ORIGINAL RESEARCH

Molecular Mechanism & Cytological Diagnosis of Thyroid Cancer and Their Correlation with Thyroid Hormone Profile

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Received: 24 February, 2023 Accepted: 29 March, 2023

ABSTRACT

Thyroid cancer is the most frequently diagnosed type of endocrine cancer. Its incidence rate is rising more rapidly than that of any other cancer, affecting both men and women. Around 90% of thyroid cancers belong to the DTC category, with PTC being the most prevalent subtype, accounting for 75% of cases. The FTC subtype, on the other hand, comprises roughly 10% of all diagnosed thyroid cancers. The aim of this study is to analyze the cytomorphological features of various types of thyroid lesions and classify them according to The Bethesda System for Reporting Thyroid Cytology and to investigate the relationship between the thyroid hormone levels of patients and their cytomorphological characteristics. Our findings indicate that there is no significant correlation between the T3, T4, and TSH profile and cytological diagnosis of malignant thyroid lesions. Our study suggests that FNAC diagnosis and thyroid profile are independent variables.Another study, which involved 1500 participants, reported a noteworthy rise in the risk of malignancy among individuals with elevated TSH levels. The study found that malignant thyroid lesions had significantly higher TSH levels than benign ones. The likelihood of a thyroid lesion being malignant was 1.54 times higher in patients with elevated TSH levels. In some cases with abnormal T3, T4, and TSH levels, the thyroid hormone profile may be useful for symptom management.

INTRODUCTION

Thyroid cancer remains the most commonly diagnosed form of endocrine malignancy, with an incidence rate that is currently increasing faster than any other cancer type, across both genders [1, 2]. Recent studies indicate that the incidence of thyroid cancer has been rising by an average of 3.6% annually over the past decade [3]. In the United States, thyroid cancer ranks as the ninth most frequently diagnosed cancer, accounting for 3.8% of all malignancies, with an estimated 44,280 new cases reported in 2021 alone. Fortunately, the mortality rate for thyroid cancer is low, with only 0.3% of all cancer-related deaths attributed to this type of cancer [4, 5].

Thyroid cancer is classified into three main types based on their histological features: differentiated thyroid cancer (DTC), which arises from the epithelial cells of the thyroid follicles; medullary thyroid cancer (MTC); and anaplastic thyroid cancer (ATC). Among all diagnosed thyroid cancers, approximately 90% are of the DTC type, with papillary (PTC) histology being the most common (75%), followed by follicular (FTC) (10%) **(Figure 1),** Hurthle cells (5%), and poorly differentiated carcinomas (1-6%) [6, 7]. The incidence of MTC is relatively low, accounting for approximately 10% of all thyroid tumors, while ATC represents less than 1% of cases. Thyroid cancer is a relatively uncommon form of cancer, accounting for only 1% of all solid tumors in adults. Women are three times more likely than men to develop this disease **(Figure 2),** and the incidence of differentiated thyroid cancer (DTC) has increased by 2.4 times over the past 30 years. When diagnosed at an early stage, most DTC patients have an excellent prognosis. In fact, 91% of patients treated with the classical approach of surgery followed by radioiodine ablation and suppression of thyroid stimulating hormone (TSH) are alive 20 years after treatment. This highlights the importance of early detection and prompt treatment in achieving successful outcomes for patients with thyroid cancer. Unfortunately, patients who have differentiated thyroid cancer (DTC) that is resistant to radioactive iodine or those who have medullary thyroid cancer (MTC) or anaplastic thyroid cancer (ATC) face limited options for treatment[8-12].

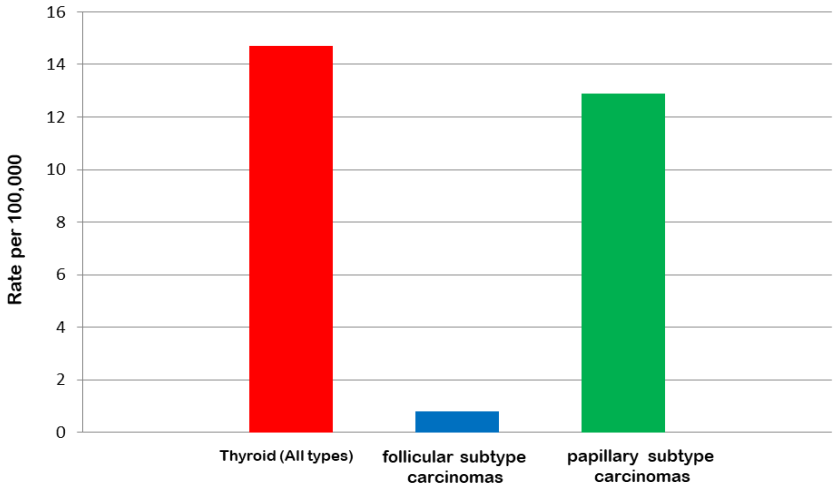


Figure 1: Papillary and follicular thyroid cancer sub type distribution (Source with courtesy:SEER Explorer https://seer.cancer.gov/statistics-network/explorer/.)

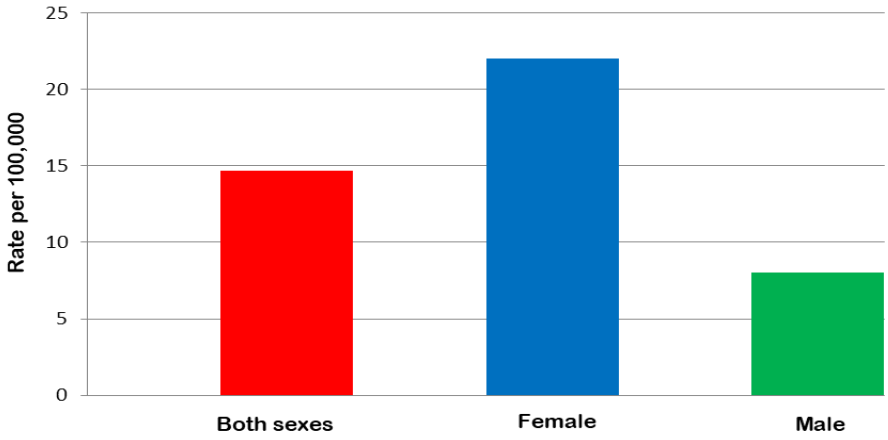


Figure 2: Thyroid cancer distribution among male and females (Source with courtesy:SEER Explorer https://seer.cancer.gov/statistics-network/explorer/.)

At present, doxorubicin and cisplatin are the most commonly utilized chemotherapy drugs worldwide for thyroid cancer treatment. However, the clinical guidelines in this area do not always recommend routine administration of these agents. While a study conducted in the 1970s involving 92 thyroid cancer patients of all types demonstrated some efficacy of doxorubicin and cisplatin, the achieved progression-free survival was only 3 months, and overall survival was 7 months post-treatment[13]. Currently, the application of chemotherapy for thyroid cancer is restricted to anaplastic thyroid cancer (ATC), patients with poorly differentiated histology and a high proliferation rate, or individuals who have severe symptoms and are not eligible for other systemic or local therapies[14].

Over the past decade, there has been substantial progress in comprehending the molecular mechanisms underlying the development and advancement of thyroid tumors **(Figure 3).** For instance, RAS/RAF/MAPK intracellular signaling pathway mutations or gene rearrangements such as RET/PTC are mainly associated with differentiated thyroid cancer (DTC). Almost all medullary thyroid cancer (MTC) tumors related to hereditary syndromes and about 45% of sporadic MTC cases involve activating mutations in the RET gene [7].

Thyroid tumors are commonly distinguished by elevated levels of vascularization and the existence of specific growth factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) [15]. The significance of angiogenesis in the development of these tumors was elucidated through studies showing a strong correlation between high levels of stromal VEGF and an increased likelihood of distant metastases and other markers of aggressive tumors [16]. Interestingly, blocking the VEGF pathway has been shown to directly inhibit the proliferation of thyroid tumor cells in culture, underscoring the potential of antiangiogenic drugs as a targeted therapy for thyroid cancer. Of particular note, VEGFR3 is involved in the process of lymphangiogenesis, which is of special interest in

papillary thyroid carcinomas that have a tendency to metastasize to regional lymph nodes [17].Tyrosine kinases play a crucial role in cellular control by transferring phosphate groups from adenosine triphosphate (ATP) to tyrosine residues of other proteins. Various tyrosine kinases have been identified in humans and are known to be involved in essential cellular processes such as differentiation, function, survival, proliferation, and cell motility. Currently, the molecular pathogenesis of different subtypes of thyroid cancer is better understood than ever before, and as a result, this area of research has become one of the busiest in the field of endocrine oncology. Translating laboratory discoveries into clinical practice, or the "bench-to-bed" transfer, is one of the greatest challenges in translational research. If successful, this could lead to thyroid tumors being utilized as a template for treatment plans based on the molecular characteristics that drive tumor progression and growth in each patient [18-21].

The etiology of thyroid cancer is still not well comprehended. Although age, female gender, a history of benign thyroid disease, exposure to ionizing radiation, and a family history of thyroid cancer are commonly acknowledged risk factors, recent studies indicate that increased body weight and height may also raise the risk of thyroid cancer [22].

Thyroid cell growth and function are regulated by thyroid-stimulating hormone (TSH), a major growth factor. The production and secretion of thyroid hormones, such as triiodothyronine (T3) and thyroxine (T4), are controlled by TSH [23]. Blood levels of thyroid hormones have a negative feedback effect on TSH levels via the pituitary gland. Studies conducted on mice have shown that elevated TSH levels are linked to the development of papillary thyroid carcinoma (PTC) [24]. Patients with differentiated thyroid cancer (DTC) are currently recommended to have their TSH levels suppressed, which has been shown to improve survival [25]. Thyroid hormones have been linked to tumor growth in various types of cancers, such as breast, pancreatic, ovarian, and prostate cancers. However, the results of epidemiological studies investigating the relationship between thyroid hormones and TSH levels and the risk of thyroid cancer have been inconclusive.

Most early studies suggested a higher risk of thyroid cancer with increased levels of thyroid-stimulating hormone (TSH), but some studies did not find a significant association, and one even reported a decreased risk [24]. However, all studies that found a positive link between TSH and thyroid cancer were either cross-sectional or case-control studies, raising concerns about the possibility of reverse causation or treatment effects, since TSH levels were measured after diagnosis.More recent prospective cohort studies have provided further insights. Three cohort studies have been conducted previously to investigate the association between TSH levels and thyroid cancer risk. Among them, one study found a significantly reduced risk of thyroid cancer with elevated TSH levels, while the other two smaller studies did not show a statistically significant difference in TSH levels between thyroid cancer cases and controls. The association between thyroid hormones and thyroid cancer risk is also unclear, with two studies showing a higher risk of thyroid cancer with lower thyroid hormone levels, while the remaining five studies did not find a significant association [26].

FNAC is a widely used diagnostic tool for both solitary and diffuse thyroid nodules. It is a rapid, minimally invasive, cost-effective, and easy-to-perform screening method. The widespread use of FNAC has resulted in a more than 50% reduction in the number of patients requiring surgery. FNAC has not only helped to prevent unnecessary thyroid surgeries for benign nodules but has also increased the rate of detecting malignancy in resected nodules from 14% to 50%. However, this procedure has some limitations, particularly in cases of suspicious cytology and follicular neoplasms where its accuracy may be lower [27, 28].

The thyroid cytopathology reporting system, known as The Bethesda System, has established a standardized approach for reporting thyroid specimens. By utilizing The Bethesda System, cytopathologists are able to effectively communicate their interpretations of thyroid FNAC to referring physicians, which not only aids in clinical decision-making but also assists in determining the most appropriate management plan [29, 30].

The objective of this study is to evaluate the cytomorphological characteristics of different types of thyroid lesions and categorize them based on The Bethesda System of Reporting Thyroid Cytology. Additionally, the study aims to determine the correlation between the cytomorphological features and the thyroid hormone status of the patients.

MATERIAL AND METHODS

This study was conducted in department of pathology, GSVM Medical College, Kanpur Nagar, Uttar Pradesh, India among 11266 patients from August 2020 to July 2022. The patients were explained about the study and confidentiality of data was ensured. The study was conducted on patients of all ages and genders who presented with complaints of thyroid swelling at the surgery or ENT outpatient department **(Figure 4).**

Clinical data, including age, sex, location, size, and duration of thyroid swelling, were documented prior to fine needle aspiration cytology (FNAC). In addition, T3, T4, and TSH hormone levels were evaluated for all patients.

FNAC was carried out using a 22 gauge needle by non-aspiration method, in accordance with usual practise. A minimum of two smears from the sample were made, and one dry smear stained with the Giemsa and another wet fixed smear with H and E stains, respectively **(Figure 5)**. In the case of cystic

lesions, fluid was aspirated first, and then the nodule was aspirated again. USG guided FNAC was carried out in non palpable lesion. The prepared smears were examined by a cytopathologist, and the final diagnosis was classified using the Bethesda system for reporting thyroid cytopathology.

The Thyroid profile was done in department of biochemistry. Approximately 5 ml of blood was withdrawn and placed in a labeled plain serum tube. The sample collected from patients was assayed using ELISA kits from Human Gesellschaft fur biochemica und Diagnostic Mbh Max -Planck-Ring 21, D - 6205 Wiesbadan, Germany serozyme ELISA.

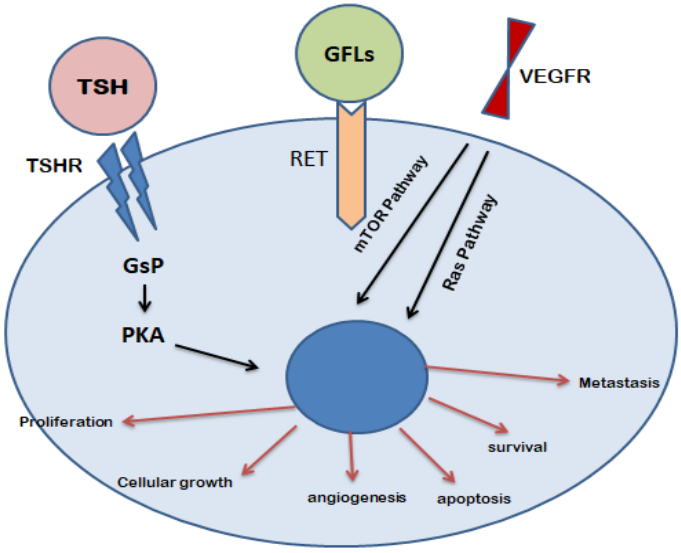
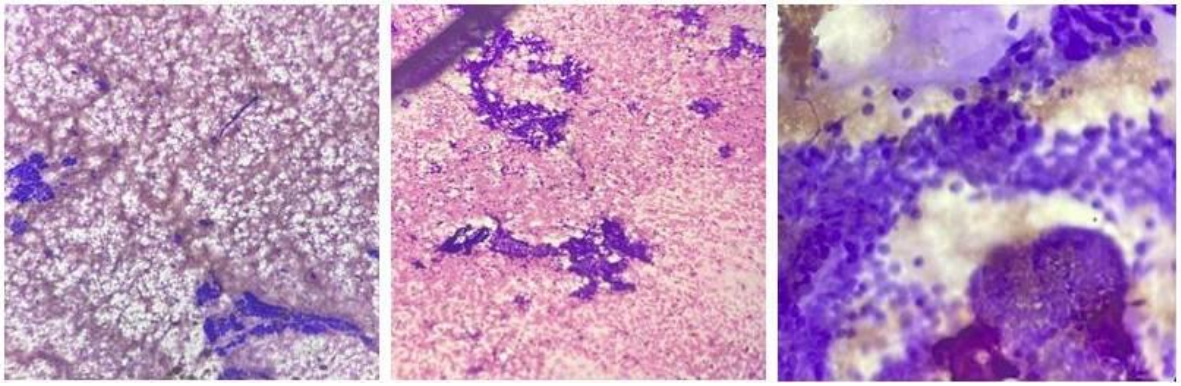


Figure 3: Molecular signalling pathways of thyroid cancer

Figure 4: Images of thyroid cancer patients investigated during present study.



(a) **(b)** **(c)**

(b) **Figure 5:** Thyroid cancer specimenstained with the Giemsa

RESULTS

11266 FNAC were done from all sites during study period, out of which 388 patients were from thyroid comprising of 3.44% of all lesions. The most common age group affected was 31-40 years (27.8 %) followed by 21-30 with frequency of 22.6%. The least affected age groups were first and over sixth decade each comprised 5% and 7.4% respectively. Female preponderance was noted with M:F ratio of 1:3.4. Majority of cases reported in present study were in benign consist of 82.21% and only 3.35 % cases were

malignant. Case distribution as per TBSRTC was summarised in **table 1.**

Table 1: Diagnosis categorization based on the Bethesda system for thyroid cytopathology (TBSRTC) reporting

S No	Cytological Diagnosis	Percentage
1	Non diagnostic	6.70%
2	Benign	82.21%
3	AUS/FLUS	3.09%
4	SFN/FN	3.86%
5	Suspicious for malignancy	1.28%
6	Malignant	3.35%

Category	Number of cases	Hormone profile available	Euthyroid	Hyperthyroid	Hypothyroid	Calcitonin level
Non-diagnostic	26	15	13 (86.6%)	0 (0%)	2(13.3%)	**0**
Benign lesion	319	282	245 (86.8%)	10 (3.5%)	27(9.5%)	**0**
AUS	12	7	6 (85.71%)	0 (0%)	1(14.29%)	**0**
SFN/FN	15	10	8 (80%)	1 (10%)	1(10%)	**0**
Suspicious for malignancy	5	3	3 (100%)	0 (0%)	0(0%)	0
Papillary thyroid carcinoma	6	5	4 (80%)	1(20%)	0(0%)	0
Follicular thyroid caricoma	4	4	3 (75%)	1 (25%)	0(0%)	0
Medullary thyroid carcinoma	2	2	2 (100%)	0 (0%)	0(0%)	2
Anaplastic carcinoma	1	1	0 (0%)	1 (100%)	0(0%)	0

Table 2: Thyroid function level in various pathological conditions

Euthyroid condition was most commonly seen in both benign and malignant lesion. Majority of patients had benign lesion including colloid goitre, Lymphocytic thyroiditis, Hashimoto's thyroiditis, of which 86.8% were euthyroid, 3.5% were hyperthyroid, and 9.5% were hypothyroid. It was noted that 86.6% cases were euthyroid in non-diagnostic while 80% cases were euthyroid in Follicular neoplasm or suspicious for follicular neoplasm, 85.71% cases were euthyroid in atypia of undetermined significance and out of 13 cases of thyroid malignant lesion, 75% cases were euthyroid and 25% were hyperthyroid.

DISCUSSION

Thyroid nodules are a common issue in India, and there is a concern about the possibility of malignancy [31]. Numerous studies have examined clinical and biochemical factors that may be associated with thyroid cancer. However, the majority of thyroid nodules are benign and confined to a particular area. Only a small percentage, approximately 1%, are malignant, although the incidence is reportedly increasing each year. As a result, diagnosing thyroid nodules can be a challenging task. Fine needle aspiration cytology of the thyroid gland is now well established and regarded as the first line diagnostic tool for the assessment of diffuse and nodular thyroid lesions. Diagnosis categorization based on the Bethesda system for thyroid cytopathology reporting helps in the reduction of unnecessary procedures and is a standardized reporting approach for identifying diagnoseson aspirated materials[32-34].

Majority of the aspirations in present study resulted in good diagnostic yield and only 6.70 % of total thyroid aspirates were non diagnostic. However percentage is higher in comparison to the other studies. This could have been due to the fact that aspirations were performed by junior residents with lesser experience. Repeat aspirations can reduce the percentage of non-diagnostic yields[35].

The age group with the highest number of cases was between 31 to 40 years, accounting for 27.83% of cases, while the 21 to 30-year-old age group accounted for 22.68% of cases. Female preponderance was noted with M :F ratio of 1:3.4. Geographically thyroid lesions are more common in Himalayan belt and regions consuming goitrogenic diet. Increased physiological demand in females makes them more prone to develop goitre and other thyroid lesions[36, 37]. Therefore, much higher incidence in females with M:F ratio 1:8 was noted in Nepalese population. Variation in male-female ratio has been reported from different parts of India, especially in the state of Karnataka (M:F ratio 1:20) due to consumption of non-iodised salt and sale of iodised salt having less quantity of iodine than stipulated. Above study was done on 350 cases out of which 334 (95.5%) were females and 16 (4.6%) were male. In concordance

with present study majority of lesions were in the age group of 21- 40 years.

The conventional methods of reporting thyroid FNAC had some notable drawbacks owing to its variable standards adopted by different laboratories, creating confusion in some instances and hindering the sharing of data among multiple institutions. Adoption of TBSRTC by us helped to compare data with other studies.

Papillary thyroid carcinoma is the commonest thyroid malignancy which presents as solitary thyroid nodule or lateral neck lymphnode. This occult malignancy is sometimes discovered as incidental finding during investigations. This calls for development of none or minimally invasive methods for diagnosis of thyroid malignancies[38]. The levels of T3, T4 and TSH were assessed and thyroid lesions were categorized as euthyroid, hyperthyroid, or hypothyroid conditions accordingly [39]. Euthyroid condition was most commonly seen in both benign and malignant lesion. Majority of patients had benign lesion of which 86.8% were euthyroid, 3.5% were hyperthyroid, 9.5% were hypothyroid. It was noted that 80% cases were euthyroid in Follicular neoplasm or suspicious for follicular neoplasm, while Out of 5 cases of suspicious for malignancy, hormone profile was available in 3 cases and all were euthyroid. Hormone profile was available in 5 out of 6 cases of Papillary thyroid carcinoma, in which 4 were euthyroid and 1 were hyperthyroid, there were 4 cases of Follicular thyroid carcinoma, in which 3 cases were euthyroid and 1 case was hyperthyroid while 2 cases of Medullary thyroid carcinomawereeuthyroid with raised calcitonin level, only one case of anaplastic thyroid carcinoma was hyperthyroid. So out of 13 cases of thyroid malignant lesions, 9 were euthyroid, 3 were hyperthyroid. It was noted that 75 % of cases were euthyroid and only 25% of cases were hyperthyroid.

In context of T3, T4 and TSH profile and cytological diagnosis of thyroid malignant lesions did not show any significant correlation.We observed that FNAC diagnosis and thyroid profile are two independent variables .The thyroid profile hormone may play role in symptomatic treatment modality in selective cases with deranged T3, T4 and TSH.

Attempts to study correlation between thyroid hormones and thyroid malignancies were first conducted in 1999 on 1005 thyroid aspirations and no correlation was noted. A similar study on 117 cases, observed that most of the benign and malignant lesion including benign follicular nodule, Follicular neoplasm/suspicious for follicular neoplasm and papillary thyroid carcinoma were euthyroid. The study showed that there is no significant difference between mean T3, T4 and TSH profile and various groups of FNAC diagnosis.

A study was conducted on a group of 42 patients to evaluate the correlation between thyroid profiles and FNA diagnosis. The majority of patients (83.3%) had nodular goitre, of which 47.6% were euthyroid. Among the patients with FNA diagnosis of non-diagnostic sample, three patients (7.1%) were euthyroid, while 2.4% each of patients with papillary carcinoma and atypia were also euthyroid. However, the study found no significant correlation between T3, T4, TSH and FNA cytological diagnosis.

Nodular goitre develops thyroid autonomy during its progression i.e thyroid hormone secretion becomes independent of levels of TSH. TSH decreases with age in nodular goitre due to thyroid autonomy but not in papillary thyroid carcinoma. The data was given by National Health and Nutrition Examination Survey III suggested that the development of thyroid autonomy reduces TSH levels which reduce the probability of mutated oncogenes, which may cause cancer that is clinically detectable. Comparison of the TSH levels between patients with papillary thyroid microcarcinomas and medullary cancer revealed that TSH is not likely involved in the oncogenesis of papillary thyroid cancer. We also observed that most of the cases (75%) of papillary thyroid cancer had TSH levels within normal range [40-42].

A similar small cohort study on 150 aspirations out of which 142 were females and 8 males. Majority of patients were in the range of 21 to 40 years (49.3%). 141 cases were non neoplastic and only 9 cases were neoplastic. Maximum number of patients (92 cases) was found to be Euthyroid, 17 cases were hyperthyroid, 4 cases were hypothyroid, 23 cases had subclinical hyperthyroidism and 14 cases were of subclinical hypothyroidism.

Studies have shown that high levels of serum TSH are associated with an increased risk of thyroid malignancy. On the other hand, treatment with thyroxine has been found to reduce this risk. In addition, higher TSH values have been linked to more advanced stages of thyroid cancer. Moreover, lower TSH levels have been associated with a reduced likelihood of papillary thyroid cancer. Taken together, these findings suggest that TSH plays a crucial role in the development of clinically detectable thyroid cancer and that levothyroxine treatment can decrease the risk of thyroid malignancy in patients with nodular thyroid disease.

Similar study also reported significant increase in risk of malignancy with higher TSH levels where 1500 patients were included. TSH levels found to be significantly higher in malignant lesions as compared to benign ones. It was 1.54 times more likely for thyroid lesion to be malignant when TSH levels were higher.

CONCLUSION

Present study noted that there is no any diagnostic role of T3, T4 and TSH level in association with cytological diagnosis of thyroid malignant lesions. We observed that FNAC diagnosis and thyroid profile are two independent variables. The thyroid profile hormone may play role in symptomatic treatment

modality in selective cases with deranged T3, T4 and TSH. Small sample size is a limitation of this study, larger studies are required. Future studies to elucidate the role of thyroid profile as a prognostic factor will be beneficial to patients. Further, Advances in diagnosis and treatment are contributing to better outcomes for patients, making it crucial to raise awareness of the importance of early detection and treatment.

ACKNOWLEDGEMENT

I acknowledge to Dr. Pravesh Verma and Dr. Navneet Yadav to help in referencing of manuscript.

CONFLICT OF INTEREST

"All the authors declare that they have no conflict of interest."

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