

THYROID FUNCTION IN THYROID CARCINOMA: A 5-YEAR RETROSPECTIVE ANALYSIS

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ABSTRACT

Background: Several studies investigated the behavior of thyroid stimulating hormone (TSH) among patients with documented thyroid carcinoma. Elevations of TSH are commonly seen and only a fraction of thyroid carcinomas present with low TSH levels.

Objective: To describe the thyroid function in thyroid carcinomas.

Setting: St. Lukes's Medical Center, Quezon City Philippines (Tertiary Institution)

Design: Retrospective study

Patients and Methods: Charts of medical records of patients diagnosed with primary thyroid carcinoma on routine biopsy, fine needle aspiration biopsy or frozen section from 2002 to 2006 were reviewed. Pertinent data such as the sex, age in years, provincial location; pertinent medical history such as previous history of head and neck radiation, family history of thyroid cancer, family history of multiple endocrine neoplasia (MEN-II); history of dysphonia/dysphagia; physical exam findings; pre-operative TSH and its interpretation; ultrasonographic assessment; official tissue biopsy results; TNM staging and overall tumor stage; and extent of surgery done. Comparison of categorical variables was done using Fisher Exact test and Kruskal Wallis ANOVA for mean TSH values across histologic types. All comparisons with p-values <.05 were considered significant.

Results: A total of 400 patients were analyzed. There was slight female predominance, with a mean age of 44 years (range 14-86), residing mostly in Metro Manila, with a family history of MEN-II in 14% and medullary carcinoma in 2%. Papillary carcinoma and follicular CA were the most common histologic types. Most underwent total thyroidectomy with neck

lymph node dissection in 63%. Mean TSH values did not statistically differ across the histologic types of cancer (p=.91). Majority (78%) had normal TSH (0.4-4.65 mIU/L) despite tumor size (p=.039) and nodal involvement (p=.035). Values of TSH did not statistically vary with metastasis and overall staging (p=.24, p=.63 respectively).

Conclusion: Normal TSH levels were commonly seen in this sample of thyroid carcinomas. TSH determination in thyroid carcinoma guide clinicians regarding suppressive thyroid hormone therapy.

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Keywords: Primary thyroid carcinoma, thyroid stimulating hormone, fine needle aspiration biopsy

INTRODUCTION

The increasing incidence of thyroid carcinoma in the Philippines warrants the need for institutions to provide the public a data base of its demographic and clinical profile, methods of diagnosis and current trends in therapy. This study focuses on the thyroid function profile of patients with histopathologically confirmed thyroid carcinoma.

Several reports have documented that well differentiated carcinoma of the thyroid expresses TSH receptors.^{1,2} Several reports show that recently discovered oncogenes and other growth factors contribute to thyroid carcinogenesis and its ultimate growth^{3,4} and there is standing point to say that TSH receptor stimulation is indeed a cancer stimuli. This postulate receives support from two published studies that demonstrated good survival in thyroid cancer patients who received suppressive doses of levothyroxine⁵ and by cases of tumor growth post T4 withdrawal or recombinant TSH.⁶ In one study by Haymart *et.al*, the risk of malignancy at TSH levels less than .06mIU/L was 16% when compared to 52% if the concentration was above 5.0mIU/L.⁷

We cannot locate similar studies in the local setting, experimental and analytical alike, dealing with TSH and its role or profile among patients with confirmed differentiated carcinoma of the thyroid.

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RATIONALE

This study was undertaken to describe the clinical as well as biochemical profile of thyroid malignancy. Because several researches continue to push the hypothesis of TSH suppression as a factor for improving overall survival, it is prudent that we present our data base derived from the past 5 years. Consequently, this study will also indirectly provide information concerning the need for TSH suppression for the overall improvement of this subset of patients.

Research Question

What is the predominant thyroid function profile of patients with thyroid carcinoma in a retrospective analysis?

General Objective

To describe the thyroid function of patients with thyroid carcinoma.

Specific Objectives

1. To describe the clinical profile of patients with thyroid carcinoma according to demographics, diagnostic imaging results, histopathologic assessment and extent of surgery done.
2. To describe the thyroid function status across histopathologic subtypes of thyroid carcinoma.
3. To compare the TSH levels across tumor size and stage.

Scope and Limitations of the Study

This is a five-year retrospective analysis of medical records of patients with a diagnosis of thyroid carcinoma. Due to the absence of guidelines that dictate such, free serum T3 and T4 as well as thyroglobulin are not routinely requested preoperatively and therefore are not included in this final analysis. Lastly, data on mortality is not further investigated in this study.

MATERIALS AND METHODS

We identified all patients who underwent biopsy (either fine needle aspiration biopsy, frozen section or routine tissue biopsy) and at least a thyroid stimulating hormone (TSH) assay from years 2002

to 2006, at the St. Luke's Medical Center, Quezon City Philippines.

Inclusion criteria included 1) complete medical records for data abstraction; 2) official histopathology reports; 3) official thyroid function work-up done in this institution. We excluded those with previously documented hyperthyroid states (e.g. Grave's disease) who subsequently underwent radioactive therapy; documented primary hypothyroidism under thyroid hormone replacement therapy; and those patients whose diagnostic work-up were thoroughly performed outside of St. Luke's Medical Center.

Data Abstraction

From each patient, we collected the following information. Pertinent socio-demographic data such as the sex, age in years, provincial location; pertinent medical history such as previous history of head and neck radiation, family history of thyroid cancer, family history of multiple endocrine neoplasia (MEN-II); history of dysphonia/dysphagia; physical exam findings of a growing nodule, firm consistency, cervical adenopathy, fixed nodule; pre-operative TSH and its interpretation; ultrasonographic assessment; FNAB and routine tissue biopsy results; TNM staging and overall tumor stage; and extent of surgery done.

All data were collected using a standard data collection form.

Statistical Analysis

All data were analyzed using STATA intercooled version 7. Continuous data were summarized as mean and standard deviation while categorical data were summarized as percentage frequency distribution. Comparison of categorical factors was carried out using Fisher exact test. Kruskal Wallis ANOVA was used to compare mean TSH across histologic types. All tests of significance were carried out at .05 alpha level of significance and 95% confidence limits precision.

RESULTS

A total of 1,726 medical records of patients from 2002 to 2006 were identified. Only 400 patients (23.2%) had complete histopathology for analysis. Their clinical and demographic data are summarized at tables I and II. (See below).

The youngest patient was a 14 year old female diagnosed with papillary carcinoma, who subsequently underwent lobectomy who had high pre-operative TSH level, while the oldest was an 86-year old female with normal TSH with papillary carcinoma. The mean age was 44 years old, with female predominance (85% vs 15%, female to male ratio of 6:1); with half coming from Metro Manila.

Table I. Demographic and Clinical Profile of Patients with Thyroid Carcinoma, St. Luke's Medical Center, 2002-2006

Characteristic	Frequency (n=400)	Percentage (%)
Age (Years)		
Mean \pm SD	44 \pm 14	-
Range	14-86	
Sex		
Male	61	15
Female	339	85
Location		
Metro Manila	200	50
North Luzon	86	21.5
South Luzon	73	18.3
Visayas	30	7.5
Mindanao	11	2.8
Family Medical History		
Medullary carcinoma	6	1.5
MEN-II	6	1.5
Physical Exam Findings		
Growing nodule	207	52
Cervical adenopathy	358	89
Fixed nodule	66	17
Dysphonia/or dysphagia	153	38
Defined margins	6	2
Ultrasonography		
Solitary	46	11.5
Multiple	90	22.5
No nodule	9	2.3
No data	255	63.8

TSH Levels and Histopathology

A total of 188 subjects had a single TSH determination. Among these, 146 subjects (78%) were normal (within 0.4 to 4.65) while 38 (20%) had low hormone levels (below <0.4) and only four (2%) were high (above 4.65). The range of TSH was from 0 to 5.4 (mean=1.1 mIU/L). (Table II)

Papillary carcinoma was the most common histologic type accounting for 66%, followed by follicular carcinoma (14%); micropapillary carcinoma (11.8%); Hurthle cell (3.8%); medullary carcinoma (1.5%) and the anaplastic type (0.8%).

Table II. TSH Assay and Histopathology of Thyroid Carcinoma, St. Luke's Medical Center, 2002-2006

Assessment	Frequency (n=400)	Percentage (%)
TSH Levels* (mIU/L)		
High (> 4.65)	4	2
Normal (0.4-4.65)	146	78
Low (<0.4)	38	20
None	212	-
Mean TSH Levels (mIU/L)		
Mean \pm SD	1.1 \pm 0.96	-
Range	0 - 5.4	
Routine Biopsy		
Papillary CA	267	66.0
Follicular CA	59	14.0
Micropapillary CA	47	11.8
Hurthle cell CA	18	3.8
Medullary CA	6	1.5
Anaplastic	3	.8

*Reference range- (0.4 -4.65 mIU/L)

TNM Staging in Thyroid Malignancy

In 174 patients (43.5%) tumor size ranged from 2 to 4 cm. 37.8% had masses less than 2cms while in 56 patients (4.8%), the tumors were more than 4cms. (See table III)

Majority had no lymph node involvement (188 or 47%). Forty (10%) had central node involvement and another 10% had lateral node involvement. Thirty one patients (9%) had metastasis. Most patients had stage I cancer (33.8%), while in 42.3% staging could not be done.

Table III. TNM Staging in Thyroid Carcinoma, St. Luke's Medical Center, 2002-2006

Staging	Frequency (n=400)	Percentage (%)
Tumor		
< 2 cm	151	37.8
2-4 cm	174	43.5
> 4 cm	56	14.0
Local extension	19	4.8
Nodal Status		
Negative	188	47.0
Central	40	10.0
Lateral	40	10.0
No data	132	33.0
Metastasis		
Negative	196	49
Positive	31	9
No data	169	42
Overall Stage		
Cannot be staged	169	42.3
Stage 1	135	33.8
Stage 2	42	10.5
Stage 3	18	4.5
Stage 4	36	9.0

Extent of Surgery

Majority had total thyroidectomy (80.3%), with 63 patients (16%) undergoing neck lymph node dissection.

Table IV. Extent of Surgery in Thyroid Carcinoma, St. Luke's Medical Center, 2002-2006

Treatment	Frequency (n=400)	Percentage (%)
Extent of Surgery		
Total thyroidectomy	321	80.3
Subtotal thyroidectomy	12	3.0
Lobectomy	26	6.5
Lobectomy + Isthmusectomy	41	10.3
Neck lymph node dissection		
Yes	63	16
No	337	84

Comparison of TSH Levels and Histopathologic Type of Malignancy

We found no statistically significant difference in the distribution TSH levels across histologic types of cancer. A higher proportion of patients with papillary cancer had normal TSH (34.5% vs high-1.1% vs low 8.7%), similar to those with follicular cancer (46.4% vs low-8.9%). Majority of those with Hurthle cell cancer (67% vs 33%), micropapillary carcinoma (53% vs 47%), and medullary carcinoma (33.3% vs 16.7% low) as well as the single patient with anaplastic type had normal TSH levels.

Table V. TSH Levels Across Histopathologic Types of Thyroid Carcinoma, St. Luke's Medical Center, 2002-2006

Assessment	Normal TSH n=146 (%)	High TSH n=4 (%)	Low 38= (%)	Total	p-value*
Routine Biopsy					
Papillary	91 (77.7)	3 (2.5)	23 (19.5)	117	.91 (NS)
Follicular	26 (84)	0	5 (16)	31	
Medullary	2 (33.3)	0	1 (16.7)	3	
Hurthle cell	6 (67)	0	3 (33)	9	
Anaplastic	1 (100)	0	0	1	
Micropapillary	15 (68)	1 (4.5)	6 (27.2)	22	

%-reflect horizontal sum, NS-not significant

* Significant association if p-value is < .05, by Fisher Exact Test

Comparison of Exact TSH Values

There was no statistically significant difference in the mean TSH levels across the six types of thyroid carcinoma. (p=.19). (Table VI)

Table VI. Comparison of Exact TSH Values in Thyroid Carcinoma, St. Luke's Medical Center, 2002-2006

Assessment	Serum TSH		Range	p-value*
	No. of Subjects	Mean ± SD		
Routine Biopsy				
Papillary	117	1.21 ± 1.0	0 -5.44	.19 (NS)
Follicular	31	1.16 ± 1.0	0 - 4.35	
Medullary	3	1.04 ± .04	1.01-1.08	
Hurthle cell	9	0.63 ± 0.43	0.18 - 1.45	
Anaplastic	1	2.76	-	
Micropapillary	22	0.86 ± 0.69	0 - 2.41	

*Significant difference if p-value is <.05, Kruskal Wallis ANOVA
Reference Range= 0.4 -4.65 mIU/L

TNM Staging and TSH Levels

TSH levels and tumor size statistically varied (p=.039) as well as nodal status (p=.035).

Levels of TSH did not differ significantly across staging for metastasis (p=.24) and overall surgical stage. (p=.63) (Table VII)

Table VII. TSH Levels Across TNM Staging of Thyroid Carcinoma, St. Luke's Medical Center, 2002-2006

Staging	Normal TSH n=146 (%)	High TSH n=4 (%)	Low n=38 (%)	Total	p-value*
Tumor					
< 2 cm	49 (70)	2 (3)	19 (27)	70	.039
2-4 cm	60 (79)	1 (1)	15 (20)	76	
> 4 cm	31 (92)	0	3 (8)	34	
Local extension	6 (75)	1 (12.5)	1 (12.5)	8	
Nodal Status					
Negative	66 (73)	1 (1)	24 (26)	91	.035
Central	17 (94)	1 (6)	0	18	
Lateral	17 (81)	0	4 (19)	21	
No data	46 (79)	2 (4)	10 (17)	58	
Metastasis					
Negative	75 (48)	2 (2)	78 (50)	155	.24 (NS)
Positive	12 (60)	0	8 (40)	20	
No data	59 (80)	2 (2)	13 (18)	74	
Overall Stage					
Cannot be staged	59 (80)	2 (3)	13 (17)	74	.63 (NS)
Stage 1	55 (79)	1 (1)	13 (19)	69	
Stage 2	14 (67)	0	7 (33)	21	
Stage 3	6 (75)	1 (12.5)	1 (12.5)	8	
Stage 4	12 (75)	0	4 (25)	16	

* Significant association if p-value is < .05, by Fisher Exact Test
NS-not significant, % reflect horizontal sum

DISCUSSION

This study shows convincing evidence that thyroid stimulating hormone is normal on the average, in almost all types of malignancy of the thyroid. This is in contrast with the previously cited studies (Haymart *et.al* and Boelaert *et.al.*) that claim that TSH is more often than not elevated in thyroid cancer. In our study, only four subjects (2%) demonstrated high TSH values. By cautious interpretation of TSH levels, we found only 38 patients (20%) who had levels below the lower end of the cut-off range. These patients did not demonstrate signs of hypofunctioning or hyperfunctioning thyroid. In this study, the malignancy did not co-exist with hyperthyroidism such as Grave's disease. Previous reports at the Philippine General Hospital showed two cases of concomitant Grave's disease and thyroid cancer.⁸ Although the relationship of thyroid carcinoma to Grave's disease remains unclear, the possible role of thyroid stimulating antibodies, growth factors, immunological derangements inpatients with Grave's disease, and HLA-haplotype associations in thyroid carcinogenesis are well discussed in foreign literature. We found no local reports of patients with low TSH results in malignant neoplasms of the thyroid gland.

Significant findings in this study include a statistical difference in the distribution of patients with elevated and normal TSH levels across the size of thyroid carcinomas. Despite a small size (less than 2 cm) TSH elevation was seen. Similarly, those with tumors above 4 cm and those with local extension altogether had elevated hormones. This finding has significant implications inasmuch as it is unlikely that TSH suppression reduces benign nodule size, however it may prevent the development of new nodules and decrease the rate of growth.^{9,10,11}

We found no similar study that backs up our claims of a statistical difference in the TSH levels across the nodal involvement, although this finding is equated with tumor aggressiveness.

The cut-off of TSH levels utilized in this study was between 0.4 to 4.65mIU/L, similar to that of the Haymart study. However, in the absence of a normal control (benign population), we cannot derive a predictive cut-off of TSH levels that will point to an increased likelihood of carcinoma. In previous studies, there was non significant trend in the decrease in cancer risk if TSH was below the normal range.¹¹ In one cohort analytical study, there was an increased risk of malignancy among those with solitary nodules with TSH of above 0.9mIU/L. Although there was a

trend towards increased cancer risk with rising TSH range, no significant difference existed between normal range TSH levels above 0.9mIU/L due to the small number of malignancies.¹²

It was previously believed that the low incidence of thyroid cancer among those with low TSH below the normal range was due to the autonomous functioning nodules having a lower malignancy rate or gradual thyroid failure secondary to autoimmune thyroid disease.¹³ The low cancer risk in hyperfunctioning nodules is attributed to the constitutive activating mutations of TSH receptors driving cyclic AMP pathway through G receptors and very rarely the cancer associated RAS dependent MAPK pathway.¹⁴

Our study has shown that in papillary, follicular, medullary, Hurthle cell, anaplastic and micropapillary cancer, pre-operative TSH levels were normal and thus the need for suppressive doses of levothyroxine was not advocated at this point.

Despite the previously documented association of TSH with certain forms of thyroid cancer, several reports also negate the association of increased cancer risk and elevated TSH. First, TSH receptor mutations in certain types of thyroid cancer in regions functionally associated with increased signal transduction do not commonly occur in thyroid cancer,¹⁵ secondly, in vitro studies has shown that other factors such as IGF-1 may have a role in thyroid cancer growth¹⁶ and lastly there is an inverse relationship between mRNA level and cancer aggressiveness.¹⁷

This study is not without methodologic flaws. First, the exact mean values of TSH levels were not completely collated and we rely more on the categorical interpretation of the levels. Second, the study did not include an analysis of factors influencing survival or even the likelihood of being treated with suppressive doses of thyroxine among those with elevated TSH and lastly the study did not consider other medical management which could indirectly affect TSH concentrations.

CONCLUSION

- The sample constituted 400 patients with histopathologically confirmed thyroid carcinoma, with female predominance, residing in metropolitan Manila.
- A significant family history of MEN-II (14%)

and medullary carcinoma (2%) was identified. More common presenting signs include cervical adenopathy, growing nodule and dysphonia and or dysphagia.

- Common thyroid carcinomas include papillary cancer accounting for 66%, follicular carcinoma- 14% and micropapillary carcinoma-11.8%. Most tumors were 2-4 cm in size, without nodal involvement and without metastasis.
- A greater proportion of patients (78%) with confirmed thyroid carcinoma have TSH levels were within the normal cut-off level (0.4 to 4.65mIU/mL).
- No difference in the TSH levels across the histologic types of thyroid carcinoma was identified.

RECOMMENDATIONS

In the light of these findings, we therefore advocate that the following suggestions be considered:

- A prospective cohort analysis across the lower, normal and high end range of levels of TSH be analyzed.
- The sample to include a heterogenous mix of normal and benign tumors of the thyroid as documented by FNAB, frozen section and routine biopsy.
- A study examining the likelihood of cancer patients getting TSH suppression therapy by clinicians and the factors which influences this be undertaken
- Include other thyroid function tests such as thyroglobulin, free T3 and T4 as outcome measures.

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