60.0)	2 (40.0)
IV	10 (16.4)	6 (60.0)	4 (40.0)
V	0 (0)	0 (0)	0 (0)
VI	1 (1.6)	0 (0)	1 (100)

Figure 4: Cyto-histopathological correlation



Among 14 patients with malignant histological findings, 12 (85.7%) were female and only two (14.3%) were male. With regard to the various type of malignant lesions, the result showed that papillary cancers (n=11; 79%) were the most common type of thyroid cancer, followed by Hürthel cell cancer (n=2; 14%) and medullary cancer (n=1; 7%) as shown in figure 5.

Figure 5: Types of malignancy



Out of 28 benign cases on FNAC, 23 (82.1%) were also confirmed as benign on histopathological examination, showing true negative rate of 82.1%. There were five (17.9%) false negative cases, which were diagnosed as benign upon FNAC but turned out to be malignant after histopathological examination. Out of 11 cases diagnosed as malignant on FNAC, five (45.5%) were diagnosed as malignant on histopathological examination, and therefore considered as true positive cases. Six (54.5%) cases yielded false positive results, which were cytologically diagnosed as malignant but turned out to be benign upon histopathological examination, as shown in Table III.

Table III. Cytological and histopathological diagnoses of thyroid nodules

Fine needle aspiration cytology (FNAC)	**Histopathology**	
	Benign (n=29)	**Malignant (n=10)**
	n (%)	**n (%)**
Benign (n=28)	23 (82.1) (TN)	5 (17.9) (FN)
Malignant (n=11)	6 (54.5) (FP)	5 (45.5) (TP)

TN = True Negative; TP = True Positive; FN = False Negative; FP = False Positive

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of NFCA were calculated as follows:

Sensitivity

True positive ÷ (true positive + false negative) = 5 ÷ (5 + 5) x 100 = 50.0%

Specificity

True negative ÷ (true negative + false positive) = 23 ÷ (23 + 6) x 100 = 79.3%

Positive predictive value (PPV)

True positive ÷ (true positive + false positive) = 5 ÷ (5 + 6) x 100 = 45.5%

Negative predictive value (NPV)

True negative ÷ (true negative + false negative) = 23 ÷ (23 + 5) x 100 = 82.1%

Accuracy

(True positive + true negative) ÷ total number of cases = (5 + 23) ÷ 39 x 100 = 71.8%

The sensitivity rate for thyroid FNAC was 50.0% (95% CI 19–81%) and the specificity rate was 79.3% (95% CI 60–92%). The positive predictive value was 45.5% (95% CI 17–77%) and the negative predictive value was 82.1% (95% CI 63–94%). The diagnostic accuracy of FNAC was calculated as 71.8% (95% CI 55–85%). The comparison of these findings with studies published in the literature is shown in Table IV.

Table IV. Comparison of the current study's results with studies previously published in the literature.

Study	Year	No. of patients	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Al-Sayer et al.[16]	1985	70	86.0	93.0	80.0	96.0	92.0
Cusick et al.[17]	1990	283	76.0	58.0	72.0	64.0	69.0
Bouvet et al.[18]	1992	78	93.5	75.0	85.3	88.2	79.6
Afroze et al.[19]	2002	170	61.9	99.31	92.86	94.74	94.58
Ko et al.[20]	2003	207	78.4	98.2	99.0	66.3	84.4
Al-Hureibi et al.[21]	2003	196	38.0	89.9	66.7	73.2	72.0
Kessler et al.[22]	2005	170	79.0	98.5	98.7	76.6	87.0
Mahar et al.[23]	2006	125	98.0	70.0	91.0	93.0	91.0
Haberal et al.[24]	2009	260	92.6	91.6	83.5	96.5	91.9
Muratli et al.[25]	2013	126	87.1	64.6	76.1	79.5	77.3
Current study	2019	61	50.0	79.3	45.5	82.1	71.8

Discussion

Nodular thyroid disease is a common occurrence globally. The principal aim of evaluating thyroid nodules is to recognise potentially malignant nodules. The clinician has the choice of a variety of diagnostic tests, such as ultrasound, thyroid nuclear scan, and Fine Needle Aspiration Cytology (FNAC), in order to evaluate these nodules. Although ultrasonography and nuclear scans may contribute to differentiate between benign and malignant lesions, tissue diagnosis is mandatory to exclude malignancy and FNAC is the first-line investigation in this regard.

Our study was conducted to determine the accuracy of FNAC in differentiating benign thyroid lesions from the malignant nodules. Generally, FNAC is mandatory before thyroidectomy. FNAC being the most important initial investigation for the work up of the thyroid nodules also has certain disadvantages. Despite its accuracy that has been reported as high as 95–98%, false positive and false negative outcomes may also occur.[25]

The success of FNAC primarily depends on a satisfactory sample obtained from the thyroid nodule being investigated. The smear obtained must be representative of the lesion, be of a sufficient quantity and excellent cyto-preparation should be performed. Our unsatisfactory rate was 27.9%, which was higher than many of the studies conducted earlier. For example, the unsatisfactory rate reported by Khan et al.[27] was 6.2%, 10% reported by Jat[28] and 12.52% reported Machała et al.[29] However, a higher non-diagnostic rate of FNAC has been reported in the literature where the unsatisfactory or non-diagnostic rate was as high 33%.[30] Many factors are responsible for inadequate fine needle aspiration samples.

Grani et al.[31] described that certain ultrasound characteristics are linked to inadequate cytology samples. They reported that a thyroid nodule of less than 10 mm in size, especially with ill-defined margins, might be indicative of a poor cytology sample. In contrast, if the nodules are isoechogenic on sonar examination, these are more predictive of a good diagnostic cytology sample.[31] Alexander at el. reported that a cystic content of a nodule resulted in non-diagnostic cytology.[32] Similarly, Richards et al. found that nodules larger than 3 cm in size were also associated with non-diagnostic cytology.[33] Some other factors that might affect cytology adequacy include use of smaller needles (24–25 gauge) for aspiration and capillary sampling technique (versus suction aspiration method).[29] Both of these factors favour the possibility of obtaining adequate samples. The age and sex of the patient and the timing of the repeat biopsy after a first inadequate sample had no effect on non-diagnostic rates.[33–35]

A strong female preponderance has been observed in our study, which was higher than those reported in similar studies conducted on this topic. The female-to-male ratio in our study was 15.2:1, compared to 4:1 observed by Khan et al.[27] and 3.4:1 by Mochala et al.[29] Thyroid diseases are more common among the females, which can be explained by hormonal factors and the fact that women attend healthcare facilities more often than men, including antenatal and postpartum visits, and therefore, women are screened both clinically and through investigations more often than males.[36,37]

With regard to the age distribution of patients in our study, the minimum and maximum ages were 20 and 90 years, respectively. The highest numbers of cases

occurred in patients between 51 and 60 years, with more than of half of our study population being 40–60 years of age. The age distribution of patients in our study was in keeping with those reported by similar studies, but other research data showed the peak age of incidence in the second and third decades of life.[38]

Among the total study sample of 61 cases, 22 patients fell under BSRTC category I (17 patients) and category III (5 patients) therefore no cyto-histopathological correlation could be made. The remaining 39 patients belonged to categories 11,IV and IV where the correlation could be established between cytology and histology. Twenty-eight of these 39 cases showed positive correlation between FNAC and histopathology results. The discordant results were found in the remaining 11 cases.

The false negative rate was 17.8% in cases of malignant lesions, which constitutes a significant drawback of FNAC at our institution, as false negative reporting would preclude these malignant lesions from being excised. The false negative results reported in the literature ranges from 1% to as high as 30%.[39] Discrepancies such as these reflect the shortcomings of FNAC in diagnosing certain lesions, such as follicular pattern lesions, cystic papillary thyroid carcinoma (PTC) and microcarcinoma.[26] The term "follicular pattern lesions" includes lesions such as hyperplastic nodule (nodular goiter), follicular neoplasm (follicular adenoma and carcinoma) and follicular variants of PTC. Cytologists designate different descriptions of the findings in this category, such as atypical, indeterminate, favour, cannot exclude, possible, or probable and suspicious, which can cause uncertainty among the clinicians. Therefore, excision of such lesions is recommended for accurate diagnosis. The false negative rate could also be due to an inappropriate sample taken from a cystic lesion in the thyroid, which may be associated with another underlying malignant nodule.[26]

The false positive rate reported in the literature ranges from 1.9% to 8%.[26,40–43] In our study, the false positive rate of 54.6% was substantially higher than that reported in similar studies. The reason for these false positive cases could be the presence of some similar cytological characteristics shared by both papillary carcinoma and benign thyroid conditions, such as Hashimoto's thyroiditis, nodular goiter or follicular neoplasms.[29] The pathologist, therefore, must be aware of such cytological similarities

to avoid over- or under-diagnoses, as over-diagnosis will lead to unnecessary thyroidectomies putting the patient at risk of postoperative complications or permanent hypothyroidism. Contrarily, misdiagnosing malignant lesions to a benign condition will result in the malignancy being left untreated.[26]

According to the literature, the sensitivity of thyroid FNAC ranges from 38% to 98%, and the specificity from 72% to 99%.[17,19,21,23] The sensitivity, specificity, and diagnostic accuracy of FNAC in our study was 50.0%, 79.3%, and 71.8%, respectively, whereas sensitivity, specificity, and accuracy of FNAC were 76%, 58%, and 69%, respectively, in a study by Cusick et al.,[17] and 92.6%, 91.6%, and 91.9%, respectively, in a study by Haberal et al.[24] A comparison of the results of the current study with various previous studies is shown in Table IV. Our study showed a sensitivity of 50.0%, which is only better than the 38% sensitivity reported by Al-Hureibi et al.[21] The highest sensitivity was found by Mahar et al.,[23] which was 98%.

With regard to the positive predictive value, our study also has not performed well. The value was 45.5% compared to 99% by Ko et al.[20] However, with respect to specificity and the negative predictive value, our results of 79.3% and 82.1%, respectively, were better than some of the studies included in the comparison. Our diagnostic accuracy was71.8%, whereas most of the studies referred to in Table IV have shown a diagnostic accuracy of more than 80%.

The low sensitivity in our study could be due to multiple factors, such as the low sample size, operator's skills regarding the aspiration of cytology sample, inadequate cytology slide preparation, and the wrong classification of suspicious lesions. Another important factor that could be responsible for the poor sensitivity at our institution might be that there is no single radiologist responsible for fine needle aspiration sampling of thyroid nodules. Furthermore endocrinologists and surgeons also take fine needle aspiration cytology samples at our institution. The relatively low diagnostic accuracy of 71.8% at our institution might compromise the trust among clinicians to use FNAC as a reliable diagnostic tool for thyroid nodules.

In our study, 14 cases were found to be malignant on histology reports, where 11 (79%) were papillary carcinoma, 2 (14%) were Hürthle cell carcinomas and 1 (7%)

was a medullary carcinoma. According to the, papillary carcinoma constitutes around 75% to 85% of all thyroid cancers,[29] which was in agreement with 78.6% of malignant nodules being papillary carcinomas in our study. The malignancy rate in our study was 22.9%, which was similar to findings reported by Gupta et al.[39] However, a wide range of malignancy rates has been reported in the literature, ranging from 13.8% found by Haberal et al.,[24] to as high as 54% reported by Muratli et al.[25]

Out of 128 thyroidectomies performed during our study period, 56 patients were excluded from our study because FNAC had not been done prior to the thyroidectomy. The majority of these patients (75.0%) had a benign histology on histopathology examination. Therefore, thyroidectomy could potentially have been avoided if FNAC had been performed prior to surgery, and if FNAC had a high sensitivity and specificity in our unit. However this does not apply to the patients on whom the thyroidectomy was performed because of obstructive symptoms or where the sonar findings were highly suspicious of malignancy and thus thyroidectomy was performed without prior FNAC. More research is needed to determine the reasons behind patients not having FNAC before thyroid surgery at our institution, as FNAC has been proven to reduce the number of thyroid surgeries performed for non-neoplastic lesions.[7]

Conclusions

Literature has proven the enhanced efficacy of ultrasound-guided FNAC as the initial diagnostic tool of choice when evaluating thyroid nodules. However, FNAC at our institution has not performed that good, especially pertaining to its sensitivity, positive predictive value and diagnostic accuracy. Many explanations could be offered for this relatively poor performance, including, but not limited to, the wrong nodule selected for the biopsy, variability in the skill levels of different operators, the poor sample aspiration technique, inadequate slide preparation, difficulties in classification and interpretations of certain thyroid pathologies by the cytologists, and surgeons having little faith in FNAC. Further research should be conducted at our institution to determine the factors behind the suboptimal performance of FNAC.

References

1. Pang HN, Chen CM. The incidence of cancer in nodular goiters. Ann Acad Med Singapore. 2007;36(4):241–3.
2. Belfiore A, La Rosa GL, Padova G, et al. The frequency of cold thyroid nodules and thyroid malignancies in patients from an iodine-deficient area. Cancer. 1987;60(12):3096–102.
3. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167–214.
4. Luo J, Zhang C, Huang F, et al. Risk of malignancy in thyroid nodules: predictive value of puncture feeling of grittiness in the process of fine-needle aspiration. Sci Rep. 2017;7(1):13109.
5. Soderstrom N. Puncture of goitres for aspiration biopsy. Acta Med Scand. 1952;144(3):237–44.
6. Gharib H. Fine-needle aspiration biopsy of thyroid nodules: advantages, limitations, and effect. Mayo Clin Proc. 1994;69(1):44–9.
7. Kendall CH. Fine needle aspiration of thyroid nodules: three years' experience. J Clin Pathol. 1989;42(1):23–7.
8. Prades JM, Querat C, Dumollard JM, et al. Thyroid nodule surgery: predictive diagnostic value of fine- needle aspiration cytology and frozen section. Eur Ann Otorhinolaryngol Head Neck Dis. 2013;130(4):195–9.
9. Alexander EK. Approach to the patient with a cytologically indeterminate thyroid nodule. J Clin Endocrinol Metab. 2008;93(11):4175–82.
10. Seningen JL, Nassar A, Henry MR. Correlation of thyroid nodule fine needle aspiration cytology with corresponding histology at Mayo Clinic, 2001–2007: an institutional experience of 1,945 cases. Diagn Cytopathol. 2012;40(Suppl. 1):E27–32.
11. Baier ND, Hahn PF, Gervais DA, et al. Fine- needle aspiration biopsy of thyroid nodules: experience in a cohort of 944 patients. Am J Roentgenol. 2009;193(4):1175–9.
12. Nyawawa E, Yongolo S, Tupa J. Radionuclide scan and other diagnostic studies in goitre patients in Tanzania. East Centr Afr J Surg. 2006;11(2):15–20.

13. Costamagna D, Pagano L, Caputo M, et al. Incidental cancer in patients surgically treated for benign thyroid disease. Our experience at a single institution. G Chir. 2013;34(1–2):21–6.
14. Wang CC, Friedman L, Kennedy GC, et al. A large multicenter correlation study of thyroid nodule cytopathology and histopathology. Thyroid. 2011;21(3):243–51.
15. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Am J Clin Pathol 2009; 132(5): 658–665.
16. Al-Sayer HM, Krukowski ZH, Williams VM, et al. Fine needle aspiration cytology in isolated thyroid swellings: a prospective two year evaluation. Br Med J (Clin Res Ed). 1985;290(6480):1490–2.
17. Cusick EL, MacIntosh CA, Krukowski ZH, et al. Management of isolated thyroid swellings: a prospective six year study of fine needle aspiration cytology in diagnosis. Br Med J. 1990;301(6747):318–21.
18. Bouvet M, Feldman JI, Gill GN, et al. Surgical management of the thyroid nodule: patient selection based on the results of fine-needle aspiration cytology. Laryngoscope. 1992;102(12 Pt 1):1353–6.
19. Afroze N, Kayani N, Hasan SH. Role of fine needle aspiration cytology in diagnosis of palpable thyroid lesions. Indian J Pathol Microbiol. 2002;45(3):241–6.
20. Ko HM, Jhu IK, Yang SH, et al. Clinicopathologic analysis of fine needle aspiration cytology of the thyroid. A review of 1,613 cases and correlation with histopathologic diagnoses. Acta Cytol. 2003;47(5):727–32.
21. Al-Hureibi KA, Al-Hureibi AA, Abdulmughni YA, et al. The diagnostic value of fine needle aspiration cytology in thyroid swellings in a university hospital, Yemen. Saudi Med J 2003; 24(5): 499–503.
22. Kessler A, Gavriel H, Zahav S, et al. Accuracy and consistency of fine-needle aspiration biopsy in the diagnosis and management of solitary thyroid nodules. Isr Med Assoc J. 2005;7(6):371–3.
23. Mahar SA, Husain A, Islam N. Fine needle aspiration cytology of thyroid nodule: diagnostic accuracy and pitfalls. J Ayub Med Coll Abbottabad. 2006;18(4):26–9.
24. Haberal AN, Toru S, Ozen O, et al. Diagnostic pitfalls in the evaluation of fine needle aspiration cytology of the thyroid: correlation with histopathology in 260 cases. Cytopathology. 2009;20(2):103–8.

25. Muratli A, Erdogan N, Sevim S, et al. Diagnostic efficacy and importance of fine-needle aspiration cytology of thyroid nodules. J Cytol. 2014;31(2):73–8.
26. Sharma C. Diagnostic accuracy of fine needle aspiration cytology of thyroid and evaluation of discordant cases. J Egypt Natl Cancer Inst. 2015;27(3):147–53.
27. Khan I, Naz S, Akhter ZM, et al. Diagnostic accuracy of fine needle aspiration of thyroid nodule verses biopsy in thyroid lesions. J Ayub Med Coll Abbottabad. 2010;22(4):179–81.
28. Jat MA. Comparison of surgeon-performed ultrasound-guided fine needle aspiration cytology with histopathological diagnosis of thyroid nodules. Pak J Med Sci. 2019;35(4):1003–7.
29. Machała E, Sopiński J, Javorska J, et al. Correlation of fine needle aspiration cytology of thyroid gland with histopathological results. Pol Przegl Chir. 2018;90(6):13–9.
30. Degirmenci B, Haktanir A, Albayrak R, et al. Sonographically guided fine-needle biopsy of thyroid nodules: the effects of nodule characteristics, sampling technique, and needle size on the adequacy of cytological material. Clin Radiol. 2007;62(8):798–803.
31. Grani G, Calvanese A, Carbotta G, et al. Intrinsic factors affecting adequacy of thyroid nodule fine needle aspiration cytology. Clin Endocrinol. 2013;78(1):141–4.
32. Alexander EK, Heering JP, Benson CB, et al. Assessment of nondiagnostic ultrasound-guided fine needle aspirations of thyroid nodules. J Clin Endocrinol Metab. 2002;87(11):4924–7.
33. Richards ML, Bohnenblust E, Sirinek K, Bingener J. Nondiagnostic thyroid fine-needle aspiration biopsies are no longer a dilemma. Am J Surg. 2008;196(3):398–402.
34. Lubitz CC, Nagarkatti SS, Faquin WC, et al. Diagnostic yield of nondiagnostic thyroid nodules is not altered by timing of repeat biopsy. Thyroid. 2012;22(6):590–4.
35. Houlton JJ, Sun GH, Fernandez N, et al. Thyroid fine-needle aspiration: does case volume affect diagnostic yield and interpretation? Arch Otolaryngol Head Neck Surg. 2011;137(11):1136–9.
36. Nikiforov YE, Fagin JA. Risk factors for thyroid cancer. Trends Endocrinol Metab. 1997;8(1):20–5.

37. Alwahaibi N, Alsalami J, Rani Bai U, et al. Accuracy of fine needle aspiration cytology of thyroid lesion with corresponding histopathology: a single institutional experience. Thyroid Res Pract. 2016;13(3):140–3.
38. Rout K, Ray CS, Behera SK, et al. A comparative study of FNAC and histopathology of thyroid swellings. Indian J Otolaryngol Head Neck Surg. 2011;63(4): 370–2.
39. Gupta M, Gupta S, Gupta VB. (2010). Correlation of fine needle aspiration cytology with histopathology in the diagnosis of solitary thyroid nodule. J Thyroid Res. 2010;2010:379051.
40. Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med. 1993;118(4):282–9.
41. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Am J Clin Pathol 2009; 132(5): 658–665.
42. Sangalli G, Serio G, Zampatti C, et al. Fine needle aspiration cytology of the thyroid: a comparison of 5469 cytological and final histological diagnoses. Cytopathology. 2006;17(5):245–50.
43. Jogai S, Al-Jassar A, Temmim L, et al. Fine needle aspiration cytology (FNAC) of the thyroid: a cytohistologic correlation with critical evaluation of discordant cases. Acta Cytol. 2013;49(5):483–8.

Appendix A: Letter of approval from Health Sciences Research Ethics Committee

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

24-Jun-2019

Dear **Dr Fayyaz Ahmad**

Ethics Clearance: **Diagnostic accuracy of ultrasound guided Fine Needle Aspiration Cytology of thyroid nodules at Universitas Academic Hospital Bloemfontein**

Principal Investigator: **Dr Fayyaz Ahmad**

Department: **Internal Medicine Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2019/0738/3007**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa

Appendix B: DOH approval letter

health
Department of Health
FREE STATE PROVINCE

12 July 2019

Dr F Ahmad
Dept. of Internal Medicine
UFS

Dear Dr F Ahmad

Subject: Diagnostic accuracy of ultrasound guided Fine Needle Aspiration Cytology of thyroid nodules at Universitas Academic Hospital Bloemfontein

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **Universitas Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeelats@fshealth.gov.za / koekoeel@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with National Hospital CEO's on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 11/07/19

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemj@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za

Appendix C: Permission letter from HOD Internal Medicine

UNIVERSITY OF THE FREE STATE
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YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

6 May 2019

Dr. E. le Grange
The Chairperson,
Ethics Committee,
Faculty of Health Sciences
University of the Free State

Dear Dr Le Grange

Title: ***"Diagnostic accuracy of fine needle aspiration cytology at Universitas Academic Hospital Bloemfonetein"***

I hereby grant Dr F Ahmad (Registrar - Internal Medicine) permission to conduct research in the Endocrinology division, Department of Internal Medicine.

Kind regards

Dr TRP Mofokeng
BS(Lewis & Clark) USA, M.Med (Int) UFS
MBChB (UCT), Cert Endocrinolog + Met(SA)
Head: Dept. Internal Medicine
Tel: 051 405 3154 - Fax: 051 401 2659

Dr TRP Mofokeng
Head: Department Internal Medicine

Department of Internal Medicine/Departement Interne Geneeskunde
205 Nelson Mandela Drive/Rylaan, Park West/Parkwes, Bloemfontein 9301, South Africa/Suid-Afrika
P.O. Box/Posbus 339 (G73), Bloemfontein 9300, South Africa/Suid-Afrika,
T: +27(0)51 4053154, Fax/faks: +27(0)51 4012659
www.ufs.ac.za

Appendix D: Copy of approved research protocol

Diagnostic accuracy of ultrasound guided Fine Needle Aspiration Cytology of thyroid nodules at Universitas Academic Hospital Bloemfontein

Principal researcher: Dr F.Ahmad

0834535975

fayyaz307@hotmail.com

Supervisor: Prof A.Moodley

084 595 5077

MoodleyAA@ufs.ac.za

Table of contents

1.Summary of the research in layman's terms.....3

2.Title……..5

3.Introuction……5

4.Aim……..6

5.Methodology……6

5.1:Study design……..6

5.2:Sample…….6

5.3:Inclusion criteria……..6

5.4:Exclusion criteria…….6

5.5:Measurements……..6

5.6:Methodological and measurement errors……7

5.7:Pilot study……...7

6.Analysis……...7

7.Time Schedule…….8

8.Budget……..8

9.Ehical aspects……..8

10.References……9

1.Summary of the research in layman's terms

Thyroid lumps are localised swellings inside thyroid gland and are common occurrence in the world population. These are more common in females than males. The thyroid lumps can be either cancerous or non cancerous. It is crucial to differentiae between the two categories so as to diagnose earlier the lumps that are cancerous in order to treat effectively and timely.it is also important to diagnose the non-cancerous lumps so as to avoid unnecessary surgery and to reassure the patient that their lump is not a cancer.

To differentiate between cancerous and non-cancerous lumps, there is a variety of tests available, both invasive and non invasive. Invasive tests entail obtaining actual thyroid tissue sample from thyroid gland and sending it to he laboratory for confirmation of cancer. The non-invasive tests are ultrasonography, computerized tomography (CT) and Magnetic Resonance Imaging (MRI) scans of thyroid gland. The non-invasive tests do help to differentiate between the two categories however are unable to accurately diagnose whether the lump is a cancer or not. To accurately diagnose the lumps, invasive tests described below are mandatory.

There are two invasive tests available to obtain tissue sample from thyroid gland. In the first test a needle is inserted into the thyroid gland under ultrasound guidance and a very small piece of thyroid gland is sucked into the needle. The sample obtained is sprayed onto a glass slide, which is examined under a microscope by a laboratory doctor to diagnose the nature of the lump. The medical term used for his procedure is Fine Needle Aspiration Cytology (FNAC).

FNAC is a quick, easy to perform and first line invasive investigation in order to diagnose the lump with great certainty. However this test is not 100% accurate because the size of the tissue obtained from the thyroid gland is very small. Also the needle may miss the lump and may enter into nearby structures in the neck and therefore can obtain a wrong sample.

In the second invasive test, the thyroid gland must surgically be removed and then sent to the laboratory to be examined under he microscope for accurate diagnosis. This procedure is called Thyroidectomy and is 100% diagnostic. However not all patients who have thyroid lumps can be exposed to thyroidectomy as this is a major surgery and has many complications. Therefore the FNAC is performed first and if it shows suspicious results then Thyroidectomy is considered.

The aim of this research study is to compare the diagnostic accuracy of FNAC procedures against Thyroidectomies performed at Universitas academic hospital over the last 5 years (1st January 2014 till 31st December 2018).

The researcher will obtain the laboratory reports of both procedures (FNAC and thyroidectomy) performed during the study period. The data will be used to complete a data-sheet that will then be sent to biostatistician for analysis.

The researcher will obtain consent from relevant authorities including Health Sciences Research Ethics Committee and Department of Health Free State.

The data collection procedure will be kept strictly confidential and no identifying information (for example personal particulars) of the patients will appear in the study.

2.Title

Diagnostic accuracy of ultrasound guided Fine Needle Aspiration Cytology of thyroid nodules at Universitas Academic Hospital Bloemfontein.

3.Introduction:

Nodular thyroid disease is common throughout the world, and the incidence has been rising in recent decades[1]. Worldwide, thyroid nodules have been reported in 4 - 7% of the population on neck palpation and in 30 - 50% when investigated by ultrasonography. [1,2] Nodules are more frequent in females, however are more malignant in males[3]. Male to female ratio is 1.2 to 4.3[3].Thyroid nodules can be benign (adenoma, nodules of multinodular goiters (MNGs), localised thyroiditis, including autoimmune disease and cysts) or malignant (papillary adenocarcinoma, follicular adenocarcinoma, medullary carcinoma, undifferentiated carcinoma or lymphoma). Most nodules are benign[4]. About 10-15 % thyroid nodules are malignant and require surgical intervenion[4]. Usually patients with nodular thyroid disease present to a surgical clinic with a neck mass, with or without toxic symptoms, with pressure symptoms or for cosmetic reasons.

The main goal of evaluating these nodules is to identify nodules with malignant potential. A variety of diagnostic tests like ultrasound, thyroid nuclear scan, and fine needle aspiration cytology (FNAC) is available to the clinician for evaluation of thyroid nodules. Although ultrasonography and nuclear scans help in differentiating between benign and malignant lesions, however tissue diagnosis is mandatory to exclude malignancy and FNAC is the first line investigation in this regard.

Fine Needle Aspiration Cytology (FNAC) has been in use since the 1950s for the pre operative diagnosis of thyroid nodules and is a safe, cost effective method of diagnosing thyroid nodules[5]. The main aim of FNAC is to identify nodules that require surgery and those benign nodules that can be observed clinically and decrease the overall thyroidectomy rate in patients with benign diseases.

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 [6-7] and its diagnostic performance has been shown to vary across different studies[8].
The diagnostic performance of thyroid FNAC at Universitas Academic Hospital is unknown. The purpose of this study is to determine the accuracy of FNAC by estimating its sensitivity, specificity, positive and negative predictive value in detecting malignancy for thyroid nodules using histopathology of excised specimen as a gold standard.

4.Aim

The aim of this study is to determine the diagnostic accuracy of Fine Needle Aspiration Cytology performed at our institution over a period of past 5 years from 1st January 2014 till 31st December 2018 by correlating Fine Needle Aspiration Cytology results with histopathological diagnoses.

5. Methodology

5.1 Study design

A retrospective descriptive study

5.2 Sample

The researcher will retrieve histopathological and cytology reports of all thyroidectomies done for the diagnosis/treatment of nodular thyroid disease during the study period as well as information about age and sex of the patients from National Health Laboratory Services Labtrack system.

On average 3 thyroidectomies are performed per month at Universitas Hospital, therefore we are estimating about 180 patients over the study period of 5 years.

5.3 Inclusion criteria

Adult patients (18 years and above)

Reports of all patients who underwent both thyroidectomy and FNAC

Thyroidectomies done for the diagnosis/treatment of nodular thyroid disease

5.4 Exclusion criteria

Thyroidectomies done for reasons other than nodular disease (hyperthyroidism)

Patients who underwent only one procedure

5.5 Measurement

The principal researcher will collect the data in a private room at the department of Internal Medicine from 7 July - 31 July 2019.

The data will be noted on attached data form. This information will then be placed on Excel spread sheet by the researcher.
The following patient's data will be collected from the NHLS record;

i) Age
ii) Sex
iii) Bethesda category (table below)

iii) Histological category (benign or malignant)

Bethesda System[9]

Diagnostic category	Risk of malignancy (%)	Usual management
I. Nondiagnostic or unsatisfactory		Repeat FNA with ultrasound guidance
II. Benign	0–3	Clinical follow-up
III. Atypia of undetermined significance or follicular lesion of undetermined significance	5–15	Repeat FNA
IV. Follicular neoplasms or suspicious for a follicular neoplasm	15–30	Surgical lobectomy
V. Suspicious for malignancy	60–75	Near-total thyroidectomy or surgical lobectomy
VI. Malignant	97–99	Near-total thyroidectomy

5.6 Methodological and Measurement Errors

Researcher is aware of the missing information because of the retrospective nature of this study. With regards to data typing errors, the researcher will check every fifth file to match the data figures between data form and the excel spread sheet.

5.7 Pilot study

A pilot study will be performed, evaluating the information of first 10 patients to test data capturing apparatus and if no changes are made to the data form then pilot study data will be included in the study.

6.ANALYSIS

Using the Bethesda FNAC reporting system only individuals with a "benign"(Bethesda ii) report will be considered benign cases on FNAC, whereas cases with "follicular neoplasm" (Bethesda IV), "suspicious for malignancy" (Bethesda V) or "malignancy"
(Bethesda VI) reports will constitute malignant cases on FNAC.

The histopathology diagnosis would be classified as non-neoplastic (benign) or neoplastic
(malignant).

Descriptive statistics namely means and standard deviations or medians and percentiles will be calculated for continuous data. Frequencies and percentages will be calculated for categorical data. Diagnostic test statistics namely sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios will be calculated for the comparison of the Bethesda category and histology. The analysis will be performed by the Department of Biostatistics, University of the Free State (UFS).

7.TIME SCHEDULE

Ethics committee submission: May 2019
Department of Health approval: 1 June – 30 June 2019
Pilot Study: 1 July – 7 July 2019
Data Collection: 7 July - 31 July 2019
Data Analysis: 1 August - 31 August 2019
Writing up: 1 September - 31 September 2019
Submission for evaluation: October 2019

8.BUDGET

Wi-Fi/ Data: R1500 per month
Stationery: White papers R250
Ink for the printer: R1000
Language Editor: R2500
Total: R5250

The researcher will apply for funding, if unsuccessful then researcher will bear all of the expenses.

9.ETHICAL ASPECTS

To obtain Ethics Committee's approval.
To obtain permission from appropriate authorities;

Head of Department Internal Medicine
The Department of Health Free State

The data collecting procedure will be kept strictly confidential. No identifying information (for example personal particulars) of the patients will appear in the study. No known conflicts of interest to be declared.

10.REFERENCES

1. Pang H-N, Chen C-M. The incidence of cancer in nodular goiters. Ann Acad Med Singapore 2007;36(4):241-243.

2. Belfiore A, La Rosa GL, Padova G, Sava L, Ippolito O, Vigneri R. The frequency of cold thyroid nodules and thyroid malignancies in patients from an iodine-deficient area. Cancer 1987;60(12):3096-3102.

3.Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, et al. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19:1167–214.

4. Luo J, Zhang C, Huang F, et al. Risk of malignancy in thyroid nodules: predictive value of puncture feeling of grittiness in the process of fine-needle aspiration. *Sci Rep*. 2017;7(1):13109. Published 2017 Oct 12. doi:10.1038/s41598-017-13391-3

5. Solderstrom N. Puncture of Goitres for aspiration biopsy. Acta Med Scand. 1952;144:237–244. PubMed. [PubMed]

6. 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.

7. Costamagna D, 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):21–26. [PubMed]

8. 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):243–251. PubMed. [PMC free article] [PubMed].

9. Ali SZ, Cibas ES. The Bethesda System for Reporting Thyroid Cytopathology. New York, NY: Springer; 2010.

10. Bagga PK, Mahajan NC (2010) Fine needle aspiration cytology of thyroid swellings: how useful and accurate is it? Indian J Cancer 47:437–442.

Appendix E: Data Collection Sheet

Data Form

1.Patient No ----------

2. Age (in years)----------

3.Sex
- 3.1 Male
- 3.2 Female

4.FNAC Bethesda category
- 4.1 Category ii
- 4.2 Category iv
- 4.3 Category v
- 4.4 Category vi

5. Histology
- 5.1 Benign
- 5.2 Malignant

Appendix F: Turnitin summary report

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by Fayyaz Ahmad

Submission date: 05-Jun-2020 06:23PM (UTC+0200)
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4. Declaration regarding authorship.
5. Ethics committee approval.
6. Conflicts of interest.

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Correspondence to the Editor-in-Chief:

Prof Jeffrey Wing, e-mail: Jeffrey.Wing@wits.ac.za,

Technical manuscript preparation

All JEMDSA papers must comply with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (Ann Intern Med 2000; 133:229-231 [editorial]; http://www.icmje.org, full text). All articles must be typed in 12 pt Times New Roman with 1.5 spacing. Small tables and figures (1/4–1/2 page) may be included in the manuscript. If tables are large (i.e. 1 page landscape) or if images are large in file size (> 500 KB), they must be uploaded as separate supplementary files. Research articles should have a structured abstract not exceeding 200 words (50 for short reports) comprising: Objectives, Design, Setting, Subjects, Outcome measures, Results and Conclusions. Refer to articles in recent issues for guidance on the presentation of headings and subheadings.

Abbreviations

These should be spelt out when first used in the text and thereafter used consistently. Scientific measurements: These should be expressed in SI units except: blood pressure should be given in mmHg and haemoglobin values in g/dl. If in doubt, refer to 'uniform requirements' above. Illustrations: Figures consist of all material that cannot be set in type, such as photographs and line drawings. If any tables or illustrations submitted have been published elsewhere, the author should obtain written consent to republication from the copyright holder and the author(s). All illustrations, figures etc must be of high resolution/quality, preferably jpeg or equivalent but not PowerPoint, and must be uploaded as separate supplementary files.

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Articles in Journals

- *Standard journal article*
  Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002 Jul 25;347(4):284-7.
- *More than six authors:*
  Rose ME, Huerbin MB, Melick J, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.

Books

- *Personal author(s)*
  Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Electronic Material

- *Journal article on the Internet*
  Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm. Accessed 3 June 2007
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  Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap.edu/books/0309074029/html/. Accessed 6 January 2007
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9. All photographs must be at 300 dpi and clearly marked according to the figure numbers in the text. (Figure 1, Table II, etc.)
10. Scientific measurements: These should be expressed in SI units except: blood pressure should be given in mmHg and haemoglobin values in g/dl. If in doubt, refer to 'uniform requirements' above.
11. All numbers below ten, without percentages or units, must be written in words.
12. Figure numbers: Arabic; Table numbers: Roman,
13. Abbreviations: These should be spelt out when first used in the text and thereafter used consistently.
14. The submission must be reviewed by a language expert proficient in UK English.

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