

Original Research Article

Preoperative significance of thyroglobulin, thyroid stimulating hormone and thyroglobulin antibody in differentiated papillary thyroid carcinoma

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ABSTRACT

Background: The objective of the study was to compare the levels of preoperative thyroglobulin (TG), thyroid stimulating hormone level (TSH), FT3, FT4 and TG Ab among 50 malignant and 50 benign thyroid swellings. Papillary thyroid cancer (PTC) is the most common malignancy in thyroid gland. TG antibodies (Ab) occur in around 20% of patients with papillary thyroid cancer (PTC), and the presence of TG Ab complicates the follow-up of these patients because TG-Ab interferes with the assay of serum TG7.

Methods: A prospective and retrospective study conducted on 100 patients with thyroid nodule diagnosed by neck ultrasound and confirmed by histopathological evaluation in Faculty of Medicine, Menoufia University Hospital, Egypt, during January 2017 to July 2019. History taking, levels of TG, TSH free T3, free T4 and TG Ab, neck ultrasound or CT and pathological evaluation were done.

Results: There were statistically significant differences between malignant and benign thyroid swellings regarding, TG level, TSH and T4 level. Also, there was statistically significant difference between the level of TG and tumor recurrence ($p=0.01$). While, there was no statistical significance between focality, staging, lymph node status, capsular invasion, lymphovascular embolization, and evidence of hashimoto thyroiditis and the level of TG.

Conclusions: Preoperative serum TG concentration is a useful marker for predicting the presence of initial distant metastasis of PTC and tumor recurrence. TSH level considered an important prognostic factor for papillary thyroid cancer patients.

Keywords: Papillary thyroid carcinoma, Recurrence, Thyroglobulin, TSH

INTRODUCTION

Papillary thyroid cancer (PTC) is the most common malignancy of endocrine system and accounts for over 85% of all malignant thyroid tumors. The incidence is increasing owing to various reasons as increased use of imaging methods and early detection of micro carcinomas.¹

The prognosis of papillary thyroid cancer is good while a small ratio of patients might have recurrent disease and a minority dies from thyroid cancer.²

Patients with PTC generally have a very good prognosis, with 10-year overall mortality of less than 4%. However, persistent or recurrent disease, which is mainly loco-regional, occurs in approximately 20% of patients, thus

accurate risk stratification is important to determine those patients who need aggressive therapy.³ Because PTC can recur at any time for years after initial treatment, long-term follow-up is necessary and should be guided by an approach with a high negative predictive value to exclude patients with a non-significant risk of recurrence.⁴

Serum thyroglobulin (TG) levels is one of the most important modalities used to monitor patients for residual or recurrent disease. Tg has high sensitivity and specificity in detecting thyroid cancer, especially after total thyroidectomy and remnant ablation, with the highest sensitivity noted after thyroid hormone withdrawal or stimulation with recombinant human TSH.⁵

Higher TSH values even normal ranges were reported to be associated with a higher risk of thyroid cancer and more advanced disease. However, the role of TSH in the development and the progression of thyroid cancer is not clear yet. More evidence is required to display the possible effect of serum TSH as a risk factor for thyroid cancer.⁶ Because thyrotrophic is a well-known stimulant of thyroid cells, TSH suppression is recommended after thyroidectomy. This approach was shown to reduce recurrence and increase disease specific survival. In many various studies serum TSH was presented as an independent predictor for the diagnosis of thyroid cancer.⁵

TG antibodies occur in around 20% of patients with PTC, and the presence of TG Ab complicates the follow-up of these patients because TG Ab interfere with the assay of serum TG.⁷

The objective of the study was to compare the levels of preoperative TG, TSH, FT3, FT4 and TG Ab among 50 malignant and 50 benign thyroid swellings.

METHODS

A prospective and retrospective study carried out on 100 patients with thyroid nodule diagnosed by neck ultrasound and confirmed by histopathological evaluation. All patients attended to General Surgery Department, Clinical Pathology Department, Pathology Department and followed up in Clinical Oncology Department, Faculty of medicine Menoufia university during January 2017 to June 2019.

Patients were divided into two groups: Group A (patient group) included 50 patients diagnosed as papillary thyroid cancer. Group B (control group) included 50 patients diagnosed as benign thyroid swelling.

Ethical consideration

The study was approved by the ethical committee of Menoufia Faculty of Medicine and an informed consent

obtained from all subjects before the study was commenced.

Inclusion criteria

All patients with pathological evidence of PTC and cervical lymph nodes metastasis were included.

Exclusion criteria

Other types of thyroid cancer and distant metastasis were excluded.

For retrospective archived cases, all clinical and histopathological data were retrieved from the patients' medical records.

All patients in the study were subjected preoperatively to history taking regarding: name, age, family history, residence, radiation exposure.

Laboratory investigations were done on all patients for evaluation of the levels of TG, TSH free T3, free T4 and TG Ab. Radiology that included neck ultrasound or CT was done.

Pathological evaluation was done which includes fine needle aspiration cytology from thyroid nodules or suspicious LN, true cut biopsy or excisional LN biopsy.

Total thyroidectomy and central neck dissection for group (A) with bilateral or unilateral modified neck dissection and total thyroidectomy only for group (B) was done.

Pathological evaluation of the specimen for assessment of primary tumor size, bilateralism, the number of tumor foci, cervical lymph node status, extrathyroidal extension, capsular, vascular invasion, and histological variants as well as staging according to TNM classification. After surgery the patients followed up by thyroglobulin and TSH.

Statistical analysis

Results were tabulated and statistically analyzed by using a personal computer using Microsoft excel 2016 and SPSS v. 21 (SPSS Inc., Chicago, IL, USA. Statistical analysis was done using: Descriptive: e.g. percentage (%), mean and standard deviation. Analytical: that includes: Mann-Whitney U, one-way ANOVA, Kruskal Wallis H, Chi-squared (χ^2), McNemar test and Pearson correlation. A value of p less than 0.05 was considered statistically significant.

RESULTS

In the current study, there was no statistically significant difference between benign and malignant cases regarding free T3 level and TG Ab level. While, there was

statistically significant difference between malignant and benign patients regarding free T4 ($p=0.02$), TSH ($p=0.05$) and TG ($p=0.005$) (Table 1).

Also, there was statistically significant difference between malignant and benign patients regarding capsular invasion, lymphovascular embolization and recurrence. While, there was no statistically significant difference between malignant and benign patients

regarding focality, lymph node status and side of dissected lymph nodes (Table 2).

Results in the present study revealed that there was statistically significant positive correlation between the number of affected LNs and level of TSH ($p=0.01$), (Figure 1). While, TSH level was not correlation between with age, tumor size among malignant group and serum, (Table 3).

Table 1: Correlation between T3, T4, TSH, TG and TG Ab and the studied groups.

	Studied groups		U test	P value
	Malignant (n=50)	Benign (n=50)		
T3				
Mean \pm SD	2.23 \pm 1.05	2.36 \pm 1.26	0.52	0.60
Range	0.53-4.92	0.77-6.22		
T4				
Mean \pm SD	3.88 \pm 3.71	2.58 \pm 1.39	2.29	0.02
Range	1.1-23.84	0.87-6.2		
TSH				
Mean \pm SD	2.65 \pm 1.70	1.96 \pm 1.20	1.95	0.05
Range	0.01-6.3	0.77-0.6		
TG				
Mean \pm SD	63.99 \pm 110.32	24.18 \pm 62.86	2.82	0.005
Range	0.2-500	0.02-300		
TG Ab				
Mean \pm SD	71.76 \pm 121.18	47.72 \pm 113.55	1.78	0.08
Range	0.63-500	0.89-500		

SD=stander deviation; U=Mann Whitney U test.

Table 2: Pathological criteria of thyroid swelling among both studied groups.

	Studied groups				Test	P value
	Malignant n=50		Benign n=50			
Size of largest focus						
Mean \pm SD	2.97 \pm 1.77		2.36 \pm 0.91		U test 1.06	0.29
Range	0.5-8		0.7-5.1			
	N	%	N	%	χ^2	
Focality						
Unifocal	25	50.0	40	80.0	9.89	0.002 S
Multifocal	25	50.0	10	20.0		
Lymph node status						
Positive	41	82.0	0	0.0	69.5	<0.001
Negative	9	18.0	50	100		
Side of dissected nodule						
Unilateral	13	26.0	0	0.0	100	<0.001
Bilateral	37	74.0	0	0.0		
No	0	0.0	50	100		
Capsular invasion						
Positive	13	26.0	0	0.0	14.9	<0.001
Negative	37	74.0	50	100		
Lymphovascular embolization						
Positive	11	22.0	0	0.0	12.36	<0.001
Negative	39	78.0	50	100		
Recurrence						
Positive	6	12.0	0	0	Fisher's 6.88	0.03
Negative	44	88.0	50	100		

Continued.

	Malignant=50		Benign n=50		X ²	P value
	No	%	No	%		
Duration of recurrence						
Mean ±SD	11.33±12.42					
Range	4-36					
Evidence of Hashimoto thyroiditis						
Positive	4	8	1	2.0	Fisher's 1.89	0.36
Negative	46	92	49	98.0		
Number of affected lymph nodes						
Mean ±SD	8.3±6.3					
Range	1-25					
T stage						
Stage 1a	9	18.0				
Stage 1b	13	26.0				
Stage 2	17	34.0				
Stage 3a	11	22.0				
T stage						
Stage 1&2	39	78.0				
Stage 3	11	22.0				

SD: standard deviation, U=Mann Whitney U test, X² = Chi square test, Fisher's= Fisher's Exact test.

Table 3: Correlation between age, tumor size, number of affected lymph nodes among malignant group and serum TSH level.

	TSH	
	r	P value
Age	0.05	0.72
Tumor size	-0.07	0.61
Number of affected LNs	0.38	0.01

TSH: thyroid-stimulating hormone; r=correlation coefficient.

Table 4: Correlation between tumor characters among malignant group and TSH level.

	TSH		U test	P value
	Mean±SD	Range		
Sex				
Male	2.59±1.77	0.01-6	0.29	0.77
Female	2.68±1.68	0.05-60		
Focality				
Unifocal	2.01±1.32	3.76±5.86	2.41	0.02
Multifocal	0.01-6.0	0.06-36		
T stage				
Stage 1a	2.95±1.86	0.05-6.3	K	
Stage 1b	2.57±1.51	0.33-5.5		
Stage 2	2.73±1.99	0.05-6	0.32	0.57
Stage 3a	2.36±1.46	0.01-4.6		
T stage				
Stage 1&2	2.42±1.76	0.01-6.3	2.18	0.03
Stage 3	3.45±1.22	1.35-4.86		
Lymph node status				
Positive	2.98±1.67	0.01-4.6	2.99	0.003
Negative	1.14±0.72	0.05-2.31		
Capsular invasion				
Positive	4.41±1.42	1.77- 6.3	4.10	<0.001
Negative	2.02±1.31	0.01-4.6		
Lymphovascular embolization				
Positive	2.62±1.69	0.05-6	0.07	0.94
Negative	2.65±1.72	0.01-6.3		

Continued.

	TSH		U test	P value
	Mean±SD	Range		
Recurrence				
Positive	1.37±1.45	2.81±1.67	2.06	0.04
Negative	0.01-3.2	0.05-6.3		
Evidence of Hashimoto thyroiditis				
Positive	4.33±1.82	1.77-6	2.01	0.045
Negative	2.46±1.60	0.01-6.3		

U=Mann Whitney U test K=Kruskal Wallis test.

Table 5: Correlation between tumor characters and TG level.

	TG		U test	P value
	Mean±SD	Range		
Sex				
Male	51.50±96.80	0.01 -350	0.16	0.88
Female	40.09±89.10	0.2-500		
Focality				
Unifocal	35.89±72.87	0.02 -300	0.23	0.81
Multifocal	59.30±118.48	0.2-500		
T stage				
Stage 1a	63.32±100.45	0.22-270	3.35	0.34
Stage 1b	129.71±170.95	0.2-500		
Stage 2	39.76±53.19	0.2-200		
Stage 3a	24.31±60.23	0.2-200		
T stage				
Stage 1&2	71.62±117.0	0.2-500	1.35	0.18
Stage 3	36.96±81.19	0.2-270		
Lymph node status				
Positive	70.81±117.33	0.2-500	0.63	0.53
Negative	32.91±66.31	0.22-200		
Capsular invasion				
Positive	66.67±142.62	0.74-500	0.39	0.70
Negative	63.05±63.05	0.20-350		
Lymphovascular embolization				
Positive	89.46±162.43	0.33-500	0.66	0.51
Negative	56.81±92.25	0.20-350		
Recurrence				
Positive	183.86±183.86	2.88-500	2.48	0.01
Negative	47.64 ±87.52	0.2-350		
Evidence of Hashimoto thyroiditis				
Positive	45.89±80.29	0.2-200	0.19	0.86
Negative	43.97±92.60	0.02-500		

U=Mann Whitney U test K=Kruskal Wallis test.

Table 6: Correlation between tumor characters and TG Ab level.

	TG Ab		Test	P value
	Mean±SD	Range		
Sex				
Male	27.60±32.10	0.63-121.2	1.26	0.21
Female	98.83±146.20	0.83-500		
Focality				
Unifocal	97.93±150.23	1.04-500	1.94	0.05
Multifocal	45.54±77.33	0.63-300		

Continued.

	TG Ab		Test	P value
	Mean±SD	Range		
T stage				
Stage 1a	45.85±99.58	0.63-305.5	K 4.62	0.20
Stage 1b	99.0±150.55	1.7-500		
Stage 2	44.30±73.87	0.72-250		
Stage 3a	103.21±155.41	1.32-500		
T stage				
Stage 1&2	64.06±112.51	0.63-500	1.45	0.15
Stage 3	99.06±150.99	1.06-500		
Lymph node status				
Positive	64.48±107.0	0.72-500	0.28	0.78
Negative	104.95±176.59	0.63-500		
Capsular invasion				
Positive	69.11±81.22	0.83-250	0.96	0.33
Negative	72.69±133.69	0.63-500		
Lymphovascular embolization				
Positive	76.35±145.54	0.83-500	0.05	0.96
Negative	70.47±115.55	0.63-500		
Recurrence				
Positive	14.13±18.35	79.62±127.15	1.64	0.10
Negative	1.33-49.2	0.63-500		
Evidence of Hashimoto thyroiditis				
Positive	34.63±48.83	1.96-121.2	0.32	0.75
Negative	75.89±126.34	0.63-500		

U=Mann Whitney U test K=Kruskal Wallis test.

Table 7: Correlation between tumor characters among malignant group and FT4 level.

	T4		U test	P value
	Mean±SD	Range		
Sex				
Male	3.69±2.43	1.23-10.1	1.63	0.10
Female	4.0±4.35	1.1-23.84		
Focality				
Unifocal	2.91±1.54	3.82±4.35	0.09	0.93
Multifocal	0.87-7.8	0.99-23.84		
T stage				
Stage 1a	2.91±2.14	1.1-7.8	K 2.96	0.40
Stage 1b	4.95±5.95	1.8-23.84		
Stage 2	4.5 ±3.22	1.1-12.31		
Stage 3a	2.70±0.83	1.44-4.7		
T stage				
Stage 1&2	4.25±4.11	1.1-23.84	1.17	0.24
Stage 3	2.59±1.10	1.1-4.9		
Lymph node status				
Positive	4.16±4.03	1.1-23.84	0.66	0.51
Negative	2.66±1.05	1.26-4.6		
Capsular invasion				
Positive	3.02±1.38	1.77-6.22	0.47	0.64
Negative	4.19±4.22	1.10-23.84		
Lymphovascular embolization				
Positive	2.18±1.77	1.1-6.22	1.38	0.17
Negative	4.19±4.07	1.10-23.84		

Continued.

	T4		U test	P value
	Mean±SD	Range		
Recurrence				
Positive	1.94±0.73	4.15±3.88	2.56	0.02
Negative	1.1-3.05	1.1-23.84		
Evidence of Hashimoto thyroiditis				
Positive	3.40±0.88	2.34-4.53	0.83	0.41
Negative	3.94±3.91	1.10-23.84		

U=Mann Whitney U test K=Kruskal Wallis test

Additionally, the level of TSH was no statistically significant correlation with sex, and Lymph vascular embolization. Whereas, the level of TSH was statistically significant correlation with focality, TNM staging, lymph node status, capsular invasion, recurrence and evidence of Hashimoto thyroiditis (Table 4).

Furthermore, our results showed that there was no statistically significant relation between level of TG with focality, staging, lymph node status, capsular invasion, Lymph vascular embolization, and Evidence of Hashimoto thyroiditis. On the other hand, a statistically significant relation was observed between the level of TG and tumor recurrence ($p=0.01$), (Table 5).

Moreover, our results showed that there was statistically significant relation between focality and the level of TG. AB (Table 6). Also, no-statically significant correlation was observed between tumor characters among malignant group and FT4 level (Table 7).

DISCUSSION

Differentiated papillary thyroid cancer (DPTC) accounts for 0.5-1.5% of all malignancy.⁸ DPTC derived from thyrocytes. DPTC represents the majority (90%) of all types of thyroid cancer.⁹ Clinical presentation of DPTC, symptoms of recurrent laryngeal nerve involvement as dysphagia, odynophagia, hoarseness, or aspiration of liquids and tracheal invasion symptoms as cough, dyspnea, hemoptysis, and stridor.¹⁰

The present study was conducted to compare the levels of preoperative TG, TSH, FT3, FT4 and TG Ab among 50 malignant and 50 benign thyroid swellings. In this study there was no statistically significant difference between malignant and benign patients regarding age, sex, residence and family history. While, statistically significant difference was recorded between malignant and benign patients regarding free TSH ($p=0.05$). Similar results confirmed by El gammal et al, there were no significant relation between nodular size with age and sex.¹¹ Also, Fiore et al who reported significantly higher serum TSH in patients with PTC compared to patients with benign disease.¹⁰

Also, in the study by Zafon et al patients with benign lesions had the lowest, PTMC (n=36) had intermediate

and DTC had the highest levels of TSH.¹² However, the differences in TSH were only significant between benign and thyroid cancer of larger size groups and this was partly explained by small number of cancers cases.¹³

In contrary to these findings, Kim et al and Castro et al did not find a significant relation between serum TSH and thyroid malignancy.¹³ In our study we demonstrated that high preoperative TSH levels were significantly correlated with extrathyroidal extension, lateral lymph node metastasis. Similar to the previous studies that reported the relationship between high TSH level and extrathyroidal extension. Fiore et al showed that TSH values in patients with neck lymph nodes metastasis were significantly higher than those without neck lymph nodes metastasis.¹⁰ All these findings suggest a role of TSH on thyroid cancer promotion and aggressiveness.

Additionally, our study demonstrated that higher level of TSH was related to recurrence of the tumor and one of the prognostic factors. In the study by Rageh et al capsular invasions are another factor that affect recurrence which is a strong predictor factor for recurrence that was noticed in multifocal PTC.¹⁴ A study by Cady et al showing that the degree of infiltration and recurrence was a powerful prognostic factor and related to the levels of TSH.¹⁵ This result come in line with our results.

Also, the current study indicated that there was statistically significant difference between malignant and benign patients regarding TG levels ($p=0.005$). Previous studies have used preoperative serum TG for differential diagnosis of DPTC. Petric et al, differentiated between papillary adenoma and carcinoma, and between follicular carcinoma and Hurtle cell carcinoma using preoperative serum TG.¹⁶ While, another study Haymart et al found that preoperative serum TG concentrations are not useful for differential diagnosis of DPTC. The reason for this may be many factors that affect preoperative serum TG concentration.^{17,18}

Also, this study demonstrated that preoperative serum TG concentration well predicted initial distant metastasis in DPTC patients also proposed a specific TG cutoff value of 63.4 ng/ml as an optimal threshold with the greatest accuracy for practical use in clinics.^{19,20} In the study done by Oltmann et al showed that preoperative serum TG concentration was significantly higher with initial distant

metastasis. However, a cutoff for serum TG was not presented.²¹

In our study, there was statistically significant difference between malignant and benign thyroid patients regarding level of FT4 ($p=0.02$). A study by Choi et al, the odds ratio (OR) calculated in patients with thyroid nodules of all sizes supports the initial hypothesis that patients without thyroid malignancy are less likely to have higher levels of FT4.²²

However, this was not in agreement with Jonklaas et al who found no significant relationship between these variables.^{22,23} This relationship can be explained simply as Jonklaas only considered patients to have high FT4 when it was greater than 23.2 pmol/L (1.80 ng/dL). Furthermore, the low OR in both case groups when compared to the controls is evidence suggesting that low T4 indicates a lower chance of thyroid malignancy.

The line created by the logistic regression is further evidence of a relationship between probability of cancer and serological level of FT4.²⁴ In fact, using the regressed line gives a cut-off value which could prove to be a margin of safety in future studies.

Results of the present study demonstrated that high preoperative TG. AB levels were not significant between malignant and benign thyroid swellings regarding socio-demographic criteria and pathological criteria. Also, there was statistically significant relation between preoperative TG. AB levels with focality of the tumor in DPTC. Kim et al was the first to report that a positive Tg. Ab test was an independent predictor of thyroid nodules malignancy.¹³

Also, in this study, we found that high preoperative FT3 levels were not significant regarding socio-demographic criteria and pathological criteria. Choi et al found no significant relationship between these variables, or with Rinaldi et al found non-significantly observed high FT3 to be indicative of cancer risk.^{22,24} Also, Jonklaas et al no significant relationship between low FT3 and malignancy was identified in this study.²³ Other study correlate level of free T3 with papillary thyroid cancer. These studies observe size of nodules in cases of malignancy and attempts to determine FT3 change with thyroid nodule size.¹⁸

CONCLUSION

Although high preoperative TSH level is considered an important prognostic factor for differentiated thyroid cancer patients, increased preoperative TSH levels may be also correlated with advanced cancer stages and its high-risk features including extrathyroidal extension, lateral lymph node metastases and recurrence in population. As a result, TSH could be considered as a supplementary marker when determining the scope of required treatment before operation. Also, Preoperative

serum TG concentration is a useful marker for predicting the presence of initial distant metastasis of PTC.

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