

# A Study to Evaluate the Size of Thyroid Nodules as an Indicator for Malignancy

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## Abstract

**Background:** Several authors have questioned the accuracy of fine-needle aspiration cytology (FNAC) in large thyroid nodules. It's the current practice to provide thyroidectomy to patient with thyroid nodules 4 cm or larger regardless of the FNAC results. The aim of the study is to answer two questions: is the size of nodule associated with higher risk of malignancy and is the size indication for surgery. **Subjects and Methods:** This study included 20 patients who underwent thyroidectomy. We compared all thyroid nodules with benign FNAC and their final histopathology reports. Patients were divided into two groups based on the size of the nodule (< 4cm or >4cm) and indication of surgery. **Results:** 20 patients with thyroid nodule underwent thyroid surgery. 13 patients had nodule <4cm and 7 patients were ≥4 cm. For patients with nodules <4 cm, 3 patients had a malignancy, and for those with nodules ≥4 cm, 1 patients had a malignancy. For benign cases FNAC and histopathology reports are showing same results, (p<0.05). **Conclusion:** Thyroid nodules ≥4 cm are not risk factor of malignancy. Thyroid nodules ≥4 cm with benign FNAC should not undergo thyroidectomy as false negative rate is low. Therefore, the decision for surgery ought not to be taken based on the size of the nodule.

**Keywords:** Biopsy, Diagnostic accuracy, Fine-needle, Large nodules, Thyroid neoplasms, Thyroid nodule

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## Introduction

Thyroid nodules are common diseases of the endocrine system, with prevalence of 3%–7% by palpation and 19%–67% by high resolution ultrasound.<sup>[1,2]</sup> Thyroid cancer accounts for approximately 5% to 15 % of thyroid nodules.<sup>[3]</sup> In recent years; the number of thyroid cancer has been on the rise.

Due to early identification of thyroid nodule, diagnosis and management of thyroid cancer have been expanded. History and physical examination, thyroid function test (TFT), ultrasound of the neck and fine-needle aspiration cytology (FNAC) are all part of initial evaluation of a thyroid nodule.<sup>[4]</sup>

Fine needle aspiration cytology is gold standard tool to define nature of thyroid nodule.<sup>[5]</sup> FNAC was introduced in the 1950s and has become a commonly used procedure, its accuracy improved with ultrasound guided. Sensitivity and specificity >90%. Based on its evaluation surgeon can plan extent of surgery and further treatment. The most valuable information that FNAC provides is whether a nodule has neoplastic

potential.<sup>[6,7]</sup>

The false negative rate for thyroid FNAC is low. The expected incidence of malignancy in cytological benign nodules is 0% to 3% according to the Bethesda system for reporting thyroid cytopathology.<sup>[2,7]</sup> Skilled FNA technique and the availability of experienced cytologists are vital to achieving high diagnostic accuracy. Several diagnostic pitfalls have been described in the literature, including inadequate sampling, insufficient cellular material from cystic or hemorrhagic lesions, and limited experience of those who perform and interpret FNAC. Additionally, number of punctures and the smear preparation techniques also affect results.<sup>[2]</sup>

Number of studies have attempted to associate size of thyroid nodule with accuracy of FNAC. Several studies in the past reported the larger the nodule size the higher false negative rate for FNAC due to sampling error, these studies concluded nodular size 4cm and larger more likely to harbor cancer cell and considered thyroidectomy even when FNAC result is benign.

In other hand other studies showed false negative rate in larger thyroid nodule is not higher than those with small nodule. Therefore, the size of the nodule is not independent risk factor for malignancy, should not take part in therapeutic decision making and it would prevent unnecessary surgery with its possible complications, including injury to the recurrent laryngeal nerve, hypoparathyroidism, and lifelong thyroid hormone.

Other study concludes that male gender, age  $\geq 60$  years old, microcalcification, cervical lymphadenopathy was risk factor of malignancy. [4,8-10] Based on benign cytology features and low false negative rate of the FNAC patient required regular follow up with annual clinical examination and repeat ultrasound. Repeat cytology was recommend for patient with abnormal feature in ultrasound and changes in the size of the nodule. [4,11] Therefore, the purpose of this study was to investigate the relationship between the size of thyroid nodules and malignancy risk.

### Subjects and Methods

This prospective study was conducted at ANMMCH, Gaya. The study was approved by the institutional research committee. A total of 20 cases who underwent thyroidectomy were included in this study with prior informed consent. The study was carried out over a time period of six months from January 2019 and June 2019. The present study was observational.

All thyroid nodule  $>5\text{mm}$  with abnormal sonographic feature or high-risk history and nodule  $>1\text{ cm}$  (the solid and hypoechoic areas) underwent ultrasound guided FNAC. Thyroid nodule FNA cytology was reported using diagnostic group outlined in the Bethesda system for reporting thyroid cytopathology.

Pathology reports were reviewed and nodules with benign FNAC were matched with the histologic results. In addition, physical examination, ultrasound exam and location of the nodule were correlated with size of the nodule in operative and pathology reports. The results of the final pathology were classified as either benign or malignant. Patients were divided into two groups based on nodule size:  $<4\text{ cm}$  or  $\geq 4\text{ cm}$ , clinical factors and rate of malignancy were compared.

### Statistical Analysis

Statistical analysis was performed by the SPSS program for Windows, version 13.0. Continuous variables were presented as mean $\pm$ SD, and categorical variables as absolute numbers and percentage. Chi-Square test was applied as appropriate for comparison of nominal data. Normally distributed continuous variables were compared using paired T-test. A “p” value of less than 0.05 was considered significant.

### Results

This prospective study included 20 cases who presented with neck swelling with thyroid nodule and they were subsequently underwent thyroid surgery between January 2019 and June 2019. The average age of the patient population was  $45.0\pm 12.31$ . Among 20 patients, 16 (80%) were female and 4 (20%) were males. 13 patients had nodules that were  $<4\text{ cm}$  and 7 patients had nodules that were  $\geq 4\text{ cm}$ . 5 patients were diagnosed to have malignancy based on final histopathology report.

Out of 13 patients with nodules  $<4\text{ cm}$ , 4 patients had a malignancy, and among those 7 patients with nodules  $\geq 4\text{ cm}$ , 1 patients had a malignancy. There was no significant difference found in the rate of malignancy in these two Groups ( $p=0.27$ ) [Table 1].

The primary indications for thyroidectomy included compressive symptoms ( $n=5$ ), follicular lesion ( $n=1$ ), papillary carcinoma ( $n=1$ ), thyrotoxicosis ( $n=1$ ), and Progression in size ( $n=5$ ).

Most of them had multiple indications for surgery. Of these indications, patients with compressive symptoms were equal in number in both the group were observed [Table 1].

Of the total 20 patients, FNAC results were reported as benign in 14 cases (70 %), malignant in 6 patients (30 %). FNAC results of 13 patients with  $<4\text{cm}$  nodules were reported as benign in 70% cases, malignant in 30% cases. Also, FNAC results of 7 patients with  $\geq 4\text{cm}$  nodules were reported as benign in 70% cases and malignant in 30%. But this association is statistically not significant ( $p=0.07$ ) [Table 2].

According to postoperative pathologic survey of the nodules that underwent FNAC; 3 patients with  $<4\text{ cm}$  nodules and 1 patients with  $\geq 4\text{ cm}$  nodules were diagnosed having thyroid cancer on FNAB [Table 3].

Of total 20 cases FNAC diagnosed, 4 cases as Malignant, final histopathology reports declared 3 cases having malignancy. For benign cases FNAC and histopathology reports showed no malignancy. This relation is statistically significant ( $p<0.05$ ). This proves that for surgical removal one can rely on the FNAC results than nodule size [Table 4].

### Discussion

Some studies have concluded that thyroid nodule size can be considered as an independent indication to predict the risk of malignancy in people with thyroid nodules, but other studies did not support these data and even reported against their results. [12-15] Furthermore, diagnostic accuracy of FNAC in large thyroid nodules is still controversial. [13,16-19] Therefore,

**Table 1: Demographic and pathologic data.**

Variables	Total cohort nodule	Nodule <4 cm	Nodule ≥4 cm	P value
Number of patients	20	13	7	
Mean age ±SD	45.0±12.31	45.0±12.02	44.8±12.98	0.35
Gender (% female)	16	10	5	<0.05*
Gender (%male)	4	3	2	<0.05*
Mean nodule size±SD (cm)	3.2±1.62	2.2±0.93	4.9±1.06	0.46
Malignancy	5	4	1	0.27
Compressive symp-toms	5	3	1	<0.05*
Thyrotoxicosis	1	1	0	<0.05*

\*significant

**Table 2: Association of size of nodule and FNAC results.**

Size	FNAC2 results		
	Benign	Malignant	Total
<4cm	9	4	13
≥4cm	5	2	7
Total	14	6	20

\*p= 0.07 (not significant)

**Table 3: Association of size of nodule and histopathology results.**

Size	Histopathology result		
	Malignant	Benign	P value
≥4cm	1	5	6
<4cm	3	11	14
Total	4	16	20

\*p= 0.27 (not significant)

**Table 4: Comparison between histopathology and FNAC outcome.**

FNAC result	Histopathology result		
	Malignant	Benign	TOTAL
Malignant	3	1	4
Benign	0	16	16
Total	3	17	20

\*p<0.05 (significant)

this study is designed to investigate the relationship between the size of thyroid nodules and malignancy risk.

Authors found in present study that, nodule size did not show any association with risk of malignancy in nodules ≥4 cm. Present findings are similar to those of several other studies. Raj et al evaluated the prevalence of thyroid cancer in 223 patients who underwent thyroidectomy for thyroid nodules 4 cm or larger. Sixteen patients (7.2%) had malignancy on final

pathology. There was no association between nodule size and malignancy rate. [20]

Kamran et al. reported that increasing thyroid nodule size had an influence on cancer risk in a nonlinear fashion, and there was no increase in the risk beyond the 2cm threshold. [18] While, Berker et al. reported no significant difference between 1 cm nodules and >1cm in malignancy risk. [21] Some studies have shown higher prevalence of thyroid carcinoma in ≥4

cm nodules.<sup>[13,22]</sup> Conversely, Rausei et al and Mc Henry et al reported higher prevalence of thyroid carcinoma in smaller nodules.<sup>[17,23]</sup> In this study, there was no statistically significant ( $p=0.27$ ) difference between malignant and benign nodules size. These contradictory results show that the size of the nodule is not reliable at predicting malignancy and should not be applied for medical decision making.<sup>[15,17,23–25]</sup>

Shrestha et al performed a retrospective study of 540 patients with 695 nodules, who underwent FNAB and subsequent thyroid surgery. There was no set size criterion for surgical referral. The overall malignancy rate was 18.6% and did not vary significantly based on size. The overall false negative rate was 7% and did not differ significantly according to size. The authors noted that the accuracy of FNAC increased with increasing nodule size.<sup>26</sup> Similarly, Magister et al performed a retrospective study of 297 patients with 326 thyroid nodules, who underwent FNAB and subsequent thyroidectomy. The overall rate of malignancy on final pathology was 43.9%. The false negative rate was 6% for all nodules combined, and 3.8% for nodules 3 cm or greater. Higher probability of malignancy was found in smaller nodules.<sup>[26]</sup> In these studies finding of increased risk of malignancy and decreased diagnostic accuracy in smaller nodules could be due to selection bias. The smaller nodules included in the study may have undergone thyroidectomy due to the presence of unmeasured risk factors for malignancy.

The discrepancy in the risk of malignancy and accuracy of FNAC reported in the literature for large thyroid nodules may be due to variability in sampling and interpretation of cytopathological findings. The accuracy of FNAC depends on adequate sampling and correct interpretation. Furthermore, the post-test probability of malignancy is significantly influenced by the overall prevalence of malignancy in the population, which varies among institutions. These factors need to be accounted for when counseling patients about the need for thyroidectomy for large nodules.

## Conclusion

Risk of malignancy was not associated with nodule size. Patients with thyroid nodules  $\geq 4$  cm and benign FNAC should not automatically undergo thyroidectomy. FNAC as well as the presence of symptoms are important factors to consider when recommending thyroidectomy for these patients. Selection of the appropriate treatment option (thyroidectomy versus observation) should involve shared decision making between the patient and the healthcare provider. The overall accuracy of FNAC and the prevalence of malignancy in the population need to be considered.

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