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Patterns of thyroid tumors in Northern Saudi Arabia with a specific focus on CK19, CD56, and Galectin-3 tumor markers

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Abstract. – OBJECTIVE: The goal of this study was to look at the patterns of thyroid tumors and how thyroid cancer markers showed up in immunohistochemistry in Northern Saudi Arabia.

PATIENTS AND METHODS: This study investigated retrospectively 190 patients who attended with thyroid complaints. About 140 thyroid biopsies were diagnosed in the Department of Pathology at King Salman Hospital, Ha'il, from November 2019 to November 2020.

RESULTS: Out of the 190 patients who attended with thyroid complaints, 140/190 (73.7%) were detected with thyroid lesions (58 malignant and 82 benign). Benign lesions included goiter 49/82 (60%), follicular adenoma 17/82 (21%), Hashimoto's thyroiditis 13/82 (16%), and toxic goiter 3/82 (3%). 5/6 (83.3%) of males with benign lesions had goiters. CK19 was positive in 68.5% of the cases; 71.8% were papillary, 66.7% were follicular, and 100% were undifferentiated carcinomas. Out of the 26/54 (48%) CD56-positive cases, 18/39 (46%) were papillary, 7/12 (58.3%) were follicular, and 3/3 (100%) were undifferentiated carcinomas. Out of the 35/54 (64.8%) Galectin-3-positive cases, 69.2% were papillary, 7/12 (58.3%) were follicular, and 3/3 (100%) were undifferentiated carcinomas.

CONCLUSIONS: Thyroid cancer is prevalent in northern Saudi Arabia, with the predominant type being papillary thyroid carcinoma. Most patients are female and younger. The combined use of CK19, CD56, and Galectin-3 tumor markers assists in the accurate differential diagnosis of thyroid neoplasms.

Key Words:
Thyroid cancer, Carcinoma, CK19, CD56, Galectin-3, Saudi Arabia

Introduction

Thyroid cancer is the most prevalent, with an increasing yearly incidence[1]. Thyroid cancer is Saudi adults' third most frequent cancer[2]. In Saudi Arabia, thyroid cancer is a leading head and neck cancer, particularly among females, which necessitates deep searches into the possible modifiable risk factors[3,4].

Many modifiable risk factors have been implicated in the etiology of thyroid cancer, which significantly differs according to geographical area, sex, age, and ethnicity. Women are more susceptible than men, particularly during the fertile period. Irrespective of sex and the presence of risk factors, papillary carcinoma is encountered as the most common histological type. Goiter, ionizing radiation exposure, miscarriage or abortion, cigarette smoking, and contraceptive usage are the most confronting modifiable risk factors[5].

The assessment of surgically removed thyroid cancer tissues by immunohistochemistry has diagnostic, prognostic, and therapeutic impacts[6]. Cytokeratin 19 (CK19) immunohistochemistry expression is valuable in determining the overall survival of patients with thyroid carcinoma[7]. CD56 immunohistochemistry expression is lower in high-grade thyroid carcinomas than in benign thyroid tumors. Therefore, it helps differentiate thyroid malignant from benign tumors[8]. Besides the fact that Galectin-3 immunohistochemistry has applicable diagnostic value in thyroid papil-

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lary carcinoma, its absence is usually associated with less aggressive papillary thyroid carcinoma pathogenesis than positive[9]. Thus, the present study aimed to assess the patterns of thyroid tumors and immunohistochemistry expression of thyroid cancer markers in Northern Saudi Arabia.

Patients and Methods

This study investigated retrospectively 190 patients who attended with thyroid complaints. About 140 thyroid biopsies were diagnosed in the Department of Pathology at King Salman Hospital, Ha'il, Northern Saudi Arabia, from November 2019 to November 2020. Out of the 140 biopsies, 58/140 (41.4%) were diagnosed as thyroid carcinomas and 82/140 (58.6%) as benign thyroid lesions.

Conventional histopathology confirmed the diagnosis of thyroid lesions. The histopathological diagnosis of the tissue samples was re-evaluated to verify the prior diagnosis and categorize the lesion into benign and malignant types. The expression of CK19, CD56, and Galectin-3 tumor markers was demonstrated using immunohistochemistry, applying the avidin-biotin-peroxidase complex method.

Immunohistochemical Staining Procedure

The 5 μm thyroid tissue sections on poly-L-lysine coated slides were stained by immunohistochemistry (IHC), applying antibodies raised against CK19, CD56, and Galectin-3 tumor markers. The slides were initially heated overnight at 56°C, followed by deparaffinization through graded ethanol concentrations toward rehydration. Then the tissue sections were treated with 10 μM sodium citrate buffer at 100°C for 15 minutes for antigenic epitope retrieval (previously masked by fixation). After that, the tissues were treated with 0.3% hydrogen peroxide (in methyl alcohol) for 30 minutes (to block endogenous peroxidase activity), then washed in three changes of phosphate-buffered saline (PBS). Then non-specific antigenic sites were blocked using normal serum (horse) diluted in PBS, and then slides were washed in two changes of distilled water (DW) for five minutes. Then the primary antibodies (CK19, CD56, or Galectin-3) were applied and incubated for 8 hours in the humidity chamber, followed by two changes of PBS for five minutes. After that, the secondary antibody was applied and incubated for 30 minutes. Then the detection system using the avidin-biotin-peroxidase complex was used. The slides were counterstained with hematoxylin, mounted, and analyzed with a light microscope. All slides were performed at the same time and submitted using standard methods. Identified positive and negative cases were employed as external controls.

- Positive staining was considered when > 10% of the specific tissue sites showed brown 3, 3-diaminobenzidine (DAB) staining.
- Positive CK19: showing cytoplasmic/membranous staining.
- Positive CD56: showing diffuse cytoplasmic staining.
- Positive Galectin-3: showing cytoplasmic expression.

Statistical Analysis

Retrieved information sets were entered into computer software, Statistical Package for Social Sciences, version 16 (SPSS Inc., Chicago, IL, USA). The Chi-square test was employed for statistical significance ($p < 0.05$ was considered significant).

Results

Demographic and Pathologic Characteristics

Out of 190 patients, 136 (71.6%) were female and 58 (28.1%) were male, ranging in age from 11 to 71, with a mean age of 40. In general, most cases were aged 25-34 years (32%), followed by 35-44 years (30.5%).

Out of the 190 patients who attended with thyroid complaints, 140/190 (73.7%) had thyroid lesions. About 82/140 (58.6%) of the thyroid tumors were found to be benign, and the other 58/140 (41.4%) were found to be thyroid carcinoma. Goiters made up 49 of the 82 benign lesions (60%), follicular adenomas made up 17 (21%), Hashimoto's thyroiditis made up 13 (16%), and toxic goiters made up 3 (3%). Most males with benign lesions had goiters (5/6) (83.3%).

Regarding malignant lesions, most cases were diagnosed with follicular variant papillary carcinoma, followed by papillary microcarcinoma and classical type papillary carcinoma, representing 17/58 (29.5%), 15/58 (26.2%), and 12/58 (20.7%), as indicated in Table I and Figure 1. All males with cancer were seen with classical-type papillary carcinoma.

Table I. Distribution of the patients by diagnosis, age, and gender.

Variable	Males	Females	Total
< 25 years	5	5	10
25-34	16	45	61
35-44	12	46	58
45-54	11	27	38
55+	10	13	23
Total	54	136	190
Diagnosis			
Colloid goiter	5	44	49
Follicular adenoma	1	16	17
Hashimoto's thyroiditis	0	13	13
Toxic goiter	0	3	3
Classical Type Papillary carcinoma	3	9	12
Follicular variant Papillary carcinoma	0	17	17
Papillary microcarcinoma	0	15	15
Tall cell variant Papillary carcinoma	0	1	1
Widely invasive Follicular carcinoma	0	4	4
Minimally invasive Follicular carcinoma	0	7	7
Medullary carcinoma	0	2	2
Total	**9**	**131**	**140**

Table II and Figure 2 summarize the distribution of the diagnosis by age. Goiter was increasingly seen in the age range 35-44 years (22/49; 45%), followed by 45-54 years (12/49; 24%). Follicular adenoma was more frequent in the age range 25-34 years (7/17; 41%), followed by 35-44 years (6/17; 35%). Hashimoto's thyroiditis was more common in the age range 25-34 years (5/13) (38.5%), followed by 45-54 years (4/13) (31%).

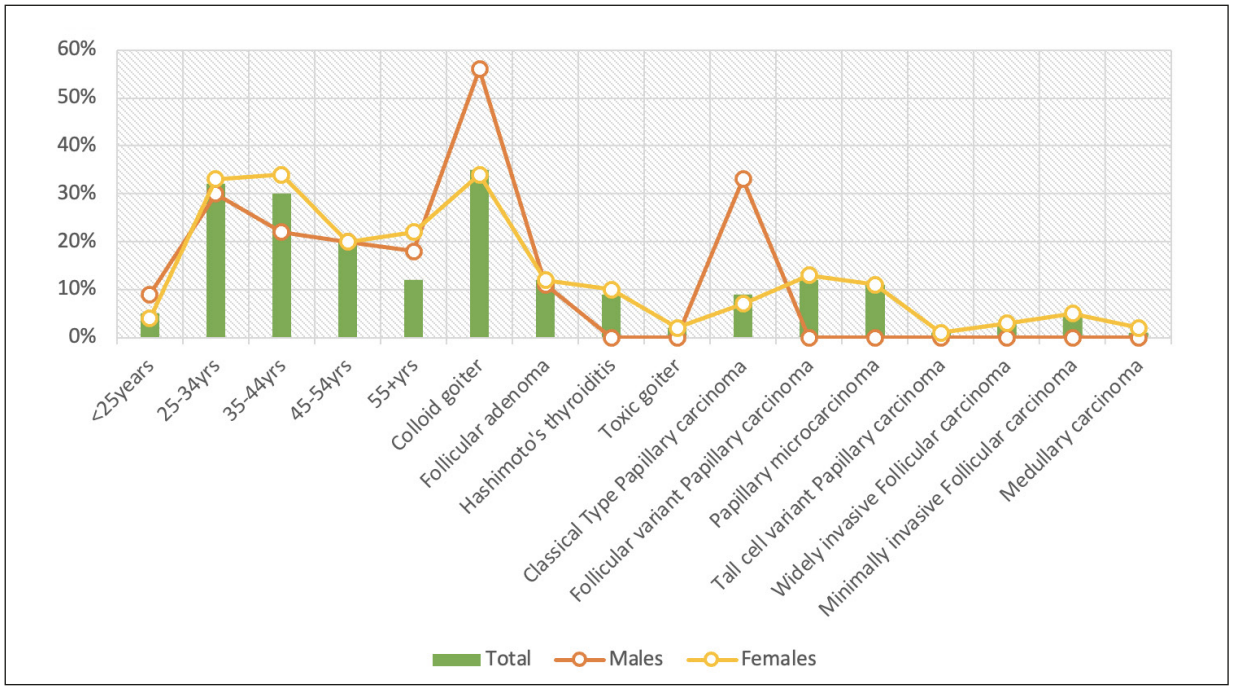

Figure 1. Description of the diagnosis and age within the entire gender group.

Table II. Distribution of the study subjects by diagnosis and age.

Diagnosis	< 25 yrs	25-34	35-44	45-54	55+	Total
Colloid goiter	2	8	22	12	5	49
Follicular adenoma	2	7	6	1	1	17
Hashimoto's thyroiditis	0	5	3	4	1	13
Toxic goiter	0	1	0	2	0	3
Classical Type Papillary carcinoma	2	1	5	3	1	12
Follicular variant Papillary carcinoma	0	6	7	2	2	17
Papillary microcarcinoma	1	8	5	1	0	15
Tall cell variant Papillary carcinoma	0	0	1	0	0	1
Widely invasive Follicular carcinoma	0	4	0	0	0	4
Minimally invasive Follicular carcinoma	0	4	1	0	2	7
Medullary carcinoma	0	0	1	1	0	2
Total	7	44	51	26	12	140

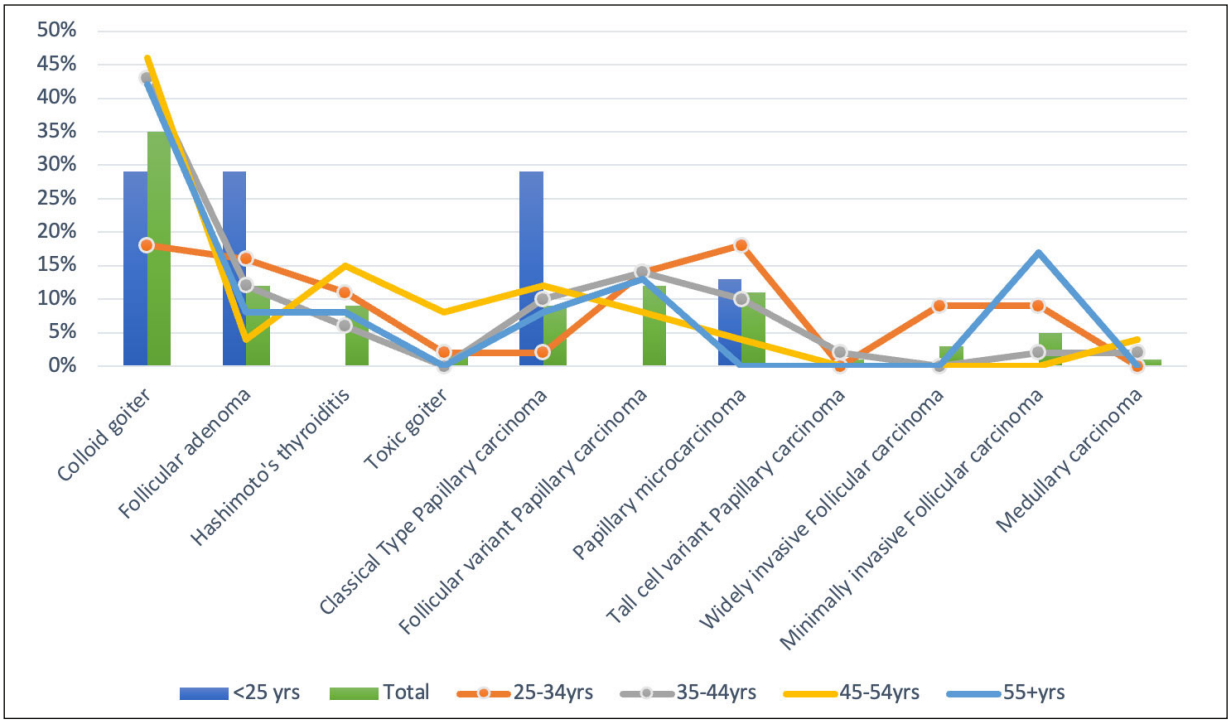

Figure 2. Description of the patients by diagnosis within the entire age group.

Classical-type papillary carcinoma is more common in adults aged 35-44 years (5/12; 42%). Follicular papillary carcinoma increased in age 35-44 years (7/17; 41%), followed by 25-34 years (6/17; 35%). Papillary microcarcinoma increased in the age group 25-34 years (8/15, 53.3%), followed by 35-44 years (5/15, 33.3%). All cases of widely invasive follicular carcinoma were seen in the age range of 25-34 years (100%). Minimally invasive follicular carcinoma was increasingly seen in ages 25-34 (4/7; 57%).

Table III summarizes the distribution of patients by thyroid tumor site and side, and diagnosis. Most classical-type papillary carcinoma, papillary microcarcinoma, widely invasive follicular carcinoma, and minimally invasive follicular carcinoma were seen in the left lobe. Most follicular variant papillary carcinoma, minimally invasive follicular carcinoma, and medullary carcinoma were seen in the right lobe. Available lesions size (< 2 cm), indicating small lesions in the right isthmus, followed by the left lobe. Large-size lesions were relatively similar in most sites.

Table III. Distribution of patients by thyroid tumor site and side and diagnosis.

Variable	Right lobe	Left lobe	Right & isthmus	Isthmus	Bilateral	Total
Classical Type Papillary carcinoma	2	3	1	1	1	8
Follicular variant Papillary carcinoma	5	3	0	2	0	10
Papillary microcarcinoma	3	7	0	0	0	10
Widely invasive Follicular carcinoma	1	2	0	0	0	3
Minimally invasive Follicular carcinoma	2	2	0	0	0	4
Medullary carcinoma	1	0	0	0	0	1
Total	14	17	1	3	1	36
Lesion size						
Smaller than 2 cm	5	9	13	1	3	1
Bigger than 2 cm	7	7	2	3	4	1
Total	12	16	15	4	7	2

CK19, CD56, and Galectin-3 IHC Expression

Table IV and Figure 3 summarize the distribution of the thyroid carcinoma type by CK19, CD56, and Galectin-3 tumor markers. CK19 was positive in 37/54 (68.5%) cases. Out of the 37 positive cases, 28/39 (71.8%) were papillary, 8/12 (66.7%) were follicular, and 3/3 (100%) were undifferentiated carcinomas. Out of the 26/54 (48%) CD56-positive cases, 18/39 (46%) were papillary, 7/12 (58.3%) were follicular, and 3/3 (100%) were undifferentiated carcinomas. Out of the 35/54 (64.8%), Galectin-3-positive cases, 27/39 (69.2%) were papillary, 7/12 (58.3%) were follicular, and 3/3 (100%) were undifferentiated carcinomas.

Discussion

Thyroid tumors are prevalent in Saudi Arabia, particularly among females. The present study shows a high percentage of thyroid tumors (30.5%), particularly among females (71.6%) of relatively younger age. A recent study[10] from Saudi Arabia reported that thyroid cancer represents 12.9% of all cancers and is the 3rd most common adult cancer in the country[11]. Studies[12-13] from Saudi Arabia also reported that it was most prevalent among females and in the younger population. According to a recent study[14], females developed thyroid nodules at a younger age than males. Multicentric malignancy was common in multinodular goiter (MNG) in papillary carcinomas, and the risk of MNG increased with age.

Table IV. Distribution of the thyroid carcinoma type by Ck19, CD56, and Galectin3 tumor markers.

Variable	Thyroid carcinoma type						
	Papillary	*p*-value	Follicular	*p*-value	Undifferentiated	*p*-value	Total
CK19		0.9089		0.6494		0.0001	
Positive	28		8		3		37
Negative	11		4		0		13
Total	39		12		3		54
CD56		0.1437		0.5933		0.0001	
Positive	18		7		3		26
Negative	21		5		0		24
Total	39		12		3		54
Galectin-3		0.8584		0.4409		0.0001	
Positive	27		7		3		35
Negative	12		5		0		15
Total	39		12		3		54

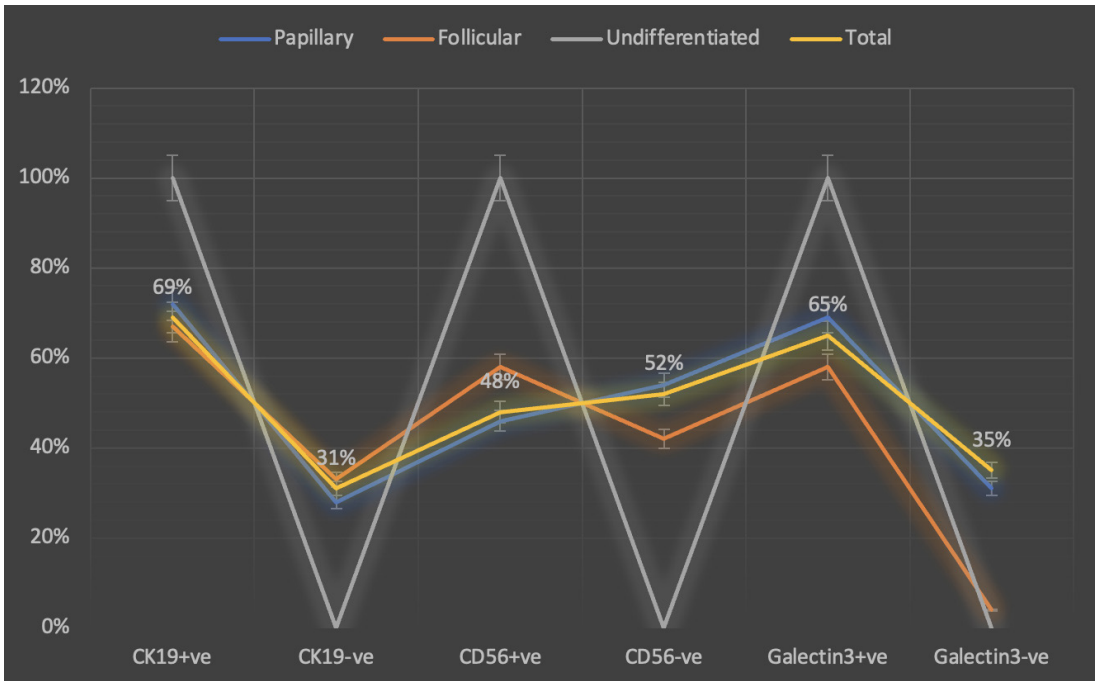

Figure 3. Thyroid carcinoma type by Ck19, CD56, and Galectin-3 tumor markers.

Most cases in the present study were diagnosed with papillary thyroid cancer, the most prevalent type of thyroid cancer globally and in Saudi Arabia[15,16]. The most common thyroid benign lesion was goiter, which represented 60% of all benign lesions in the present study, which was previously reported from Saudi Arabia[17].

In a similar study, 31 of 94 complete thyroidectomy patients had thyroid cancer. 18 had nodules, but 13 without nodules had thyroid cancer. 31 patients had these cancer subtypes: 22 had papillary microcarcinoma, 8 carcinoma, and 1 benign follicular thyroid tumor with papillary-like nuclear characteristics. Thyroid cancer was found in 30% of patients operated for other causes and 50% of those operated for anti-thyroid drug-related significant adverse events[18].

CK19 was found positive in 71.8% of the cases of papillary thyroid carcinomas, 66.7% of follicular thyroid carcinomas, and all the cases of undifferentiated thyroid carcinoma (100%). Similar findings were reported regarding CK19 immunohistochemistry expression (80%) in papillary thyroid carcinoma[7].

CD56 was immunoexpressed in 48% of the cases of thyroid carcinoma. Including 69% papillary carcinoma, 27% follicular carcinoma, and 4% undifferentiated carcinoma. In the literature was shown relatively lower immune expression of CD56 in thyroid carcinomas (44.4%). CD56 is highly immunoexpressed in benign thyroid lesions compared to malignant tumors. Therefore, CD56 is an excellent tumor marker for distinguishing thyroid carcinomas from other benign thyroid lesions[19]. In a study to differentiate between follicular thyroid carcinoma and adenomas, CD56 was expressed in only 5% of thyroid carcinomas compared to 93% of the benign thyroid lesions, which indicated a sensitivity of 94.8% and a specificity of 92.3%. Therefore, CD56 immunohistochemistry testing is a useful diagnostic marker, particularly for differentiating benign thyroid lesions from papillary thyroid carcinoma[20].

In the present study, Galectin-3 was positive in 64.8% of the thyroid carcinoma cases, including 77% papillary carcinomas, 20% follicular carcinomas, and 3% undifferentiated carcinoma. Galectin-3 is a beta-galactoside that has increased expression in many malignant types, including thyroid cancer[21]. Metastasized thyroid carcinomas usually show high Galectin-3 immunoexpression[22]. Galectin-3 immuno-expression is usually increased in thyroid carcinoma rather than benign thyroid tumors. Galectin-3 immuno-expression was also noted in some thyroid follicular adenomas, suggesting the involvement of this marker in thyroid tumorigenesis, as well as the probability of progression of these benign tumors towards cancerous change[23]. The pattern of immune expression of Galectin-3 can be used to differentiate between benign and malignant thyroid tumors.

Galectin-3 immuno-expression was significantly higher in malignant thyroid tumors than in benign lesions. Therefore, diffuse and galectin-3 solid immune expression differentiates malignant tumors from benign thyroid lesions. Moreover, it can differentiate thyroid neoplasms with ambiguous morphological features[24].

Although CK19 diffuse immune expression is characteristic of papillary thyroid carcinoma compared to focal immune expression in benign lesions, it still has lower specificity and is inaccurate for the diagnosis of thyroid carcinoma[25]. CD56 is a negative marker rather than a positive marker for papillary thyroid carcinoma compared to CK19, and therefore, CD56 is encountered as a more specific and sensitive marker than CK19[26]. In the literature was shown that Galectin-3 is more sensitive than CK19 for thyroid carcinoma, while the absence of CD56 immuno-expression is very specific for thyroid carcinoma. Thus, applications of the three markers can effectively assist in the accurate differential diagnosis of thyroid neoplasms[27].

The present study provided the first time such data for Saudi Arabia; nonetheless, its main limitation is its retrospective setting.

Conclusions

Thyroid cancer is prevalent in Northern Saudi Arabia, with the predominant type being papillary thyroid carcinoma. Most patients are female and younger. The combined use of CK19, CD56, and Galectin-3 tumor markers assists in the accurate differential diagnosis of thyroid neoplasms in terms of specificity and sensitivity.

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Authors' Contributions
HGA: Conception, administration, analysis, drafting, and approval of the final version.
ABE: Conception, design, data acquisition, practical part, approval of the final version.
HMA: Conception, analysis, drafting, practical part, approval of the final version.
KKA: Conception, design, data acquisition, and approval of the final version.
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Conflict of Interest
The authors declare no competing interests.

Ethics Approval
The protocol of this study was approved by the Human Research Ethics Committee of the College of Medicine, University of Hai'il, Saudi Arabia, No. HREC 00069/CM-UOH.12/20. We confirm that all experiments were performed following relevant guidelines and regulations.

Informed Consent
Although the study was retrospective, we confirm that informed consent was obtained from legal guardians.

Data Availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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