Histopathological Evaluation of Non-Tumorous Areas of Thyroid Gland In Thyroid Malignancy

Jahan S[1], Kamal M[2], Huq MH[3], Rahman MM[4], Islam S[5]

Abstract

Thyroid carcinoma is common and represents 1% of all human neoplasia. Incidence increases if occult carcinoma are taken into consideration. Some of the cancers of the thyroid gland have got relashionship with non-neoplastic conditions such as Hashimoto thyroiditis, Graves' disease and multinodular goiter. This cross sectional study was performed on a total of 50 cases of thyroid carcinoma at the Department of Pathology Bangabandhu Sheikh Mujib Medical University, Dhaka for a period of six months from March 2012 to August 2012 for histopathological evaluation of tumor and non-tumorous areas of thyroid gland. The age range of patients with malignant thyroid tumor was 12 to 65 years with a male to female ratio 1:3.2. Lymphocyte infiltration and lymphoid follicle formation were the predominant changes in the non-tumorous areas adjacent to thyroid malignancy which are found mostly with papillary thyroid carcinoma. This study suggested that if these changes are found in thyroid specimen which are operated due to any cause including clinically benign cases, we should thoroughly search for thyroid carcinoma inside the gland.

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Introduction

Thyroid carcinoma is a common malignancy. Incidence increases if occult carcinoma are taken into consideration[1]. Some of the cancers of the thyroid gland have got relashionship with non-neoplastic conditions such as Hashimoto thyroiditis, Graves' disease and multinodular goiter[2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17]. The frequency of the association of Hashimoto thyroiditis and Graves' disease with differentiated thyroid carcinomas is approximately 30% and 16.9%, respectively[3]. The association between thyroiditis and carcinoma has been reported mostly in Hashimoto thyroiditis (HT) and papillary carcinoma. It has also been reported in follicular carcinoma, follicular adenoma, medullary carcinoma[8,9,10,15] and in non-Hodgkin lymphoma[14]. However, the association between lymphocytic thyroiditis and papillary thyroid carcinoma, and the prognostic significance of lymphocytic infiltrate in patients with thyroid malignancy, remains controversial[3, 4, 5, 7]. The survival of patients who have papillary thyroid cancers may be superior in coexistent Hashimoto's thyroiditis[4, 6, 17] and reduced risk of recurrence[16]. Multinodular goiter (MNG) is one of the commonest presentations of thyroid disorders in Bangladesh[11]. The incidence of occult malignancy in MNG varies from 4 to 17 percent[12] and the common type is papillary carcinoma (62.5%). The incidence is high in nontoxic single nodule, common in female and generally occurrs at older age[1, 13].

1. * *Dr Shahanaz Jahan*
   Assistant Professor, Dept of Pathology,
   Community Based Medical College Mymensingh,
   Bangladesh.

2. *Professor Mohammed Kamal*
   Chairman, Department of Pathology,
   Bangabandhu Sheikh Mujib Medical University
   Shahbag, Dhaka-1000, Bangladesh.

3. *Professor Dr. Mirza Hamidul Huq*
   Professor, Dept of Pathology & Principal
   Community Based Medical College Mymensingh,
   Bangladesh.

4. *Dr. Mohammad Mosiur Rahman*
   Lecturer, Dept. of Cytopathology
   National Institute of Cancer Research & Hospital,
   Dhaka.

5. *Dr. Shamina Islam*
   Rearch Assistant, Department of Pathology
   Bangabandhu Sheikh Mujib Medical University
   Shahbag, Dhaka-1000, Bangladesh.

Address of Correspondence:
Email : mmsk1995@gmail.com
Phone: 01716235481

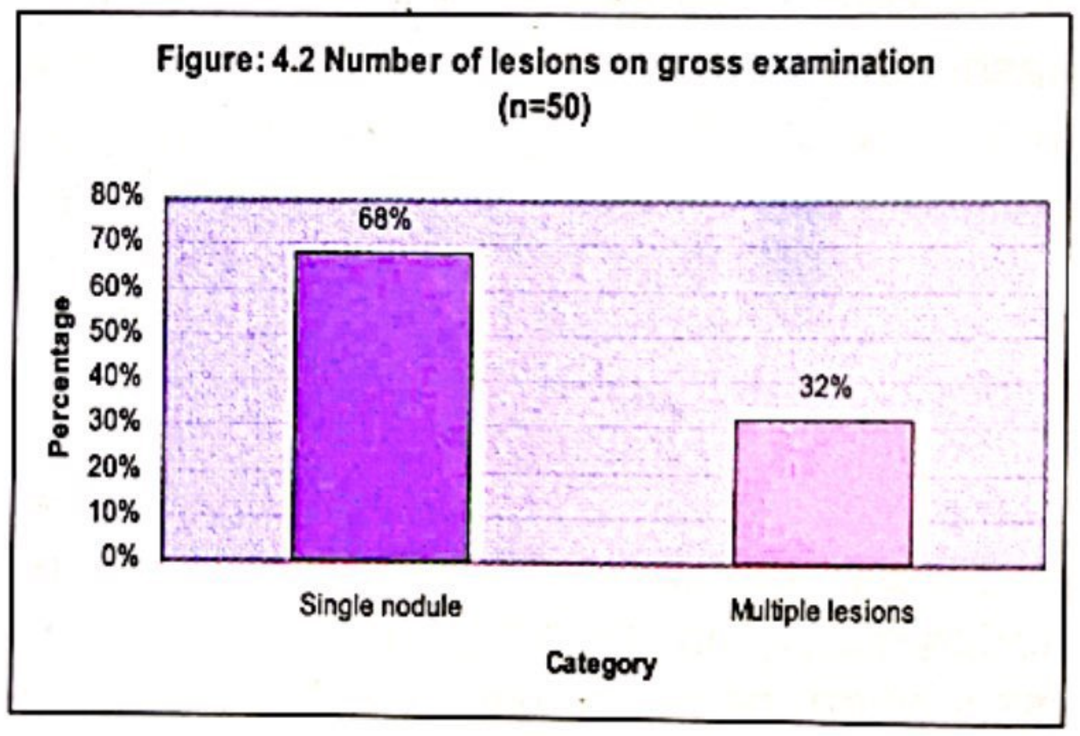
Methods

This Cross sectional study was carried out in the Department of Pathology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka during the period of March 2012 to August 2012. A total of 50 cases of thyroid malignancy were selected on the basis of histopathological diagnosis and presence of grossly detectable non-tumourous thyroid tissue for examination. Clinically and cytologically suspected cases of thyroid malignancy subsequently proved to be non-malignant lesions in histopathological examination were excluded. Also excluded from the study were: non-malignant, secondary or metastatic cancer and thyroid malignancy with no detectable normal tissue grossly or less than one cm non-tumorous area. Clinical information was obtained by taking history and recorded in clinical proforma. Specimens were obtained after surgical resection and were collected in a container containing 10% neutral buffered formalin and properly labeled. The specimens were grossly examined and recorded at the Department of Pathology of BSMMU with a particular emphasis on size of the tumor and non-tumorous area, multicentricity, consistency, presence or absence of capsule, cystic contents and appearance of cut surface. In all cases three blocks (3-5 mm thick) were taken from the tumorous area and in most cases four representative tissue blocks were taken from the non-tumorous area of the thyroid gland. After fixation tissue blocks were submitted for routine processing and paraffin embedding. For microscopic examination, routine paraffin sections were stained with haematoxylin and eosin staining method. In one case of medullary carcinoma, Crystal violet and Congo red stain was done. Tissue processing and staining were performed in autoprocessor and auto-stainer following standard protocol. Routinely stained sections were first examined under low power and then high power magnifications. Both the tumor and the non-tumorous areas were examined thoroughly. The following points were noted during examination: cellular morphology, follicular architecture, capsular invasion, vascular invasion, growth patterns, stromal changes e.g. hyaline change, fibrosis etc, presence of lymphoid follicle, inflammatory cell infiltration and presence of other co-existent disease or any other abnormalities. Regarding the stromal changes, the predominant change was recorded in relation to tumor type. All the necessary and relevant data were arranged in systemic manner, presented in various tables and figures and statistical analyses were made with the help of SPSS (version 16).

Results

The age range of patient with malignant thyroid tumor was 12 to 65 years with mean age 42.8 years with a male to female ratio 1:3.2. The average age of female patients was 44.42 years and the average age of male patients was 37.66 years. No case was found in 1st decade and beyond 7th decade with the highest frequency of malignancy 20(40%) in 3rd decade. Among 50 cases, 24(48%) specimen were total thyroidectomy sample followed by 14(28%) left hemithyroidectomy and 12(24%) right hemithyroidectomy sample. In this study, 34(68%) were found single lesion and 16(32%) were multicentric lesion (figure 1).

Figure-1: Bar diagram showing number of lesions on gross examination.



The size of the tumors in this study ranges from 0.5 cm to 9.5 cm with a mean value of 1.2 cm. In most of the cases 36 (72%) show non-tumorous area at one side of the tumor and 14(28%) show this area surrounding the tumor. Grossly the range of this area was 1.2 cm to 4 cm. On histopathology, the highest frequency of thyroid malignancy was papillary thyroid carcinoma (PTC) 43 (86%) followed by

follicular thyroid carcinoma (FTC) 4 (8%), anaplastic thyroid carcinoma (ATC) 2 (4%) and medullary thyroid carcinoma (MTC) 1 (2%). Among the PTC, the predominant type was conventional 28 (65%) followed by follicular variant 13 (31%) and papillary microcarcinoma 2 (4%) (table 1).

Table-1: Histopathological types of thyroid malignancy (n=50):

Name of tumor	No. of cases
Papillary carcinoma -Conventional -follicular variant -papillary microcarcinoma	43 (86%) -28 (65%) -13 (31%) -02 (4%)
Follicular carcinoma	4 (8%)
Anaplastic carcinoma	2 (4%)
Medullary carcinoma	1 (2%)

Inflammatory cells within tumor and non-tumorous areas were predominantly lymphocytes. In non-tumorous area, the infiltrate were evaluated and found mostly near the adjacent area of tumor. Among the other inflammatory cells macrophages, plasma cells and eosinophils were present. All the cases were found in association with papillary carcinoma and predominantly in non-tumorous areas. Among the 43 cases of PTC, 14 (32%) cases show presence of inflammatory cells in non-tumorous area. Follicular, anaplastic and medullary carcinomas do not show inflammatory cells. Small sample size may be the cause (table 2).

Table-2. Percentage of type of inflammatory cells in non-tumorous areas

	Distribution in non- tumorous area/100 cells
Lymphocyte	56%
Macrophage	28%
Plasma cell	10%
Eosinophil	06%

Lymphoid follicles were present focally, near the adjacent area of tumor and predominantly in non-tumorous areas. All the cases were found in association with PTC. Among 43 cases of PTC 4 (9%) and 10 (23%) show lymphoid follicles in tumor and non-tumorous areas respectively (table 3).

Table-3. Distribution of lymphoid follicles in tumor and non-tumorous areas in papillary carcinoma cases.

Area involved	Distribution in tumor	Distribution in non-tumorous area
Focal	3 (7%)	7 (16%)
Diffuse	1 (2%)	3 (7%)
Total	4 (9%)	10 (23%)

Lymphoid follicles are more frequently present in non-tumorous area than tumor.
(P = > o.o5)

Distribution of stromal changes was more or less similar between tumor (56%) and non-tumorous areas (54%). These changes were most pronounced in PTC. All type of changes was found in PTC as nearly similar distribution in both the tumor and non-tumorous areas. Fibrosis, hemorrhage and hyalinization were found in variable amount in some of the cases of FTC, ATC and MTC both in tumor and in non-tumorous areas. Areas of dystrophic calcification and Psammoma bodies were found only in PTC, both within tumor and in non-tumorous areas. The cases those show presence of MNG in non-tumorous areas, a few of the cases also show foci of dystrophic calcification and fibrosis (table-4).

Table-4. Stromal changes in tumour and non-tumourous areas of thyroid.

Indicator	Distribution in tumor	Distribution in non-tumorous area
Fibrosis	12	10
Hemorrhage	6	5
Hyalinization	4	3
Calcification	4	8
Psammoma body	2	1
Total	28 (56%)	27 (54%)

Stromal changes are more frequently present in tumor than non-tumorous area.
(P = > o.o5) except calcification.

MNG and HT was found as co-existent disease. All the cases was found in non-tumorous areas of papillary carcinoma. Among 43 cases of PTC, 6(14%) show MNG and 3(7%) show HT. All the cases of HT were biochemically hypothyroid and shown positive antibody titer. The FTC, ATC and MTC do not show any co-existent disease in non-tumorous areas (table 5).

Table-5. Distribution of co-existent diseases in non-tumorous area.

Co-existent disease	No. of cases
Multinodular goiter	6 (14%)
Hashimoto thyroiditis	3 (7%)
Total	9 (21%)

Discussion

In the present study, age range of patient with malignant thyroid tumor was 12 to 65 years with mean age 42.8 years. The average age of female patients was 44.42 years and the average age of male patients was 37.66 years with a male to female ratio 1:3.2.

Among the 50 cases, the highest frequency of malignancy was 20 cases (40%) in 3rd decade followed by 8 cases (16%) in 4th decade, each 7 cases (14%) in 2nd and 6th decade, 6 cases (12%) in 5th decade and 2 cases (4%) in 7th decade. Out of these, 12 cases (24%) were male patients and 38 cases (76%) were female patients. In a study, Darwish et al found malignant thyroid cases at the age ranges from 21 to 82 years and out of 26 malignant cases he found 18 cases in female and 08 cases in male [18], Another study by Mader et al shows the age ranges from 5-87 years[19]. The present study is a short-period study and has a small sample size. So no case was found in 1st decade and beyond 7th decade.

In total thyroidectomy sample, multiple and single lesions were found. In this study, 34 (68%) cases show single lesion and 16 (32%) cases show multicentric lesions. In a review by Leung et al (2011), 57% cases had single tumor focus and 43% had 2 or more foci[25]. Several studies revealed solitary thyroid lesions as thyroid carcinoma and also multicentric lesions that are mostly found in PTC and also FTC and MTC [19,20]. In one study, of the 65 patients of FTC, 52 (80%) were presented as solitary thyroid nodule[21].

The size of the tumors in this study ranges from 0.5 cm to 9.5 cm with a mean value of 1.2 cm. Among the 50 cases, 21 (42%) had the diameter of >1-2 cm followed by 14 (28%) cases >2 cm, 13 (26%) cases >4 cm and only 2 (4%) cases were <1 cm. Most of the tumors were in TNM stage T1, followed by stage T2 and stage T3. In a review of 368 cases of thyroid malignancy, 89% tumor were >1cm in diameter[22].

Amount of non-tumorous area was detected on gross examination. Most of the cases 36 (72%) show non-tumorous area at one side of the tumor and 14 (28%) show this area surrounding the tumor. Grossly the range of this area was 1.2 cm to 4 cm. Among 50 cases, 27 (54%) cases were 1-2 cm in diameter and 23 (46%) were 2-4 cm in diameter.

In this study, the highest frequency of thyroid malignancy was PTC 43 (86%) followed by FTC 4 (8%), ATC 2 (4%) and MTC 1 (2%). In many studies of thyroid gland, PTC was found as the commonest malignancy[7,16,21,22,23]. In the current study, most of the PTC were found in 2nd to 5th decade, FTC were in 3rd to 7th decade ,ATC were in 4th to 7th decade and the MTC were found in 4th decade. This is consistent with a study by A. Sofiadis [23]. Among the PTC, the predominant type was conventional 28 (65%) followed by follicular variant 13 (31%) and papillary microcarcinoma 2 (4%). In a study by Lars et al, among the 128 cases of PTC most of the cases were conventional type[24].

In the present study, Inflammatory cells within tumor and non-tumorous areas were

predominantly lymphocytes. In non-tumorous area, the infiltrate were evaluated and found mostly near the adjacent area of tumor. Among the other inflammatory cells macrophages, plasma cells and eosinophils were present. All the cases were found in association with papillary carcinoma and predominantly in non-tumorous areas. Among the 43 cases of PTC, 14 (32%) cases show presence of inflammatory cells in non-tumorous area. FTC, ATC and MTC do not show inflammatory cells. Small sample size may be the cause. Many experimental evidence suggest, inflammatory cells are present in thyroid cancer that exert a pro-tumorigenic function and moreover oncoproteins typically expressed in human PTCs, trigger a pro-inflammatory programme in thyrocytes[2]. The co-existence of lymphocytic thyroiditis (LT) and PTC has been variously reported[4].

In this study, lymphoid follicle with or without formation of germinal center were evaluated within tumor and non-tumorous areas . In most of the cases it was present focally, near the adjacent area of tumor and predominantly in non-tumorous areas. All the cases were found in association with PTC. Lymphoid follicles may also found in FTC but because of small sample size only 4 cases were follicular carcinoma and no significant changes were found. The ATC and MTC also do not show follicles within tumor and non-tumorous areas. Among 43 cases of PTC, 4 (9%) and 10 (23%) show lymphoid follicles in tumor and non-tumorous areas, respectively. In an immunohistochemical study of inflammatory markers, Ardito et al found inflammatory cytokines in all cases in the tumor-adjacent normal thyroid gland and he found it mostly in association with PTC [28]. Another study shows the majority of PTC (65%) and FTC (75%) containing lymphocytes in the immediate vicinity of thyroid cancers and the number of lymphocytes per high powered field was greater for multifocal PTC, and the number of proliferating lymphocytes was greatest for PTC with regional lymph node involvement[16].

Distribution of stromal changes was more or less similar between tumor 28 (56%) and non-tumorous areas 27 (54%) in this study. These changes were most pronounced in PTC. All type of changes was found in PTC as nearly similar distribution in both the tumor and non-tumorous areas. Fibrosis, hemorrhage and hyalinization were found in variable amount in some of the cases of FTC, ATC and MTC both in tumor and in non-tumorous areas. Areas of dystrophic calcification and Psammoma bodies were found only in PTC, both within tumor and non-tumorous areas. In non-tumorous area, most of the cases show fibrosis 10 (20%) followed by hemorrhage 8 (16%), hyalinization 5 (10%), calcification 3 (6%) and Psammoma body in 1 (2%) cases. It has been reported that PTC is associated with a variable degree of fibrosis [26] and in ATC stromal fibrosis is one of the main feature[27].

In this study, MNG and HT were found as co-existent disease. All the cases were found in non-tumorous areas of PTC. Among 43 cases of PTC, 6 (14%) show MNG and 3 (7%) show HT. The FTC, ATC, and MTC do not show any co-existent disease in non-tumorous areas. Many studies have found co-existence of HT with PTC [5,6,7,8,9,10,15]. In this study, co-existence of HT with PTC was 7% and in a study by Elias et al (2010) it was 8.6% [7]. The incidence of MNG in this study was 12% of total cases of thyroid carcinoma. Many studies show incidence of occult carcinoma in MNG that varies from 4-17% [1,11,12,13]. According to published works, the histopathological type of carcinoma more frequently related to MNG was shown to be PTC (62.5%) [11].

Conclusion

In non-tumorous area of thyroid malignancy, two-thirds of cases showed no change. In other cases lymphocyte infiltration and lymphoid follicle formation were predominant change. These were` mostly limited with papillary thyroid carcinoma. Psammoma body was also found in non-tumorous area of papillary carcinoma of thyroid gland in addition to its presence within tumor. If these changes are found in non-tumorous area, we should thoroughly search for thyroid carcinoma inside the gland.

References

1. *Gandolfi PP, Frisina A, Raffa M, Rena F, Rocchetti O, Ruggeri C, Alberto Tombolini A. The incidence of Thyroid Carcinoma in Multinodular Goiter: retrospective analysis. Acta Bio Medica Agene Paramense. 2004;75:114-117.*
2. Guarino V, Castellone MD, Avilla E, Melillo RM. *Thyroid cancer and inflammation. Mol Cell Endocrinol. 2010;321:94-102*
3. Ciri J, Beleslin-Nedeljkovi B. *Differentiated thyroid carcinoma in previously manifested autoimmune thyroid disease.* Srp Arh Celok Lek. *2005;133:74-6.*
4. *Chuan LK, Francis S. Greenspan, Dong F, Theodore RM, Peter PBY. Influence of Lymphocytic Thyroiditis on the Prognostic Outcome of Patients with Papillary Thyroid Carcinoma. J Clin Endocrinology and Metabolism. 1999;84:458.*
5. *Matesa AD, Matesa N, Dabelie N, Kusie Z. Coexistence of Papillary carcinoma and Hashimoto thyroiditis. Acta Clin Croat. 2009;48:9-12.*
6. Singh B, Shaha AR, Trivedi H, Carew JF, Poluri A, Shah JP. *Coexistent Hashimoto's thyroiditis with papillary thyroid carcinoma: impact on presentation, management and outcome.* Surgery. *1999;126:1070-7.*
7. *Elias EM, Anastasios AT, Elpida ID, Athanasios NT, Periklis KS, Christos MK, Maria GP, Ioannis KS. Coexistence of Hashimoto's thyroiditis with papillary thyroid carcinoma: a retrospective study. Hormones. 2010;9:312-317.*
8. *Conwell LS, Greer ML, Stewart A, Perry CF. (2009). Differentiated thyroid carcinoma associated with histological features of Hashimoto's thyroiditis. J Ped Endocrinology & Metabolism. 2009;22:991-993.*
9. Liu LH, Bakhos R, Wojcik EM. *Concomitant papillary thyroid carcinoma and Hashimoto's thyroiditis.* Semin Diagn Pathol. *2001;18:99-103.*
10. Kollur SM, Sayed S, Hag IA. *Follicular thyroid lesions coexisting with Hashimoto's thyroiditis: incidence and possible sources of diagnostic errors. Diagn Cytopathol. 2003;28:35-8.*
11. *Rahman MM. Biochemical Status and Cytopathological Profile of Patients Presenting with Multinodular Goiter. J Medicine. 2011;12:26-29.*
12. *Pedamallu R, Pedamallu SB, Rao KR , Pedamallu CS. Incidence of occult carcinoma in multinodular goiter using histopathological findings. J Surgery. 2008; 17.*
13. *Warren HC, Alvin LW. Incidence of carcinoma of the thyroid in nodular goiter. Semin Surg Onc. 1991;7:61–63.*
14. *Seeriweera EH, Ratnatunga NV. Profile of Hashimoto's Thyroiditis in Sri Lankas: Is There an Increased Risk of Ancillary Pathologies in Hashimoto's Thyroiditis? Journal of Thyroid Research. 2010, Article ID 124264, 5 pages*
15. *Wijayawardena MA, Gunawardane HD, Sheriffdeen AH, Silva MV. Medullary carcinoma of the thyroid gland associated with Hashimoto thyroiditis. The Ceylon Med J. 2004;49:96.*
16. *Gupta S, Patel A, Folstad A, Fenton C, Dinauer CA, Tuttle RM, Conran R, Francis GL. Infiltration of Differentiated Thyroid Carcinoma by Proliferating Lymphocytes Is Associated with Improved Disease free Survival for Children and Young Adults. J Clin Endocrinology and Metabolism. 2004;86:1346-54.*
17. *Filipovic A, Paunovic I, Vuckovic L. Influence of lymphocytic thyroiditis on prognostic outcome of differentiated thyroid carcinoma. Acta Chir Iugosl. 2010;57:85-94.*
18. *Darwish A H, Sindi K A A, Kafsi J E, Pattern of Thyroid Diseases - A Histopathological Study Bahrain Medical Bulletin 2006: 28(4).*
19. Verburg *F A,* Uwe Mäder, Luster *M and* Christoph Reiners. *Histology does not influence prognosis in differentiated thyroid carcinoma when accounting for age, tumour diameter, invasive growth and metastases European Journal of Endocrinology 2009:160, 619–624*
20. *Dionigi G, Castano P , Bertolini V, Boni L, Rovera F, Maria L T, Capella C, Bartalena L and Renzo D. Simultaneous medullary and papillary thyroid cancer: two case reports Journal of Medical Case Reports 2007, 1:133. 23. Dionigi G, Castano P , Bertolini V, Boni L, Rovera F, Maria L T, Capella C, Bartalena L and Renzo D. Simultaneous medullary and papillary thyroid cancer: two case reports Journal of Medical Case Reports 2007, 1:133.*
21. *Geoffrey T. Emerick, Quan-Yang Duh, Allan E. Siperstein, Gerard N. Burrow , Orlo H. Clark. Diagnosis, treatment, and outcome of follicular thyroid carcinoma, Cancer 1993: 72 (11) : 3287–3295.*
22. Angela M Leung, Shalini Dave, Stephanie L Lee, Francis X Campion, Jeffrey R Garber, *and* Elizabeth N Pearce *Factors determining the persistence or recurrence of well-differentiated thyroid cancer treated by thyroidectomy and/or radioiodine in the Boston, Massachusetts area: A retrospective chart review. Thyroid Res. 2011; 4: 9.*
23. *A. Sofiadis. In search of diagnostic and prognostic markers for thyroid cancer: A proteomics approach. Karolinska Institute, Sweden, 2010.*
24. *Lars A. Asklen, Virginia A Livolsi. Prognostic Significance of Hitologic Grading Compared With Subclassification of Papillary Thyroid Carcinoma. American Cancer Society, 2000*
25. *Guglielmo Ardito et al. Immunohistochemical evaluation of inflammatory and proliferative markers in adjacent normal thyroid tissue in patients undergoing total thyroidectomy: results of a preliminary study. Journal of Experimental & Clinical Cancer Research 2010, 29:77.*
26. Michiko Inaba , Shinobu Umemura , Haruhiro Satoh , Yasuko Ichikawa , Yoshifumi Abe , Kiyoshi Kurokawa, Hideto Sakai , R. Yoshiyuki Osamura. *Papillary thyroid carcinoma with fibromatosis-like stroma: A report of two cases.* Endocrine Pathology, *2002, Volume 13,* Issue 3, *pp 219-225.*
27. *E Lammerts, Tumor Stroma In Anaplastic Thyroid Carcinoma, Acta University Upsaliensis, Uppasala, 2002.*