

ACCURACY OF THYROID FINE NEEDLE
ASPIRATION CYTOLOGY BY USING BETHESDA
SYSTEM: A HOSPITAL BASED STUDY

By:

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Dissertation Submitted In Partial Fulfilment Of The
Requirements For The Degree Of
Master Of Pathology
(Anatomic Pathology)



UNIVERSITI SAINS MALAYSIA

2017

ACKNOWLEDGEMENT

The author would like to express deepest gratitude to the following individuals for their advice, guidance, comments, cooperation and support during the preparation of this dissertation, and thus, with their patience, help and encouragement making this dissertation possible.

- Dr. Safiya/Thin Thin Win – Anatomy Pathologist and senior lecturer, Pusat Pengajian Sains Perubatan, Universiti Sains Malaysia.
- All lecturers and supporting staffs in Jabatan Patologi, Pusat Pengajian Sains Perubatan, Universiti Sains Malaysia.

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ABBREVIATIONS

A	Accuracy
ATA	American Thyroid Association
AUS	Atypia of undetermined significant
BTA	British Thyroid Association
CK	Cytokeratin
FN	False negative
FNA	Fine needle aspiration
FNAC	Fine needle aspiration cytology
FP	False positive
HPE	Histopathological examination
HUSM	Hospital Universiti Sains Malaysia
LIS	Laboratory Information System
MNG	Multinodular goiter
NPV	Negative predictive value
PPV	Positive predictive value
SN	Sensitivity
SP	Specificity
TBSRTC	The Bethesda System of Reporting Thyroid Cytology
TN	True negative
TP	True positive
TSH	Thyroid stimulating hormone
US	Ultrasound

KETEPATAN SITOLOGI SEDUTAN JARUM HALUS TIROID DENGAN MENGGUNAKAN SISTEM BETHESDA: KAJIAN BERASASKAN SEBUAH HOSPITAL

ABSTRAK

Tujuan: Di Hospital Universiti Sains Malaysia, *The Bethesda System of Reporting Thyroid Cytology (TBSRTC)* tidak digunakan secara meluas oleh ahli patologi atau pakar bedah/doktor. Sebaliknya, sistem laporan konvensional telah digunakan dan hasilnya tidak diberi klasifikasi berperingkat seperti dalam *TBSRTC*. Ini adalah satu kajian retrospektif untuk mengkaji semula semua FNACs tiroid dengan korelasi pemeriksaan histopatologi dalam tempoh 5 tahun (2010-2014) berdasarkan Sistem Bethesda 2010 dan untuk mencari ketepatan serta sensitiviti dan spesifisiti.

Kaedah: Kami telah mengenal pasti sebanyak 563 kes FNAC tiroid dilakukan dari Januari 2010 hingga Disember 2014 di Hospital Universiti Sains Malaysia (HUSM), sebuah hospital pengajaran di Kelantan, yang membentuk populasi kajian kami. Semua kes-kes telah dikenal pasti dari pangkalan data Sistem Maklumat Makmal (LIS) di Jabatan Patologi, Hospital Universiti Sains Malaysia. Selepas memansuhkan kes-kes yang mempunyai kriteria pengecualian, sejumlah 110 kes FNAC tiroid telah dimasukkan dalam kajian ini. Kes-kes tersebut adalah FNAC tiroid yang mempunyai kualiti slaid yang baik dan yang mempunyai keputusan pemeriksaan histopatologi (HPE). Penyiasat utama, pakar patologi dan sitopatologis yang mengkaji semua slaid daripada 110 kes akan memberi diagnosis sepakat dengan menggunakan kriteria yang telah

ditetapkan oleh TBSRTC. SPSS versi 20.0 digunakan untuk kemasukan data dan analisis. Statistik deskriptif digunakan untuk data sosio-demografi. Perisian Stata digunakan untuk nilai-p dengan menggunakan ujian Fisher Exact untuk nombor Objektif 2. Formula statistik digunakan untuk mengira ketepatan,spesifikasi dan sensitiviti.

Keputusan:Umur pesakit adalah dari 11 hingga 80 tahun. Min umur pesakit termasuk dalam kajian ini adalah 44,70 +/- 14.52 (min +/- SD) tahun. Terdapat 94 atau 85.5% wanita dan 16 atau 14.5% pesakit lelaki. Antara 110 kes yang telah dikaji semula menggunakan TBRSTC, 78 kes atau 70.9% telah dilaporkan sebagai benigna pada sitologi, 1 kes atau 0.9% dilaporkan 'Atypia of Undetermined Significant', 9 kes atau 8.2% telah dilaporkan sebagai 'follicular neoplasm', 9 kes atau 8.2% telah dilaporkan sebagai 'suspicious of malignancy' dan 13 kes atau 11.8% telah dilaporkan sebagai 'malignant'. Korelasi sito-histopatologi menunjukkan 29 kes atau 26.4% adalah TP, 75 kes atau 68.2% adalah TN, 3 kes atau 2.7% adalah FP dan 3 kes atau 2.7% adalah FN. Pemeriksaan histopatologi menunjukkan, 25 kes atau 22.7% adalah malignan dan 85 kes atau 77.3% adalah benigna. Antara pesakit wanita, 76 kes atau 81% adalah benigna dan 18 kes atau 19% adalah histologi malignan. Manakala, di kalangan pesakit lelaki, 7 kes atau 44% adalah benigna dan 9 kes atau 56% malignan. 18 kes atau 66.7% kes malignan adalah wanita dan 9 kes atau 33.3% kes malignan adalah lelaki. 76 kes atau 91.6% kes benigna adalah wanita dan 7 kes atau 8.4% daripada kes-kes benigna adalah lelaki.

Korelasi sito-histopatologi menunjukkan 96.2% benigna dan 3.8% malignan dalam Bethesda II (benign), 100% malignan dalam Bethesda III (AUS

/ FLUS), 55.6% benigna dan 44.4% malignan dalam Bethesda IV (neoplasma folikel), 33.3% benigna dan 66.7% malignan dalam Bethesda V (kecurigaan malignan) dan 100% malignan dalam Bethesda VI (malignan). Secara statistik, ketepatan keseluruhan tiroid FNAC dengan menggunakan Sistem Bethesda adalah 94.5%, sensitiviti adalah 90.6% dan spesifisiti adalah 96.1%. Nilai ramalan positif adalah 90.6% dan nilai ramalan negatif adalah 96.1%. Dengan melihat setiap kategori, benign (kategori II) mempunyai 96% ketepatan, AUS (kategori III) mempunyai ketepatan 100%, neoplasma folikel (kategori IV) mempunyai 100% ketepatan, kecurigaan malignan (Kategori V) mempunyai 66% ketepatan dan malignan (kategori VI) mempunyai 100% ketepatan.

Kesimpulan:Dari kajian ini, kami membuat kesimpulan bahawa FNA adalah kaedah yang paling tepat dan kos efektif untuk menilai nodul tiroid. Kajian ini juga menyimpulkan bahawa *The Bethesda System of Reporting Thyroid Cytology, 2010* mempunyai ketepatan yang tinggi, spesifisiti dan sensitiviti.Sistem ini juga boleh meningkatkan ketepatan dalam kategori malignan (kategori VI).

ACCURACY OF THYROID FINE NEEDLE ASPIRATION CYTOLOGY BY USING BETHESDA SYSTEM: A HOSPITAL BASED STUDY

ABSTRACT

Aim: In Hospital University Science of Malaysia, The Bethesda System of Reporting Thyroid Cytology (TBSRTC) was not widely used by pathologist or surgeon/clinician. Instead, conventional reporting system was used and the result was not given tiered classification as in TBSRTC. This study is a retrospective study to review all thyroid FNACs with histopathological correlation in 5 years (2010 to 2014) base on Bethesda System and to look for the accuracy as well as sensitivity and specificity.

Methods: We identified total of 563 thyroid FNACs cases performed from January 2010 till December 2014 in Hospital Universiti Sains Malaysia (HUSM), a teaching hospital in Kelantan, which form our study population. All cases were identified from the database of Laboratory Information System (LIS) in the Department Pathology, HUSM. After excluding the cases with exclusion criteria, total of 110 FNAC cases were included in this study. These cases were thyroid FNAC with good quality of slides and with histopathology examination (HPE) result. Primary investigator, a pathologist and a cytopathologist reviewed all slides from 110 cases and consensus diagnosis was given using TBSRTC. SPSS version 20.0 is used for data entry and analysis. Descriptive statistic is used for socio demographic data. Stata software is used for p-value by using

Fisher Exact test for objective number 2. Statistic formulas are used to calculate the accuracy, sensitivity and specificity.

Results:The patients age were range from 11 to 80 years. The mean age of the patient included in this study was 44.70+/-14.52 (mean+/-SD) years. There were 94 or 85.5% female and 16 or 14.5% male patients. Among 110 cases which were reviewed using TBRSTC, 78 cases or 70.9% were reported as benign on cytology, 1 case or 0.9% was reported as Atypia of Undetermined Significant (AUS), 9 cases or 8.2% were reported as follicular neoplasm, 9 cases or 8.2% were reported as suspicious of malignancy and 13 cases or 11.8% were reported as malignancy. Cyto-histopathological correlation shows 29 cases or 26.4% were true positive, 75 cases or 68.2% were true negative, 3 cases or 2.7% were false positive and 3 cases or 2.7% were false negative. Histopathological examination shows, 25 cases or 22.7% were malignant and 85 cases or 77.3% were benign. Among female patients, 76 cases or 81% were benign and 18 cases or 19% were malignant histologically. Whereas, among male patients, 7 cases or 44% were benign and 9 cases or 56% were malignant histologically. 18 cases or 66.7% of malignant cases were female and 9 cases or 33.3% of malignant cases were male. 76 cases or 91.6% of benign cases were female and 7 cases or 8.4% of benign cases were male.

Cyto-histopathological correlation shows 96.2% benign and 3.8% malignant in Bethesda II (benign), 100% malignant in Bethesda III (Atypia of Undetermined Significant/Follicular Lesion of Undetermined Significant), 55.6% benign and 44.4% malignant in Bethesda IV (follicular neoplasm), 33.3% benign and 66.7% malignant in Bethesda V (suspicious malignancy) and 100%

malignant in Bethesda VI (malignant). Statistically, the overall accuracy of thyroid FNAC by using Bethesda System is 94.5%, the sensitivity is 90.6% and the specificity is 96.1%. The positive predictive value is 90.6% and the negative predictive value is 96.1%. By looking at each categories, benign (category II) had 96% accuracy, AUS (category III) had 100% accuracy, follicular neoplasm (category IV) had 100% accuracy, suspicious of malignancy (category V) had 66% accuracy and malignancy (category VI) had 100% accuracy.

Conclusion: From this study, we conclude that FNA is the most accurate and cost effective method for evaluating thyroid nodule. This study also concludes that The Bethesda System of Reporting Thyroid Cytology have high accuracy, sensitivity and specificity. This system also can increase the accuracy in malignant category.

CHAPTER 1

INTRODUCTION

Over the past decades, fine needle aspiration (FNA) has become an essential step in the evaluation of a thyroid nodule. The clinical application of FNA as an initial diagnostic tool for thyroid nodules is widespread because thyroid nodules are quite common. Within the general population, palpable thyroid nodules are present in 4% to 7% of adults, and sub-clinical (non-palpable) nodules are present in up to 70% of individuals. Of these thyroid nodules, 90% to 95% are benign, and include a wide variety of lesions such as adenomatous nodules, simple thyroid cysts, colloid nodules, follicular adenomas, and inflammatory and developmental conditions, among others (Clark and Faquin, 2010).

The extremely large number of benign thyroid nodules and the small number of admixed malignant ones creates a clinical dilemma on how to manage these patients with a detectable thyroid lesion that is most likely benign. FNA has emerged as the most effective method for dealing with this problem. As a screening test for thyroid carcinoma, FNA assists in guiding the clinical management of patients by helping to select those individuals who are more likely to have a malignancy and need surgical intervention from the larger group of patients with benign nodules that can be managed without surgery.

Fine needle aspiration is now widely accepted by endocrinologists and thyroid surgeons as a safe, cost-effective, and accurate for evaluating a thyroid nodule. Wide- spread use of FNA has reduced the number of patients requiring thyroid surgery by more than 50%, it has increased the yield of malignancies at thyroidectomy by two to three times, and it has decreased the overall cost of managing a thyroid nodule by more than 25% (Clark and Faquin, 2010).

The Bethesda System of Reporting Thyroid Cytopathology (TBSRTC) was established during the *National Cancer Institute Thyroid FNA State of Science Conference* hosted by National Cancer Institute in October 2007. The conference which was attended by 154 participants, including pathologists, endocrinologists, surgeons, and radiologists, gave the committees an in-depth opportunity to present their conclusions and debate controversial areas (Cibas and Ali, 2009a).

The conference is to aim a uniform reporting system for thyroid FNA that will facilitate effective communication among health care providers; facilitate cytologic-histologic correlation for thyroid diseases; facilitate research into the epidemiology, molecular biology, pathology, and diagnosis of thyroid diseases, particularly neoplasia; and allow easy and reliable sharing of data from different laboratories for national and international collaborative studies

Many studies favor a tiered system for classifying thyroid FNA; this ranges from 5 to 6 diagnostic category schemes (Bongiovanni et. al., 2012). For clarity of communication, the Bethesda System for Reporting Thyroid Cytopathology recommends that each report begin with a general diagnostic category. The 6 general diagnostic categories are: category I for non-diagnostic

or unsatisfactory; category II for benign; category III for atypia of undetermined significant; category IV for follicular neoplasm; category V for suspicious for malignancy and category VI for malignancy. Each category has an implied cancer risk, which ranges from 0% to 3% for the “Benign” category to almost 100% for the “Malignant” category. As a function of these risk associations, each category is linked to evidence-based clinical management guidelines (Cibas and Ali, 2009).

In Hospital Universiti Sains Malaysia, TBSRTC was not widely used by pathologist or surgeon/clinician. Instead, conventional reporting system was used and the result was not given tiered classification as in TBSRTC. The reason TBSRTC was not widely used could be multifactorial. One of the factor might be due to lack of communication between pathologist, clinician and radiologist. This study is a retrospective study to review all thyroid FNACs with histopathological examination correlation in 5 years (2010 to 2014) base on Bethesda System and to look for the accuracy as well as sensitivity and specificity.

Although the study was done in many other institution and countries, this study which is specific to Bethesda system was never been done in Malaysia. Thus, this study might be helpful for the pathologist and surgeon or clinician in Malaysia, particularly in Hospital Universiti Sains Malaysia.

CHAPTER 2

LITERATURE REVIEW

2.1 ANATOMY OF THE THYROID GLAND

It is essential for all cytopathologists and histopathologists to know the anatomy of the thyroid glands. This includes the surrounding structures nearby the thyroid gland, arteries and veins supplying the thyroid gland and the lymphatic drainage of each thyroid lobe.

The normal adult thyroid has a shape like a butterfly, with two bulky lateral lobes connected by a thin isthmus. Each lateral lobe is 2 to 2.5 cm wide, 5 to 6 cm long, and 2 cm deep. Their upper and lower extremities are referred to as upper and lower thyroid poles, respectively. One lobe may be larger than the other, and the isthmus may be exceptionally wide. The pyramidal lobe, a remnant of the thyroglossal duct, is found in about 40% of thyroids; it appears as a narrow projection of thyroid tissue that extends upward from the isthmus to lie on the surface of the thyroid cartilage. (Mills et al., 2007)

The thyroid gland is located at the anterior of the neck, where it is attached to the trachea by loose connective tissue. The two lateral lobes surround the ventral and lateral aspects of the larynx and trachea, reaching the lower halves of the thyroid cartilage and covering the second, third, and fourth tracheal rings (Figure 2.1).

The normal weight of the adult thyroid is 15 to 25 g. However, there are significant individual variations, most of them related to gender, age, corporal weight, hormonal status, functional status of the gland, and iodine intake. In women, the thyroid volume is known to increase during the secretory phase of the menstrual cycle (Mills et al, 2007).

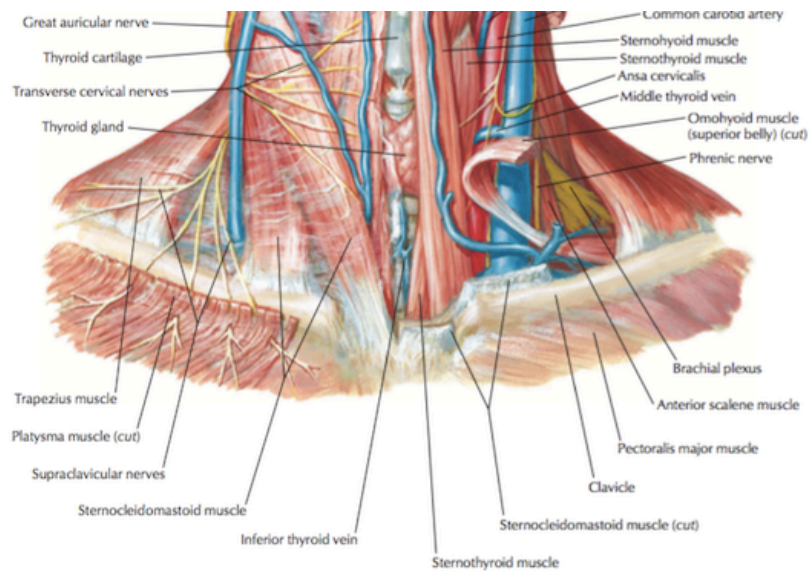


Figure 2.1: Anatomy of the thyroid gland and its surrounding structures

Adapted from Atlas of Human Anatomy

Grossly, the color of the normal thyroid is beefy and brown. Occasionally, elderly individuals have accumulation of a melanin-like pigment in the follicular cells that give coal black stain, which can be seen on gross examination. The

terms melanosis thyroid and black thyroid are used to refer to this phenomenon. These changes are qualitatively identical to those seen in more florid form in thyroids of patients on chronic minocycline. Nodularity of thyroid parenchyma is identified grossly in about 10% of the glands of endocrinologically normal individuals (Mills et al, 2007).

The blood supply of the thyroid gland derives primarily from the inferior thyroid artery, which originates from the thyrocervical trunk of the subclavian artery, and the superior thyroid artery, which arises from the external carotid. A thyroidea ima artery also may be present, which varies widely in size from a small vessel to one the size of the inferior thyroid artery. The superior and medial thyroid veins and the inferior vein drain (via a venous plexus in the thyroid capsule) into the internal jugular and the brachiocephalic vein, respectively (Mills et al., 2007).

The lymphatic network permeates the thyroid gland, encircling the follicles and it empties into subcapsular channels, which in turn give rise to collecting trunks within the thyroid capsule. The lymph vessels draining the superior portion of the thyroid lobes and isthmus collect into the internal jugular lymph nodes, whereas those draining the inferior portion of the gland collect into the pre- and paratracheal and prelaryngeal lymph nodes. The pretracheal lymph node situated close to the isthmus is also known as the Delphian node. Other lymph node stations are the recurrent laryngeal nerve chain and the retropharyngeal and retroesophageal groups. The anterosuperior mediastinal nodes are secondary to the recurrent laryngeal nerve chain and pretracheal groups; however, injection studies have shown that dye injected into the thyroid isthmus can drain directly into the mediastinal nodes (Mills et al., 2007).

Correlations exist between the site of a thyroid tumor within a given lobe and the location of the initial lymph node metastasis. However, the degree of anastomosing between these various nodal groups is such that any of them can be found to be the site of disease regardless of the precise location of the primary tumor (Mills et al., 2007).

2.2 PREVALENCE OF THYROID LESION

2.2.1 Prevalence in the world

Thyroid nodules are common and are commonly benign. The reported prevalence of nodular thyroid disease depends on the population studied and the methods used to detect nodules. The incidence increases with age, and is increased in women, in people with iodine deficiency, and after radiation exposure. Numerous studies suggest a prevalence of 2–6% with palpation, 19–35% with ultrasound, and 8–65% in autopsy data (Dean and Gharib, 2008). In US, there are between 5% to 7% of adults have a clinically detectable nodule in the thyroid and 30% to 50% of adults have one or more nodules in the thyroid when the gland is examined by ultrasound. (McDougall, 2007)

However, in one study the prevalence of thyroid nodules in a healthy population is high. In the German Papillon study, nationwide ultrasound screening of more than 90 000 people using 7.5 MHz scanners revealed the presence of thyroid nodules in 33% of the normal population and a study using 13MHz ultrasound examination showed 68% of thyroid lesion were detected in 635 candidates (Guth et al., 2009). In another study in China, the prevalence of

thyroid nodule among men and women was 24.1% and 34.7%, respectively (Xu et al., 2014). The majority of clinically diagnosed thyroid nodules are non-neoplastic; only 5%–30% are malignant and require surgical intervention (Gupta et al., 2010).

2.2.2 Prevalence in Malaysia and Kelantan

In West Malaysia, the northeastern region including Kelantan has a high incidence of multinodular goiter, with incidence of 31.4% in coastal/ lowland areas to 45.0% in the inland areas (Mafauzy et al., 1995). Thyroid cancer is the fourth most common cancer among female in Kelantan comprising 7.2% from all cancer patients. This is much higher compared to 3% incidence of thyroid cancer, which is 9th most common cancer among female in Malaysia (Zainal and Nor Saleha, 2011).

The number of thyroid samples received in pathology laboratory in Hospital Universiti Sains Malaysia were increasing in number which were quadruple in 10 years (Othman et al., 2009) (Figure 2.2). This increment is similar to the thyroid cancer cases worldwide, which is inversely proportionate (Figure 2.3). Eleven years of study in Pathology Laboratory Hospital Universiti Sains Malaysia showed that 76.5% of thyroid nodules were benign and 23.5% were malignant.

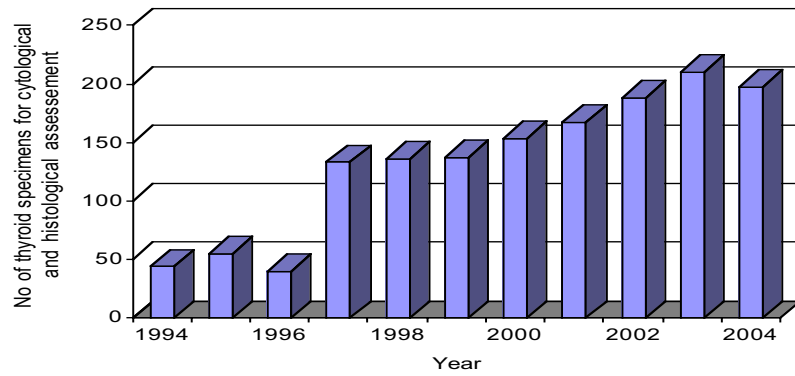


Figure 2.2: The number of thyroid samples received in Pathology Laboratory, Hospital University Sains Malaysia 1994-2004.

Adapted from (Othman et al., 2009)

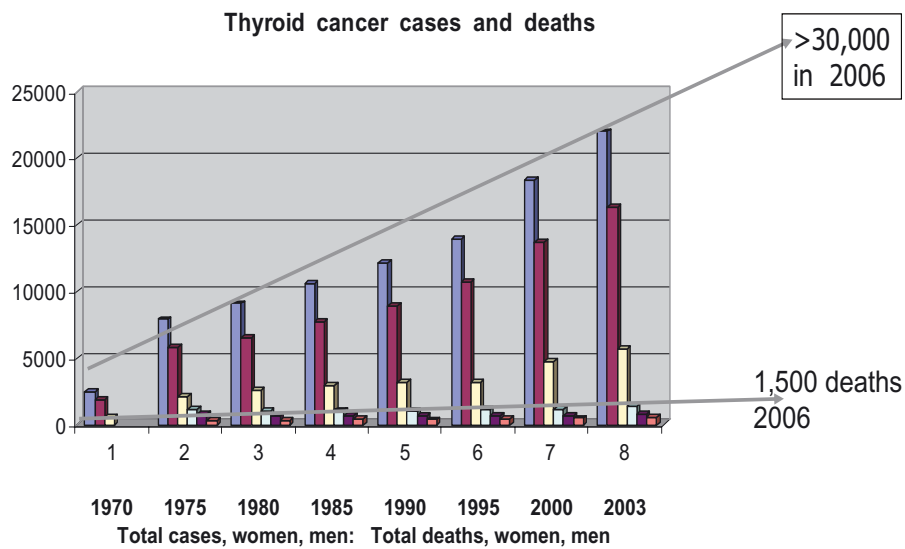


Figure 1.1. The graph shows increases in cases of thyroid cancer between 1976 and 2003 in the US. The increases in mortality are less marked. (Adapted from McDougall IR. Management of Thyroid Cancer and Related Nodular Disease. London: Springer-Verlag; 2006:2.)

Figure 2.3: Number of thyroid cancer from 1976 to 2003

Adapted from (Mcdougall, 2007)

2.3 Fine needle aspiration cytology

2.3.1 Introduction

FNAC of the thyroid gland is now a well-established, first line diagnostic test for the evaluation of diffuse thyroid lesions as well as of thyroid nodules with the main purpose of screening thyroid lesions and thereby, reducing unnecessary surgery and avoiding possible injury of the recurrent laryngeal nerve, hypoparathyroidism, and thyroid hormone dependence in patients with benign thyroid nodules. However, the distinction of these benign lesions from malignant nodules cannot be based reliably on the clinical presentation alone.

Different imaging techniques are now used for diagnosis of thyroid nodules like radionuclide scanning or high-resolution ultrasonography. However, FNAC is still regarded as the single most accurate and cost-effective procedure, particularly if ultrasound is used as a guide for better sample collection, especially for cystic lesions.

Published data suggest that FNA has an overall accuracy rate around 95% in the detection of thyroid malignancy. Nevertheless, like any other test, FNAC has its limitations and diagnostic pitfalls. These limitations include false negative and false positive results. Some of FNA results are not obviously benign or malignant and fall into the indeterminate (AUS/FLUS) or suspicious group.

The reported pitfalls are those among others, related to specimen adequacy, sampling techniques, the skill of the physician performing the aspiration, the experience of the pathologist interpreting the aspirate and the overlapping cytological features between some benign and malignant thyroid lesions.

2.3.2 Indication for FNA thyroid

Before a decision is made to perform an FNA, a complete history should be obtained; a physical examination directed to the thyroid gland and cervical lymph nodes should be performed; and a serum thyrotropin level (TSH) and thyroid ultrasound (US) should be obtained (Baloch and LiVolsi, 2006) (Baloch et al., 2008).

Significant history or physical examination findings that increase the likelihood of malignancy include a family history of thyroid cancer, prior head and neck or total body irradiation, rapid growth of the nodule, a very firm or hard nodule, hoarseness or vocal cord paralysis, ipsilateral cervical lymphadenopathy, and fixation of the nodule to surrounding tissues.

Patients with a normal or elevated serum TSH level should proceed to a thyroid US to determine if an FNA needs to be performed, those with a depressed serum TSH should have a radionuclide thyroid scan, the results of which should be correlated with the sonographic findings (Kendall-Taylor, 2003) (Hussein, 2012). Functioning thyroid nodules in the absence of significant clinical findings do not require an FNA because the incidence of malignancy is exceedingly low. A nodule that appears either iso- or hypo-functioning on radionuclide scan should be considered for FNA based on the US findings (Hussein, 2012).

A palpation-guided FNA can be considered in the following scenarios:

1. A thyroid nodule > 1 cm in diameter has been confirmed via US examination of the thyroid. The sonographic examination is important

because physical examination can be imprecise in determining nodule size and its origin from the thyroid rather than adjacent tissues.

2. The thyroid nodule is discrete and readily identified on physical examination.
3. The nodule is primarily solid (<25% cystic) on US examination.
4. The patient has no other head or neck illnesses or prior head or neck surgery that may affect the thyroid anatomy.
5. A prior non-diagnostic biopsy of the nodule has not occurred. In such cases, an US-guided FNA should be performed.
6. Obtaining US guidance for FNA is logistically difficult or not readily available.

According to 2015 American Thyroid Association (ATA) Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer (Haugen *et al.*, 2016), diagnostic thyroid/neck US should be performed in all patients with a suspected thyroid nodule, nodular goitre, or radiographic abnormality suggesting a thyroid nodule incidentally detected on another imaging study (e.g., computed tomography (CT) or magnetic resonance imaging (MRI) or thyroïdal uptake on 18FDG-PET scan) (Figure 2.4). Not all patient with thyroid nodule are indicated for FNA. The clinician should refer the patient to radiologist first to evaluate the thyroid nodule. The ultrasound patterns will guide the clinician for further management. Below is an algorithm for evaluation and management of patients with thyroid nodules (Figure 2.4) and table of thyroid nodule sonographic patterns (Table 2.1):

ATA THYROID NODULE/DTC GUIDELINES

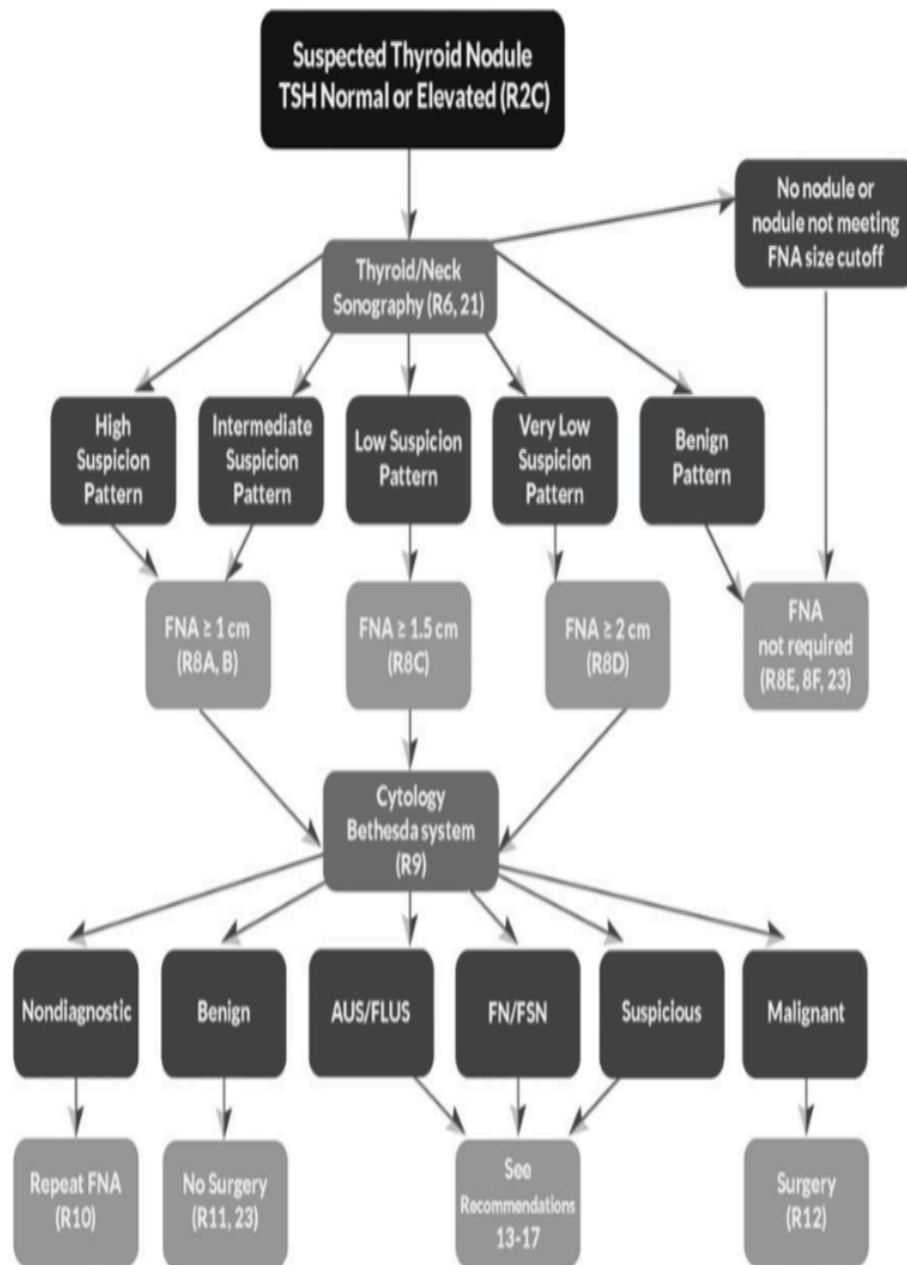


Figure 2.4: Guideline for management of thyroid lesion

Adapted from American Thyroid Association guideline 2016

Table 2.1: Ultrasound patterns for thyroid lesion and FNA guidance

Adapted from American Thyroid Association guideline 2016

TABLE 6. SONOGRAPHIC PATTERNS, ESTIMATED RISK OF MALIGNANCY, AND FINE-NEEDLE ASPIRATION GUIDANCE FOR THYROID NODULES

<i>Sonographic pattern</i>	<i>US features</i>	<i>Estimated risk of malignancy, %</i>	<i>FNA size cutoff (largest dimension)</i>
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE	>70–90 ^a	Recommend FNA at ≥1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins without microcalcifications, ETE, or taller than wide shape	10–20	Recommend FNA at ≥1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or ETE, or taller than wide shape.	5–10	Recommend FNA at ≥1.5 cm
Very low suspicion	Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate, or high suspicion patterns	<3	Consider FNA at ≥2 cm Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	<1	No biopsy ^b

US-guided FNA is recommended for cervical lymph nodes that are sonographically suspicious for thyroid cancer (see Table 7).

^aThe estimate is derived from high volume centers, the overall risk of malignancy may be lower given the interobserver variability in sonography.

^bAspiration of the cyst may be considered for symptomatic or cosmetic drainage.
ETE, extrathyroidal extension.

Meanwhile, The British Thyroid Association (BTA) has recently produced an US classification (U1–U5) of thyroid nodules to facilitate the decision-making process regarding the need to perform fine-needle aspiration cytology (FNAC) for suspicious cases (Figure 2.5 to Figure 2.10). Almost similar to the breast classification (BIRADS), this classification of sonographic findings can help determine whether aspiration is necessary (Xie et al., 2016). Similar to the American Thyroid Association, benign (U2) thyroid lesion is not indicated for FNAC.

Below is pictorial review taken from the similar literature:

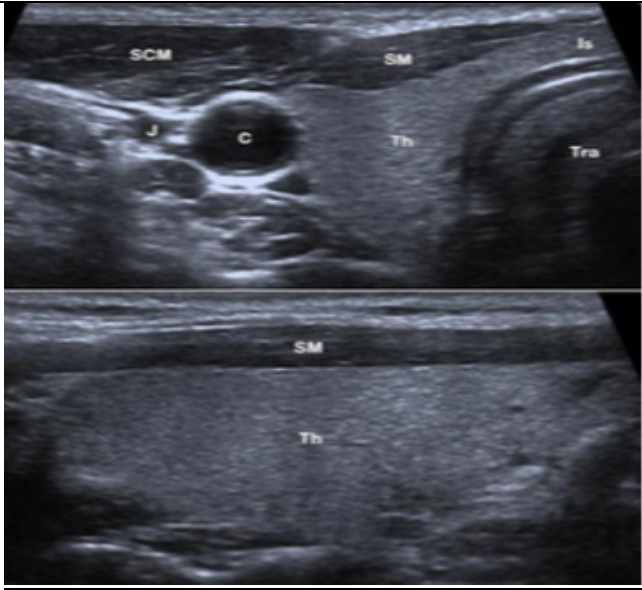
BTA U- classification	Thyroid Ultrasound and description	FNAC
U-1-Normal	 <p data-bbox="497 1137 1141 1299">a. Axial view of right thyroid lobe (Th). Isthmus (Is) is anterior to the trachea (Tra). The carotid artery (C) is round and hypoechoic located laterally to the thyroid. Internal jugular vein (J) is lateral to the carotid artery. Strap muscle (SM) and sternocleidomastoid muscle (SCM) wrap around the anterior aspect of the thyroid.</p> <p data-bbox="497 1332 949 1361">b. Longitudinal view of the right thyroid lobe.</p>	Not required

Figure 2.5: Ultrasound classification U1 (BTA)
Adapted from (Xie et.al, 2016).


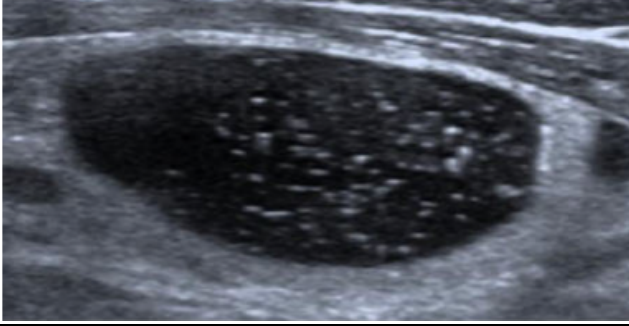
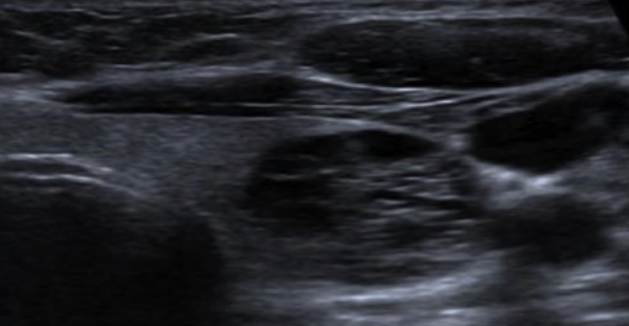
BTA U-classification	Thyroid Ultrasound and description	FNAC
U2(a)- Benign: Halo, iso-echoic, mild hyper-echoic	 <p>a. A benign nodule</p>	Not required
U2(b)- Benign: cystic change +/- ring down sign, (colloid)	 <p>b. A benign cystic nodule with multiple colloid, which are seen as multiple hyperechoic spots with comet-tail.</p>	Not required
U2(c)- Benign: Microcystic, spongiform	 <p>c. A benign nodule with hypo-echoic cystic spaces resulting in spongiform appearance.</p>	Not required

Figure 2.6: Ultrasound classification U2
Adapted from (Xie et.al.,2016)


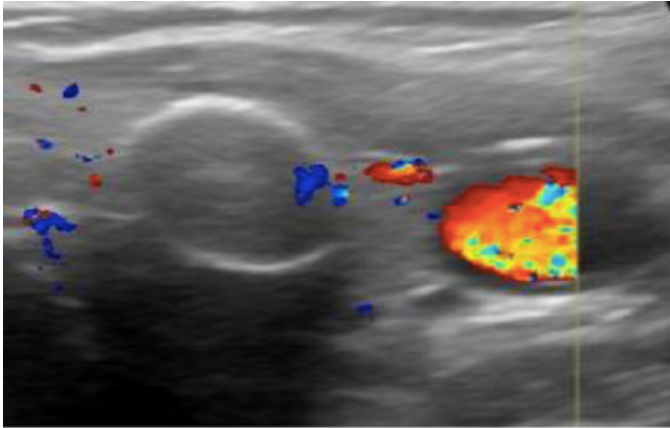
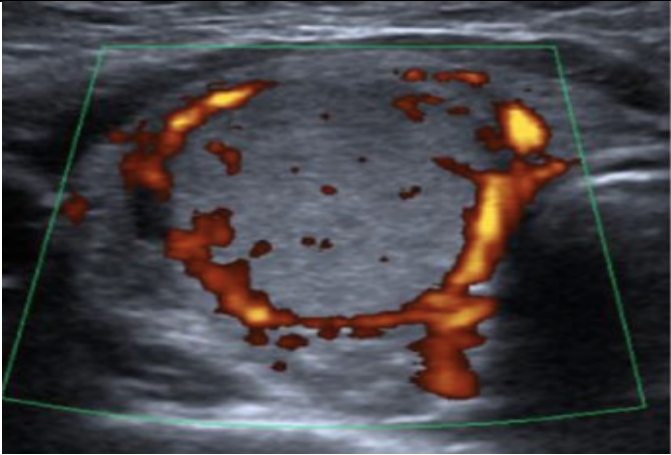
<p>U2(d&e)- Benign: egg shell calcification</p>	 <p>d. A benign nodule with egg shell calcification.</p>  <p>e. A benign nodule with egg shell calcification.</p>	<p>Not required</p>
<p>U2(f)- Benign: Peripheral vascularity</p>	 <p>f. A benign nodule with peripheral vascularity.</p>	<p>Not required</p>

Figure 2.7: Ultrasound classification U2
Adapted from (Xie et.al,2016)

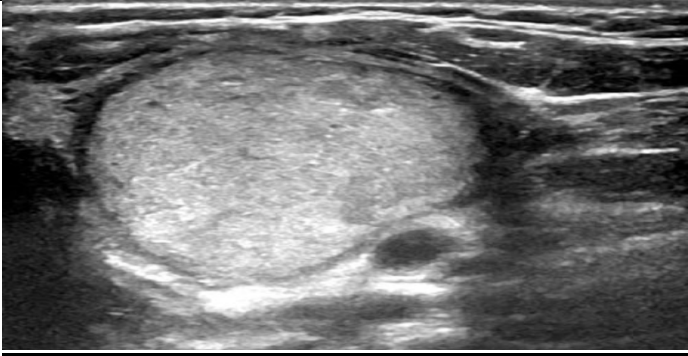
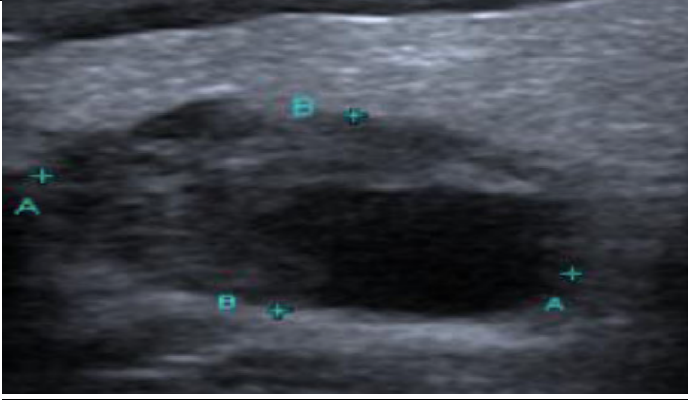
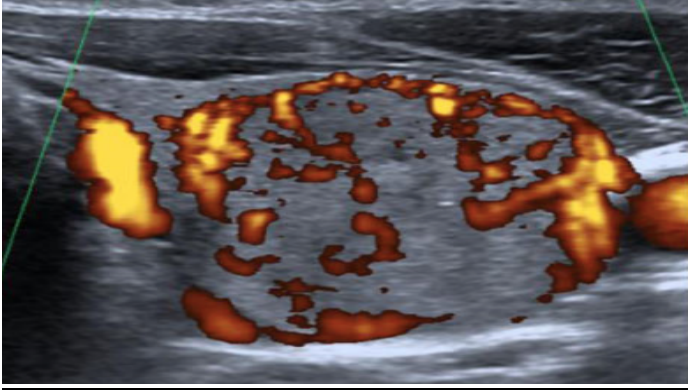
BTA U-classification	Thyroid ultrasound & description	FNAC
U3 (a) – Indeterminate: Homogenous, hyper-echoic (markedly), solid, halo (follicular lesion)	 <p data-bbox="483 763 1134 819">a. A markedly hyper-echogenic nodule is considered indeterminate regarding its malignant risk.</p>	Required
U3 (b) – Indeterminate: ?Hypo- echoic, equivocal echogenic foci, cystic change	 <p data-bbox="483 1288 1158 1344">b. A nodule containing an echogenic focus that appears to be cystic is indeterminate.</p>	Required
U3 (c) – Indeterminate: Mixed vascularity	 <p data-bbox="483 1805 1153 1861">c. Doppler assessment of a nodule showing mixed vascularity, which consists of both peripheral and intra-nodular vasculature.</p>	Required

Figure 2.8: Ultrasound classification U3
 Adapted from Xie et.al

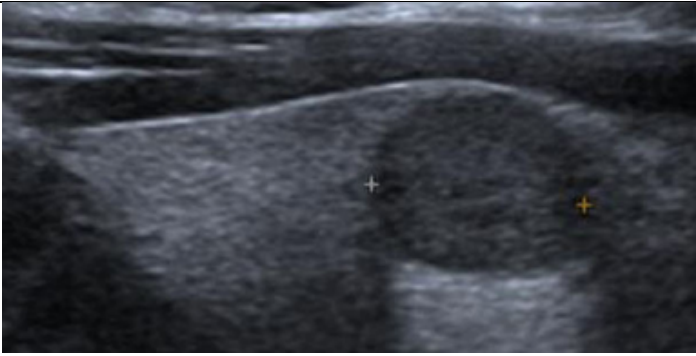
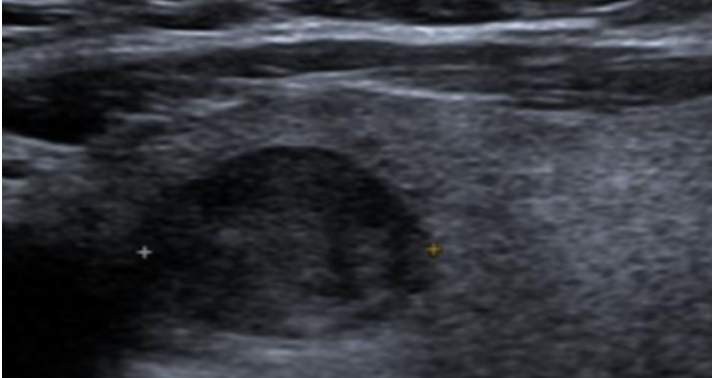
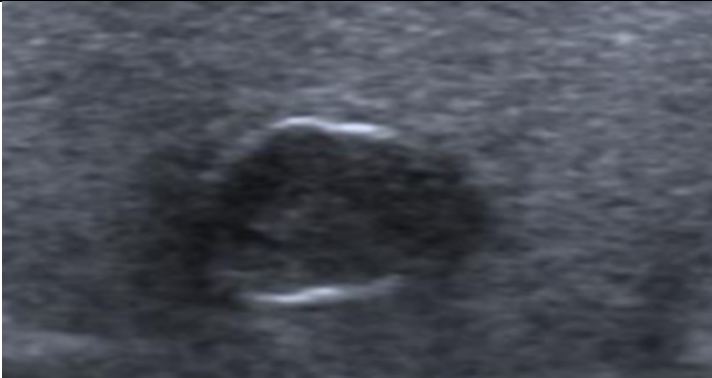
BTA U-classification	Thyroid ultrasound & description	FNAC
U4 (a) – Suspicious: Solid, hypo- echoic (cf thyroid)	 <p data-bbox="472 689 1171 741">a. A suspicious hypo-echoic nodule with signal lower than the surrounding thyroid tissue but higher than the strap muscle above.</p>	Required
U4 (b) – Suspicious: Solid, very hypo-echoic (cf strap muscle)	 <p data-bbox="472 1191 1187 1243">b. A suspicious hypo-echoic nodule with signal lower than both thyroid tissue and strap muscle.</p>	Required
U4 (c) – Suspicious: Disrupted peripheral calcification, hypo- echoic	 <p data-bbox="472 1697 1187 1749">c. A suspicious hypo-echoic nodule with interrupted eggshell calcification around the edges.</p>	Required

Figure 2.9: Ultrasound classification U4
 Adapted from (Xie et.al.,2016)


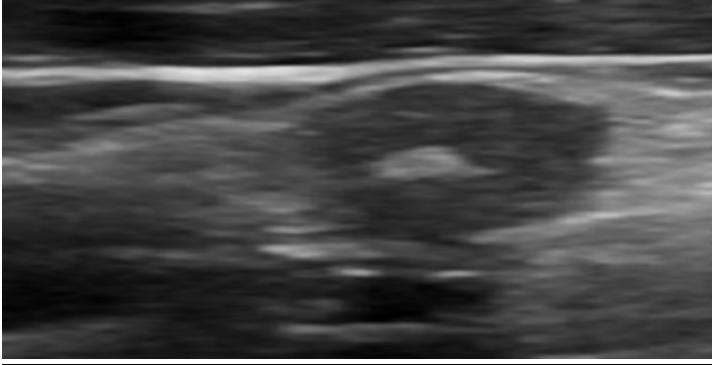
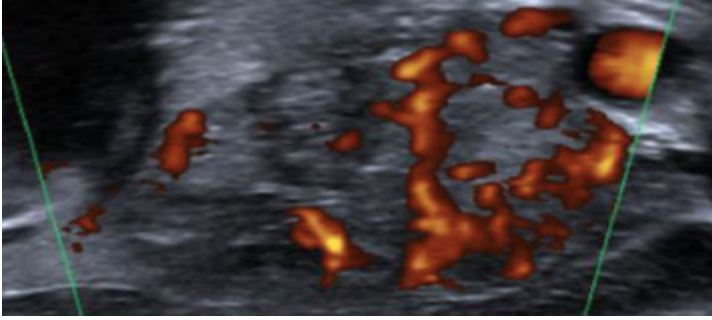
BTA U-classification	Thyroid ultrasound & description	FNAC
<p>U5 (a) – Malignant: Solid, hypo-echoic, lobulated / irregular outline, micro- calcification (?Papillary carcinoma)</p>	 <p>a. This hypo-echoic nodule has small hyper-echoic foci of calcification and an irregular lobulated contour. FNAC confirmed papillary thyroid cancer.</p>	<p>Required</p>
<p>U5 (b) – Malignant: Solid, hypo-echoic, lobulated / irregular outline, globular calcification (?Medullary carcinoma)</p>	 <p>b. This hypo-echoic nodule has a single coarse globular calcification and an irregular contour. FNAC confirmed medullary thyroid cancer.</p>	<p>Required</p>
<p>U5 (c) – Malignant: Intra- nodular vascularity</p>	 <p>c. Thyroid nodule with intra-nodular vascularity. Later confirmed to be papillary thyroid cancer.</p>	<p>Required</p>

Figure 2.10: Ultrasound classification U5

Adapted from (Xie et.al,2016)

Published data suggest that FNA has an overall sensitivity rate around 62% to 94%, specificity rate around 58% to 99% and accuracy rate around 64% to 95% in the detection of thyroid malignancy (Tables 2.2) and Pitman et al. (2008), in her synopsis stated that the median sensitivity of FNAC of thyroid is 96%. One study using 170 samples show 98.5% specificity (Kessler et. al.,2005).

Table 2.2: Comparison of sensitivity, specificity, accuracy, negative predictive value and positive predictive value

Adapted from (Gupta et.al,2010)

TABLE 7: Comparison of results of present study with previous studies.

Study	Year	Number of patients	Sensitivity	Specificity	Accuracy	Negative predictive value	Positive predictive value
Al-Sayer et al.	1985	70	86	93	92	96	80
Cusick et al.	1990	283	76	58	69	64	72
Bouvet et al.	1992	78	93.5	75	79.6	88.2	85.3
Afroze et al.	2002	170	61.9	99.3	94.5	94.7	92.8
KO HM et al.	2003	207	78.4	98.2	84.4	66.3	99
Kessler et al.	2005	170	79	98.5	87	76.6	98.7
Present series	2006	75	80	86.6	84	86.6	80

2.3.3 The Bethesda System of Reporting Thyroid Pathology

The Bethesda System of reporting thyroid pathology is a uniform terminology for reporting thyroid FNA results. A uniform reporting system for thyroid FNA will facilitate effective communication among cytopathologists, endocrinologists, surgeons, radiologists, and other health care providers; facilitate cytologic-histologic correlation for thyroid diseases; facilitate research into the epidemiology, molecular biology, pathology, and diagnosis of thyroid diseases, particularly neoplasia; and allow easy and reliable sharing of data from different laboratories for national and international collaborative studies (Cibas and Ali, 2009a)

Beside the primary purpose of the terminology that is clarity of communication, the interpretation should provide clinically relevant information that will assist referring physicians in the management of patients. The terms for reporting results should have an implied risk of malignancy on which recommendations for patient management (eg, annual follow-up, repeated FNA, surgical lobectomy, near total thyroidectomy) can be given (Cibas and Ali, 2009).

Table 2.3: Recommended diagnostic categories in TBSRTC

Adapted from (Cibas and Ali, 2009)

The Bethesda System for Reporting Thyroid Cytopathology: Recommended Diagnostic Categories*

-
- I. Nondiagnostic or Unsatisfactory**
 - Cyst fluid only
 - Virtually acellular specimen
 - Other (obscuring blood, clotting artifact, etc)
 - II. Benign**
 - Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc)
 - Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
 - Consistent with granulomatous (subacute) thyroiditis
 - Other
 - III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance**
 - IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm**
 - Specify if Hürthle cell (oncocytic) type
 - V. Suspicious for Malignancy**
 - Suspicious for papillary carcinoma
 - Suspicious for medullary carcinoma
 - Suspicious for metastatic carcinoma
 - Suspicious for lymphoma
 - Other
 - VI. Malignant**
 - Papillary thyroid carcinoma
 - Poorly differentiated carcinoma
 - Medullary thyroid carcinoma
 - Undifferentiated (anaplastic) carcinoma
 - Squamous cell carcinoma
 - Carcinoma with mixed features (specify)
 - Metastatic carcinoma
 - Non-Hodgkin lymphoma
 - Other
-

Table 2.4: Implied risk of malignancy and recommended management

Adapted from (Cibas and Ali, 2009)

The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management

Diagnostic Category	Risk of Malignancy (%)	Usual Management [†]
Nondiagnostic or Unsatisfactory	1-4	Repeat FNA with ultrasound guidance
Benign	0-3	Clinical follow-up
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	~5-15 [‡]	Repeat FNA
Follicular Neoplasm or Suspicious for a Follicular Neoplasm	15-30	Surgical lobectomy
Suspicious for Malignancy	60-75	Near-total thyroidectomy or surgical lobectomy [§]
Malignant	97-99	Near-total thyroidectomy [§]

A study reported 100% of accuracy in thyroid FNAC study title 'A histological assessment of the Bethesda system for reporting thyroid cytopathology (2010) abnormal categories: a series of 219 consecutive cases' (Tepeoğlu et al., 2014). Another study reported sensitivity of 92.8%, a specificity of 94.2%, and a total accuracy of 93.6% in one study (Sinna and Ezzat, 2012). In one latest study showed 100% sensitivity using Bethesda system compared to 77% sensitivity using conventional system (M. Mamatha et al., 2015). Another study using 6362 cases showed 97% sensitivity, 50.7% specificity and 68.8% accuracy using TBSRTC (Bongiovanni et. al., 2012).