Hellenic Journal of Surgery (2017) **89**:2, 73-78

Coexistence of Hashimoto's Thyroiditis and Papillary Thyroid Carcinoma

Avgoustou C., Avgoustou Eirini

Abstract

Aim: The coexistence of Hashimoto's thyroiditis (HT) and papillary thyroid carcinoma (PTC) has been a widely debated issue. In view of the current controversy, as well as the high prevalence of both diseases, the objective of the present paper is to evaluate the association between them and to propose the proper therapeutic management.

Methods: We herein review previous pertinent literature on the subject of concomitant HT and PTC, with respect to epidemiology, clinical presentation, carcinogenesis, and appropriate treatment.

Results: Studies to date establish 6.5-43.8% of patients with PTC and coexisting HT, while 11-58.3% of all HT patients will develop PTC. Coexistence of the diseases is significantly related to younger women. Malignant lesions tend to be microcarcinomas, at times multifocal (13.5-44%) and occasionally metastasising to the central cervical compartment (10.8-49%). Mostly, patients have a good prognosis with total thyroidectomy, accompanied by central compartment node dissection in cases with nodal involvement. Many issues, including molecular biological characteristics of carcinogenesis in Hashimoto's thyroiditis, remain to be clarified and further studies need to be undertaken.

Conclusions: The close relationship between HT and PTC lends credence to the hypothesis that autoimmune thyroiditis is a predisposing factor to the development of thyroid carcinoma but patients tend to have favorable clinicopathological characteristics and long recurrence-free survival. A careful surveillance of these patients is required for an early detection of malignant lesions, which should constitute indication for radical surgical treatment.

Key words: *Hashimoto's thyroiditis; papillary thyroid carcinoma; epidemiology; clinical presentation; carcinogenesis; treatment*

Introduction

First described in 1912, Hashimoto's thyroiditis (HT) is the most common non-iatrogenic cause of hypothyroidism. The condition is definitely more prevalent in the female population, with published gender prevalence ratios ranging from 5 to 20:1, and occurs in all age groups [1,2]. Its etiopathogenesis is not yet completely clear, but available data from the literature strongly indicate a gradual autoimmune-mediated thyroid failure with occasional goiter development: T-helper lymphocytes (CD4+) are activated by class II human leukocyte antigen system cells (MHC class II: HLA-DR3, HLA-DR4, HLA-DR5) and recruit B lymphocytes, which infiltrate the entire gland and produce specific anti-thyroglobulin, anti-thyroid peroxidase, or anti-TSH receptor antibodies, as well as cytotoxic T lymphocytes (CD8+), which release cytokines that directly damage the thyroid follicular cells [3]. The condition should be differentiated from the relatively frequent histopathologic finding of focal lymphocytic changes. Clinically, the condition presents with hypothyroidism in most of the patients; however, in a small minority of cases, an early manifestation of symptoms of hyperthyroidism (Hashitoxicosis) may be observed [3].

Non-medullary differentiated thyroid cancer comprises a group of tumors including papillary thyroid carcinoma (and its follicular variant), follicular thyroid carcinoma and

Avgoustou C., MD
General Surgeon, Director of Surgery, Surgical Department, General Hospital of N. Ionia "Constantopoulion - Aghia Olga", Athens, Greece

Avgoustou Eirini, MD
Medical School Graduate, National and Kapodistrian University of Athens, Athens, Greece

Corresponding author: Avgoustou C., MD
Ploutarchou 13, Gerakas Attikis, 15344, Athens, Greece
Telephone: +30-6977218339, Fax: +30-2106612673,
e-mail: avgoustouk@yahoo.gr

Received 15 Jan 2017; Accepted 7 July 2017

Abbreviations

AGES scoring system= Age of the patient, histological Grade of the tumor, Extent of the tumor (extrathyroidal invasion or distant metastases), Size of the primary tumor
AMES scoring system= Age of the patient, presence of distant Metastases, Extent of the primary tumor, Size of the primary cancer

carcinoma with Hürthle cells. Papillary thyroid carcinoma (PTC) is the most frequent manifestation of thyroid cancer, comprising about 85% of cases [4,5]. Similarly to HT, it affects more frequently women with gender prevalence ratios ranging from 2.5 to 4.0:1 [2].

In their study in 1955, Dailey *et al.* [6] were the first to propose a possible association between Hashimoto's thyroiditis and thyroid cancer. Numerous studies followed this initial description and attempted to prove and explain the relationship between the two diseases [7-32]. Despite this abundant literature, the hypothesis that chronic lymphocytic thyroiditis may predispose to the development of papillary thyroid carcinoma remains to date a subject of intense controversy.

Materials and methods

We searched the Medline online database via PubMed (www.ncbi.nlm.nih.gov/pubmed), updated to June 2016, using the keywords "Hashimoto's thyroiditis" and "papillary thyroid cancer" without language restrictions. We also manually screened the reference lists of all identified studies, and relevant articles were retrieved for detailed analysis. We only included articles, in which the coexistence of PTC and HT was proven by histopathologic examination and was, at least, briefly discussed. This review article summarises what is known so far about the association between HT and PTC, especially in terms of epidemiology, clinical presentation, etiology, treatment, clinical course and outcome, and makes recommendations.

Results

According to the numerous case control studies and one meta-analysis retrieved, among all thyroid specimens resected for PTC, HT was histologically proven in 6.5 to 43.8 % of patients [7-24]. Inversely, among all HT patients, the overwhelming majority of malignancies were papillary carcinomas with occurrence rates ranging from 11.1 to 58.3% (Figure 1) (Table 1) [7,16,25-32]. These findings were more common among women (female prevalence of more than 90% in most studies) of younger age groups (fourth decade of life). Furthermore, as far as the characteristics of the primary focus are concerned, the coexistence of the autoimmune disease and PTC affected its size, which in most of the cases was about 10 mm, thus providing the basis for microcarcinoma diagnosis. Nevertheless, it did not limit the number of primary foci, since, although the majority of the patients have isolated or dominant nodules, a considerable number present the multifocal PTC form (rates ranging in different studies between 13.5 and 44%) and HT was more often observed in multifocal PTCs than in single PTCs. Moreover, even these forms have the possibility of capsular infiltration and nodal metastases, especially to the central cervical compartment [7-32]. Central lymph node invasion was reported in 10.8 to as much as 49% of cases and is discussed immediately after (Table 2).

Histopathology shows lymphocytic infiltrations with reaction center formation both in the thyroid tissue and around the primary focus. Some authors support the thesis that these infiltrations create a breeding ground for the development of neoplastic lesions [7,18,30,31,33], while others consider them as the response of the gland to the tumor, suggesting that the autoimmune response to thyroid-specific antigens in chronic lymphocytic thyroiditis patients may be involved in destruction of cancer cells expressing these antigens in PTC, thus preventing recurrence and improving survival [9,19,20]. Notably, Paulson et al. [20] suggest that a coexisting autoimmune disease may limit the neoplastic spread beyond the primary focus area and result in a lower number of cervical lymph node metastases. A lower incidence of nodal involvement is similarly supported by many authors [19,21,23,31,34,35]; there are others, though, who report no impact or even an increased risk of nodal metastases [17,18,24,36].

From the surgical point of view, in most cases, total thyroidectomy was the procedure of choice for the management of HT and PTC, along with central neck dissection in patients with nodal invasion.

Discussion

In their 10-year retrospective study of patients who underwent initial thyroidectomy for PTC, Kebebew *et al.* [12] correlated the presence of chronic lymphocytic thyroiditis with a better prognosis. The potentially improved

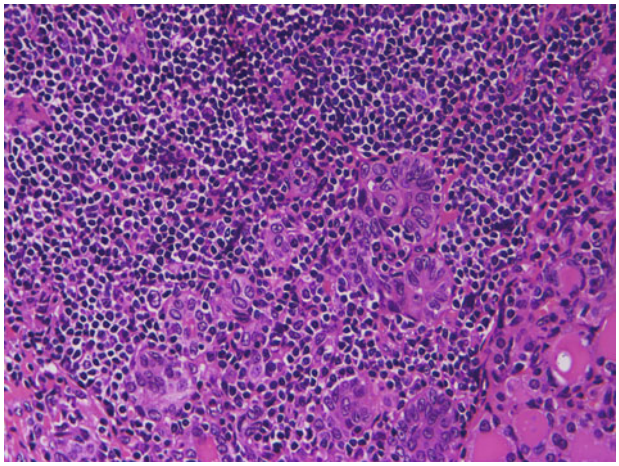

Figure 1. Histopathology image of PTC in a background of HT (own material).

Table 1. *Coexistence of HT and PTC. Brief literature review.*

Authors	Patients with PTC	Patients with PTC and coexistent HT, n (%)
Dailey et al. [6]	278 with PTC	35 (12.6)
Ott et al. [7]	161 with TC	61 (38.0)
Eisenberg et al. [8]	120 with TC	13 (10.8)
Matsubayashi et al. [9] [17]	95 with PTC	36 (37.9)
Schäffler et al. [10]	153 with TC	10 (6.5)
Singh et al. [11]	388 with PTC	57 (15.0)
Kebebew et al. [12]	136 with PTC	41 (30)
Pisanu et al. [13]	344 with PTC	33 (9.6)
Kurukahveciglu et al. [14]	199 with PTC	37 (18%)
Kim EY et al. [15]	1441 with PTC	214 (14.9)
Mazokopakis et al. [16]	32 with PTC	12 (37.5)
Kim HS et al [17]	323 with PTC	105 (32.5)
Kim KW et al. [18]	1028 with PTC	307 (29.9)
Yoon et al. [19]	195 with PTC	56 (28.7)
Paulson et al. [20]	139 with PTC	61 (43.8)
Lee et al. [21]	10648 with PTC	2471 (23.2)
Girardi et al. [23]	417 with PTC	148 (35.4)
Qu et al. [10]	1250 with PTC	364 (29.1)
Authors	Patients with HT	Patients with HT and coexistent PTC, n (%)
Ott [7]	267 with HT	61 (23)
Mazokopakis et al. [16]	42 with HT	12 (28.6)
Chesky VE et al. [25]	432 with HT	48 (11.1)
Sclafani et al. [26]	48 with HT	8 (17.0)
Avgoustou et al. [27]	62 with HT	23 (37.1)
Bradly et al.[28]	74 with HT	21 (28)
Gul et al. [29]	92 with HT	42 (45.7)
Consorti et al. [30]	69 with HT	25 (36.2)
Zhang et al. [31]	653 with HT	381 (58.3)
Kapan et al. [32]	44 with HT	10 (22.7)

prognosis and longer duration of recurrence-free survival in this group of patients are more and more documented and attributed to various of their clinicopathological characteristics, among which the most important and well-known prognostic factors remain the younger age, the female predominance and the smaller size of tumor at presentation [9-12,19,21,22,37-39].

The causative mechanism which is responsible for the relationship between HT and PTC is still ambiguous, despite a number of hypotheses that have been made in the literature. One proposed mechanism for both diseases implies a genetic predisposition to tumor development. According to the findings of numerous investigations in recent years on the molecular basis of carcinogenesis in the thyroid gland, neoplastic lesions may originate from mutations, thus activation of oncogenes, leading to genetic defects of the signaling cascades. For the time being, the best understood and most frequent form of such mutations in PTC concerns the oncogenes RET/PTC1 and RET/PTC3 [40-43]. The finding that these sequences are also present in the autoimmune thyroiditis demonstrates that both diseases have similar morphological features, immunohistochemical

Table 2. *Coexistence of HT with PTC. Clinicopathological characteristics of patients.*

Authors	Females (%)	Age (years)	Nodule size (cm)	Multifocality (%)	Extrathyroidal extension (%)	Central lymph node metastases (%)
Singh et al. [11]	79	41	2		30	26
Kurukahveciglu et al. [14]	97.3			13.5		10.8
Kim EY et al. [15]	95.8	46	2	39.2	50	43
Kim KW et al. [18]	95.7	47.5	1.08	44	58	40
Yoon et al. [19]	96.4	45.9	0.77	42.8	21.4	12.5
Paulson et al. [20]						49
Girardi et al. [23]	91.8	45.97	1.2	21.6	22.2	15.5
Zhang et al. [31]	92.2	42.64	1.21		19.2	42.7

staining pattern, and most importantly, molecular profile [43]. Consequently, performing a polymerase chain reaction (PCR) assay in material obtained by fine-needle aspiration biopsy (FNAB) could permit the use of mutations detected in the RET/PTC oncogenes as a molecular marker of early malignant lesions and thus, the diagnosis of papillary thyroid microcarcinoma before it even manifests clinically, which would be of great importance in early initiation of targeted therapy [41].

The coexistence of papillary thyroid cancer and Hashimoto's thyroiditis has also been attributed to the activation of a tirosine kinase cascade, the phosphatidylinositol 3-kinase (PI3k)/Akt pathway, and thus, overexpression of the p63 protein, a cellular apoptosis inhibitor. Unger, *et al.* reported expression of p63 in both PTC and HT [44]. This potential pathobiologic link between the two disorders was also confirmed by Larson, *et al.* [45] and Burstein, *et al.* [46], who proposed that both diseases may originate by the same population of pluripotent p63-positive embryonal stem cell remnants.

The high prevalence of PTC in HT provides a foundation for ensuring a close clinical monitoring of patients with nodular lesions present in immunologically altered thyroid gland; this strategy would permit early diagnosis of thyroid cancer [13,18,21,29,33,42] and considering radical surgical treatment in these cases. Ultrasonography, or even computed tomography at times, are useful, but most of all, FNA is extremely valuable for diagnosing PTC in such patients with a sensitivity of more than 90%. In addition, the negative prognostic value of FNA for the identification of PTC is also excellent (96%) [11].

The optimum strategy of surgical treatment of Hashimoto's thyroiditis with nodular lesions should include total thyroidectomy, which, not only allows treating the disease, but also contributes to a decrease in reoperation rates in cases of subtotal thyroidectomies with excessive remnant and postoperative diagnosis of thyroid cancer, limiting therefore the risk of permanent complications, such as the damage of recurrent laryngeal nerves or the accidental excision of inferior parathyroid glands, which, despite rare, pose though a considerable threat in the postoperative quality of life of these patients [30,47-49]. Similarly, the treatment in cases with known HT and malignant lesions already diagnosed by FNAB should not be different from the treatment of patients with conventional PTC: i.e. total thyroidectomy with consideration for radioactive iodine therapy, if poor prognostic factors are present (high-risk group of patients as determined by scoring systems such as AGES or AMES by Mayo and Lahey Clinic respectively) [14,50,51]. As far as lymph node excision is concerned, although all major endocrine societies agree that therapeutic central compartment node dissection is recommended in all patients with clinically node-positive PTC, whether prophylactic central compartment node dissection should be performed in patients with no clinical, sonographic or intraoperative evidence of abnormal lymph nodes is controversial. The potential benefits include reduced rates of recurrence, accurate staging to help determine the need for radioiodine ablation and ^{131}I dosing and reduced reoperation in the central neck with its potential higher morbidity. The opposers support that there is no proven oncologic benefit since only 10% of patients with microscopic lymph node metastases ever develop clinically significant nodal disease while there is, instead, an increased risk of the aforementioned complications. It seems that the balance between the risks and the benefits favors total thyroidectomy alone for clinically node-negative PTC [52,53].

Conclusion

The association between Hashimoto's thyroiditis and PTC has been widely disputed and no consensus exists yet. The literature concludes that the coexistence of Hashimoto's thyroiditis and papillary thyroid carcinoma is a common

phenomenon and occurs more frequently in younger women. Malignant lesions tend to present with a small diameter of the primary focus, and, at times, have a multifocal form, but the prognosis is statistically more favourable as compared to other patient groups. The early detection of lesions, the radical surgical strategy with appropriate adjuvant therapy, and the careful surveillance may improve significantly the therapeutic outcomes and the quality of life in this group of patients. Further studies are required to confirm the genetic and clinical association between HT and PTC.

Conflict of Interest: *The authors declare that they have no conflict of interest.*

References

1. Lal G, Clark OH. Textbook of endocrine surgery. Philadelphia: Saunders; Chronic Thyroiditis 2005;38-40.
2. Bloodworth JMB, Lechago J, Gould VE. Bloodworth's endocrine pathology. Baltimore, Md: Williams & Wilkins: The thyroid 1997. pp. 178-81, 197-206.
3. Kumar V, Robbins SL. Robbins basic pathology. Philadelphia, PA: Saunders/Elsevier: The endocrine system; 2007. pp. 731-2, 735-6.
4. Carhill A, Cabanillas M, Jimenez C, et al. The oninvestigestional use of tyrosine kinase inhibitors in thyroid cancer: establishing a standard for patient safety and monitoring. J Clin Endocrinol Metab 2013;98:31-42.
5. Rajhbeharrysingh U, Taylor M, Milas M. Medical therapy for advanced forms of thyroid cancer. Surg Clin N Am 2014;94:541-71.
6. Dailey ME, Lindsay S, Skahen R. Relation of thyroid neoplasms to Hashimoto's disease of the thyroid gland. Arch Surg 1955;70:291-7.
7. Ott RA, McCall AR, McHenry C, et al. The incidence of thyroid carcinoma in Hashimoto's thyroiditis. Am Surg 1987;53:442-5.
8. Eisenberg BL, Hensley SD. Thyroid cancer with coexistent Hashimoto's thyroiditis. Clinical assessment and management. Arch Surg 1989;124:1045-7.
9. Matsubayashi S, Kawai K, Matsumoto Y, et al. The correlation between papillary thyroid carcinoma and lymphocytic infiltration in the thyroid gland. J Clin Endocrinol Metab 1995;80:3421-4.
10. Schäffler A, Palitzsch KD, Seiffarth C, et al. Coexistent thyroiditis is associated with lower tumor stage in thyroid carcinoma. Eur J Clin Invest 1998;28:838-44.
11. Singh B, Shaha AR, Trivedi H, et al. Coexistent Hashimoto's thyroiditis with papillary thyroid carcinoma: impact on presentation, management, and outcome. Surgery 1999;126:1070-6.
12. Kebebew E, Treseler PA, Ituarte PH, et al. Coexisting chronic lymphocytic thyroiditis and papillary thyroid cancer revisited. World J Surg 2001;25:632-7.
13. Pisanu A, Piu S, Cois A, et al. Coexisting Hashimoto's thyroiditis with differentiated thyroid cancer and benign thyroid diseases: indications for thyroidectomy. Chir Ital 2003;55:365-72.
14. Kurukahvecioglu O, Taneri F, Yuksel O, et al. Total thyroidectomy for the treatment of Hashimoto's thyroiditis coexisting with papillary thyroid carcinoma. Advances in Therapy 2007;24:510-6.
15. Kim EY, Kim WG, Kim WB, et al. Coexistence of chronic lymphocytic thyroiditis is associated with lower recurrence rates in patients with papillary thyroid carcinoma. Clinical Endocrinology 2009;71:581-6.
16. Mazokopakis EE, Tzortzinis AA, Dalieraki-Ott EI, et al. Coexistence of Hashimoto's thyroiditis with papillary thyroid carcinoma. A retrospective study. Hormones 2010;9:312-7.
17. Kim HS, Choi YJ, Yun JS. Features of papillary thyroid microcarcinoma in the presence and absence of lymphocytic thyroiditis. Endocrine Pathology 2010;21:149-53.
18. Kim KW, Park YJ, Kim EH, et al. Elevated risk of papillary thyroid cancer in Korean patients with Hashimoto's thyroiditis. Head & Neck 2011;33:691-5.
19. Yoon YH, Kim HJ, Lee JW, et al. The clinicopathologic differences in papillary thyroid carcinoma with or without coexisting chronic lymphocytic thyroiditis. European Archives of Oto-Rhino-Laryngology 2012;269:1013-7.
20. Paulson LM, Shindo ML, Schuff KG. Role of chronic lymphocytic thyroiditis in central node metastasis of papillary thyroid carcinoma. Otolaryngol Head Neck Surg 2012;147:444-9.
21. Lee JH, Kim Y, Choi JW, et al. The association between papillary thyroid carcinoma and histologically proven Hashimoto's thyroiditis: a meta-analysis. Eur J Endocrinol 2013;168:343-9.
22. Lun Y, Wu X, Xia Q, et al. Hashimoto's thyroiditis as a risk factor of papillary thyroid cancer may improve cancer prognosis. Otolaryngol Head Neck Surg 2013;148:396-402.
23. Girardi FM, Barra MB, Zettler CG. Papillary thyroid carcinoma: does the association with Hashimoto's thyroiditis affect the clinicopathological characteristics of the disease? Braz J Otorhinolaryngol 2015;81:283-7.
24. Qu N, Zhang L, Lin DZ, et al. The impact of coexistent Hashimoto's thyroiditis on lymph node metastasis and prognosis in papillary thyroid microcarcinoma. Tumor Biol 2016;37:7685-92.
25. Chesky VE, Hellwig CA, Welch JW. Cancer of the thyroid associated with Hashimoto's disease: an analysis of forty eight cases. Am Surg 1961;28:678-85.
26. Sclafani AP, Valdes M, Cho H. Hashimoto's thyroiditis and carcinoma of the thyroid: optimal management. Laryngoscope 1993;103:845-49.
27. Avgoustou C, Schizas V, Sioros Ch, et al. Hashimoto thyroiditis in benign and malignant surgical diseases of the thyroid gland. Abstracts of the 26th Hellenic Congress of Surgery and International Surgical Forum. Hell J Surg, Supplementary Issue 2008;80:140-1.
28. Bradly DP, Reddy V, Prinz RA, et al. Incidental papillary carcinoma in patients treated surgically for benign thyroid diseases. Surgery 2009;146:1099-104.
29. Gul K, Dirikoc A, Kiyak G, et al. The association between thyroid carcinoma and Hashimoto's thyroiditis: the ultrasonographic and histopathologic characteristics of malignant nodules. Thyroid 2010;2:873-8.
30. Consorti F, Loponte M, Milazzo F, et al. Risk of malignancy

from thyroid nodular disease as an element of clinical management of patients with Hashimoto's thyroiditis. European Surgical Research 2010;45:333-7.
31. Zhang L, Li H, Ji QH, et al. The clinical features of papillary thyroid cancer in Hashimoto's thyroiditis patients from an area with a high prevalence of Hashimoto's disease. BMC Cancer 2012;12:610.
32. Kapan M, Onder A, Girgin S, et al. The reliability of fine-needle aspiration biopsy in terms of malignancy in patients with Hashimoto thyroiditis. Int Surg 2015;100:249-53.
33. Ma H, Yan J, Zhang C, et al. Expression of papillary thyroid carcinoma-associated molecular markers and their significance in follicular epithelial dysplasia with papillary thyroid carcinoma-like nuclear alterations in Hashimoto's thyroiditis. Int J Clin Exp Pathol. 2014;7:7999-8007.
34. Anand A, Singh KR, Kushwaha JK, et al. Papillary Thyroid Cancer and Hashimoto's Thyroiditis: An Association Less Understood. Indian J Surg Oncol 2014;5:199-204.
35. Zhu Y, Zheng K, Zhang H, et al. The clinicopathologic differences of central lymph node metastasis in predicting lateral lymph node metastasis and prognosis in papillary thyroid cancer associated with or without Hashimoto's thyroiditis. Tumor Biol 2016;37:8037-45.
36. Konturek A, Barczyński M, Nowak W, et al. Risk of lymph node metastases in multifocal papillary thyroid cancer associated with Hashimoto's thyroiditis. Langenbecks Arch Surg 2014;399:229-36.
37. Souza SL, da Assumpção LVM, Ward LS. Impact of previous thyroid autoimmune diseases on prognosis of patients with well-differentiated thyroid cancer. Thyroid 2003;13:491-5.
38. Siassakos D, Gourgiotis S, Moustafellos P, et al. Thyroid microcarcinoma during thyroidectomy. Singapore Med J 2008;49:23-5.
39. Feldt-Rasmussen U, Rasmussen AK. Autoimmunity in differentiated thyroid cancer: significance and related clinical problems. Hormones 2010;9:109-17.
40. Cyniak-Magierska A, Wojciechowska-Durczyńska K, Krawczyk-Rusiecka K, et al. Assessment of RET/PTC1 and RET/PTC3 rearrangements in fine-needle aspiration biopsy specimens collected from patients with Hashimoto's thyroiditis. Thyroid Res 2011;10:4-5.
41. Wirtschafter A, Schmidt R, Rosen D, et al. Expression of the RET/PTC fusion gene as a marker of papillary carcinoma in Hashimoto's thyroiditis. Laryngoscope 1997;107:95-100.
42. Sheils OM, O'Leary JJ, Uhlmann V, et al. RET/PTC-1 activation in Hashimoto thyroiditis. J Surg Pathol 2000;8:185-9.
43. Arif S, Blanes A, Diaz-Cano SJ. Hashimoto's thyroiditis shares features with early papillary thyroid carcinoma. Histopathology 2002;41:357-62.
44. Unger P, Ewart M, Wang BY, et al. Expression of p63 in papillary thyroid carcinoma and in Hashimoto's thyroiditis: a pathobiologic link? Hum Pathol 2003;34:764-9.
45. Larson SD, Jackson LN, Riall TS, et al. Increased incidence of well-differentiated thyroid cancer associated with Hashimoto's thyroiditis and the role of the PI3k/Akt pathway. J Am Coll Surg 2007;204:764-73, discussion 773-5.
46. Burstein DE, Nagi C, Wang BY, et al. Immunohistochemical detection of p53 homolog p63 in solid cell nests, papillary thyroid carcinoma, and hashimoto's thyroiditis: A stem cell hypothesis of papillary carcinoma oncogenesis. Hum Pathol 2004;35:465-73.
47. Barczyński M, Konturek A, Hubalewska-Dydejczyk A, et al. Five-year follow-up of a randomised clinical trial of total thyroidectomy versus Dunhill operation versus bilateral subtotal thyroidectomy for multinodular nontoxic goiter. World J Surg 2010;34:1203-13.
48. Barczyński M, Konturek A, Stopa M, et al. Total thyroidectomy for benign thyroid disease: is it really worthwhile? Ann Surg 2011;254:724-9.
49. Alecu L, Bărbulescu M, Ursuț B, et al. Occult thyroid carcinoma in our experience -- should we reconsider total thyroidectomy for benign thyroid pathology? Chirurgia (Bucur) 2014;109:191-7.
50. Chow SM, Law SC, Chan JK, et al. Papillary microcarcinoma of the thyroid—prognostic significance of lymph node metastasis and multifocality. Cancer 2003;98:31-40.
51. Mercante G, Frasoldati A, Pedroni C, et al. Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients. Thyroid 2009;19:707-16.
52. So YK, Son YI, Hong SD, et al. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. Surgery 2010;148:526-31.
53. McHenry C, Stulberg J. Prophylactic central compartment neck dissection for papillary thyroid cancer. Surg Clin N Am 2014;94:529-40.