



## Malignancy rates in thyroid nodules classified as Bethesda categories III and IV; a subcontinent perspective

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### ABSTRACT

**Background:** Bethesda category III and IV thyroid nodules fall in the indeterminate risk of malignancy category. These nodules have been a relatively elusive entity to manage as previous studies have shown a wide variation in malignancy rates in different regions and institutions across the world. However, data from the subcontinent with regards to this is scarce.

**Aim and objective:** This study aimed to determine the characteristics and malignancy rates of cytology proven Bethesda Category III and IV thyroid nodules and its association with clinical, histopathological and laboratory variables, in the regional population.

**Method:** A retrospective search was performed on all patients with thyroid nodules who presented to this hospital, from January 2011 to September 2018. Patients who had cytology proven Bethesda category III and IV thyroid nodules that underwent surgery were included in the study.

**Results:** Malignancy in Bethesda Category III and Bethesda Category IV thyroid nodules was 29.6% and 47.1%, respectively. There was no significant association determined between malignancy rate and various clinical, histopathological, and radiological characteristics.

**Conclusion:** The malignancy rates in Bethesda category III and IV thyroid nodules in this study are significantly higher than that initially suggested by the Bethesda consensus publication but is comparable to international data present.

### Introduction

Thyroid nodules are common in adults. Studies using ultrasonography have estimated the prevalence of thyroid nodules to be 20–76% in the adult population [1]. The incidence of malignancy among nodules is approximately 5% [2]. However, there are studies which have suggested that it may be as high as 15% [3]. In the last three decades, the overall incidence of thyroid cancer has increased dramatically, and it is considered as one of the fastest-growing cancers among women [4].

Ultrasound-guided fine-needle aspiration (FNA) is an acknowledged diagnostic modality for evaluating thyroid nodules [5–7]. Nodules that undergo FNA, their cytology is assessed using the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) and hence further managed accordingly [8]. This system categorizes specimens into six categories (I–VI), each having a different malignant potential. The malignant potential of Bethesda Category II, V, and VI nodules are well-established, and

they have set recommendations for management [9]. On the contrary, Bethesda Category III and IV nodules' malignancy potential is variable, and the management depends on the stratification of risk factors such as family history of thyroid cancer, history of radiation therapy to the neck, rapid growth of the nodule, above normal thyroid stimulating hormone (TSH) [10], and ultra-sonographic characteristics (nodule, shape, echogenicity, regularity of borders, calcification and vascularity) [11]. The management can consist of observational clinical follow-up with no intervention, repeating FNA, or surgery (lobectomy/thyroidectomy) [12–14].

The literature on the malignancy potential of Bethesda Category III and IV nodules is very variable across different institutes and regions. It has been suggested that local malignancy rate should be determined, and management should be tailored, accordingly. Studies from different institutes from various parts of the world show a malignant potential of Bethesda category III nodules to be as variable as from 15.7% to 54.6%

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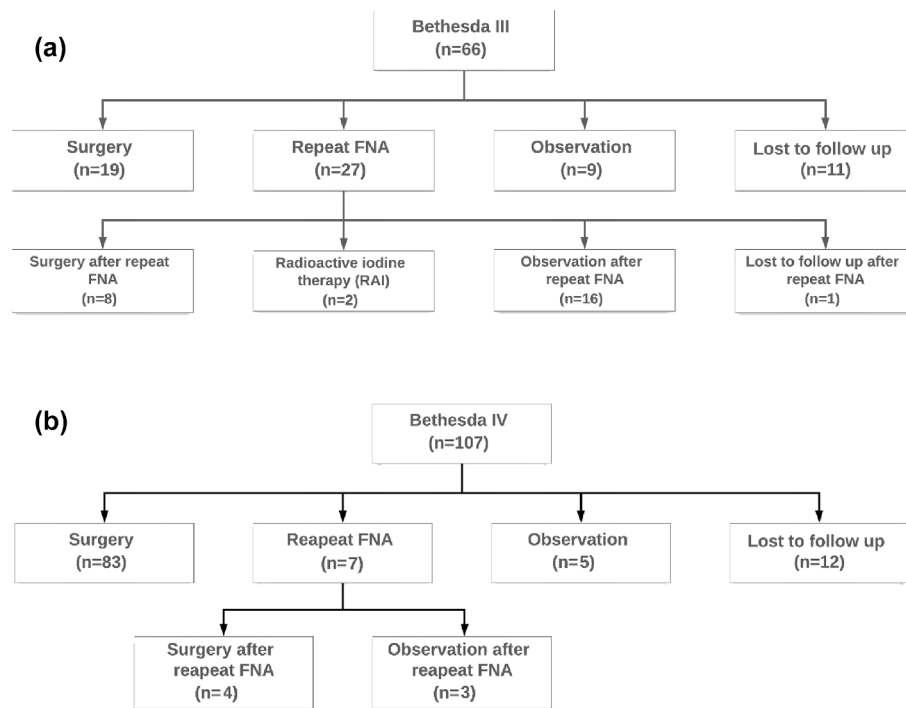
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**Fig. 1.** Summary of management strategies of patients with Bethesda Category III & IV thyroid nodules. Patients that subsequently underwent surgery were included in the present investigation.

and of category IV nodules to be 16.8% to 72.4% [15,16]. This is much higher than what was initially reported by Cibas et al, where malignancy rate for Bethesda Category III thyroid nodule was estimated to be 5–15% and for Bethesda category IV thyroid nodules was estimated to be 15–30% [12].

Furthermore, data for malignancy rate of Bethesda Category III and IV thyroid nodules in the sub-continent is scarce and limited to a handful of studies. This study aims to determine the characteristics and malignancy rates of cytology proven Bethesda Category III and IV thyroid nodules and its association with clinical, histopathological and laboratory variables, in the regional population.

## Materials and methods

### Subjects, study design, and clinical setting

We performed a retrospective chart analysis of all patients with cytology proven Bethesda Categories III and IV thyroid nodules presenting to the hospital from January 2011 to September 2018. The study was approved by the local Institutional Review Board.

During the hospital visit, all patients had a thorough clinical, laboratory and radiological evaluation. This consisted of a thorough history and examination, thyroid function tests, and imaging studies consisting of at least one of the following: magnetic resonance imaging (MRI) neck, ultrasound thyroid, or technetium (Tc – 99 m) pertechnetate thyroid scan. All patients underwent ultrasound- guided-FNA.

The cytopathological assessment was done using the Bethesda System of Reporting Thyroid Cytology [12,17]. The FNA cytology smears were air-dried and stained using Diff Quik stain. Once dried, specimens were fixed in alcohol and stained with Papanicolaou stain. Category III lesions were called follicular lesion of undetermined significance (FLUS)/atypia of undetermined significance (AUS) [18]. Both terminologies were used and depicted similar cytological findings. These included follicular cells with minimal cytological atypia, including slight nuclear irregularity, minimal increase in size, and overlap.

Bethesda Category IV lesions were called follicular neoplasm (FN)

[19] and included cellular smears with cells showing nuclear irregularity and atypia and arranged in microfollicle formation. The FNA smears were compared to histology as the gold standard (where available). The tissue was serially sectioned and preserved in 10% buffered formalin. These were then embedded into the paraffin and stained with hematoxylin and eosin and reviewed under a microscope. The histology specimens were assessed for the presence of a capsule and a capsular or vascular invasion, including the number of vessels involved.

Based on the risk factors (>40 years of age, female gender, positive family history, or history of radiation), clinical features (lymphadenopathy, new onset of voice changes, or a sudden increase in the size of growth), radiological features (size, and the number of nodules), and preference of physicians and patients, patients were either placed on observational clinical follow-up with no intervention, underwent a repeat FNA, or had surgery (lobectomy/thyroidectomy) [20].

All males and females who presented to the SKMCH&RC, Lahore, for assessment of thyroid nodules, which were categorized as Bethesda Category III or IV, and underwent surgical excision of the gland were included in the study. Patients with thyroid nodules, of any other Bethesda category, were excluded.

### Clinical information

The data of the subjects were deidentified. Electronic medical records were reviewed to collect information regarding demographics, baseline clinical characteristics, laboratory findings, histopathological, and radiological analysis, and treatment modalities. Malignancy rate was determined for subjects that underwent surgery, by correlating the cytopathology report with the histopathological report.

### Statistical analysis

The statistical analysis was performed using SPSS software (version 22.0; SPSS, Chicago, IL). Descriptive statistics were computed for each variable. If any study variable was missing for the included subjects, it was excluded in the statistical analysis. Chi-Square and t-tests were used

**Table 1a**  
Baseline characteristics of subjects with Bethesda Category III thyroid nodules.

Study characteristic	Category	Number (%)
Age (Years)	Median (Range)	40 (18–69)
Gender	Males	9 (33.3%)
	Females	18 (66.7%)
Demographics	Punjab	19 (70.4%)
	Khyber Pakhtunkhwa	5 (18.5%)
	Others (Baluchistan, Afghanistan, Kashmir)	3 (11.1%)
Presenting symptom	Neck Swelling	24 (88.9%)
Family history	Positive	3 (11.1%)
Radiation exposure	Present	1 (3.7%)
Thyroid function	Euthyroid	26 (96.3%)
	Altered (hyperthyroidism or hypothyroidism)	1 (3.7%)
Thyroid scan	Cold nodule(s)	8 (80%)
	Hot nodule(s)	2 (20%)
Nodularity (ultrasound)	Multinodular goiter	8 (50%)
	Solitary nodule	8 (50%)
Size (ultrasound)	Less than 2 cm	2 (12.5%)
	2 cm or more	14 (87.5%)
Size (magnetic resonance imaging)	Less than 2 cm	4 (14.8%)
	2 cm or more	23 (85.2%)

**Table 1b**  
Baseline characteristics of subjects with Bethesda Category IV thyroid nodules.

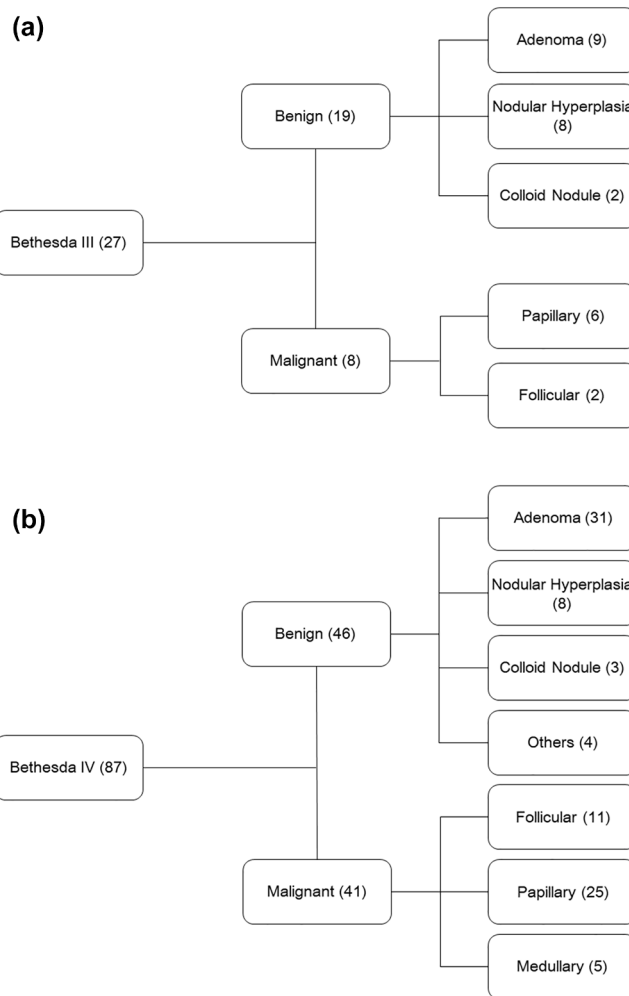
Study characteristic	Category	Number (%)
Age (Years)	Median (Range)	39 (7–78)
Gender	Males	22 (25.3%)
	Females	65 (74.7%)
Demographics	Punjab	59 (67.8%)
	Khyber Pakhtunkhwa	18 (20.7%)
	Others (Baluchistan, Afghanistan, Kashmir)	10 (11.5%)
Presenting symptom	Neck Swelling	82 (94.3%)
Family history	Positive	12 (13.8%)
Radiation exposure	Present	3 (3.4%)
Thyroid function	Euthyroid	76 (87.4%)
	Altered (hyperthyroidism or hypothyroidism)	11 (12.6%)
Thyroid scan	Cold nodule(s)	35 (97.2%)
	Hot nodule(s)	1 (2.8%)
Nodularity (ultrasound)	Multinodular goiter	24 (57.1%)
	Solitary nodule	18 (42.9%)
Size (ultrasound)	Less than 2 cm	10 (23.8%)
	2 cm or more	32 (76.2%)
Size (magnetic resonance imaging)	Less than 2 cm	19 (23.8%)
	2 cm or more	61 (76.3%)

for the analyses between independent and dependent variables. However, if the assumptions for the chi-square test were not met, Fisher exact test was used. A p-value of <0.05 was considered statistically significant.

**Results**

A total of 66 charts of patients with Bethesda Category III and 107 charts of patients with Bethesda Category IV thyroid nodules were identified and reviewed. Among the 66 patients with Bethesda Category III thyroid nodules, 39 patients were excluded because they were either lost to follow-up (12), had radioactive iodine therapy (RAI) (2), or they were put under clinical observation and follow up, without any intervention (25) (Fig. 1a). On the contrary, of the 107 patients with Bethesda Category IV thyroid nodules, 20 patients were excluded. These patients were lost to follow-up (12) or followed in the clinic without intervention (8) (Fig. 1b).

Of the 27 subjects with Bethesda Category III thyroid nodules, 18 (66.7%) were females. The median age of the cohort was 40 years (range: 18–69 years). The majority of subjects were from Punjab



**Fig. 2.** Histopathological diagnoses of Bethesda Category III & IV thyroid nodules.

province (70.4%). Neck swelling was reported by 24 (88.9%) subjects at the time of initial presentation, 11.1% (3) had a positive family history for thyroid cancer, and 1 (3.7%) subject had higher than normal levels of thyroid-stimulating hormone (TSH). Ten subjects underwent a Tc-99 m pertechnetate thyroid scan, and among these, 8 (80%) had cold nodules. On the ultrasound thyroid imaging, 50% (8) of the subjects had a solitary nodule, and 14 (87.5%) subjects had a nodule of at least 2 cm or more. Similarly, on MRI of the neck, 85.2% (23) of the subjects had a nodule of at least 2 cm or more. These results have been summarized in Table 1a.

Among the 87 subjects with Bethesda Category IV thyroid nodules, 65 (74.7%) were females. The median age was 39 years (range: 7–78 years), and most of the subjects were from Punjab province. In 94.3% (82) of the subjects, neck swelling was the presenting symptom. There was a positive family history of thyroid cancer in 12 (13.8%) subjects, 3 (3.4%) subjects had a history of radiation exposure, and in 12.6% (11) of the subjects, the levels of TSH were abnormal. Thirty-six subjects completed the Tc-99 m pertechnetate thyroid scan, and 1 (2.8%) subject had a hot nodule. Ultrasound thyroid imaging indicated that 24 (57.1%) subjects had a multinodular goiter, and 76.2% (32) of the subjects had a nodule of at least 2 cm or more in size. On the MRI of the neck, in 61 (76.3%) subjects, the size of the nodules was at least 2 cm or more (Table 1b).

The malignancy rate of Bethesda Category III thyroid nodules was 29.6%, and the most common malignant diagnosis was papillary thyroid carcinoma. On the contrary, among benign nodules, adenoma and

**Table 2a**

Stratification of the subjects with Bethesda Category III based on malignancy status of the thyroid nodules.

Study characteristic	Category	Malignant	Not Malignant	P-Value
Age (Years)	Median (Range)	41 (18–58)	34 (20–69)	0.99
Gender	Males	2 (25%)	7 (36.8%)	0.68
	Females	6 (75%)	12 (66.7%)	
Demographics	Punjab	4 (50%)	15 (78.9%)	0.30
	Khyber Pakhtunkhwa	3 (37.5%)	2 (10.6%)	
	Others (Baluchistan, Afghanistan, Kashmir)	1 (12.5%)	2 (10.6%)	
Presenting symptom	Neck Swelling	8 (100%)	16 (84.2%)	0.53
Family history	Positive	1 (12.5%)	2 (10.5%)	1.00
Radiation exposure	–	–	1 (5.3%)	1.00
Thyroid function	Euthyroid	8 (100%)	18 (94.7%)	1.00
	Altered (hyperthyroidism or hypothyroidism)	–	1 (5.3%)	
Thyroid scan	Cold nodule (s)	2 (100%)	6 (75%)	1.00
	Hot nodule (s)	–	2 (25%)	
Nodularity (ultrasound)	Multinodular goiter	2 (40%)	6 (54.5%)	1.00
	Solitary nodule	3 (60%)	5 (45.5%)	
Size (ultrasound)	Less than 2 cm	2 (40%)	–	0.08
	2 cm or more	3 (60%)	11 (100%)	
Size (magnetic resonance imaging)	Less than 2 cm	–	2 (11.1%)	1.00
	2 cm or more	4 (100%)	16 (88.9%)	

nodular hyperplasia were the most common histopathologies (Fig. 2a). There was no significant association present between the malignancy status of the Bethesda Category III thyroid nodules and demographic, clinical, histopathological, and radiological parameters (Table 2a).

The malignancy rate of Bethesda Category IV thyroid nodules was 47.1%. The most common diagnosis among malignant nodules was papillary thyroid carcinoma, and in benign lesions, it was of adenoma (Fig. 2b). The Bethesda Category IV thyroid nodules' malignancy status was found to have no significant associations with any of the demographic, clinical, histopathological, and radiological parameters (Table 2b).

## Discussion

The purpose of this single institutional retrospective analysis was to determine the characteristics and malignancy rates of cytology proven Bethesda Category III and IV thyroid nodules and its association with clinical, histopathological, and laboratory variables in the regional population. The malignancy rate for Bethesda category III and IV thyroid nodules was 29.6% and 47.1%, respectively. No statistically significant associations were identified between malignancy rate and clinical, histopathological, and laboratory characteristics.

The malignancy rate for Bethesda category III and IV thyroid nodules is inconsistent. Prior investigations have reported a 15.7%–54.7% and a 16.8%–72.4% malignancy rate for Bethesda category III and IV thyroid nodules [15,16], respectively (Table 3). An important reason for this disparity in reporting is the criteria for selecting the patients to undergo surgical intervention. Similarly, there are differences in the study population. Studies that have been conducted on similar populations have comparable malignancy rates. The cohort of the present investigation is closest to the study by Pasha et al. The malignancy rates of both studies for the Bethesda Category III thyroid nodules are analogous.

The median age of subjects with Bethesda Category III thyroid nodules was 40 years (18–69 years), and the median age of participants with Bethesda Category IV thyroid nodules was 39 years (7–78 years).

**Table 2b**

Stratification of the subjects with Bethesda Category IV based on malignancy status of the thyroid nodules.

Study characteristic	Category	Malignant	Not Malignant	P-Value
Age (Years)	Median (Range)	39 (17–72)	39 (7–78)	0.75
Gender	Males	11 (26.8%)	11 (23.9%)	0.76
	Females	30 (73.2%)	35 (76.1%)	
Demographics	Punjab	26 (63.4%)	33 (71.7%)	0.15
	Khyber Pakhtunkhwa	10 (24.4%)	8 (17.4%)	
	Others (Baluchistan, Afghanistan, Kashmir)	5 (12.2%)	5 (10.9%)	
Presenting symptom	Neck Swelling	40 (97.6%)	42 (91.3%)	0.37
Family history	Positive	6 (14.6%)	6 (13%)	0.83
Radiation exposure	–	–	3 (6.5%)	0.244
Thyroid function	Euthyroid	36 (87.8%)	40 (87%)	0.91
	Altered (hyperthyroidism or hypothyroidism)	5 (12.2%)	6 (13%)	
Thyroid scan	Cold nodule (s)	18 (100%)	17 (94.4%)	1.00
	Hot nodule (s)	–	1 (100%)	
Nodularity (ultrasound)	Multinodular goiter	6 (42.9%)	18 (64.3%)	0.19
	Solitary nodule	8 (57.1%)	10 (35.7%)	
Size (ultrasound)	Less than 2 cm	2 (14.3%)	8 (28.6%)	0.45
	2 cm or more	12 (85.7%)	20 (71.4%)	
Size (magnetic resonance imaging)	Less than 2 cm	7 (17.9%)	12 (29.3%)	0.30
	2 cm or more	32 (82.1%)	29 (70.7%)	

This is relatively younger than the average age of the study population reported by others. The exact reason for this difference is unknown and beyond the scope of this study. However, this could be associated with genetic variations. The investigations that have been conducted on similar cohorts have reported comparable mean age at the time of presentation [21–24]. The most common presenting symptom was neck swelling in the present study.

This is not surprising, as the level of medical awareness and health consciousness is low, and there are limited medical facilities. Patients do not undergo routine medical visits and only present to the hospital after the nodules become symptomatic.

There were no statistically significant risk factors identified for malignancy in the present study. Previously, investigators have reported a positive family history of thyroid cancer, history of radiation therapy to the neck, rapid or sudden growth of nodule, and above normal TSH levels as risk factors for malignancy [25]. Lack of association in the present study is likely due to a smaller number of subjects and limited level of education and history of symptoms, due to which majority of the subjects were unable to provide an adequate history of risk factors. Similarly, in most subjects, detailed reports of ultrasonography of the thyroid gland were not available, as they had been conducted at outside healthcare facilities.

Among the cancer subtypes, papillary thyroid cancer was the most common malignant variant in both Bethesda category III and IV thyroid nodules followed by follicular cancer. At the same time, adenoma was the most common benign histopathology seen in subjects with Bethesda category III and IV thyroid nodules. Other investigators worldwide have reported a similar distribution of histopathology [26].

There were a few limitations in this study. This was a retrospective

**Table 3**

Malignancy rates in Bethesda Category III and IV thyroid nodules, international and regional comparison.

Reference	Bethesda III			Bethesda IV		
	Cytology (N)	Underwent surgical resection (% of total cohort)	% Malignancy	Cytology (N)	Underwent surgical resection (% of total cohort)	% Malignancy
Ho et al. 2014[21]	541	369 (68.2)	37.9	NR	NR	NR
Deniwar et al. [22]	65	45 (69)	34.0	42	41 (97.7)	50.0
Godoi Cavalheiro B et al. [15]	478	478 (100)	15.7	137	137 (100)	16.8
Chandra S, et al. [24]	63	31 (49.2)	28.5	NR	NR	NR
Abbas al-Kurd et al. 2019 [27]	14	14 (100)	35.7	162	162 (100)	64.2
Chirayath et al. [16]	140	75 (53.6)	54.7	36	29 (80.6)	72.4
Yaparak Bayrak, et al. 2020 [28]	510	108 (21.2)	25.0	440	47 (10.7)	27.6
Pasha HA, et al. [23]	81	81 (100)	33.0	NR	NR	NR
<b>Present study</b>	<b>66</b>	<b>27 (40.9)</b>	<b>29.6</b>	<b>107</b>	<b>87 (81.3)</b>	<b>47.1</b>

N: No of nodules.

NR: Not reported.

chart review. Due to the study's inherent nature, it was not possible to account for all clinical, histopathological, and radiological characteristics. Furthermore, due to the lack of randomization and blindness, there is a high likelihood of magnifying or understating associations. Nonetheless, in the present study, data were extracted from the electronic hospital information system, and records from all hospital visits were correlated to reduce the risk of reporting bias. Another limitation of the study was the unavailability of standardized ultrasonography report of the subjects. As indicated earlier, most of the subjects had their scans from outside healthcare facilities, and it was not possible to retrieve the raw files of these studies. Similarly, the total number of participants in the present study was small. However, these are comparable to other investigations. Lastly, molecular testing was not used for stratifying the risk of malignancy in this study. This is because, at the time of writing, this test is unavailable in Pakistan.

## Conclusion

To our knowledge this is the first study in Pakistan which has determined the malignancy rates in both Bethesda category III and IV thyroid nodules. The malignancy rate for Bethesda category III thyroid nodules in this study is significantly higher than that initially suggested by the Bethesda consensus publication (5–15%) but is comparable to global data. The malignancy rate for Bethesda category IV thyroid nodules is also significantly higher than estimated by the Bethesda consensus publication (15–30%). Our study implies that Bethesda Category III and IV thyroid nodules in our practice setting have a higher potential of malignancy than traditionally believed. Further, larger studies are needed in this region to determine the malignancy potential of Bethesda category III and IV thyroid nodules to establish guidelines for management of these indeterminate category nodules.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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