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ORIGINAL ARTICLE

Thyroid cancer risk assessment indicators: A correlation between preoperative and postoperative criteria

Noora Al Moosa, Mai Abdulla Nasser, Mohamed Alshehabi

Bahrain Defense Force, Royal Medical Service, Riffa, Kingdom of Bahrain

Correspondence to: Noora Al Moosa, MD
Department of General Surgery, Bahrain Defense Force Hospital, Royal Medical Services, Kingdom of Bahrain
e-mail: doctor888111@gmail.com

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Abstract

BACKGROUND AND OBJECTIVES: To differentiate preoperatively between benign nodule and thyroid cancer (TC) is highly important. Therefore, we investigated the risk assessment indicators that correlate preoperative clinical, radiological, and pathological features with post-operative TC characteristics.

METHODS: An observational retrospective study was performed in Bahrain Defense Force (BDF) hospital for all patients suspected of having thyroid cancer from January 2016 to October 2020. All the medical records, including clinical, laboratory, radiological, and pathological assessments of these patients, were retrieved and analyzed for association using binary and multivariate logistic regression analysis to estimate significance, odds ratio (OR), and 95% confidence interval.

RESULTS: A total of 87 patients were included in the study with a mean age of 40 ± 12.5 years old. The histopathology revealed that 27 patients had TC with a mean age of 38.1±10.8 years (p>0.05 vs. benign conditions). Furthermore, the TC frequencies within gender were 29.9% and 36.4% for females and males, respectively. Besides, most patients (85.2%) had papillary TC cancer, whereas 7.4% had follicular cancer, and 3.7% had either medullary TC or minimally invasive follicular TC. The correlation results between demographic, clinical characteristic evaluations, laboratory findings of the study patients, and TC as reported by the histopathology were all not significant except for ultrasound features including solitary nodule (p<0.05), lymph node involvement, and consistency (p<0.01). The sensitivity and specificity values of FNAC for detection of TC were 77.8% and 86.3%, respectively. Multivariate analysis revealed that only solid consistency of the tumor (OR = 9.88) and lymph node involvement (OR = 14.78) were correlated with TC detection. On the other hand, gender, symptoms of hypothyroidism, hyperthyroidism, or compression, family history of TC, abnormal thyroid function tests, neck swelling, and ultrasounds imaging with regards to vascularization and microcalcification were not correlated with the detection of TC.

CONCLUSION: Preoperative nodule and FNAC assessments need further research and development to approach higher sensitivity in detecting TC.

INTRODUCTION

Although thyroid diseases are the most common endocrine disorders, thyroid cancer (TC) is a somewhat rare disease with an incidence of 15/100,000 population per year (Gharib *et al.* 2010). Since it is rare cancer, the diagnosis of thyroid cancer preoperatively remains difficult for surgeons and endocrinologists. On the other hand, nodular thyroid disease is prevalent at 5% (Singh *et al.* 2020; Bernet & Chindris 2021). These thyroid nodules are frequently identified in asymptomatic patients without symptoms and are detectable by clinical examination, laboratory findings, followed by either ultrasound imaging, fine needle aspiration cytology (FNCA), and/or thyroid biopsies (Polyzos *et al.* 2007; Dean & Gharib, 2008; Cairncross & Panieri 2013; Singh *et al.* 2020; Bernet & Chindris 2021). Therefore, it is very important to reduce unnecessary thyroid biopsies and have a confident preoperative diagnosis.

To differentiate preoperatively between benign nodule and TC is of high importance and helps proper surgical intervention and reduces unnecessary operation and its consequences (Cairncross & Panieri 2013; Singh *et al.* 2020). Therefore, in the current study, we investigated the risk assessment indicators that correlate preoperative clinical, radiological, and pathological features with post-operative TC characteristics. The goal, however, is to evaluate our common diagnostic approach, especially for intermediate FNCA results, to enhance patients' prognoses better.

Tab. 1. Demographic and clinical characteristic evaluations of the study patients

Parameter	Type	N	%
Age (years)	40 ± 12.5	-	-
Gender	Male	11	12.6%
	Female	76	87.4%
Family history	No	79	90.8%
	Yes	8	9.2%
Radiation exposure	No	87	100.0%
	Yes	0	0.0%
Symptoms of hypothyroidism	No	71	81.6%
	Yes	16	18.4%
Symptoms of hyperthyroidism	No	77	88.5%
	Yes	10	11.5%
Neck swelling	No	3	3.4%
	Yes	84	96.6%
Compression symptoms	None	41	47.1%
	Horsiness	12	13.8%
	Dysphagia and Shortness of breath	34	39.1%
Lymph nodes (clinical)	No	86	98.9%
	Yes	1	1.1%

PATIENTS AND METHODS

Study Design and Protocol

An observational retrospective study was performed in Bahrain Defense Force (BDF) hospital from January 2016 to October 2020. A study protocol was submitted and approved by the Research & Research Ethics Committee (BDF/R&REC/2020-499) at the BDF.

Subjects and Laboratory and Radiological Data

The inclusion criteria were set for all patients suspected of having thyroid cancer from January 2016 to October 2020 at BDF. All medical records, including clinical, laboratory, radiological and pathological assessments of these patients were retrieved.

Preoperative and Postoperative Records

The preoperative measures were based on clinical examination, radiological assessment, laboratory findings, and FNAC results. Each clinical examination includes history, thyroid swelling, nodule type, compression symptoms, signs and symptoms of hypo- or hyperthyroidism. In comparison, the radiological assessment includes the size of the nodule, site, consistency, taller than wider, microcalcification, vascularization, and lymph node involvement. The laboratory results include thyroid function tests (TFT) and serum thyroglobulin tumor marker. The FNAC results were classified according to UK Royal College of Pathologists from THY 1 to THY5.

On the other hand, the postoperative measures include histopathology/type of cancer if present, thyroid size, nodule size and site, extrathyroidal extension, and tumor nodes metastases (TNM) classification.

Data Analysis

Each of the patient descriptive measures, preoperative and postoperative assessments were collected and recorded. The continuous variables were presented by mean ±SD and statistically tested using an independent-two-sided t student test. The categorical variables were analyzed using chi-square analysis. To identify risk assessment factors for thyroid cancer, multivariate logistic regression analysis was used, including adjusting the covariate age factor. The estimated risk effect was reported by the odds ratio (OR) with their 95% confidence interval (95% CI). A p value < 0.05 was considered significant.

Tab. 2. Radiological and laboratory results of the study patients

Parameter	Type	N	%
Ultrasound features	Solitary nodule	47	56.0%
	Multi nodular goiter	22	26.2%
	Diffuse goiter	15	17.9%
Site of nodule	Right	23	29.1%
	Left	30	38.0%
	Bilateral	26	32.9%
Consistency	Cystic	28	36.8%
	Solid	41	53.9%
	Mixed	7	9.2%
Microcalcification	No	64	78.0%
	Yes	18	22.0%
Vascularity	No	51	61.4%
	Yes	32	38.6%
Taller than wider	No	25	34.2%
	Yes	48	65.8%
Lymph node (ultrasound)	No	76	91.6%
	Yes	7	8.4%
TFT	Normal	67	76.1%
	Low	8	9.1%
	High	13	14.8%
Serum thyroglobulin	Normal	70	92.1%
	High	6	7.9%
FNAC results	Not Done	10	11.5%
	THY1	1	1.3%
	THY2	40	51.3%
	THY3	17	21.8%
	THY4	10	12.8%
	THY5	10	12.8%
Features of FNAC	Benign	41	52.6%
	Atypical/ FLUS/ HCL*	9	11.5%
	Follicular neoplasm	13	16.7%
	Papillary thyroid cancer	15	19.2%

* FLUS: follicular lesion of indeterminate; HCL: hurthle cell lesion

RESULTS

Patients' demographics, clinical, radiological and laboratory assessments

A total of 87 patients were included in the study with a mean age of 40 ± 12.5 years old (Table 1). Most of the patients were females (76%) and had no family history (90.8%) of thyroid cancer, no signs and symptoms of hypo- or hyperthyroidism (81.6% and 88.5%, respectively), had not been exposed to radiation (100%), no clinical observation of lymph node involvement (98.9%), but had neck swelling (96.6%) (Table 1). Besides, 59% of the patients had compression symptoms, including dysphagia, shortness of breath, and horsiness.

The radiological features revealed that over half of the patients had solitary nodules, solid consistency, no microcalcification, no hypervascularity, no lymph node involvement, but taller than wider (Table 2). As for the laboratory data, most of the patients had normal thyroid function, and thyroglobulin levels (Table 2). Furthermore, the FNAC classifications and features revealed that 52.6% of the cases were benign, 11.5% had atypical cells, 16.7% with follicular neoplasms, and 19.2% with papillary thyroid cancer.

The histopathology revealed that 27 of the patients had TC (Table 3). The TC patient's average age was 38.1 (±10.8) years and was not significantly different from patients' age (41.1 ±13.1 years) with benign thyroid conditions. Furthermore, the TC frequencies within gender were 29.9% and 36.4% for females and males, respectively. Besides, most patients (85.2%) had papillary TC (4 with micropapillary TC), whereas 7.4% had follicular cancer, and 3.7% had either medullary TC or minimally invasive follicular TC.

Correlation and Multinomial Regression

The correlation results between demographic, clinical characteristic evaluations, laboratory results of the study patients, and TC as reported by the histopathology were all not significant except for ultrasound features including solitary nodule ($p<0.05$), lymph node involvement, and consistency ($p<0.01$ for both). On the other hand, the microcalcification correlation to TC was close to significance ($p=0.064$). As for thyroid function and serum thyroglobulin, both were not correlated to TC.

The correlation between FNAC and histopathology results was significant (r= 0.71, $p<0.001$) (Table 4). To determine the sensitivity and specificity of FNAC results, we combined the neoplasms and cancer, which revealed 77.8% and 86.3% for sensitivity and specificity, respectively, and positive predictive and negative predictive values of 75% 88%, respectively.

The FNAC THY classification was highly correlated with histopathology results (r=0.984, $P<0.001$) (Fig. 1). However, through FNAC, ~10% of the considered "benign colloid thyroid" or (THY2) cases were actually positive for papillary TC by histopathology.

Furthermore, the misdiagnosed cases (TC and neoplasms) by FNAC were classified by histopathology as T1N0M0 (2) (micropapillary TC), T1N1M0 (1), and T2N0M0 (1) (Table 5). As for specificity and TNM classification, 7 cases were over-read by FNAC as neoplasms, and 7 were interpreted as atypical/FLUS or HCL cases.

When the association of patients' demographic, clinical findings, laboratory, and radiology results

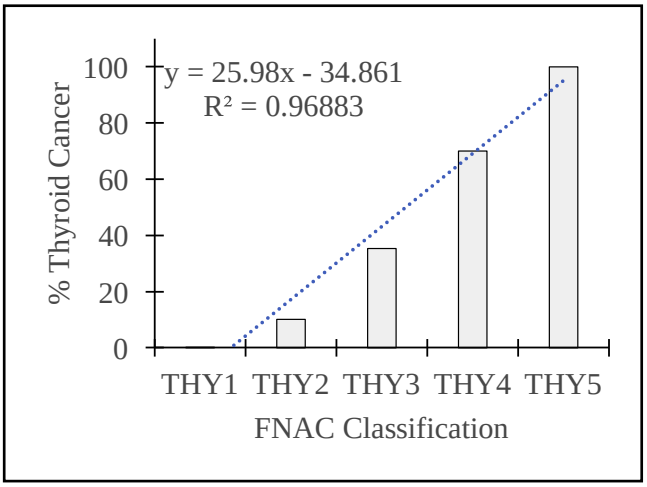

Fig. 1. Correlation of FNAC classification with % of TC

with HP findings and age as a covariate variable, solid consistency of the tumor (OR = 9.88 with 95% CI 2.26-43.30) and lymph node involvement (OR = 14.78 with 95% CI 1.19-184.2) were correlated with TC detection (Table 6). On the other hand, gender, symptoms of hypothyroidism, hyperthyroidism, or compression, family history of thyroid cancer, abnormal TFT, neck swelling, and ultrasound imaging regarding vascularization and microcalcification were not correlated with the TC detection.

DISCUSSION

In the present study, the multivariate analysis showed that the predictions of TC from demographic data, clinical assessment, laboratory, and ultrasound imaging were limited to younger age, solid composition of the nodule, and lymph nodes involvement. Gender, family history, symptoms of hypo or hyperthyroidism, microcalcification, vascularization, neck swelling, compression symptoms, and thyroid laboratory tests were not associated with TC assessment. On the contrary, a large study consisting of 59,892 TC patients conducted on the Surveillance, Epidemiology, and End Results Program database revealed that females had a significantly higher incidence of TC (Shi *et al.* 6). In the latter study, the median age of the patients was 47 years with a range of 20 - 101 years. In the current study, most patients having thyroid disease were females. However, there was no gender difference in TC patients. Secondly, the average age of TC patients was 38.1 (±10.8) years, which is significantly lower than Shi *et al.* study but higher than Yang *et al.*'s study (2007). A previous study from the same Bahrain center showed that most patients with thyroid diseases having hypo or hyperthyroidism were females (Abdulla *et al.* 2020), suggesting that benign thyroid diseases are related to hormonal imbalance and immune system dysregulations (Matalka 2003, Matalka & Ali 2005). However, the development of TC is multifactorial.

Tab. 3. Types of TC in the study group

Type of TC	Number	%
Papillary TC	23	85.2%
Follicular Cancer	2	7.4%
Medullary TC	1	3.7%
Minimally Invasive Follicular TC	1	3.7%

In the present study, the FNAC sensitivity and specificity for the detection of TC were 77.8% and 86.3%, respectively. Other centers reported ranges between 80 and 100%. These values depend on how data were analyzed (Yang *et al.* 2007; Cairncross *et al.* 2013). It has been suggested that intermediate conditions such as neoplasms should be considered malignant in calculating sensitivity and specificity (Raab *et al.* 2006, Yang *et al.* 2007). For instance, Yang *et al.* (2007) reported sensitivity and specificity values for malignancy were 94% and 98.5%, and for neoplasm were 89.3% and 74%, respectively. Since we combined cancer and neoplasm cases in the present study, the sensitivity and the positive predictive values were lower (77.8% and 75%). In our study, 3 cases (11.1%) were cytologically defined as THY1 and one case as THY2. Two of the four missed cases were defined by histopathology as micropapillary TC. For such FNAC results, a careful follow-up on evaluating clinical symptoms and more and radiograph and laboratory testing should be considered, such as molecular markers and second opinion of thyroid cytology (Eng *et al.* 2014; Singh *et al.* 2020). Since papillary TC is the most common in our region, BRAF mutation testing should be evaluated in further studies (Singh *et al.* 2020).

Several studies have studied the association of US features with malignancy. For instance, intra-nodular vascularization was more observed in benign nodules than TC ones (Moon *et al.* 2010). Furthermore, Li *et al.* (2019) showed that the diagnostic value of FNAC and US increased when the size of the tumor was equal to or less than 1 cm. In this study, US measurement size of 2 cm or less was associated with TC ($p<0.05$), and the multivariate analysis showed high OR (4.326) but close to significance. As for thyroid microcalcification, it is generally considered to be impossible to make a differential diagnosis for thyroid nodules by detecting calcifications alone. However, different features of microcalcifications, such as punctate on the US, can differentiate between benign and malignant TC (Kobayashi *et al.* 2018). In our study, 50% of the patients with microcalcification showed TC by histopathology ($p>0.05$). These findings bring to point out the sample size limitation of the present study. Furthermore, using a retrospective study design increases the limitations regarding proper assessment of risk factors associated

Tab. 4. Correlation between FNAC and histopathology results

		HP Results		Total
		Benign	TC	
Features of FNAC	Benign	37	4	41
	Atypical/FLUS/HCL*	7	2	9
	Neoplasm	7	6	13
	Cancer	0	15	15
Total		51	27	78

* FLUS: follicular lesion of indeterminate; HCL: hurthle cell lesion

Tab. 5. Correlation between FNAC and TNM classification

TNM	FNAC				Total
	Cancer	Neoplasm	Atypical/FLUS/HCL	Benign	
T4N0M0	0	1	0	0	1
T3N1M0	1	1	0	0	2
T3N0M0	2	0	0	0	2
T2N1M0	1	0	0	0	1
T2N0M0	2	2	1	1	6
T1N1M1	0	1	0	0	1
T1N1M0	3	0	0	1	4
T1N0M0	6	1	1	2	10
Benign	0	7	7	37	51
	15	13	9	41	78

Tab. 6. Multinomial regression of clinical and laboratory findings with the detection of thyroid cancer and age as a covariate variable

Variable	OR	95% CI		*P* value*
		Lower Bound	Upper Bound	
Age (Covariate Variable)	0.94	0.89	0.99	<0.05
Gender (F)	0.31	0.05	1.94	n.s.
Family History	2.36	0.23	23.86	n.s.
Symptoms of Hypothyroidism	3.23	0.57	18.22	n.s.
Symptoms of hyperthyroidism	4.46	0.31	63.71	n.s.
Symptoms of Compression	0.62	0.17	2.25	n.s.
Neck Swelling	0.79	0.04	14.89	n.s.
Ultrasound Features (Solitary vs Goiter)	1.65	0.42	6.42	n.s.
Size (2 cm or less vs. higher)	4.24	0.92	19.56	0.064
Consistency (solid)	9.88	2.26	43.30	<0.01
Microcalcification	2.43	0.57	10.33	n.s.
Vascularization	0.72	0.19	2.74	n.s.
Lymph nodes Involvement	14.78	1.19	184.20	<0.05
TFT (High)	0.53	0.069	3.99	n.s.
TFT (Low)	0.097	0.002	3.89	n.s.

*n.s.: not significant

with TC. However, large population-based studies should be conducted to determine the most relevant risk factors for TC in the Gulf region.

In conclusion, preoperative nodule and FNAC assessments need further research and development to approach higher sensitivity in detecting TC. In addition, since papillary TC is a predominant type of cancer, molecular mutations should be evaluated.

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DISCLOSURE STATEMENT

Nothing to disclose.

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DECLARATIONS OF INTEREST

The authors declare no conflict of interest related to the publication.

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