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Thyroid neoplasm in Graves' disease: A single center experience

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Abstract

Aim: Different comments are stated in the studies about the association between Graves' disease and thyroid neoplasms. The aim of this research was to evaluate the prevalance of thyroid neoplasm in patients with Graves' disease who underwent thyroidectomy.

Materials and Methods: A retrospective examination was made of 200 patients, who were followed up with the diagnosis of Graves' disease between 2008 and 2020. A total of 46 patients who underwent thyroidectomy were evaluated in the study. Euthyroidism was achieved in all patients before the operation.

Results: Thyroidectomy for Graves' disease was performed in 46 cases. Thyroid neoplasm was identified in the surgically-resected specimens of 12 patients (26.1%). The prevalence of thyroid neoplasm was higher in patients with nodules than in those without (p= 0.08). The level of white blood cells was higher in patients with neoplasm than in those without. The levels of thyroglobuline antibody and thyroid peroxidase, which are increased in autommune thyroiditis, were higher in patients without neoplasms than in those with neoplasm.

Conclusion: In addition to careful physical examination, thyroid ultrasonography should be performed in patients with Graves' disease. Surgery should be recommended for patients with suspicious or malignant findings on thyroid ultrasonography and fine needle aspiration biopsy. Also, increased white blood cell count and low thyroid autoantibody levels should raise suspicion of the presence of neoplasm.

Introduction

Graves' disease is an immune-mediated hyperthyroidism. It has been associated with genetic and environmental factors and annual incidence has been estimated to be 20-50/100.000 [1]. The disease is characterized by excessive production of thyroid hormones.

Graves' disease can be treated with antithyroid drugs, radioiodine ablation, and surgery [2]. Common surgical indications include the presence of an obstructive or very large goiter, moderate to severe, active orbitopathy, allergies to or poor compliance with antithyroid drugs, the coexistence of a suspicious or malignant thyroid nodule, and primary hyperparathyroidism [3].

As the thyroid gland can grow in a diffuse manner, nodules can be detected by palpation or imaging methods. The frequency of palpable thyroid nodules is higher in patients with Graves' disease (15%) [4, 5]. With advances in imaging methods, the incidence of thyroid nodules has increased, and when nodules are detected, there is an increased risk of thyroid neoplasm [6].

Thyroid neoplasm is the most common endocrine malignancy and it originates from the thyroid epithelium [7]. Although previous studies have showed an increased risk of thyroid neoplasm in Graves' patients, this remains a matter of debate [8]. In cases in literature, the incidence of neoplasms ranges from 2% to 33.7% in patients with Graves' disease (9]. The most common type of neoplasm seen in Graves' patients is incidentally detected micropapillary thyroid cancer [10].

The mechanisms have not been clearly established and predictive factors for thyroid neoplasm have not been confirmed. However, it has been emphasized that pathways are activated by the binding of thyroid-stimulating receptor antibodies, which stimulate growth, invasion, and angiogenesis, to activated insulin-like growth factor pathways [11, 12). While some studies have emphasized that lym-

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phocytic thyroiditis can be important risk factor for thyroid neoplasm, some reports have stated that multinodular hyperplasia is a contributor for thyroid neoplasm [13-15]. If the factors, associated with thyroid neoplasm are evaluated in detailed preoperatively, the operation procedure can be more organized.

The aim of this research was to evaluate the prevalence of thyroid neoplasm in Graves' patients who underwent thyroidectomy, and to investigate the clinicodemographic data, imaging characteristics, and laboratory parameters of those patients.

Materials and Methods

The documents of 200 patients, followed up with the diagnosis of Graves' disease between 2008 and 2020 were examined retrospectively. A total of 46 patients who underwent thyroidectomy for Graves' disease, according to the Hyperthyroidism Management Guidelines of the American Thyroid Association (ATA) were enrolled in the research [3].

Indications for thyroidectomy were upper airway obstruction or severe dysphagia in 5 patients (10.9%), a thyroid nodule with indeterminate, suspicious, or positive cytology on fine-needle aspiration in 12 (26.1%), and moderate to severe Graves' ophthalmopathy with uncontrolled thyrotoxicosis in 9 (19.6%). Surgery was also applied to 20 patients (43.4%) with persistent hyperthyroidism despite medical treatment and radioablative therapy. Euthyroidism was achieved in all patients before the operation. Based on pathological examination, 12 patients had a postoperative diagnosis of thyroid neoplasm. Patients who had received external irradiation treatment in the neck region and who had undergone thyroid surgery previously were not included in the study. Data such as smoking status, gender, age ultrasonography reports, and histopathological findings of surgically resected specimens were obtained from the hospital database. The laboratory parameters of each case were examined.

The study protocol was approved byUludag University Ethics Committe (2021-1/24).

Statistical analysis

The Statistical Package for the Social Sciences software version 23 (SPSS) was used for the statistical analysis (IBM Corp; Armonk, NY, USA). Fourty-six patients who underwent thyroidectomy for Graves' disease between 2008 and 2020 constituted the sample size after data extraction from medical files. We used the non-probability consecutive sampling technique. Presence of normal distribution was investigated using visual (histograms) and analytical methods (Kolmogorov–Simirnov/Shapiro-Wilk's test). Normally distributed quantitative variables were expressed as mean values ± standard deviation. Non-normally distributed variables were expressed as median values (range). Qualitative variables were expressed as proportions. The relationship between clinicodemographic characteristics and laboratory parameters are determined by using Chi-square test. For the purpose of testing the hypothesis of differences between Graves' disease/thyroid neoplasm+ and Graves' disease/thyroid neoplasm- and also difference between Graves' disease/diffuse goiter+ and Graves' disease/diffuse goiter-, Mann-Whitney U test and the Chi-square test were used where appropriate. A value of $p<0.05$ was considered statistically significant.

Results

Initial evaluation was made of a total of 200 patients, followed up with a diagnosis of Graves' disease between 2008 and 2020, and of these, 46 patients who underwent thyroidectomy with Graves' disease for various indications were enrolled in the study. The 46 cases comprised 37 (80.4%) females and 9 (19.6%) males with a median age at diagnosis of 43.5 years (range, 25-65 years). The median length of follow-up with the diagnosis of Graves' disease was 48 months (range, 2-156 months) and propylthiouracil or methimazole were used as antithyroid drugs in the patients. Thyroid nodules were detected on preoperative ultrasonography in 16 cases (34.8%). The most common localization of the nodules was the right thyroid lobe. Nodules with suspicious features were observed on imaging in 12 cases (26.1%), so fine needle aspiration biopsy was performed. The pathology report was consistent with suspected malignancy in 4 (8.7%) patients, atypia of undetermined significance was observed in 2 (4.3%), and suspected follicular neoplasm in 2 (4.3%). A thyroid scan was performed in 28 (60.9%) cases and cold nodules were detected in 2 (4.3%) of those.

Surgical pathology compatible with thyroid neoplasm was determined in 12 (26.1%) patients. Neck dissection was also performed concurrently on 4 patients due to suspicious lymph node involvement. The median age at diagnosis was higher in patients with nodules than in patients without nodules (50.5 years (31-65) vs. 42 years (25-65), $p= 0.016$) (Table 1). Thyroid stimulating hormone (TSH) level was significantly higher in patients with nodules than in those without ($p= 0.048$). Thyroid peroxidase antibody (anti TPO) and thyroglobuline antibody (anti tg) levels were lower in patients with nodules than in those without but not at a statistically significant level ($p= 0.924$, $p= 0.555$, respectively). The level of thyroid stimulating receptor antibody (TRab) was higher in patients with nodules ($p= 0.506$). The prevalence of thyroid neoplasm was higher in patients with nodules than in those without ($p= 0.08$) (Table 1). With the exception of nodule status, no differences were determined between the patients with and without thyroid neoplasm in respect of clinicodemographic characteristics and imaging findings (Table 2).

The white blood cell count was higher in Graves' patients with thyroid neoplasm than in those without neoplasm. Levels of anti tg and anti TPO were statistically significantly higher in patients without thyroid neoplasm in those with neoplasm ($p= 0.01$, $p <0.01$, respectively) (Table 3). The levels of TRab and TSH were higher in the patients with thyroid neoplasm than in those without neoplasm, but not at a statistically significant level ($p= 0.48$) (Table 3).

The median age of patients with thyroid neoplasm was 45.5 years (31-57 years) and 79.4% were female. The characteristics of the patients are presented in Table 4. During the follow-up period, 5 patients with thyroid neoplasm required radioactive iodine treatment, and 4 underwent a second neck dissection due to recurrence of the neoplasm in the neck region.

Table 1. Comparison of clinicodemographic characteristics and laboratory parameters of the patients with Graves' disease.

Parameters	Total patients (n=46)	GD with diffuse goiter (n=30)	GD with nodular goiter (n=16)	p value
Female (n-%)	37 (80.4)	24 (77.8)	13 (81.3)	0.787
Age (years)	43.5 (25-65)	42 (25-65)	50.5 (31-65)	0.016
TSH (mU/L)	0.006 (0.01-4.4)	0.002 (0.0001-0.75)	0.01 (0.001-1.96)	0.048
Free T3 (ng/L)	3.57 (1.02-21.9)	5.79 (2.14-21.9)	3.4 (1.46-19.02)	0.143
Free T4 (ng/dL)	1.28 (0.3-4.12)	1.47 (0.52-4.12)	1.01 (0.30-3.81)	0.38
White blood cells (K/μL)	8 (2.07-16.5)	7.97 (2.07-16.5)	8.18 (4.79-13.1)	0.651
Anti tg (KU/L)	6.7 (0.4-871.5)	8 (0.6-838.2)	1.9 (0.4-871.5)	0.555
Anti TPO (KU/L)	78.1 (0.1-1001)	482.8 (0.1-1001)	17.8 (0.5-1001)	0.924
TRab (IU/L)	2.75 (0.22-101.6)	2.35 (0.24-86.6)	4.07 (0.22-101.6)	0.506
Thyroid neoplasm (n-%)	12 (26.1)	4 (14.8)	8 (37.5)	0.089

GD: Graves' Disease, *TSH:* Thyroid Stimulating Hormone, *Anti tg:* Thyroglobulin antibody, *Anti TPO:* Thyroid peroxidase antibody, *TRab:* Thyroid stimulating receptor antibody.

Table 2. Comparison of clinicodemographic characteristics and imaging findings between patients with benign and neoplastic histopathological findings.

Parameter	Neoplasm (+) (n=12)	Neoplasm (-) (n=34)	p value
Age (years)	45 (31-57)	43 (31-65)	0.88
Female (n-%)	10 (83.3)	27 (79.4)	0.76
Never smoked (n-%)	9 (25)	27 (75)	0.80
Nodule status (n-%)	6 (50)	10 (30.3)	0.089
Median diameter of largest nodule (median-mm)	10 (8-26)	20 (10-40)	0.291
Thyroid weight (median-g)	35 (12-71)	29 (7-306)	0.943

mm: Millimeter, *g:* Gram

Table 3. Comparison of laboratory findings between patients with benign and neoplastic histopathological findings.

Parameter	Neoplasm (+) (n=12)	Neoplasm (-) (n=34)	p value
TSH (mU/L)	0.93 (0.001-4.4)	0.03 (0-0.75)	0.94
Free T3 (ng/L)	3.39 (1.46-7.75)	3.81 (1.92-21.9)	0.06
Free T4 (ng/dL)	1.11 (0.73-2.2)	1.07 (0.3-3.81)	0.16
White blood cells (K/μL)	8.61 (4.79-16.5)	7.55 (2.07-12.3)	0.02
Anti tg (KU/L)	1.35 (0.6-122.2)	12.6 (0.5-871.5)	0.01
Anti TPO (KU/L)	1.25 (0.5-7.8)	482.80 (0.1-100.1)	<0.01
TRab (IU/L)	8.81 (1.5-101.6)	2 (0.22-86.61)	0.48

TSH: Thyroid Stimulating Hormone, *Anti tg:* Thyroglobulin antibody, *Anti TPO:* Thyroid peroxidase antibody, *TRab:* Thyroid stimulating receptor antibody.

Discussion

The current study investigated relationship between Graves' disease and thyroid neoplasm. The higher levels of white blood cells determined in Graves' patients with thyroid neoplasms. Furthermore, the levels of TRab and TSH were higher in patients with thyroid neoplasm than in those without neoplasm. Although this high rate was not statistically significant, it might have clinical significance. Also, the levels of anti tg and anti TPO, which are related to autoimmunity were seen to be higher in patients without neoplasm compared to those with neoplasm.

Thyroid neoplasm is a common health problem and with advances in imaging methods, its prevalance is increasing. Graves' disease is defined as hyperfunctioning of the thyroid gland because of an autoimmune process. Although Beahrs et al and Sokal reported that coexistence of Graves' disease and thyroid neoplasm was rare, Shapirova and other authors have stated that it is more frequent than predicted [16-20]. In the current research, the rate of thyroid neoplasm in Graves' patients who underwent thyroidectomy was 26% (12/46). This rate is higher than reports in other studies [21], which could be attributed to changes in the criteria for indications of thyroidectomy or the heterogenity of populations examined in the studies.

Stocker and Burch emphasised that there was an increased incidence of nodules and thyroid neoplasm in patients with Graves' disease [22]. Although the coexistence of thyroid nodules and Graves' disease has been widely examined in previous studies, the association with neoplasm is uncertain. In the literature, the neoplasm rate in the nodules found in Graves' patients varies between 10% and 46% [5]. In a meta-analysis, Staniforth et al stated that the thyroid cancer in Graves' disease was approximately 5 times more likely to be diagnosed in cases with thyroid nodules than in those without nodules [23]. In the current study, 16 patients (34.8%) with Graves' disease had thyroid nodules on preoperative ultrasonography and the rate of thyroid neoplasm in these cases was 37.5% (6/16), which was consistent with data in literature. Keskin et al found that the frequency of nodule and thyroid neoplasm risk might increase with age in Graves' disease [10]. In the this study, it was seen that the frequency of nodule may increase with age in Graves' disease, but this association could not be established for thyroid neoplasm.

The autoimmune process that is seen in Graves' disease may induce the development of thyroid neoplasm by changing host immune responses [24]. Thyroid stimulating hormone has a basic role in thyroid growth and activation. Consistent with this thesis, TSH was found to be

Table 4. Clinicopathological characteristics of the Graves' patients with thyroid neoplasm.

Parameter		Results
Age(median-years)		45.5 (31-57)
Female (%)		79.4
Type of tumor (n-%)	Classic variant papillary microcarcinoma	3 (25)
	Classic variant papillary carcinoma	5 (41.7)
	Tall cell variant of papillary carcinoma	1 (8.3)
	Follicular adenoma	3 (25)
Maximum diameter of tumor (median-mm)		12.5 (4-35)
Localization of the tumor (n-%)	Right	5 (41.7)
	Left	3 (25)
	Multifocal	2 (16.6)
Histopathological features (n-%)	Encapsulation	1 (8.3)
	Vascular invasion	1 (8.3)
	Extrathyroidal extension	4 (33.3)
	Lymph node metastasis	5 (41.7)

mm: Millimeter

significantly higher in patients with nodules in the current study, and the prevalence of thyroid neoplasm was higher in nodules with TSH stimulation. Morever, Belfiore et al. suggested that TRab played a role in the development of thyroid neoplasm in Graves' disease [25]. It was suggested that thyroid stimulating receptor antibody reacted in the same way as TSH and stimulated thyrocytes. Consistent with this hypothesis, the levels of TRab and TSH were higher in the current study patients with thyroid neoplasm than in those without neoplasm, but not at a statistically significant level.

Chronic inflammation plays a role in tumor development [26]. Chronic inflammatory cells produce reactive oxygen species, which damage cellular DNA. This phenomenon can lead to tumor development. Chronic lymphocytic thyroiditis, seen in autoimmune thyroiditis, can increase the risk of developing papillary thyroid carcinoma [26]. However, due to lack of data, the presence of lymphocytic thyroiditis could not be evaluated in the pathology examinations of the current study. Furthermore, it is known that B and T lymphocytes play a basic role in Graves' disease. B lymphocytes produce antithyroid antibodies, whereas activated T lymphocytes produce proinflammatory cytokines [27]. IL-4, produced by T helper type 2 (Th2) cells, induces Th2 cell differentiation, proliferation, and apoptosis. These effects can lead to tumor progression and spread in most thyroid cancer cells [28]. In the current study, this hypothesis was supported by the higher levels of white blood cells determined in Graves' patients with thyroid neoplasms.

Thyroid autoantibodies are frequently detected in patients with autoimmune thyroid diseases and their high prevalence raises questions regarding a potential role in cancer [29]. Thyroid peroxidase antibodies, which are seen more commonly than anti tg, can induce oxidative stress but their contribution to thyroid damage is minor [30, 31]. In contrast, Imam et al demonstrated that the presence of high levels of anti tg and anti TPO appeared to be protective against neoplasm in patients with Graves' disease [32]. Interestingly, in the current study, the levels of anti tg and anti TPO, were seen to be higher in patients without neoplasm compared to those with neoplasm.

The higher levels of TSH and TRab, and the lower levels of anti TPO and anti tg were found to be associated with the presence of nodules. In addition, higher levels of TSH and TRab, and lower levels of anti TPO and anti tg were seen in patients with thyroid neoplasm compared to those without. This finding suggested that the presence of nodules may be an important predictive factor for the development of neoplasm in patients with Graves' disease.

Although a few follicular and medullar thyroid neoplasms have been reported in some studies, many have described papillary thyroid cancer as the most common form of cancer in hyperthyroid patients. All the cancers detected in the current study were of papillary origin, as seen in cases in the literature [33]. Of these 41.7% were the classic variant of papillary carcinoma, and in 25% of the patients, the pathology was consistent with follicular adenoma.

There were some limitations to this research, primarily the small sample size and retrospective design, so it was not possible to analyze all the pre-existing risk factors for thyroid neoplasm. The study results demonstrated that thyroid ultrasonography could reveal significant numbers of nodules with malignant features. However, as there was no long-term follow up of the patients with neoplasms, the association between prognosis of neoplasm and Graves' disease could not be investigated.

Conclusion

As the presence of thyroid nodules may be associated with a higher prevalance of thyroid neoplasm, Graves' patients should be examined carefully with physical examination or ultrasonography for the presence of nodules and thyroid neoplasm. When any suspicious finding is noticed on ultrasonography or in the laboratory analysis such as increased white blood cells and low thyroid autoantibody levels, further evaluation should be made because these

patients may be at higher risk for the development of malignancy.

Ethics approval

The study protocol was approved by Uludag University Ethics Committe (2021-1/24).

References

1. Papanastasiou A, Sapalidis K, Goulis DG, et al. Thyroid nodules as a risk factor for thyroid cancer in patients with Graves' disease: A systematic review and meta-analysis of observational studies in surgically treated patients. Clinical Endocrinology. 2019; 91: 571-77. doi: 10.1111/cen.14069.
2. S Ozçelik, Celik M, Vural A, et al. The Relationship between Third-generation TSH Receptor Antibody Positivity and Cumulative Methimazole Dose Used until Remission in Graves\\\' Disease J Coll Physicians Surg Pak. 2021 May; 30(5):517-522. doi: 10.29271/jcpsp.2021.05.517.
3. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016; 26: 1343-421. doi: 10.1089/thy.2016.0229.
4. Vander JB, Gaston EA, Dawber TR. The significance of nontoxic thyroid nodules. Final report of a 15-year study of the incidence of thyroid malignancy. Ann Int Med. 1968; 69: 537-40. doi: 10.7326/0003-4819-69-3-537.
5. Pellegriti G, Mannarino C, Russo M, et al. Increased mortality in patients with differentiated thyroid cancer associated with Graves' disease. J Clin Endocrinol Metab. 2013; 98: 1014-21. doi: 10.1210/jc.2012-2843.
6. Kraimps JL, Bouin-Pineau MH, Mathonnet M, et al. Multicenter study of thyroid nodules in patients with Graves's disease. Br J Surg. 2000;87: 1111-13. doi: 10.1046/j.1365-2168.2000.01504.x.
7. Bradley EI 3rd, Liechty RD. Modified subtotal thyroidectomy for Graves' disease: a two-institution study. Surgery. 1983 Dec; 94(6): 955-8.
8. Premoli, P, Tanda ML, Piantanida E, et al. Features and outcome of differentiated thyroid carcinoma associated with Graves' disease: results of a large, retrospective, multicenter study. J Endocrinol Invest 2020; (43), 109–16. https://doi.org/10.1007/s40618-019-01088-5.
9. Güçer H. Graves' Hastalığına Sahip Olgularda Tiroid Maligniteleri. Dicle Tıp Dergisi. 2016; 43(3): 460-7.
10. Keskin C, Sahin M, Hasanov R, et al. Frequency of thyroid nodules and thyroid cancer in thyroidectomized patients with Graves' disease. Arch Med Sci. 2019; 16 (2): 302-7. doi: 10.5114/aoms.2018.81136.
11. Hales IB, McElduff A, Crummer P, Clifton, et al. Does Graves' disease or thyrotoxicosis affect the prognosis of thyroid cancer. J Clin Endocrinol Metab. 1992 Sep;75(3): 886-9. doi: 10.1210/jcem.75.3.1517381.
12. Gabriele R, Letizia C, Borghese M, et al. Thyroid cancer in patients with hyperthyroidism. Horm Res. 2003; 60(2): 79-83. doi: 10.1159/000071875.
13. Farrell E, Heffron C, Murphy M, et al. Impact of lymphocytic thyroiditis on incidence of pathological incidental thyroid carcinoma. Head Neck 2017; 39: 122-127.
14. Can N, Ozyilmaz F, Celik M, et al. Comparison of clinicopathological features in incidental and nonincidental papillary thyroid carcinomas in 308 patients. Pol J Pathol. 2017;68(3):197-209. doi: 10.5114/pjp.2017.71527.
15. Jia Q, Li X, Liu Y, et al. Incidental thyroid carcinoma in surgery-treated hyperthyroid patients with Graves' disease: a systematic review and meta-analysis of cohort studies. Cancer Manag Res. 2018 May 21;10:1201-1207. doi: 10.2147/CMAR.S164210.
16. Beahrs OH, Pemberton JDJ, Black BM. Nodular goiter and malignant lesions of thyroid gland. J Clin Endocrinol. 195; 11: 1157-65. doi: 10.1210/jcem-11-10-1157.
17. Sokal JE. Incidence of malignancy in toxic and nontoxic nodular goiter. J Am Med Assoc. 1954: 1321-5. doi: 10.1001/jama.1954.02940500001001.
18. Shapiro SJ, Friedman NB, Pezik SL et al. Incidence of thyroid carcinoma in Graves' disease. Cancer. 1970; 26: 1261-70.
19. Farbota LM, Calandra DB, Lawrence AM, Paloyan E. Thyroid carcinoma in Graves' disease. Surgery. 1985 Dec; 98(6): 1148-53.
20. Terzioğlu T, Tezelman S, Onaran Y, Tanakol R. Concurrent hyperthyroidism and thyroid carcinoma. Br J. Surg. 1993; 80: 1301-2. doi: 10.1002/bjs.1800801027.
21. Tam AA, Kaya C, Kılıç FB, et al. Thyroid nodules and thyroid cancer in Graves' disease. Arq Bras Endocrinol Metabol. 2014; 58 (9): 933-8. doi: 10.1590/0004-2730000003569.
22. Sharma SD, Kumar G, Kaddour H. Thyroid cancer and hyperthyroidism. Otolaryngyl Head & Neck Surg. 2014; 151: 182-77. doi:10.1177/0194599814541629a140.
23. Staniforth JUL, Erdirimanne S, Eslick GD. Thyroid carcinoma in Graves' disease: A meta-analysis. Int J Surg. 2016; 27: 118-25. doi: 10.1016/j.ijsu.2015.11.027.
24. Tamatea JA, Tu'akoi K, Conaglen JV, et al. Thyroid cancer in Graves' disease: is surgery the best treatment for Graves' disease? ANZ J Surg. 2014; 84: 231-4. doi: 10.1111/j.1445-2197.2012.06233.x.
25. Belfiore A, Garofalo MR, Giuffrida D et al. Increase aggressiveness of thyroid cancer in patients with Graves' disease. J Clin Endocrinol Metab 1990; 70: 830-5. doi: 10.1210/jcem-70-4-830.
26. Chai EZ, Siveen KS, Shanmugam MK, et al. Analysis of the intricate relationship between chronic inflammation and cancer. Biochem J. 2015; 468: 1-15. doi: 10.1042/BJ20141337.
27. Salvi M, Pedrazzoni M, Girasole G, et al. Serum concentrations of proinflammatory cytokines in Graves' disease: effect of treatment, thyroid function, ophthalmopathy and cigarette smoking. European Journal of Endocrinology. 2000; 143: 197-202. doi: 10.1530/eje.0.1430197.
28. Vella V, Mineo R, Frasca F, et al. Interleukin-4 stimulates papillary thyroid cancer cell survival: implications in patients with thyroid cancer and concomitant Graves' disease. J Clin Endocrinol Metab. 2004 Jun;89 (6): 2880-9. doi: 10.1210/jc.2003-031639.
29. Fröhlich E, Wahl R. Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases. Front Immunol. 2017; 8: 521. doi: 10.3389/fimmu.2017.00521.
30. Ruggeri RM, Vicchio TM, Cristani M, et al. Oxidative stress and advanced glycation end products in Hashimoto's thyroiditis. Thyroid. 2016; 26: 504-11. doi: 10.1089/thy.2015.0592.
31. Zaletel K, Gaberscek S. Hashimoto's thyroiditis: from genes to the disease. Curr Genomics. 2011; 12: 576-88. doi: 10.2174/138920211798120763.
32. Imam S, Dar P, Paparodis R, Almotah K, et al. Nature of coexisting thyroid autoimmune disease determines success or failure of tumor immunity in thyroid cancer. J Immunother Cancer. 2019 Jan 7;7 (1): 3. doi: 10.1186/s40425-018-0483-y.
33. Boostrom S, Richards ML. Total thyroidectomy is the preferred treatment for patients with Graves' disease and a thyroid nodule. Otolaryngol Head Neck Surg. 2007; 136: 278-81. doi:10.1016/j.otohns.2006.09.011.