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Role of Serum TSH Levels in Predicting Thyroid Malignancy

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Abstract: ***In India, thyroid malignancies accounts for less than 1% of all malignancies (2% of women and 0.5% of men). Thyroid cancer is responsible for six deaths per 1 million persons annually. It is the commonest endocrine tumour that shows a geographic variation in the incidence of tumour type and natural history. Serum TSH is a well - established growth factor for thyroid nodules and suppression of TSH concentrations by administering exogenous thyroxine may interfere with growth of established nodules as well as formation of new nodules. Recent studies have found levels of serum TSH to be an independent predictor of malignancy in thyroid nodules. Present study aims at evaluating the association of Serum TSH concentration with thyroid carcinoma, and its significance in management of Thyroid carcinoma.***

Keywords: Serum TSH, Thyroid, Thyroid malignancy, Thyroid Nodule, Thyroxine

1. Introduction

Thyroid diseases have always been an conundrum. The management of thyroid diseases has undergone a tremendous change over the period, from the crude surgeries of the ancient times to the multidisciplinary approach under supervision of the modern era. However in the present scenario surgery still plays an important role especially in the management of thyroid malignancies.

In India, thyroid malignancies accounts for less than 1% of all malignancies (2% of women and 0.5% of men). Thyroid cancer is responsible for six deaths per 1 million persons annually. It is the commonest endocrine tumour that shows a geographic variation in the incidence of tumour type and natural history.

Almost all benign thyroid tumours arise from glandular epithelium and are termed adenomas. It is also noted that women are about 5 times more commonly affected than men. Thyroid carcinoma is rare in children and increases in frequency with increasing age.

Serum TSH is a well - established growth factor for thyroid nodules and suppression of TSH concentrations by administering exogenous thyroxine may interfere with growth of established nodules as well as formation of new nodules. Recent studies have found levels of serum TSH to be an independent predictor of malignancy in thyroid nodules [13, 14, 19]. Present study aims at evaluating the association of Serum TSH concentration with thyroid carcinoma, and its significance in management of Thyroid carcinoma.

2. Review of Literature

Management of Well Differentiated Carcinoma

Surgery plays as the mainstay role in managing WDC. However, the debate still revolves around the extent of thyroid tissue that should be removed during the initial operation.

Surgeries for WDC:

1) Total thyroidectomy – involves removal of the entire thyroid gland and its capsule. This may help in removal of all neoplastic tissue however, it leaves the patient with no thyroid tissue, necessitating lifelong thyroid hormone supplementation. There is also the added to the risk of bilateral dissection of the adjacent normal neck structures and damage to important structures. Alternatively, more conservative procedures may leave inconspicuous residual cancer within the patient. Unfortunately, there are no prospective randomized clinical trials evaluating the extent of thyroidectomy, adjuvant radioactive iodide therapy, and TSH suppressive therapy.

Advantages of Total Thyroidectomy in WDC are:

- Higher survival rate even for lesions >1.5 cms
- Low recurrence rate and prevention of recurrence in contra lateral lobe Decreases incidence of pulmonary metastasis
- Can be performed with same morbidity & mortality as lobectomy
- Improved sensitivity of thyroglobulin (Tg) as marker for persistent/recurrent disease Radioactive iodine can be used to treat persistent/recurrent disease.

2) Near - total thyroidectomy - entire gland is removed preserving a small portion near the posterior capsule of the thyroid.

3) Hemithyroidectomy - removal of the lobe ipsilateral to the lesion, and removal of the thyroid isthmus. Hemithyroidectomy is done in differentiated cancers <1.5cm in size without extrathyroidal extension (ETS) and no distant metastasis Arguments favouring Hemi - Thyroidectomy are:

- Differentiated thyroid cancer is an indolent disease and in

a majority of patients has a very low recurrence and mortality rate.
- Permanent hypoparathyroidism and recurrent laryngeal nerve injury are potential complications of total thyroidectomy.

Lymph Node Dissection

Approximately 80% of patients with PTC have microscopic regional lymph node metastases [41]. Microscopic occult metastases may often be ablated by adjuvant radioactive iodine therapy, but they may also be a site of persistent disease that would have easily been removed at the initial operation. Gross nodal disease occurs in 20–30% of adult cases of PTC, and is a certain justification for lymph node dissection [37]. As the central group / level VI of lymph nodes are mainly involved in thyroid malignancy it is recommended that dissection of ipsilateral central neck nodes and perithyroid lymph nodes (Delphian node and lymph nodes medial to the carotid sheath) be done in all cases of WDC. Removal of central neck lymph nodes is associated with an improvement in the regional recurrence rate, and an improved survival rate in retrospective observational studies. [27, 38]

Lateral neck node dissection

Dissection of lateral compartment nodes (levels II–V) is important for nodes that have identifiable involvement with disease. Lymph node level based resections of lateral neck nodes are preferable to "berry - picking" if they are clinically involved. For lateral compartment disease, the best approach is to perform functional modified radical neck dissection. Prophylactic lateral neck node dissection is not recommended as it is not associated with improved overall survival. However, follow - up of thyroid cancer patients by physical examination and ultrasound can identify patients with lateral neck nodal disease that can then be appropriately treated by therapeutic compartmental node dissection.

3. Methodology

This prospective observational study included 50 patients presenting with thyroid swellings clinically suspicious of malignancy at the Department of General Surgery and the Department of ENT at Kamineni Institute of Medical Sciences and Hospitals, Narketpally, Nalgonda. The duration of the study was of 2 years between October 2019 to September 2021.

Inclusion criteria:
- All cases of Thyroid cancer without overt thyroid dysfunction. Both males and females.
- Age - 12 - 85 years.

Exclusion criteria:
- Patients in whom serum TSH levels were obtained while on thyroid hormone therapy. Secondary malignancies in the thyroid (metastasis).
- Thyroid lymphomas. Thyroiditis.
- Grave's disease.

4. Results and Observation

This was a prospective observational study done in the Department of General Surgery at Kamineni Institute of Medical Sciences, Narketpally. The study period was October 2019 to September 2021.

Total number of cases - 50
Total number of confirmed malignancy – 17

Study Design:

This prospective observational study with a sample size of 50 patients was carried out at the Department of General surgery, Kamineni Institute of Medical Sciences, Narketpally. The inclusion criteria was of those Patients with suggestive clinical features of thyroid malignancy. During preoperative period TSH levels checks were conducted to analyse any relationship between TSH levels and the likelihood of a thyroid nodule being malignant. Furthermore, clinical study of those patients with confirmed thyroid malignancy was carried out. The observed results thus derived were subjected to statistical analysis and the presented as below:

Table 1: Gender distribution of patients studied (n=50)

Gender	Number of patients (%) (n=50)
Male	8 (16)
Female	42 (84)

Demographic Profile

Both Males and Females were included in the study. Female to Male Ratio – 8.4: 1.6.

Thyroid diseases are more common in female. Total number of patients with malignancy were 17.

Table 2: Age distribution of patients studied (n=50)

Age in years	Number of patients (%) (n=50)
< 20	1 (2)
21 - 30	10 (20)
31 - 40	9 (18)
41 - 50	16 (32)
51 - 60	9 (18)
> 60	5 (10)

- Patients ranged from 16 to 85 years.
- Thyroid diseases are more common in the age group of 31 to 50 years.

Clinical Presentation

Table 3: Duration of Symptoms (n=50)

Age in years	Number of patients (%) (n=50)
< 1 year	3 (6)
1 - 2 years	17 (34)
2 - 5 years	14 (28)
>5 years	16 (32)

- Most of the patients presented with a symptom duration of 1 to 2 years.

Table 4: Symptoms of patients studied (n=50)

Symptoms	Number of patients (%)
Swelling	46 (87)
Pain	4 (8)
Dyspnoea	1 (2)
Dysphagia	1 (2)
Dysphonia	1 (2)

- Majority of the patients (46) presented with thyroid swelling.
- The next common complaint was pain.
- Only 3 patients presented with compressive symptoms.

Table 5: Presentation of patients with Solitary Thyroid Nodule (STN) & Multi Nodular Goitre (MNG) (n=50)

Presentation	Number of patients (%) n=50)
STN	25 (50)
MNG	21 (42)

- Most of the patients presented with thyroid swelling.
- 50% of patients presented as STN with majority involving left lobe.
- The total incidents of MNG was 42%.
- 4 patients did not have palpable thyroid swelling.
- 2 patients presented with cystic swelling of neck which turned out to be cervical lymph node metastasis from an occult primary thyroid malignancy.

Table 6: Presentation of patients with Lymph Nodal Enlargement (n=50)

Neck Nodes	Number of patients (%) (n=50)
Palpable	10 (20)
Not Palpable	40 (80)

The involvement of neck lymph nodes were 20%

Table 7: Presentation of patients with Distance Metastasis (n=50)

Distant Metastasis	Number of patients (%) (n=50)
Present	1 (2)
Absent	49 (98)

One patient presented with distant metastasis i. e. bone metastasis to 6th cervical vertebra.

Table 8: FNAC results of patients studied (n=50)

FNAC	Number of patients (%) (n=50)
Colloid Goiter	35 (70)
Papillary Carcinoma of Thyroid	12 (24)
Benign Cyst	2 (4)
Follicular Neoplasm	1 (2)

Papillary Carcinoma of Thyroid was the most common malignancy picked up by FNAC. CG (70%) was the most common abnormality (benign) picked by FNAC.

1 patient presented as Follicular neoplasm which turned out to be follicular carcinoma on histopathology.

Table 9: Surgeries performed for Total Study Group (n=50)

Surgeries performed	Number of patients (%) (n=50)
Total Thyroidectomy + Lymph Node Dissection (TT + LND)	14 (28)
Total Thyroidectomy (TT)	20 (40)
Left Hemithyroidectomy (LHT)	8 (16)
Right Hemithyroidectomy (RHT)	8 (16)

The most common surgery performed was Total Thyroidectomy

For Papillary carcinoma of thyroid, surgery done was Total Thyroidectomy with central neck lymph node dissection.

For solitary thyroid nodules surgery performed was either left or right hemithyroidectomy.

Table 10: Histopathology findings of patients studied (n=50)

Histopathology	Number of patients (%) (n=50)
Colloid Goiter	33 (66)
Papillary Carcinoma	16 (32)
Follicular Carcinoma	1 (2)

Colloid Goitre was the most common histopathological variety.

Papillary Carcinoma of thyroid was most common histopathological variety of malignancy. Incidence of follicular carcinoma was 2%

Table 11: Serum TSH levels of patients studied (n=50)

Serum TSH level (0.40 - 5.36mlu/ ml)	Number of patients (%) (n=50)
0.40 - 1.39	16 (32)
1.40 - 4.99	30 (60)
> 5.0	4 (8)

The mean TSH value was 2.39±1.42mU/L.

Table 12: Incidence of malignancy according to Serum TSH Values in patients studied (n=50)

Serum TSH level (0.40 - 5.36mlu/ ml)	Number of patients (n=50)	Number of patients with benign diseases (%)	Number of patients with malignancy (%)	p - values
0.40 - 1.39	16	16 (100)	0	p< 0.001
1.40 - 4.99	30	17 (57)	13 (43)	
> 5.0	4	0	4 (100)	

All patients were Euthyroid

Serum TSH values were higher in histopathologically confirmed carcinoma of thyroid when compared with those benign disease

Out of 50 patients 17 patients showed malignancy with Serum TSH values more than 1.40

Incidence of Malignancy is significantly associated with higher range of TSH with the P value of less than 0.001.

Table 18: Comparisons of Mean TSH values according to histopathologically confirmed benign disease and carcinoma (n=50)

TSH values	Histopathologically Confirmed benign disease	Histopathologically confirmed carcinoma	p - values
Mean + S. D	1.76 +1.06	3.62 +1.21	t= 5.324; p< 0.001

The mean TSH value of patients studied was 2.39±1.42mIU/L.

The mean TSH value of Histopathologically confirmed benign diseases was 1.76±1.06 mIU/L which is less than the mean value studied. The mean TSH value of Histopathologically confirmed malignant diseases was 3.62±1.21 mIU/L which is more than the mean value studied. p value is less than 0.001 which indicates high significance.

Table 14: Serum TSH Concentration relation with stage of Thyroid carcinoma

Stage	Number of patients with malignancy (n=17)	Mean Serum TSH Concentration	t - value	p - value
I	13	3.78 +1.13	0.87	0.42
II	4	3.08 +1.49		

The mean serum TSH concentration was not increasing with the advanced stage of the disease. The p value across stages was 0.42 which indicates non - significance.

5. Discussion

Role of Serum TSH Levels in Predicting Thyroid Malignancy

It has been established that there is a definite relation between preoperative serum TSH levels and thyroid malignancy through many studies. More aggressive tumours have resulted in higher preoperative serum TSH concentrations among patients. Thus a baseline TSH would predict which nodules require a more aggressive approach and surgery.

TSH is a known thyroid growth factor. TSH receptors are expressed in well - differentiated thyroid cancers [45, 46]. Oncogenes along with other growth factors also determine the involvement of thyroid cancer growth and development [47, 48], however the probability of TSH acting as a cancer stimulus is high. Thus, the rationale to choose TSH levels as a predicator of malignancy.

This hypothesis is supported by improved survival in thyroid cancer patients treated with suppressive doses of levothyroxine [17] and by cases of tumour growth post - T4 withdrawal or recombinant TSH [49]. Studies have also shown that advanced stages can be associated with higher serum TSH levels. This suggesting that progression and/or development of thyroid carcinoma is a result of key role played by the TSH. Furthermore, the data on autoimmune thyroid disease and thyroid cancer supports the role of TSH receptor.

6. Present Study

In this prospective observational study a total of 50 patients were selected who presented with clinical features suspicious of thyroid malignancy. The main aim was to study the association between Serum Thyroid stimulating hormone concentration and Thyroid cancer.

For patients with confirmed malignancy the clinical presentation and management with descriptive analysis was carried out. Such observations and results were duly analysed using statistical methods and compared with other studies.

Table 18: Comparison of involvement of Cervical Lymph Nodes involvement (n=50)

Present study (n=50)	Dorairajan. N. et al (2002) (n=428)	Mazzaferri. et al (2003) (n=784)
20%	59%	33 - 61 %

- In the present study the incidence of neck nodes was 20%
- Presence of neck lymph nodes was a significant clinical indicator of malignancy (P<0.001)

Cervical lymph node involvement

- One of the common presentation in thyroid malignancy is Cervical lymphadenopathy.

At the time of diagnosis around 33% to 61% of patients with Papillary carcinoma have been found to have involvement of clinically apparent cervical lymph nodes. [36]

Histopathology

Table 20: Comparison of Histopathological Type of Malignancy (n=50)

Studies	Papillary Carcinoma	Follicular Carcinoma
Haymart et al (2008) (n= 1361)	87%	7%
Bailey & Love	60%	20%
Devita et al	80 - 85%	10%
Mazzaferri. et al (2003) (n= 784)	70 - 80%	10%
Present Study (n= 50)	93 %	7%

- In the present study papillary carcinoma was the commonest histopathological type with 93% of the studied population and followed by follicular type with 7%.
- This was found to be consistent with the literature and other comparative studies

TSH Levels and the Risk of Malignancy:

Table 21: Comparison of Mean TSH value in Benign vs Malignant Disease (n=50)

Studies	Benign disease	Malignant Disease	p Value
Haymart et al (2008) (n= 1361)	1.4 + 0.4	3.7 + 2.3	p< 0.001
Flore et al (2009) (n= 10, 178)	0.70 + 0.41	1.10 + 0.6	p< 0.001
Present Study (n= 50)	1.76 + 1.06	3.62 + 1.21	p< 0.001

- The mean TSH value was significantly higher in malignancy than in benign disease i. e. 3.62±1.21mU/L vs.1.76±1.06mU/L. This is comparable to the results of Haymart et al [14] and Fiore et al. [50]

It observed by analysis and study of data that TSH level was an independent predictor of malignancy. Patients with values of 0.40 - 1.39 mU/L had absolutely no risk of malignancy. Whereas patients with range of 1.40 - 4.99mU/L had 37% chance of being malignant and finally patients who witnessed TSH levels of >5mU/L had the highest (approx.75%) chance of malignant

7. Conclusion

Thyroid malignancies have a varied clinical presentation. The commonest presentation being that of a solitary thyroid nodule.

Though there are many predictors of thyroid malignancy, none of them can conclusively predict the nature of a thyroid nodule.

The present study evaluated the utility of preoperative serum TSH levels as a predictor of malignancy and it did show a statistically significant correlation (p=<0.001) between higher serum TSH levels and malignancy. However this relationship between higher serum TSH levels was not seen in those presenting with no primary thyroid swelling and only cervical lymph node metastasis. In the present study mean TSH concentration was not increasing with the advanced stage of the disease (p value = 0.42). The utility of serum TSH in poorly differentiated carcinoma could not be assessed as all the patients in this series had well differentiated carcinoma.

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