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Retrospective Study

# Bethesda System for Reporting Thyroid Cytopathology: A three-year study at a tertiary care referral center in Saudi Arabia

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## Abstract

### AIM

To stratify the malignancy risks in thyroid nodules in a tertiary care referral center using the Bethesda system.

### METHODS

From January, 2012 to December, 2014, a retrospective analysis was performed among 1188 patients (15-90 years) who had 1433 thyroid nodules and fine-needle aspiration at Prince Sultan Military Medical City, Saudi Arabia. All thyroid cyto-pathological slides and ultra sound reports were reviewed and classified according to the Bethesda System for Reporting Thyroid Cytopathology. Age, gender, cytological features and histological types of the thyroid cancer were collected from patients' medical chart and cytopathology reports.

### RESULTS

There were 124 total cases of malignancy on resection, giving an overall surgical yield malignancy of 33.6%.

Majority of the thyroid cancer nodules ( $n = 57$ , 46%) in Bethesda VI category followed by Bethesda IV ( $n = 25$ , 20.2%). Almost 40% of the cancer nodules in 31-45 age group in both sex. Papillary thyroid carcinoma (PTC) was the most common form of thyroid cancer among the study population (111, 89.6%) followed by 8.9% of follicular thyroid carcinoma (FTC), 0.8% of medullary carcinoma and 0.8% of anaplastic carcinoma. Among the Bethesda IV category 68% thyroid nodules were PTC and 32% FTC.

## CONCLUSION

The malignancy values reported in our research were constant and comparable with the results of other published data with respect to the risk of malignancy. Patients with follicular neoplasm/suspicious for follicular neoplasm and suspicious of malignancy categories, total thyroidectomy is indicted because of the substantial risk of malignancy.

**Key words:** Bethesda; Total thyroidectomy; Thyroid nodules; Risk of malignancy; Fine needle aspiration

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**Core tip:** The purpose of this study was to stratify the malignancy risks in thyroid nodules in a tertiary care referral center using the Bethesda system. The study found that there were 124 total cases of malignancy on resection, giving an overall surgical yield malignancy of 33.6%. Majority of the thyroid cancer nodules in Bethesda VI category followed by Bethesda IV. Almost 40% of the cancer nodules in 31-45 age group in both sex. Papillary Thyroid Carcinoma was the most common form of thyroid cancer among the study population followed by follicular thyroid carcinoma, medullary carcinoma and anaplastic carcinoma.

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## INTRODUCTION

According to epidemiological and clinical studies thyroid nodules are commonly encountered in clinical exams, palpable in 5% of the population on thyroid examination and detectable in nearly 60% of those subjected to thyroid ultrasound. While the majority of the nodules are benign (non-cancerous), they are normally the first indicators of thyroid cancer; therefore, further investigations are required to identify the cancerous nodule<sup>[1,2]</sup>.

The last decades have revealed a constant and remarkable rise in the occurrence of thyroid cancer

across the world, including Saudi Arabia<sup>[3-5]</sup>. The Saudi Cancer Registry (SCR) report has registered 890 thyroid cancer cases, in nearly 8.1% of all the newly diagnosed cases in 2012. However, studies revealed variations in the incidence of thyroid cancer globally. Thyroid cancer is the 5<sup>th</sup> most common cancer among females in the United States, whereas in Saudi Arabia it is the 2<sup>nd</sup> commonest identified cancer in females, and 8<sup>th</sup> among males<sup>[6]</sup>. However, compared with the developed countries, research regarding the malignancy risks in thyroid nodules is still insufficient due to lack of appropriate studies being conducted in these specified areas.

One of the most widely used diagnostic tools is fine-needle aspiration (FNA) cytology with ultrasound imaging to determine the necessity for the surgical excision of a thyroid nodule. Today, molecular genetic biomarker analyses are employed to increase the diagnostic accuracy of the FNA biopsies, and can at times drastically change clinical decision procedures as they become more commonly available and better assessed. FNA cytology (FNAC) continues to remain the initial investigation mode for malignancy in patients with thyroid nodules and the selection of patients for thyroid surgery<sup>[7]</sup>. This minimally invasive and useful method is highly effective in identifying a large percentage of thyroid nodules as benign and eliminating unnecessary surgery for patients with benign disease<sup>[8]</sup>. However, because a standardized reporting system is still unavailable, pathologists have been employing varying terminologies and diagnostic criteria, thus causing misunderstanding among the referring clinicians while interpreting cytopathology reports, resulting in non-definitive clinical management<sup>[9-11]</sup>. In 2007, the National Cancer Institute (NCI) established guidelines employing a standardized nomenclature to interpret thyroid FNAs called the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) which is now accepted as the proposed diagnostic categories for thyroid cancer<sup>[12]</sup>. This study attempts to stratify the malignancy risks in thyroid nodules in a tertiary care referral center in Saudi Arabia utilizing the Bethesda system.

## MATERIALS AND METHODS

### Study design and setting

From January, 2012 to December, 2014 (36 mo), a retrospective analysis was performed among 1188 patients (15-90 years old) who had 1433 thyroid nodules and FNA at Prince Sultan Military Medical City (PSMMC), a 1200 bedded tertiary care center, Riyadh, Saudi Arabia. The PSMMC caters to the patients referred from different regions of Saudi Arabia and considered a worthy representative of Saudi Arabia in general. The study protocol was approved by the Research and Ethics Committee of PSMMC, Riyadh, Saudi Arabia.

### Data collection

All thyroid cytopathological slides and ultra sound



**Table 1** The Bethesda system

Diagnostic category	Cytological diagnosis	Risk of malignancy, %	Usual management
I	Nondiagnostic or unsatisfactory	1-4	Repeat FNA with ultrasound guidance
II	Benign	0-3	Clinical follow-up
III	AUS/FLUS	5-15	Repeat FNA
IV	FNS/SFN	15-30	Surgical lobectomy
V	Suspicious for malignancy	60-75	Near-total thyroidectomy or surgical
VI	Malignant	97-99	Near-total thyroidectomy

FNA: Fine-needle aspiration; AUS/FLUS: Atypia of undetermined significance or follicular lesion of undetermined significance; FNS/SFN: Follicular neoplasm or suspicious for follicular neoplasm.

reports were reviewed and classified according to the BSRTC system. Age, gender, cytological features and histological types of the study population were collected from patients' medical chart and cyto-pathology reports.

### Bethesda system

Currently, the Bethesda system of reporting thyroid cytology (TBSRTC) is used for reporting FNAC specimens of thyroid. According to Cibas<sup>[13]</sup>, this system was innovated in 2007 and consists of six categories: (1) Unsatisfactory (UNS) or nondiagnostic (ND); (2) Benign and nonneoplastic; (3) Atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS); (4) Follicular neoplasm or suspicious for follicular neoplasm (FNS/SFN); (5) Suspicious for, but not diagnostic of, malignancy; and (6) Malignant (Table 1).

All FNAs were performed by one of five interventional radiologists under ultrasound (US) guidance, performing 3-5 passes by using 25 gauge needles. On-site FNAs stained with the Diff-Quik stain and adequacy assessment was performed for all samples. All slides interpreted by among of five accredited cyto-pathologists.

### Histological diagnoses

The histological diagnoses of thyroid nodules were classified into two types: Benign and nonneoplastic and malignant. For papillary thyroid carcinoma (PTC), subtype variants were documented such as the follicular variant, classical variant, conventional variant and tall cell variant. Also were follicular thyroid carcinoma (FTC) subdivided to minimally invasive follicular thyroid carcinoma (MIFTC) and Widely Invasive follicular thyroid carcinoma (WIFTC).

### Statistical analysis

All statistical calculations were performed using IBM SPSS Statistics (IBM SPSS Statistics for Windows, Version 22, SPSS Inc. an IBM Company) program and Microsoft Excel 2010 (Microsoft Corporation, Seattle, WA, United States). The descriptive analysis of the epidemiological data presented as frequencies, percentages and mean  $\pm$  standard deviation (SD).  $\chi^2$  test was performed to find out the variables associated with cancer among the surgical patients.

## RESULTS

A total of 1188 patients (range 15-90 years) included in

this study. The mean age of the study population was 46.3  $\pm$  15.1 (SD), median 45 years, and mode 49 years. Of the 1188 (212 male; 976 female) patients, 245 patients had two thyroid nodules, which resulted in a total of 1433 FNA cases (nodules). Among the study population, a total of 311 patients underwent surgery and 877 patients did not undergo surgery. Of the 311 patients who underwent surgery, 58 patients had two thyroid nodules, which resulted in a total of 369 cases (245 benign and 124 malignant) (Figure 1). Among patients who underwent surgery, no statistically significant differences were observed on the presence of cancer among both gender ( $P = 0.463$ ), and different age groups ( $P = 0.928$ ).

As shown in Table 2, the distribution of all cases in the six Bethesda diagnostic categories were as follows: 46 cases (3.2%) of category I, 1080 cases (75.3%) of category II, 131 cases (9.1%) of category III, 71 cases (5%) of category IV, 32 cases (2.2%) of category V and 73 cases (5.1%) of category VI.

The distributions of follow-up diagnoses for each initial Bethesda diagnostic classification are shown in Table 3. There were 124 total cases of malignancy on resection, giving an overall surgical yield of malignancy of 33.6%. Eight of (2.2%) 369 thyroid nodules were diagnosed as ND, 181 (49.1%) diagnosed as benign, 42 (11.4%) diagnosed as AUS/FLUS, 53 (14.4%) as FNS/SFN. Category V (SM) diagnoses (26 cases) reminded benign in 8 cases, but histologically confirmed as carcinoma in 18 case (69.2%). Finally, category VI diagnoses (59 cases) reminded benign in 2 cases, but histologically confirmed as carcinoma in 57 cases (96.7%).

Table 4 shows the comparison rates of malignancy on surgical resection for FNA diagnostic categories and malignancy risk of the present findings and previously published data. Table 5 shows the age and sex distribution of thyroid cancer. Majority of the thyroid cancer nodules ( $n = 57$ , 46%) in Bethesda VI category followed by Bethesda IV ( $n = 25$ , 20.2%) and Bethesda V ( $n = 18$ , 14.5%). Among the Bethesda IV category 17 (68%) were PTC and 8 (32%) were follicular carcinoma. Almost 40% of the cancer nodules in 31-45 age groups in both sex.

Type and variants of thyroid cancer among histopathological diagnosis are shown in Table 6. Papillary carcinoma was the most common form of thyroid cancer among the study population (111, 89.6%). Among PTC ( $n = 111$ ), four histologic variants exist, with classic variant PTC accounting for 51.4% of PTC followed by follicular-

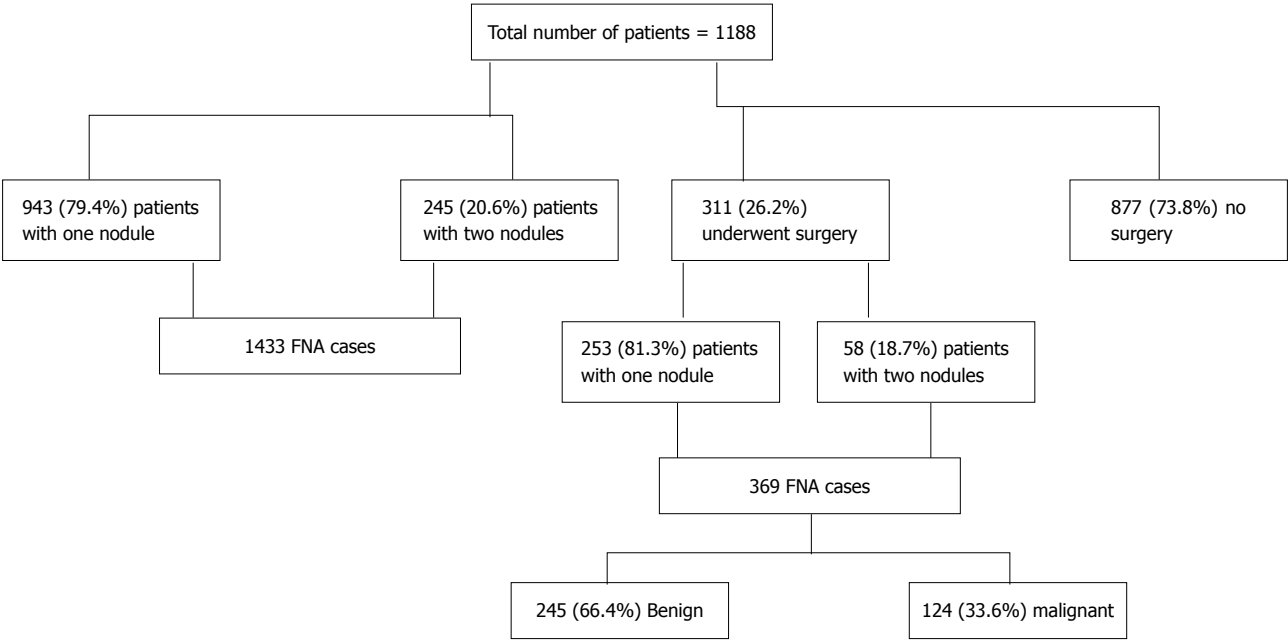


Figure 1 Flowchart of thyroid nodules description among 1188 patients and the risk of malignancy among 311 surgically excised nodules during January, 2012 to December, 2014. FNA: Fine needle aspiration.

Table 2 Age and sex distribution of thyroid lesion (based on fine-needle aspiration cytology according to Bethesda system)									
Age (yr)	Total number of patients	Gender F/M	All FNAs (n = 1433) n, %						
			Bethesda I	Bethesda II	Bethesda III	Bethesda IV	Bethesda V	Bethesda VI	Total
15-30	176 (14.8)	159/17	9 (4.5)	149 (74.9)	17 (8.5)	12 (6)	4 (2)	8 (4)	199
31-45	420 (35.4)	362/58	12 (2.4)	375 (74.7)	41 (8.2)	28 (5.6)	14 (2.8)	32 (6.4)	502
46-60	374 (31.5)	301/73	15 (3.3)	347 (75.1)	40 (8.8)	22 (4.8)	9 (2)	23 (5)	456
61-75	175 (14.7)	126/49	10 (4.5)	162 (72.3)	33 (14.7)	7 (3.1)	4 (1.8)	8 (3.6)	224
> 75	43 (3.6)	28/15	0	47 (90.4)	0	2 (3.8)	1 (1.9)	2 (3.8)	52
Total	1188	976/212	46 (3.2)	1080 (75.3)	131 (9.1)	71 (5)	32 (2.2)	73 (5.1)	1433

FNA: Fine-needle aspiration; F: Female; M: Male.

Table 3 Cyto-Histopathological correlation of thyroid lesion			
Cytopathology	Histopathological diagnosis		Total
	Benign	Malignant, n (%)	
Bethesda I	6	2 (25)	8
Bethesda II	165	16 (8.9)	181
Bethesda III	36	6 (14.3)	42
Bethesda IV	28	25 (47.2)	53
Bethesda V	8	18 (69.3)	26
Bethesda VI	2	57 (96.7)	59
Total	245	124 (33.6)	369

variant PTC (30.6%). Furthermore, 8.9% of malignancies were FTC (including 0.8% of the highest risk widely invasive phenotype), 0.8% of medullary thyroid carcinoma (MTC) and 0.8% of anaplastic thyroid carcinoma (ATC). Among the Bethesda IV category 17 (68%) thyroid nodules were PTC and 8 (32%) were FTC.

DISCUSSION

Over the last few decades thyroid cancer has been

on the rise considerably, globally, while mortality has steadily dropped, including in Saudi Arabia<sup>[14]</sup>. This reduction in the mortality resulting from thyroid cancer reflects the variations in the exposure to risk factors and alters the diagnosis and treatment of the disease, while the rise in the incidence is probably due to the improvement in the identification of this neoplasm<sup>[14]</sup>. However, in comparison with the developed countries, research on the incidence, prevalence and type of thyroid cancer in Saudi Arabia is still inadequate due to the lack of suitable studies being done on this specific aspect. Therefore, the objective of the current study is to stratify the risk of malignancy in the thyroid nodules based on the Bethesda system, which enhances the interpretation of the FNAC reports and enables a more accurate study and diagnosis of such thyroid nodules<sup>[13,15]</sup>. In this study, the distribution of age and gender among the patients is almost similar to those recorded in identical studies<sup>[1,2,16]</sup>. Besides, the female/male ratio reported in this study for thyroid cancer (4.7:1) concurs with the concept that thyroid cancer occurs more commonly among women. In the present study we found that the overall

**Table 4 Comparison rates of malignancy (%) on surgical resection for fine-needle aspiration diagnostic categories and malignancy risk of recent studies**

Published year		Comparison of diagnostic categories					
		I (ND)	II (Benign)	III (AUS/FLUS)	IV (FN/SFN)	V (SM)	VI (malignant)
Recent studies							
Park <i>et al</i> <sup>[22]</sup>	2014	13.3	40.6	9.1	0.4	19.3	17.6
Mondal <i>et al</i> <sup>[10]</sup>	2013	1.2	87.5	1	4.2	1.4	4.7
Mufti <i>et al</i> <sup>[29]</sup>	2012	11.6	77.6	0.8	4	2.4	3.6
Wu <i>et al</i> <sup>[30]</sup>	2012	20.1	39	27.2	8.4	2.6	2.7
Bongiovanni <i>et al</i> <sup>[31]</sup>	2012	2	54.7	6.3	25.3	6.3	5.4
Present study		3.2	75.3	9.1	5	2.2	5.1
Comparison of malignancy risk							
Haugen <i>et al</i> <sup>[32]</sup> (meta-analysis)	2016	9-32	1-10	6-48	14-34	53-97	94-100
Pantola <i>et al</i> <sup>[33]</sup> 2016	2016	0	0	8.3	10	100	100
Park <i>et al</i> <sup>[22]</sup>	2014	35.3	5.6	69	50	38.7	98.9
Mondal <i>et al</i> <sup>[10]</sup>	2013	0	4.5	20	30.6	75	97.8
Mufti <i>et al</i> <sup>[29]</sup>	2012	20	3.1	50	20	80	100
Wu <i>et al</i> <sup>[30]</sup>	2012	12	8	27	33	68	100
Present study		25	8.9	14.3	47.2	69.3	96.7

ND: Nondiagnostic; AUS/FLUS: Atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN: Follicular neoplasm/suspicious for follicular neoplasm; SM: Suspicious for malignancy.

**Table 5 Age and sex distribution of thyroid cancer**

Age (yr)	Total number of nodules	Gender F/M	All FNAs (n = 124) n, %					
			Bethesda I	Bethesda II	Bethesda III	Bethesda IV	Bethesda V	Bethesda VI
15-30	18 (14.5)	3/15	0	3	1	3	4	7
31-45	49 (39.5)	39/10	1	5	2	9	7	25
46-60	43 (34.7)	35/8	1	7	3	9	5	18
61-75	12 (9.7)	8/4	0	1	0	3	2	6
> 75	2 (1.6)	2/0	0	0	0	1	0	1
Total	124	87/37	2 (1.6)	16 (12.9)	6 (4.8)	25 (20.2)	18 (14.5)	57 (46)

FNA: Fine-needle aspiration; F: Female; M: Male.

**Table 6 Type and variants of thyroid cancer among histopathological diagnosis**

Type of cancer	Total = 124 ( <i>n</i> , %)	BETHESDA ( <i>n</i> , %)					
		I	II	III	IV ( <i>n</i> = 25)	V	VI
PTC							
Classic variant	57	1	5	1	3	8	39
Follicular variant	34	1	8	2	11	6	6
Conventional	19	0	2	2	3	3	9
Tall-cell variant	1	0	0	0	0	0	1
Total PTC	111 (89.6)	2	15	5	17 (68)	17	55
FTC							
MIFTC	10	0	1	1	7	1	0
WIFTC	1	0	0	0	1	0	0
Total FTC	11 (8.9)	0	1	1	8 (32)	1	0
MTC	1 (0.8)	0	0	0	0	0	1
ATC	1 (0.8)	0	0	0	0	0	1

PTC: Papillary thyroid carcinoma; MTC: Medullary thyroid carcinoma; ATC: Anaplastic thyroid carcinoma; FTC: Follicular thyroid carcinoma; MIFTC: Minimally invasive follicular thyroid carcinoma; WIFTC: Widely invasive follicular thyroid carcinoma.

malignant rate was 33.6% which exactly matches the percentage (33.8%) of 25445 thyroid FNAs used in the meta-analysis done by Bongiovanni *et al*<sup>[17]</sup>, as well as Jo *et al*<sup>[18]</sup> who reported 30.9%. However, this high malignancy rate is not unusual if it is understood that

the FNAC is consistently being performed today for most patients with thyroid nodules. This has resulted in a drop in the number of unwarranted surgeries and thereby to an increase in the percentage for reported malignancies<sup>[1]</sup>. It is noteworthy that the number of FNA



cases in this study steadily rose from 2012 ( $n = 357$ ) to 2014 ( $n = 449$ ). From various studies it was evident that the percentage of cases that were subjected to surgery differed widely among different institutions, reporting a range from 11.8%<sup>[19]</sup> to 45.1%<sup>[20]</sup> with an average rate of 25%<sup>[17]</sup>; the current study identified 26.2% of the study population who had surgical outcome.

Each Bethesda category showed a malignancy rate ranging from 1%-10% ("benign category") to 94%-100% ("malignant" category). This comprehensive range highlights the ability of the Bethesda system to differentiate and determine the likelihood of malignancy. The results recorded in our research concurred closely with the results reported in the American Thyroid Association Management Guidelines and other studies: 25% vs 9%-32% ("non-diagnostic or unsatisfactory" category), 9.3% vs 1%-10% ("benign and non-neoplastic" category), 14.3% vs 6%-48% (AUS/FLUS), 69.2% vs 53%-97% ("suspicious for malignancy" category), and 96.7% vs 94%-100% ("malignant" category)<sup>[13,17]</sup>. Among Bethesda, category IV found 47.2% malignancy risk, a value higher than the meta-analysis results of 14%-34% (FNS/SFN), published recently by Bongiovanni *et al.*<sup>[17]</sup>. However, many studies revealed the greatest variation in the risk of malignancy class IV, some of which are higher (malignancy rate 50%-67%) than the present values<sup>[21-23]</sup>.

The current study reported PTC (89.6%) as the commonest type of thyroid cancer in the population under study. Studies also reported that overall PTC as the commonest kind of thyroid cancer represents 80% of all the thyroid malignancies and more than 90% of the differentiated thyroid cancers<sup>[13,24,25]</sup>. A spurt in the occurrence of PTC over the past decades has triggered greater interest in this disease. This is one of the fastest growing kinds of cancer recording over 20000 new cases annually. Although individuals are susceptible to papillary carcinoma irrespective of age, most patients will show the disease prior to 45 years of age<sup>[26]</sup>, a fact corroborated by the current findings (42% PTC between 31-45 years of age). Unfortunately, FTC is not being diagnosed as often, although there is an increasing incidence of well-differentiated thyroid carcinomas everywhere else<sup>[27,28]</sup>, concurring with the results of the current study.

There are a two limitations to this study, mainly the retrospective design and performance in a single center. As the PSMC is a tertiary center for thyroid lesions, the data of this study may not precisely reflect the general population. More research is warranted to overcome the limitations of the study.

In conclusion, 33.6% of the cases overall among the surgically excised nodules, showed malignancy. The malignancy values reported in our research were constant and comparable with the results of other data with respect to the risk of malignancy. For the FN/SF patients and those with suspicions of malignancy, total thyroidectomy is indicated because of the substantial risk of malignancy. It is clear, that reviewing the thyroid FNAs with the Bethesda system allowed a more precise cytological diagnosis. However, the impact of Bethesda

application may vary among different institutions. Clinicians are advised to be aware of the malignancy rate in the Bethesda categories in their respective institutions to improve the investigation and decision regarding patients with thyroid nodules.

## COMMENTS

### Background

The National Cancer Institute, United States, established guidelines employing a standardized nomenclature to interpret thyroid fine-needle aspirations (FNAs) called the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) which is now accepted as the proposed diagnostic categories for thyroid cancer.

### Research frontiers

Compared with the developed countries, research regarding the malignancy risks in thyroid nodules is still inadequate due to lack of appropriate studies being conducted in these specified areas in Saudi Arabia. Hence, this present study attempts to stratify the malignancy risks in thyroid nodules in a tertiary care referral center in Saudi Arabia utilizing the Bethesda system.

### Innovations and breakthroughs

The study found that there were 124 total cases of malignancy on resection, giving an overall surgical yield malignancy of 33.6%. Majority of the thyroid cancer nodules in Bethesda VI category followed by Bethesda IV. Almost 40% of the cancer nodules in 31-45 age group in both sex. Papillary thyroid carcinoma was the most common form of thyroid cancer among the study population followed by follicular thyroid carcinoma, medullary carcinoma and anaplastic carcinoma.

### Applications

Reviewing the thyroid FNAs with the Bethesda system allowed a more precise cytological diagnosis. However, the impact of Bethesda application may vary among different institutions. Clinicians are advised to be aware of the malignancy rate in the Bethesda categories in their respective institutions to improve the investigation and decision regarding patients with thyroid nodules.

### Terminology

PTC: Papillary thyroid carcinoma; FTC: Follicular thyroid carcinoma; SCR: Saudi Cancer Registry; FNA: Fine-needle aspiration; FNAC: Fine-needle aspiration cytology; NCI: National Cancer Institute, United States; BSRTC: Bethesda System for Reporting Thyroid Cytopathology; PSMC: Prince Sultan Military Medical City; TBSRTC: The Bethesda system of reporting thyroid cytology; UNS: Unsatisfactory; ND: Nondiagnostic; AUS/FLUS: Atypia of undetermined significance or follicular lesion of undetermined significance; US: Ultrasound; MIFTC: Minimally invasive follicular thyroid carcinoma; WIFTC: Widely Invasive follicular thyroid carcinoma; ATC: Anaplastic thyroid carcinoma.

### Peer-review

The study shows a very exhaustive analysis of the throughput of thyroid cytopathology over a three-year period. The manuscript contains a detailed exposition of the results, including comprehensive tables and a comparison to other recent studies. In my opinion, this manuscript fulfills all the requirements to be published.

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