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# Study of histopathological pattern of thyroid lesions

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## Abstract

**Aim:** To study histopathological features and to find out the frequency of various lesions of thyroid and to distribute thyroid lesions according to age, sex and benign and malignant behaviour.
**Material and methods:** The test population comprised of patients with thyroid pathology, between July 2014 to August 2016, evaluated by light microscopy and immunohistochemistry.
**Results:** In our study, Age group of patients ranged from 6-70 years, with a mean age of 37.4 years and Male to Female ratio was 1:4.9. Among total 100 cases, 54 non-neoplastic masses and 44 neoplastic masses. Incidence rate of inflammatory lesions was 8%. The most common type of inflammatory lesion was lymphocytic thyroiditis (50% of total inflammatory lesion). Incidence rate of hyperplastic lesions was 46%. It was most common thyroid lesion in our study. Most of the cases presented at the age group of 21-60 years. The most common histopathological sub type of hyperplastic lesion was colloid goiter (58.7% of the total hyperplastic lesion). Incidence rate of benign lesion was 27%. The most common presenting age group for benign thyroid lesion was 21-50 years. Benign thyroid lesion was represented exclusively in this study by follicular adenoma only. One case of well differentiated tumor of uncertain malignant potential was found. Incidence rate of malignant lesions was 16%. Most of the malignant cases presented at the age group of 21-40 years. The most common histopathological sub type of thyroid malignancy was papillary thyroid carcinoma (81.3% of the total malignant lesion). Five cases were analyzed immunohistochemically, wherever light microscopy was inconclusive.
**Conclusion:** Neoplastic and non-neonlastic disorders affect thyroid gland. Non-neoplastic disorders outnumber the neoplastic disorders. Most common non-neoplastic lesion was colloid goiter. The most common benign tumor was Follicular adenoma and the most common malignant tumor was papillary carcinoma.
**Keywords:** Colloid goiter, Papillary thyroid carcinoma, Hematoxylin, Immunohistochemistry.

## 1. Introduction

Thyroid gland is a butterfly shaped endocrine gland situated in the anterior aspect of root of the neck, consists of two bulky lateral lobes connected by a relatively thin isthmus. Thyroid produces several hormones such as thyroxine (T4), triiodothyronine (T3) and calcitonin. Disorders of thyroid comprise a group of commonly encountered endocrinological disease. The incidence and prevalence of these thyroid diseases in a given community are variable depending on various factors. It is most prevalent in mountainous areas but also occurs in non-mountainous areas remote from sea. [1]

Even after 100 years, thyroid gland has been the subject of intense research and considerable attention due to the vast array of developmental, inflammatory, hyperplastic, immunologic and neoplastic disorders which are exceedingly common in clinical practice. [2] The trend toward individualized treatment has increase the importance of histopathological findings. Histopathological examination plays a major role in making a correct & accurate diagnosis of various lesions of thyroid, which has a profound impact on the further management of the patient. Differentiation of follicular lesions like follicular adenoma and follicular carcinoma requires histopathological examination to establish a definitive diagnosis, further management and prognosis of the patient.

From clinical standpoint, the major concern in person who present with thyroid nodule is the possibility of a malignant neoplasm. But fortunately, the overwhelming majority of the solitary nodules of the thyroid prove to be localized and non neoplastic lesions. Several clinical criteria provide clues to the nature of the thyroid nodule like Solitary nodules are more likely to be neoplastic than are multiple nodules, Nodules in younger and male patients are more likely to be neoplastic than are those in older patients, history of radiation therapy to the head and neck region is associated with an increased incidence of thyroid malignancy and Functional nodules that take up radioactive iodine in imaging studies are much more likely to be benign than malignant. This association and statistics however are of little comfort to a patient, in whom timely recognition of malignancy can be life saving, So morphological evaluation of thyroid nodule, by surgical resection followed by histopathological examination provides most definitive diagnosis. [3]

The purpose of study is aimed to document the frequency/prevalence of different patterns of thyroid disease and also distribute them by age and sex by histopathological examination and immunohistochemistry whenever required.

As it can be seen from the following tables, there is wide variety of the lesions that arise from thyroid gland which proposes a challenge, for the diagnosis and management of the patient.

**Non-Neoplastic**

- Goiter
- Hashimoto's or Lymphocytic thyroiditis or Granulomatous thyroiditis
- Hyperplastic nodule
- Grave's/diffuse hyperplasia

**Neoplastic**

- **Adenoma**
- **Carcinomas:** Papillary, Follicular, Medullary, Anaplastic, Squamous cell carcinoma, Metastatic carcinoma
- Lymphoma
- Plasmacytoma

Majority of clinically apparent thyroid neoplasms are primary and epithelial in origin. Traditionally, they have been divided into adenomas and carcinomas.

From a histogenetic standpoint, thyroid neoplasms are divided into three major categories, depending on the cell types involved, and subdivided them into the various benign and malignant categories such as; tumors exhibiting follicular cell differentiation (95%), tumors exhibiting C-cell differentiation, and tumors exhibiting mixed follicular and C-cell differentiation. Lesions in the later two categories comprise about 5% of tumors. Fortunately, the overwhelming majority of solitary nodules of the thyroid prove to be localized, non-neoplastic conditions or benign neoplasms such as follicular adenomas. In fact benign neoplasms out number thyroid carcinomas by a ratio of nearly 10:1. [4] While under 1% of solitary thyroid nodules are malignant.

Although tumors of the thyroid gland account for only 1% of the overall human cancer burden, they represent the most common malignancies of the endocrine system and pose a significant challenge to pathologists, surgeons and oncologists. [5]

## 2. Materials and Methods

The present cross sectional study was conducted for period of 2 years (between July 2014 and August 2016) at the Department of Pathology, Medical College Baroda and Sir Sayajirao Gaekwad Hospital of Baroda. The test population comprised of patients with thyroid pathology in specified period of time.

### 2.1 Inclusion criteria

The material for the study consisted of all the specimens and referred materials submitted to the Department of Pathology, SSG Hospital for histopathological study.

Data for study was obtained from departmental records (for retrospective study) and tissue specimens received in the histopathology section (for prospective study) in the specified period of time.

### 2.2 Tissue collection

The tissues of the test population submitted were evaluated by histopathological processing and examination (HPE). Performa designed to gather uniform necessary information was used for every case.

### 2.3 Tissue processing

Tissues were fixed in 10% Buffered formalin overnight, for an average period of 16-24 hrs. Gross examination of tissue was done, pathological areas were taken and processed in the histokinete with a cycle of 24 hours, after which the processed tissue was embedded into paraffin wax blocks and then chucked onto wooden chucks. The wax blocks were trimmed using the rotary microtome. Sections of 3-5µm thickness were cut and taken onto slides and stained by the routine H&E stain. During the HPE reporting, most of the cases were diagnosed by light microscopy. Only in certain cases where there was diagnostic dilemma, Immunohistochemistry (IHC) markers were applied.

### 2.4 IHC procedure

The selected tissue block sections were taken up on poly-l-lysine coated slides for IHC procedure. The slides were deparaffinised in xylene, thereafter brought down to water after passing through increasing grades of alcohol. The Peroxidase Antiperoxidase (PAP) method of IHC was followed. Biogenex reagents were used for the antigen

retrieval and IHC staining process. The heating cycles followed in the Biogenex temperature controlled microwave were two cycles of 10 minutes and 5 minutes each at $95^0$C, with intermittent refilling of the antigen retrieval solution.

Thereafter the slides were brought down to room temperature and taken through the steps of wash with TRIS buffer, peroxide block, power block and monoclonal antibodies. After this, slides were again washed in TRIS buffer, the secondary antibody exhibited, thereafter DAB chromogen was added. The slides were then washed with water, counterstained with hematoxylin and blued. Then slides were serially dehydrated in alcohol, cleared in xylene and thereafter mounted using DPX. After drying, the test slides were examined along with the control sections stained simultaneously.

## 3. Results and discussion

Diseases of the thyroid are of great importance because most are amenable to medical or surgical management. It is known that approximately 1-10 % of adults in the USA are reported to have solitary nodule. [6] This incidence is even significantly higher in endemic goitrous regions. Single nodules are about four times more common in women than in men and this incidence increases throughout life. In fact, benign neoplasms outnumber thyroid carcinomas by a ratio of nearly 10:1. [6,7] Overall, the incidence of thyroid malignancy is low, forming 0.5-1.0% of all cancers and 3.3-17% of all thyroid diseases[6]. Carcinomas of the thyroid are thus uncommon, accounting for less than 1% of solitary thyroid nodules and representing about 15,000 new cancer cases in North America each year [6,8,9]. Moreover, most thyroid cancers are indolent, permitting 90% survival at 20 years.

In the present study, 100 cases of thyroidectomy were received during the period between July 2014 and August 2016. Out of these, 54 were non-neoplastic masses and 44 were neoplastic masses.

**Table 1: Comparison of distribution of cases according to age**

| | Mean age | Peak age |
|---|---|---|
| Solomon *et al* [10] | 36.3 years | 30-39 years |
| Golder *et al* [11] | 35.6 years | 21-40 years |
| Present study | 37.4 years | 21-40 years |

In present study, the age of patients ranged from 6 to 70 years, with a mean age group of 37.4 years. Maximum numbers of cases were seen in the age group of 21- 40 years (59.0 %). This is very much in accordance with the past studies done by Solomon *et al* [10] and Golder *et al*[11]. This is probably because, most of malignant and benign lesions are common in these age group. So the load of thyroid lesions is tilted towards this age group.

**Table 2: Comparison of distribution of cases according to gender**

| | Female | Male | Male to female ratio |
|---|---|---|---|
| Solomon *et al* [10] | 86.4 % | 13.6 % | 1:6.4 |
| Gole *et al* [4] | 83.3 % | 16.7 % | 1:5 |
| Present study | 83 % | 17 % | 1:4.9 |

In the present study, out of 100 cases, only 17 (17.0 %) case occurred in a male and remaining 83 (83.0 %) cases were females. The male to female ratio is 1:4.9. This ratio is similar 1:6.4 and 1:5 as shown by Solomon *et al* [10] and Gole *et al* [4] respectively.

**Table 3: Comparison of incidence of inflammatory lesions**

| | Percentage of cases |
|---|---|
| Darwish *et al* [12] | 7 % |
| Sherine *et al* [13] | 7.6 % |
| Huque *et al* [14] | 2.5 % |
| Present study | 8 % |

In the present study, out of the 100 cases studied, inflammatory lesions' group contained 8 cases (8.0 %). Of these, the most common inflammatory lesion was lymphocytic thyroiditis (50%) with mean age of 36.5 years and hashimoto's thyroiditis (37.5%) with mean age of 57.3 years, As lymphocytic thyroiditis is common in younger age and hashimoto's thyroiditis in elderly.

**Table 4: Comparison of incidence of hyperplastic lesions**

| | Percentage of cases |
|---|---|
| Darwish *et al* [12] | 53.5 % |
| Sherine *et al* [13] | 51.1 % |
| Huque *et al* [14] | 52.5 % |
| Present study | 46 % |

In the present study, most common thyroid lesion was hyperplastic thyroid lesion (46%). Similar observation was done by Darwish *et al* [12], Sherine *et al* [13] and Huque *et al* [14] as shown in above table. The most common hyperplastic thyroid lesion in our study was colloid goiter (58.7%). It was followed by 19 cases of multinodular/Adenomatoid goiter (41.3%). The maximum numbers of these lesions were seen in age group of 21-60 years.

**Table 5: Comparison of distribution of benign lesions**

| | Percentage of cases |
|---|---|
| Champa *et al* [15] | 27.1 % |
| Huque *et al* [14] | 26.3 % |
| Golder *et al* [11] | 24 % |
| Present study | 27 % |

In the present study, out of 100 cases, 27 were benign neoplastic thyroid lesion. All cases were of follicular adenoma. Most of the follicular adenoma fell in the age group of 21-50 years (85.2%). It was the 2nd most common thyroid lesion in present study.

In mentioned past studies, follicular adenoma was the most common benign neoplastic thyroid lesion. In the present study, 2 cases of hurthle cell adenoma showing the oncocytic cells with granular eosinophilic cytoplasm were found.

**Table 6: Comparison of distribution of malignant thyroid lesions**

| | %of cases | Most common (% out of total malignant cases) |
|---|---|---|
| Darwish *et al*[12] | 24 % | Papillary carcinoma (100%) |
| Khadilkar *et al* [16] | 21 % | Papillary carcinoma (61.9%) |
| Huque *et al* [14] | 18.6 % | Papillary carcinoma (72.7%) |
| Solomon *et al* [10] | 12.6 % | Papillary carcinoma (53%) |
| Present study | 16 % | Papillary carcinoma (81.3%) |

In present study, thyroid malignancy was diagnosed in 16% of all the thyroid specimens received in this study. This was similar to the 18.6% and 12.6% in Huque *et al* [14] and Solomon *et al* [10] studies respectively but slightly lower than the 24% and 21% in Darwish *et al* [12] and Khadilkar *et al* [16] respectively. There is no clear explanation for the lower incidence of thyroid malignancy in present study. In this study, most of the malignant cases were found to be in the age group of 21-40 years (68.8%). The most common thyroid cancer was found to be papillary carcinoma constituting a total of 13 cases (81.3%). This is similar to the past studies conducted by Darwish *et al* [12], Khadilkar *et al* [16] and Huque *et al* [14]. By seeing the above data we can conclude that papillary carcinoma is the most common thyroid carcinoma. Other case each of follicular carcinoma, medullary carcinoma and anaplastic carcinoma was found.

Papillary Thyroid Carcinoma (PTC) is the most common type of thyroid malignancy. Most tumors manifest in age 20 – 50 years, the mean age at the time of diagnosis is approximately 40 years. The female to male ratio was 4:1[5]. The age in our study was in concordance to literature, most cases (76.9%) occurred in 21-40 years of age (mean 33.3 years), whereas, the female to male ratio was 2.3:1. The youngest patient in our series was 19 years old. Among the multiple histological variants described in literature, the only variant diagnosed in our study was, follicular (38.5%) variant of papillary carcinoma. One case (7.7%) was associated with lymphocytic thyroiditis in opposite lobe.

Involvement of cervical lymph nodes is very common in PTC. This metastasis may not be clinically apparent because of their small size and normal nodal consistency [17]. That may explain our small number of cases presented with nodal metastasis in our study (30.8%).

After exclusion of the follicular variants of other tumors, *follicular carcinoma (FC)* becomes relatively rare tumor, it accounts for 10-15% of clinically evident thyroid malignancy. It is more in women, and tends to occur in patients in the fifth decade [5]. One case of FC represents 6.3% of the malignant cases in our study at the age of only 23 years. The age was less than that mentioned in literature. So these cases were confirmed by IHC. There was only capsular invasion, no vascular invasion was present, categorised as minimally invasive follicular thyroid carcinoma.

Medullary Thyroid Carcinoma *(MTC)* comprises 5–10% of all thyroid malignancies. The mean age at presentation is 50 years [5]. This is in concordance to our study in which 1 case of MTC comprises 6.3% with age of presentation at 43 Years.

Only 1 case (6.3%) in our malignant series was *undifferentiated (anaplastic) carcinomas*, presented at 70 years in female.

In our study, we encountered one case in 50 years female in which grossly creamish white nodule was present and microscopically follicular pattern was identified but there was no capsular or vascular invasion and in-between, few areas showed questionable nuclear features (focally nuclear clearing, overcrowding and loss of polarity were seen but intranuclear inclusion and grooves were not seen). So we diagnosed these case as well differentiated tumor of uncertain malignant potential (WDTUMP).

There were 5 cases in our study where IHC markers were applied. These are discussed below:-

1) There were two cases of papillary carcinoma which were confirmed with the help of IHC markers. In first case there were papillary projections on light microscopy but definitive nuclear features like nuclear clearing and overlapping were only focally present with occasional nuclear inclusion and grooves. In second case, age of the patient was 60 years and had papillary as well as focal follicular tumor pattern with all nuclear features of papillary thyroid carcinoma but occasional nuclear inclusion. So IHC was done on both the cases. Thyroglobulin, TTF-1, CK-19, 34βE12 and β-catenin were positive in both cases which supported the diagnosis of papillary thyroid carcinoma. According to an article published in Human pathology [18], CK19 stained strongly and diffusely all cases of papillary carcinoma.[19-22]
2) There was one case of follicular carcinoma which was confirmed with the help of IHC markers. The results were thyroglobulin, TTF-1 and 34βE12 positive (20% of follicular carcinoma show 34βE12 positivity) [22] whereas, CK-19, calcitonin, synaptophysin and S-100 were negative. As this case occurred in 23 years of age, confirmation by IHC was necessary. Negative markers excluded the possibility of other carcinomas.[20,22]
3) In one case of anaplastic carcinoma, vimentin was diffuse positive, pankeratin was focally positive and thyroglobulin was negative, supporting the diagnosis of sarcomatoid variant of anaplastic carcinoma.[20-23]
4) One case of medullary carcinoma was confirmed by positive calcitonin, chromogranin and CEA. Whereas, CK-19 was negative.[20-25]

**Hyperplastic lesions**

**Figure 1: C/S Colloid Goiter (Brownish fluid-colloid present)**

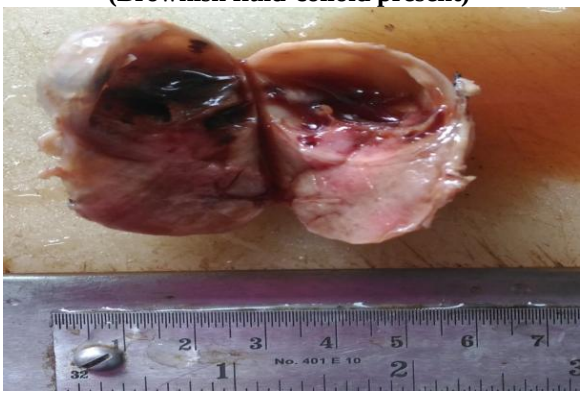


**Figure 2: Microscopy: Colloid Goiter (H&E, 100x)**

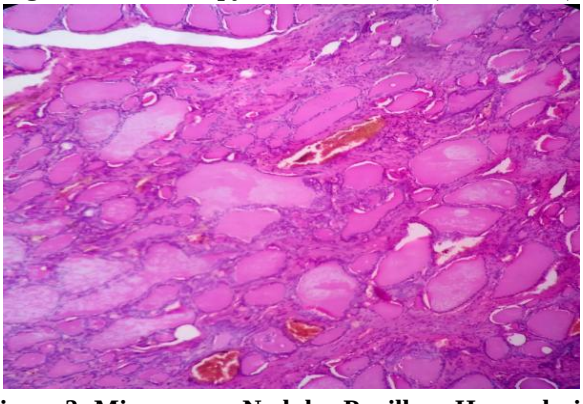
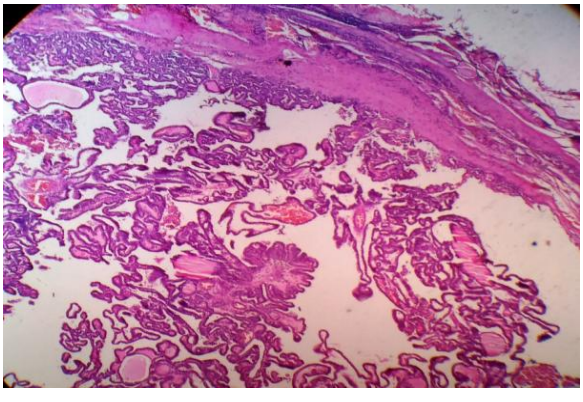


**Figure 3: Microscopy: Nodular Papillary Hyperplasia (H&E, 100x)**



**Inflammatory lesions**

**Figure 4: Microscopy: Hashimoto's Thyroiditis (H&E, 400x)**

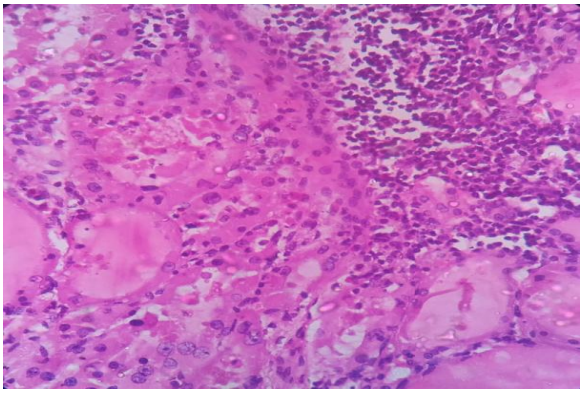


**Figure 5: Microscopy: Lymphocytic Thyroiditis (H&E, 100x)**

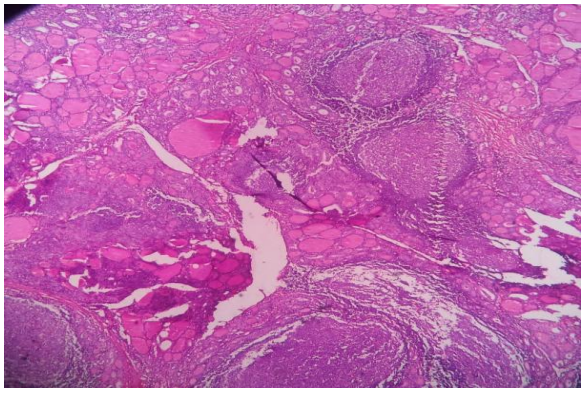
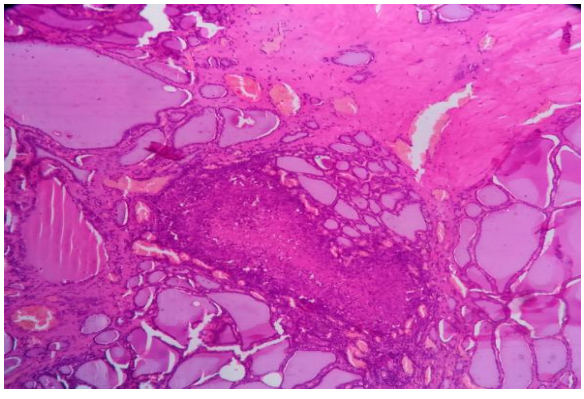


**Figure 6: Microscopy: Necrotising Granulomatous Thyroiditis (H&E, 100x)**



**Benign lesions**

**Figure 7: C/S: Follicular Adenoma (Well encapsulated)**

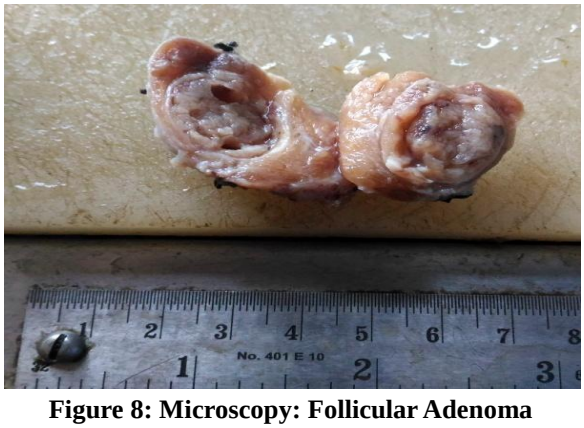


**Figure 8: Microscopy: Follicular Adenoma (Micro follicle) (H&E, 100x)**

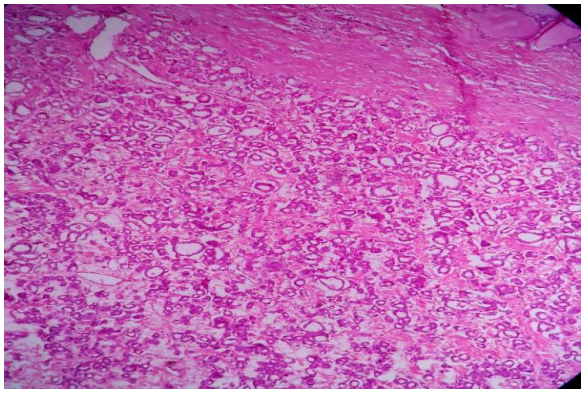


**Figure 9: Microscopy: Follicular Adenoma (macro follicle) (H&E, 100x)**

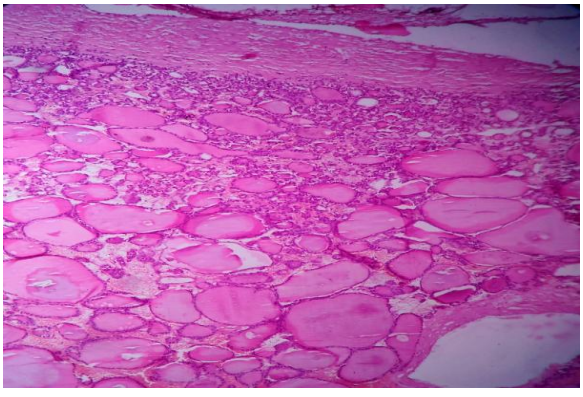


**Figure 10: C/S: Hurthle cell Adenoma (Well encapsulated)**

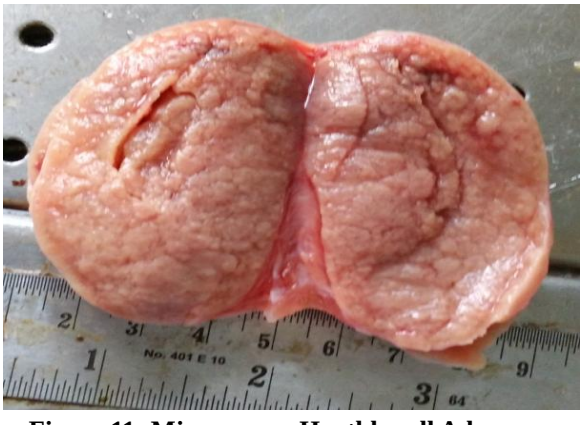


**Figure 11: Microscopy: Hurthle cell Adenoma (H&E, 100x)**

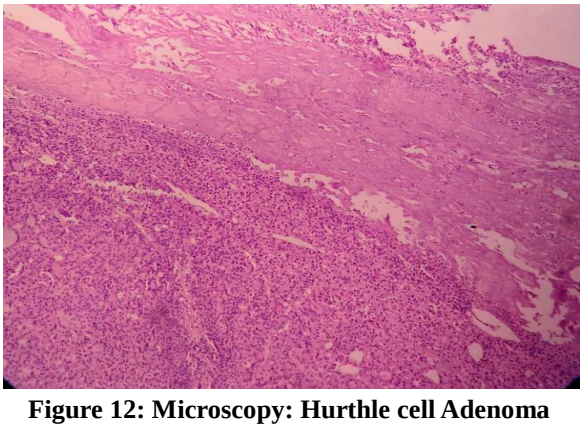
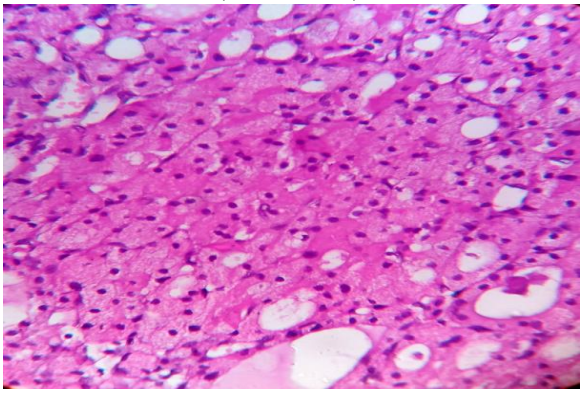


**Figure 12: Microscopy: Hurthle cell Adenoma (H&E, 400x)**



**Malignant lesions**

**Figure 13: C/S: Papillary Thyroid Carcinoma (Grayish White nodules)**

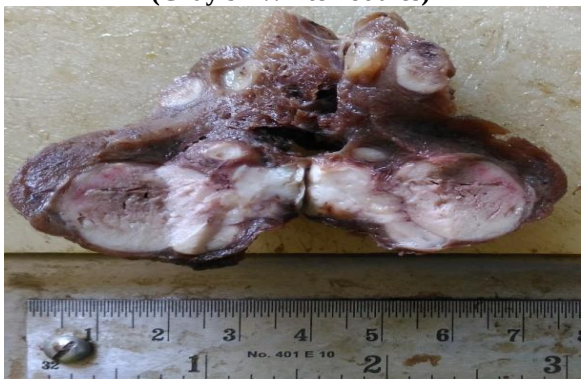


**Figure 14: Microscopy: Papillary Thyroid carcinoma (papillary projection) (H&E, 100x)**

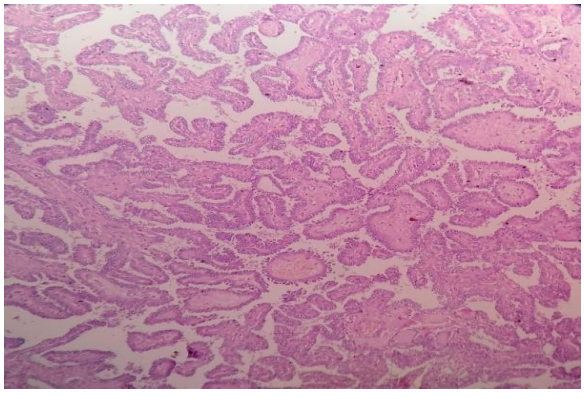


**Figure 15: Microscopy: Papillary Thyroid carcinoma (Ground Glass Nuclei/orphan Annie-eyed nuclei) (H&E, 400x)**

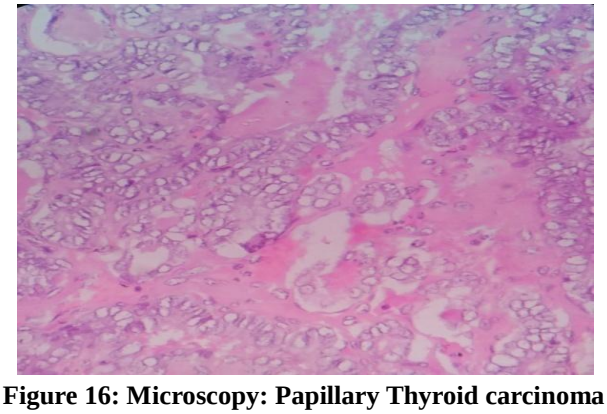


**Figure 16: Microscopy: Papillary Thyroid carcinoma (Psamomma bodies) (H&E, 100x)**

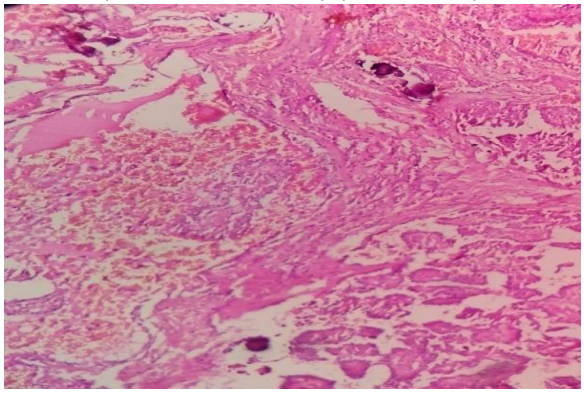


**Figure 17: Microscopy: Follicular variant of Papillary Thyroid carcinoma (Follicular lesion with nuclear features of PTC) (H&E, 400x)**

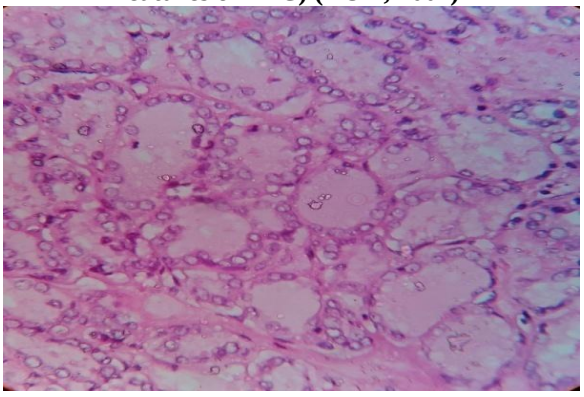


**Figure 18: Microscopy: Metastasis of PTC in lymph node (papillary projection &Psamomma bodies) (H&E, 40x)**

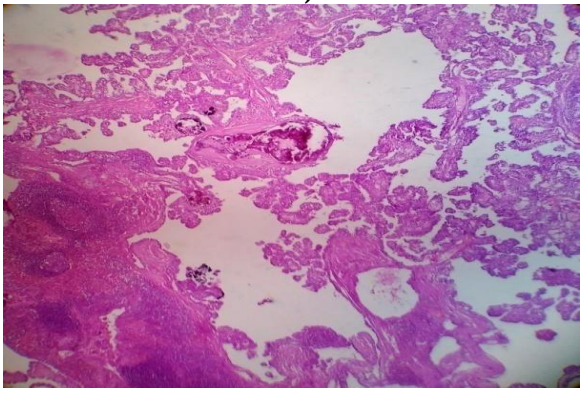


**Figure 19: Microscopy CK19 Positivity papillary thyroid Carcinoma (IHC, 100x)**

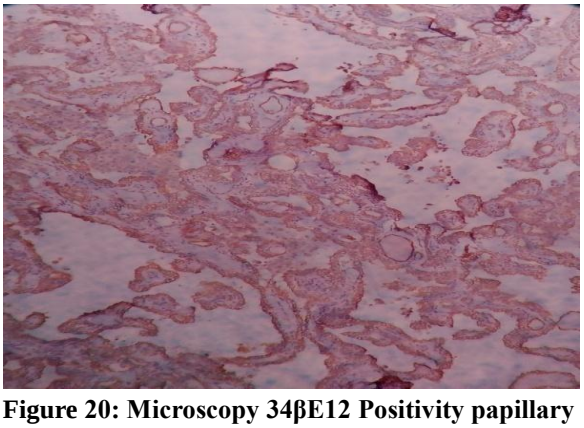


**Figure 20: Microscopy 34βE12 Positivity papillary thyroid Carcinoma (IHC, 100x)**

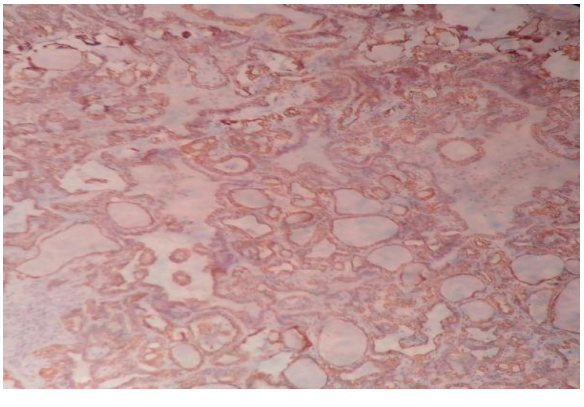


**Figure 21: Microscopy: Follicular Thyroid carcinoma (Capsular invasion) (H&E, 40x)**

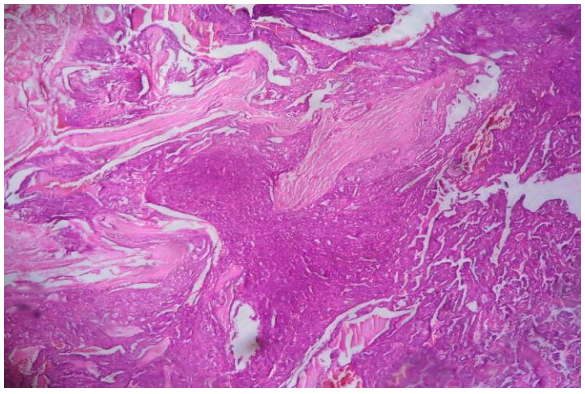


**Figure 22: Microscopy: Follicular Thyroid carcinoma (Trabecular pattern) (H&E, 400x)**

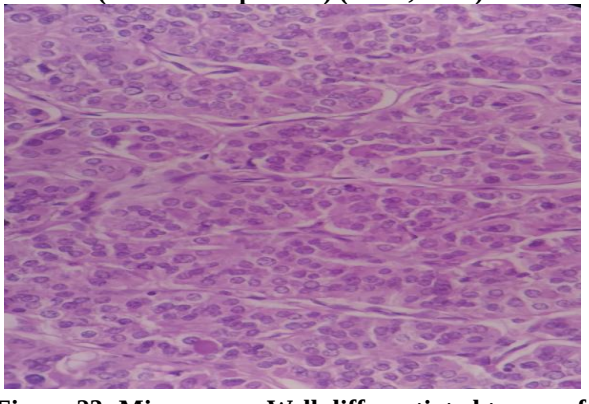


**Figure 23: Microscopy: Well differentiated tumor of uncertain malignant potential (encapsulated follicular lesion) (H&E, 100x)**

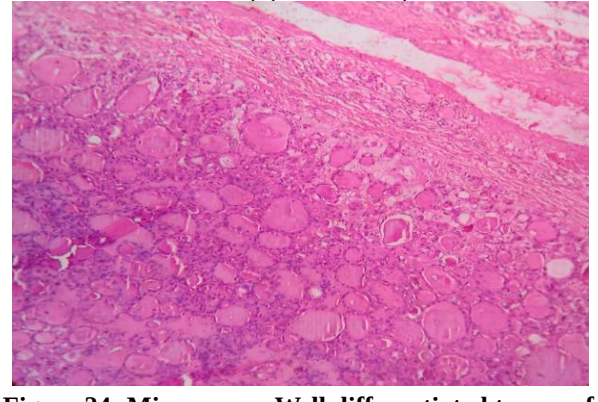


**Figure 24: Microscopy: Well differentiated tumor of uncertain malignant potential (focal incomplete nuclear features of PTC) (H&E, 400x)**

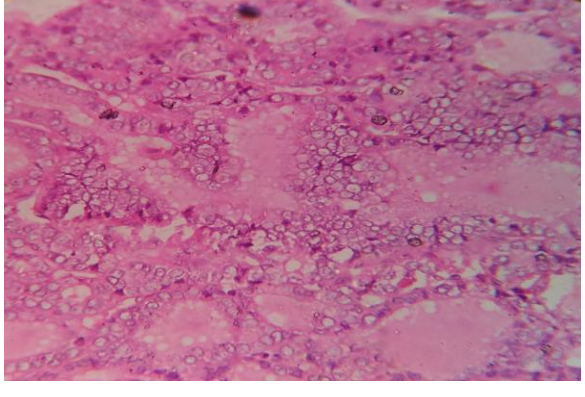


**Figure 25: Microscopy: Anaplastic Thyroid carcinoma (Sarcomatoid variant) (H&E, 100x)**

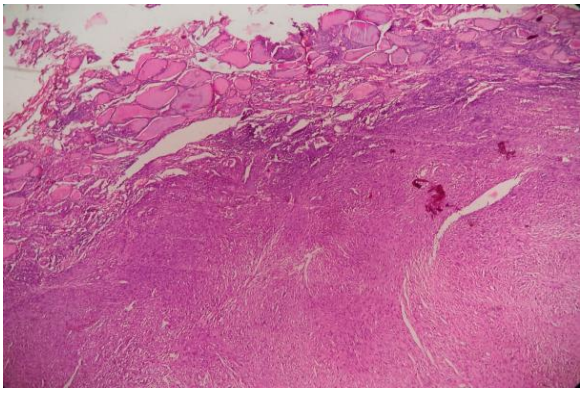


**Figure 26: Microscopy: Anaplastic Thyroid carcinoma (tumour giant cell & large pleomorphic tumour cells) (H&E, 400x)**

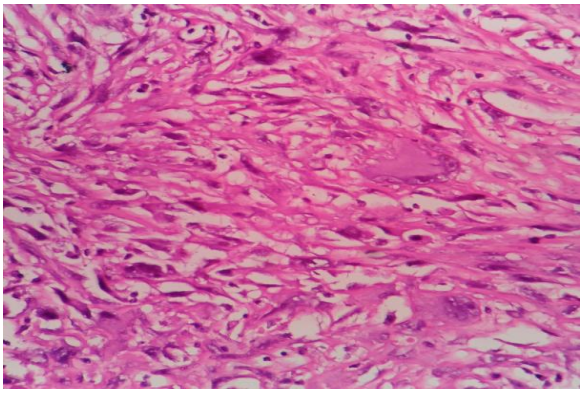


**Figure 27: Microscopy: Anaplastic Thyroid carcinoma (surrounding fat infiltration) (H&E, 100x)**

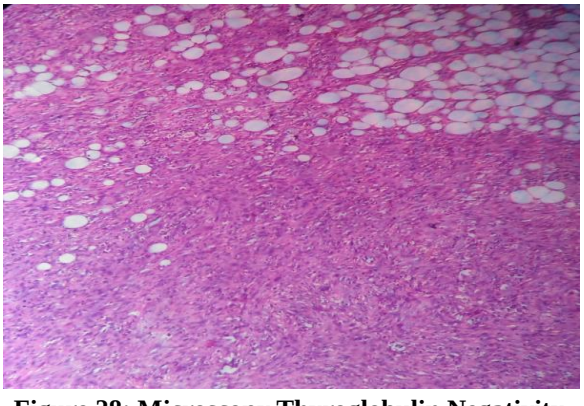


**Figure 28: Microscopy Thyroglobulin Negativity Anaplastic thyroid Carcinoma (IHC, 100x)**

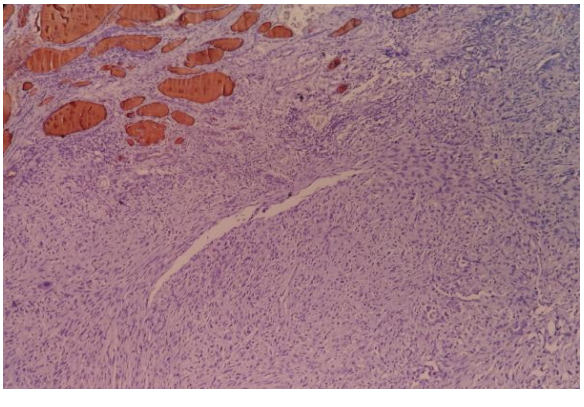


**Figure 29: Microscopy Vimentin Positivity Anaplastic thyroid Carcinoma (IHC, 400x)**

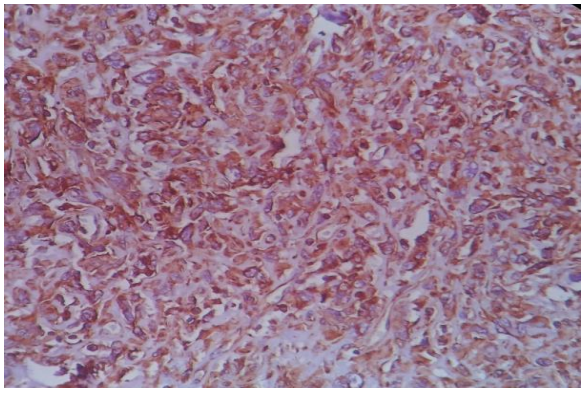


**Figure 30: Microscopy Focal Pankeratin Positivity Anaplastic thyroid Carcinoma (IHC, 400x)**

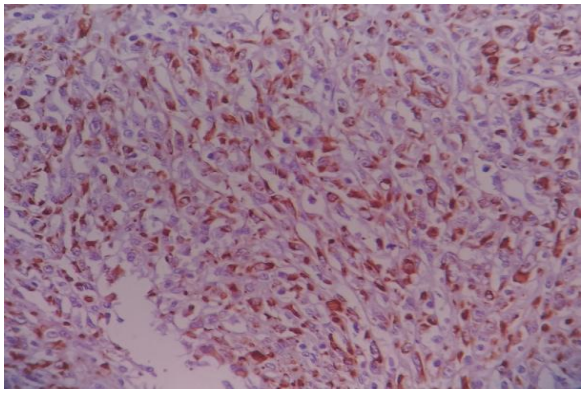


**Figure 31: Microscopy: Medullary Thyroid carcinoma (solid pattern of growth & amyloid deposition) (H&E, 100x)**

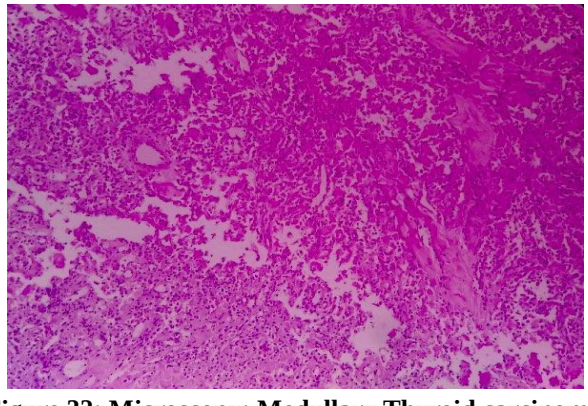


**Figure 32: Microscopy: Medullary Thyroid carcinoma (Plasmacytoid cells & amyloid deposition) (H&E, 400x)**

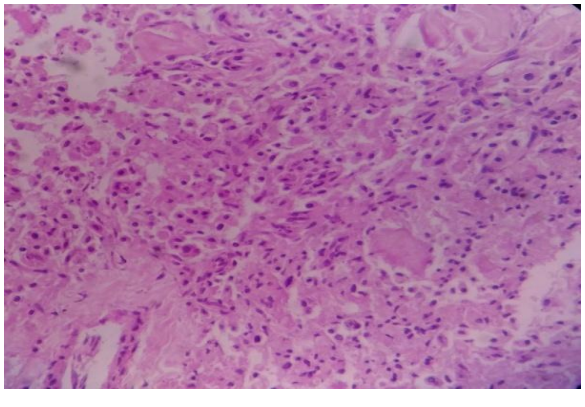


**Figure 33: Microscopy Calcitonin Positivity medullary thyroid Carcinoma (IHC, 400x)**

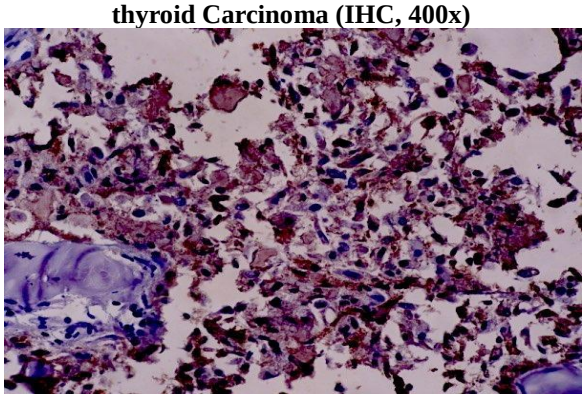


**Figure 34: Microscopy CEA Positivity medullary thyroid Carcinoma (IHC, 400x)**

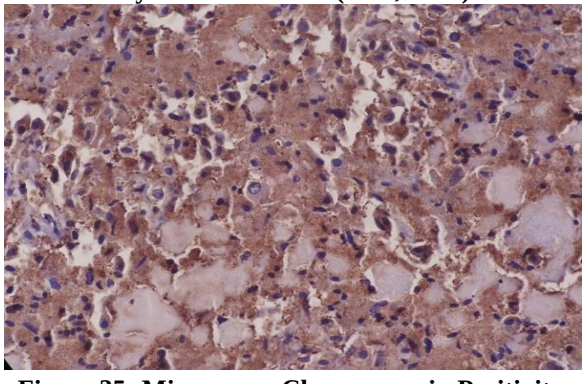
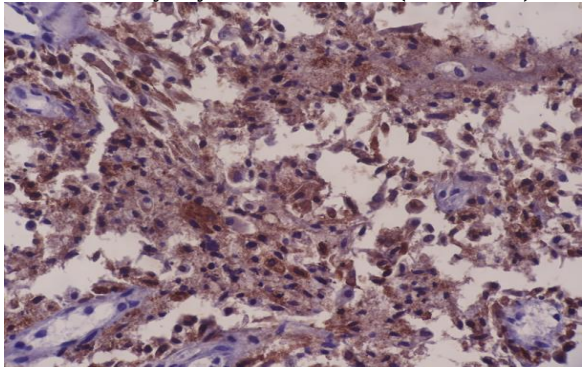


**Figure 35: Microscopy Chromogranin Positivity medullary thyroid Carcinoma (IHC, 400x)**



## 4. Conclusion

Thyroidectomy may have both therapeutic and diagnostic value. Thyroid lesions are more common in females. Most of the lesions were non- neoplastic. Colloid goiter was the most common non- neoplastic lesion. The most common benign tumor was Follicular adenoma. Papillary carcinoma accounted for the most common malignancy affecting the thyroid gland.

## References


[1]. Tsegaye B, Ergete W. Histopathologic Pattern of Thyroid Disease. *East Arf Med J* 2003; 80:525- 528.

[2]. Chandanwale S, Singh N, Kumar H, Pradhan P, Gore C, Rajpal M. Clinicopathological correlation of thyroid nodules. *Int J Pharm Biomed Sci* 2012; 3(3): 97-102.

[3]. Vinay Kumar, Abul Abbas, Jon Aster. Robbins and Cotran, Pathologic Basis of Disease: South Asia Edition, Elsevier India 2014; 2(chapter 24).

[4]. Gole S *et al*. Profile Of Thyroid Neoplasms With Special Focus On Interesting Cases: A Hospital Based 12 Year Longitudinal Study. *The Internet Journal of Pathology*. 2013; 14(1):1-13.

[5]. De Lellis RA, Lloyd RV, Heitz PU, Eng C. World Health Organization Classification of tumors. Pathology and genetics of tumors of endocrine organs. Lyon, France: IARC Press; 2004.

[6]. Mackenzie EJ, Mortimer RH. Thyroid nodules and thyroid cancer. *Med J Aust.* 2004; 180:242-7.

[7]. Elhamel A, Sherif I, Wassef S. The Pattern of Thyroid Disease in Closed Community of 1.5 Million People. *Saudi Med J*. 1988; 9:481-4.

[8]. Welker MJ, Orlov D. Thyroid nodules. *Am Fam Physician*. 2003; 67:559-66.

[9]. AACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. *Endocr Pract.* 2006; 12:63-102.

[10]. Raphael Solomon, Yawale Iliyasu1, A. Z. Mohammed. Histopathological pattern of thyroid lesions in Kano, Nigeria: A 10-year retrospective review (2002-2011). *Nigerian Journal of Basic and Clinical Sciences*. 2015; 12(1): 55-60.

[11]. Golder Samir, Satpathy Shanta Nibedita, Padhy Rajesh Kumar, Panigrahi Rajlaxmi, Ghata Swarupjit. A Clinicopathological Study of Solitary Thyroid Nodule. *J Pharm Biomed Sci* 2015; 05(03): 233-237.

[12]. Abdulla H. Darwish, Khalid A. Al Sindi, Jihene El Kafsi, B Acantab. Pattern of Thyroid Diseases- A Histopathological Study. *Bahrain Medical Bulletin*, 2006; 28 (4).

[13]. Sherine I. Salama, Layla S Abdullah, Mohamed H. Al-Qahtani, Jaudah A. Al-Maghrabi. Histopathological pattern of thyroid lesions in western region of Saudi Arabia. *The New Egyptian Journal of Medicine*, 2009; 40(6): 580-585.

[14]. Huque SM Nazmul, Ali Mohammad Idrish, Huq Md. Mahmudul, Rumi Sk. Nurul Fattah, Sattar Md. Abdus, Khan AF Mohiuddin. Histopathological pattern of malignancy in solitary thyroid nodule. *Bangladesh J Otorhinolaryngol* 2012; 18(1): 5-10.

[15]. Champa Sushel, Tariq Wahab Khanzada, Imrana Zulfikar, Abdul Samad. Histopathological Pattern of Diagnoses in Patients Undergoing Thyroid Operations. *Isra University Hospital* 2008; 1-7.

[16]. Khadilkar UN, Maji P. Histopathological study of solitary nodules of thyroid. *Kathmandu University Medical Journal* 2008; 6(4) 24: 486-490.

[17]. Frazell EL, Foote FW, Jr. Papillary thyroid carcinoma: pathological findings in cases with and without clinical evidence of cervical node involvement. *Cancer* 1955; 8(6): 1164-6.

[18]. Zubair W Baloch, Susan Abraham, Shelly Roberts, Virginia A LiVolsi, Differential expression of cytokeratins in follicular variant of papillary carcinoma: An immunohistochemical study and its diagnostic utility. *Human Pathology*, 1999; 30 (10): 1166-1171.

[19]. Mi Kyung Shin. Jeong Won Kim Young- Su Jul Cd 56 and high molecular weight cytokeratin as diagnostic marker of papillary thyroid carcinoma. *The Korean Journal of Pathology* 2011; 45: 477-484.

[20]. Haiyan Liu, Fan Lin, Application of Immunohistochemistry to Thyroid Neoplasms, *Arch Pathol Lab Med*; 2015; 139: 67-82.

[21]. Ivana Subotica. Histopathological and immunohistochemial features of thyroid carcinoma. *Review Article of Oncology* 2003; 11(3):173-174.

[22]. David Dabbs, Diagnostic immunohistochemistry Theranosticandgenomic application, third edition, 2010; 1:3-13.

[23]. Ordonez NG, El Naggar AK, Hickey RC, Samaan NA. Anaplastic thyroid carcinoma. Immunocytochemical study of 32 cases. *American Journal of Clinical Pathology*, 1991; 96 (1).

[24]. Holm R, Sobrinho-Simoes M, Nesland JM, *et al*. Medullary carcinoma of the thyroid gland: An immunocytochemical study. *Ultrastruct Pathol*. 1985; 8: 25-41.

[25]. Kimura N *et al*. Dept. of pathology, Tohoku University school of medicine, sendai, Japan Virchow. Immunohistochemical study of chromogranin in 100 cases of pheochromocytoma, carotid body tumor, medullary carcinoma of thyroid and carcinoid tumor: *Arch Pathol Anat Histopathol*.1988; 413(1): 33-8.