

## Research Article

# Role of Fine-needle Aspiration Cytology & Ultrasound in the Management of Solitary Thyroid Nodule

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### Abstract

#### Objectives

To evaluate the effectiveness of fine-needle aspiration cytology (FNAC) & ultrasound scanning (US) in the diagnosis and management of solitary thyroid nodules.

#### Materials & Methods

A retrospective study was carried out on 63 patients who were euthyroid and had a clinically palpable solitary thyroid nodule, who underwent either total or hemi-thyroidectomy, during a period of two years (January 2018 to December 2019) in the ENT unit of a tertiary care hospital in Sri Lanka. All patients with FNAC of Bethesda  $\geq 5$  underwent total thyroidectomy. Diagnostic hemi-thyroidectomy was performed only in patients with a FNAC of Bethesda  $\leq 4$ , irrespective of US suspicious features.

#### Results

Mean age was 46.9 years ( $\pm 13.2$ ). 53(84.1%) patients were females and 10 (15.9%) of them were male. 28(44.4%) patients had histologically proven malignancy while the other 35(55.6%) had benign histology. Sensitivity, specificity, positive predictive values and negative predictive values for FNAC and ultrasound were calculated. Out of 34 patients who underwent diagnostic hemi-thyroidectomy, 12(35%) had to undergo completion surgery due to malignant histology. 58% who underwent completion surgery had suspicious features of malignancy in their pre-op US.

#### Conclusion

Both ultrasonography and FNAC are cost-effective, minimally invasive investigations in the diagnosis of malignancy in patients with solitary thyroid nodules. However, there is a notable false negative rate in FNAC; hence it is best to incorporate US findings with FNAC in the decision making process in management of solitary thyroid nodules.

**Keywords** – Solitary Thyroid nodule, FNAC, Ultrasound, Thyroid malignancy, Hemi-thyroidectomy

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## Introduction

Prevalence of thyroid nodules is higher in women (5%) compared to men (1%) [1]. Thyroid cancer prevalence also shows similar pattern with 1.5% in women and 0.5% in men [2,3]. Out of all thyroid malignancies, papillary and follicular cancer (Differentiated Thyroid cancer) represents >90% of cases [4].

Surgery for the thyroid gland is a common procedure, but carries certain post-operative complications such as stridor, voice change, transient and permanent hypocalcaemia; although uncommon, have significant morbidity and financial strain on affected patients. Therefore prevention of unnecessary surgery while selecting relevant candidates for the surgical intervention has been a challenge for the surgeon.

A detailed history and physical examination may reveal certain risk factors for malignancy, however, they are absent in vast majority of patients. This fact puts the surgeon in the reliance of biochemical, imaging and cytological investigations in the decision making in the management of a solitary thyroid nodule.

Both American Thyroid Association (ATA) guidelines (2015) and British Thyroid Association (BTA) guidelines (2014) recommends Ultrasound Scan (US) of the neck should be performed in all individuals with a clinically suspected nodule [5,6]. It can confirm the presence of nodules, nodule size and suspicious features of malignancy. Multiple studies have been conducted in this regard and the results have been highly correlated with the histological diagnosis [5,6].

According to the ATA guidelines, the most accurate and cost-effective method for assessing nodules of the thyroid gland is fine-needle aspiration cytology (FNAC) [5]. The Bethesda system of cytological categorization in 2009 have been updated by the ATA in this regard. Even though similar, multiple studies show evidence suggesting high efficacy of both US and FNAC, sensitivity and specificity varies among these studies [7,8,9]. Research conducted on Sri Lankan population is lacking in this regard. Hence this research was conducted in a tertiary care hospital in Sri Lanka where trained experienced staff are present with a patient population which is high in density and variety.

## Materials and methods

A retrospective study was carried out on 63 patients consecutively, who presented to the ENT clinic during a period of two years (January 2018 to December 2019) in an ENT unit of Colombo-North Teaching Hospital, Ragama, Sri Lanka. All were clinically diagnosed to have a solitary thyroid nodule and had undergone either total or diagnostic hemi-thyroidectomy.

Inclusion criteria were patients with a clinically palpable solitary thyroid nodule, presence of solitary nodule confirmed by US, having a biochemically euthyroid status and undergone FNAC with palpation method.

Exclusion criteria were patients with a clinically or ultrasonically detected multi-nodular thyroid enlargement, a biochemical hypo or hyperthyroid status or patients who underwent FNAC with US-guidance.

All patients had undergone an US and a FNAC within 4 months of the date of surgery. Details of the US reports were recorded including confirmation of solitary nodule, nodule size and presence of any suspicious features of malignancy.

FNAC (palpation method) had been carried out by trained medical officers in the department of pathology of the same hospital. A 23 gauge needle was used for aspiration. Smears were fixed with 95% alcohol solution and stained with Haematoxylin and Eosin (H&E) staining. All were reported under the supervision of the Consultant Histo-pathologist. Cytopathology reporting was done using Bethesda system.

Cytological reports in Bethesda system were classified into two groups; Non-malignant / test negatives and Malignant / test positives. Bethesda 2 (benign) and 3 (atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS)) were considered as “non-malignant or test negatives”. Bethesda 4 (follicular neoplasm/suspicious for follicular neoplasm (FN/SFN)), 5 (suspicious for malignancy (SUSP)) and 6 (malignant) were considered as “malignant or test positives”.

Presence of one or more suspicious features including solid nodules, hypoechoic nodules, irregular margins and micro-calcifications in the US were regarded as “malignant or test positive”. Absence of such features was regarded as “non-malignant or test negative”.

All patients had either underwent total thyroidectomy or diagnostic hemi-thyroidectomy depending on clinical, ultrasonographical and cytological findings and after patient’s written informed consent. All patients with FNAC findings of Bethesda 5 or above underwent total thyroidectomy. Other indications for total thyroidectomy were retrosternal extension, obstructive symptoms and cosmesis. Diagnostic hemi-thyroidectomy was performed only in patients with a FNAC findings of Bethesda 4 or below, irrespective of ultrasonic suspicious features. Histopathological reporting was done by the same hospital’s consultant histopathologist. Histopathology reports of all patients were recorded.

All recorded data were entered and analyzed using SPSS software (Version 19). Data was analyzed as frequency distribution, crosstabs and mean values with standard deviation and expressed as percentages, odds ratios and P values (Significance level was taken as <0.05). Sensitivity, Specificity, Positive predictive Value (PPV), Negative Predictive Value (NPV), false positive rate and false negative rate for Ultrasound and FNAC were calculated separately and expressed as percentages.

## Results

**Table 1. Demographic data and distribution of Histology reports**

Variable	Mean $\pm$ SD / Frequency (%) (n=63)
Age (years)	47.5 $\pm$ 13.2
Sex	
Male	10 (16%)
Female	53 (84%)
Duration of goiter (years)	1.75 $\pm$ 1.5
Histology	
Malignant	28 (44.4%)
Papillary cancer	24 (38.1%)
Follicular cancer	4 (6.3%)
Non-malignant	35 (55.6%)
Colloid goiter	27 (42.9%)
Multi-nodular goiter	6 (9.5%)
Follicular Adenoma	2 (3.2%)

SD = Standard Deviation

Among the study group, mean age was 47.5 years ( $\pm$ 13.2). Female population predominated the vast majority; 53(84%) female patients and only 10(16%) male patients. Mean duration of goiter was 1.75( $\pm$ 1.5) years. 28 (44.4%) patients had histologically proven malignancy while 35(55.6%)patients had benign histology reports (Table 1). Mean age of patients with a malignant nodule was 44.1( $\pm$ 14.4) years while mean age of patients with a benign nodule was 50.1( $\pm$ 11.7) years.

**Table 2. Risk of malignancy Vs. Sex & Nodule size**

Variable	Non-malignant	Malignant	OR	P value
Sex				
Male	5(50%)	5(50%)	0.767	0.700
Female	30 (56.6%)	23(43.4%)		
Nodule Size				
4cm or less	27(55.1%)	22(44.9%)	0.92	0.892
> 4cm	8(57.1%)	6 (42.9)		

OR = Odds Ratio

Malignancy risk was slightly higher in the male subjects; 50% of males had a malignant nodule, while only 43.4% of females had the same, although this was not statistically significant (P =

0.7). There was no significant difference (P=0.892), of the risk of malignancy between smaller sized nodules (4cm or less) and larger nodules (>4cm), having percentages of 44.9% and 42.9%, respectively. (Table 2.)

**Table 3. Surgical Interventions**

<b>Surgery</b>	<b>Non-malignant</b>	<b>Malignant</b>	<b>Total</b>
Total Thyroidectomy	13 (44.8%)	16 (55.2%)	29 (46%)
Hemi-thyroidectomy	22 (64.7%)	12 (35.3%)	34 (54%)
<i>Presence of US suspicious features</i>	2/22 (9%)	7/12 (58%)	
<b>Total</b>			63 (100 %)

Out of all surgeries, 29 (46%) patients had undergone total thyroidectomy and 34(54%) patients had only diagnostic hemi-thyroidectomy. Out of the latter, 12 (35%) patients had to undergo completion thyroidectomy, due to their histology reports being malignant, needing radioiodine ablation. Interestingly, 7 out of 12 (58%) hemi-thyroidectomies, which had malignant histology had US features of malignancy and 2 out of 22 (9%) hemi-thyroidectomies, which were benign had the same. (Table 3.)

Histology reports and FNAC & US findings comparison is given in Table 4. Number of true positives, true negatives, false positives and false negatives for FNAC and US as well as Sensitivity, specificity, positive predictive values and negative predictive values for FNAC and US, along with false positive rates and false negative rates for FNAC and US are shown in Table 5.

**Table 4. Ultrasound and FNAC vs Final Histology**

<b>Investigation</b>	<b>Histology Malignant</b>	<b>Histology Benign</b>
<b>Ultrasound</b>		
Malignancy features Present	21 (33.3%)	4 (6.3%)
Malignancy features Absent	7 (11.1%)	31 (49.2%)
<b>FNAC</b>		
Malignant/Suspicious of malignancy	17(27.0%)	3(4.8%)
Non-malignant	11(17.5%)	32(50.8%)

**Table 5. Comparison of Ultrasound and FNAC as diagnostic tools for malignancy**

<b>Variable</b>	<b>Ultrasound</b>	<b>FNAC</b>
Sensitivity	75.0%	60.7%
Specificity	88.6%	91.4%
Positive Predictive value	84.0%	85.0%
Negative Predictive Value	81.6%	74.4%
False Positive Rate	11.4%	8.6%
False Negative Rate	25.0%	39.3%

## **Discussion**

An enlarged euthyroid gland can present with diffuse or nodular enlargement but the latter is known to be commoner. A clinically palpable nodule can either be a solitary nodule or a dominant nodule in a multinodular goiter. In either case, risk of malignancy is a concern for the clinicians dealing with such pathologies.

Prevalence of thyroid nodules are 5-10 times more common in women than in men <sup>[1]</sup>. However, malignancy is more likely among men having a thyroid nodule than in a woman. Therefore, prevalence of thyroid cancer is 1.5% in women and 0.5% in men, respectively <sup>[2,3]</sup>. Similar observation was found among our study group, as the male to female ratio was almost 1:5. The rate of malignancy was slightly higher in the male subjects which was 50%, compared to 43.4% in females and it was not statistically significant ( $P = 0.7$ ). This increase of malignancy rate among the female subjects in our study may be due to exclusion of subjects with multinodular goiters, which has a high prevalence rate in females. Exclusion of multinodular goiters from this study was done to reduce procedural bias during FNAC and US when assessing different sizes and types of nodules in the same patient.

Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) together are termed Differentiated Thyroid Cancer (DTC) and comprises >90% of all thyroid malignancies <sup>[4]</sup>. Out of the malignant subjects in our study, 24(~85%) had PTC while 4(~15%) had FTC. This is similar to the worldwide prevalence which is 72-85% for PTC and 10-20% for FTC, respectively <sup>[10]</sup>. Among non-malignant individuals, colloid goiter comprised the majority, involving 27 (77%) of them, while 2(6%) had follicular adenoma. Interestingly, 6(17%) of the benign histology' came as "multi-nodular goiter" (MNG), although we excluded those according to preoperative clinical and US assessment.

US of the neck is recommended in all individuals with a clinically suspected nodule <sup>[5,6]</sup>. It is a non-invasive and relatively cost-effective imaging study, compared to high-end investigations like Computed Tomography(CT) or Positron Emission Tomography(PET) scans. Nowadays, in Sri Lanka, it is a widely available mode of investigation in most government and private

healthcare institutions. However, the validity of the reports depends on skills and expertise of the performing radiologist.

US can confirm the presence of nodules, nodular size, and suspicious features and associated cervical lymphadenopathy. Solid hypoechoic nodules, irregular margins, micro-calcifications, taller than wide shape and increased internal vascularity are some of the features of malignancy. Current evidence does not suggest that an increase in nodule size, increases the risk of malignancy [5, 11]. Similar results were evident in our study as well, where there was no significant difference ( $P=0.892$ , Odds ratio = 0.92) of the risk of malignancy between smaller sized nodules (4cm or less) and larger nodules (>4cm).

Multiple studies have been conducted regarding US and the results have been highly correlated with the histological diagnosis [5]. Sensitivity, specificity varies among the different researches, but ranges between 40-80% [10]. A recent study in Pakistan revealed sensitivity ranging from 50-80% and specificity of 52-96% in US for each different feature of malignancy [12].

In our study, overall sensitivity, specificity, positive predictive values and negative predictive values for US were 75%, 88.6%, 84%, 81.6% respectively. Further, false positive rates and false negative rates for US were 11.4% and 25.0% respectively. However, in our retrospective study, the US were performed by different radiologists, though they were well trained and experienced staff.

FNAC is the most accurate and cost-effective method for assessing nodules of the thyroid gland [5]. A large retrospective study conducted in 2014 in Turkey revealed high rates of correlation between FNAC and histological diagnosis [7]. Similarly, multiple study evidence suggests high efficacy of FNAC. Sensitivity and specificity varied among these studies, ranging from 80-88% and 64-86% respectively [7,8,9]. In our study, specificity (91.4%) was similar to the above studies, however, a notable reduction in sensitivity (60.7%) was observed. This was due to relatively high false negative rate (39.3%).

Number of factors contribute to the accuracy of FNAC including operator's skill and experience, technique, method of preparation of specimen and interpretation of cytology. In our study, we only included FNAC done by palpation method. It has been found that nodules being >50% cystic consistency and being posteriorly located might reduce the efficacy of palpation method FNAC [13,14]. Multiple study evidence has revealed significantly reduced false negative rates with "ultrasound-guided" FNAC in contrast to palpation method [15,16].

In our study, total thyroidectomy was performed on 29 (46%) patients. All patients with a cytology of Bethesda 5 or above underwent total thyroidectomy. Other indications for total thyroidectomy were retrosternal extension, obstructive symptoms and cosmesis. Diagnostic hemi-thyroidectomy was performed in 34(54%) patients who had a cytologically indeterminate/ benign nodule (Bethesda 4 or below). Ultrasonic suspicious features were not considered in this decision.

Out of the hemi-thyroidectomies performed, 12 (35%) patient's histology became malignant and had to undergo completion thyroidectomy after Multi-Disciplinary Team (MDT) meeting and also as recommended by ATA guidelines [5]. Interestingly, majority (~58%) of hemi-thyroidectomies which had malignant histology had suspicious features in their pre-op US. Conversely, only 9% of hemi-thyroidectomies, which had benign histology had suspicious US features pre-op. This depicts that if US features of malignancy had been considered for the

decision making of the surgery, more second surgeries could have been prevented. Although research evidence shows that on account of surgical risk, two stage surgery is similar to a total thyroidectomy, it's not very cost-effective, especially for a middle-income country like Sri Lanka [17,18]. The physical and mental strain on the patient who undergoes two surgeries in a short period of time is significant and should be taken into consideration.

## **Conclusions**

Both ultrasonography and FNAC are cost-effective, minimally invasive investigations in the diagnosis of malignancy in patients with solitary thyroid nodules. Sensitivity and specificity of both US and FNAC are high, but fluctuates due to various factors. There was a notable amount of false negative rates in FNAC in this study; hence it is best to incorporate US findings as well on the management as the US and FNAC findings are complementary to each other.

## **Limitations of the study**

This research was a retrospective study, therefore the researches were not able to control and standardize the FNAC and US process. They were not performed by the same person, therefore, errors might have occurred depending on the operator's technique and skill, which may have affected both FNAC and US results.

Number of cases was a major limitation. Study population could have been larger than 63. This smaller number was due to exclusion of large number of thyroid surgeries done on hyperthyroid and multi-nodular goiters.

Our study only included FNAC done with palpation method which is a simple, cost-effective, involving less expertise and time than an US-guided FNAC.

## **Key Messages**

1. Both ultrasonography and fine-needle aspiration cytology are cost-effective, minimally invasive investigations in the diagnosis of malignancy in patients with solitary thyroid nodules.
2. Sensitivity and specificity of both ultrasonography and fine-needle aspiration cytology varies from center to center depending upon various factors including performer's skill and experience.
3. Ultrasonography and fine-needle aspiration cytology findings are complementary to each other. Management decisions should be made taking both reports into account.
4. Correct interpretation of ultrasonography and fine-needle aspiration cytology results help prevent over- and under-treatment of patients with thyroid nodules, resulting in reduction of health care costs.

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