

## REVIEW

**CHRONIC THYROIDITIS AND DIFFERENTIATED THYROID CANCER: FROM OVERLAPPING HIGH PREVALENCE TO A SHIFT ON MULTIFOCAL INTRA-THYROID PAPILLARY THYROID CARCINOMA****Ana Valea<sup>1</sup>, Simona Elena Albu<sup>2</sup>, R. Petrescu<sup>3</sup>, Mara Carsote<sup>4</sup>**<sup>1</sup>"I.Hatieganu" University of Medicine and Pharmacy & The Clinical County Hospital, Cluj-Napoca, Romania<sup>2</sup>"Carol Davila" University of Medicine and Pharmacy & The University Emergency Hospital, Bucharest, Romania<sup>3</sup>The Department of Surgery, Medlife Hospital, Brasov, Romania<sup>4</sup>"Carol Davila" University of Medicine and Pharmacy & "C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania

Corresponding author: Mara Carsote

Phone no. 0040213172041

E-mail: carsote\_m@hotmail.com

**Abstract**

*The autoimmune background as found in chronic thyroiditis (CT), also known as Hashimoto's thyroiditis or autoimmune lymphocytic thyroiditis, does not represent an indication of surgery but the discovery of macro-nodules may represent a risk for thyroid cancer, thus thyroidectomy becomes an important tool of approach. Environmental triggers, less or more described up to this moment, are a contributor to higher prevalence of CT and to the shift through more frequent cases of papillary thyroid cancers (PTC) rather than follicular type. This is a mini-review of literature focused on the association between CT and differentiated thyroid cancer, especially PTC. The research used as key words all the mentioned synonyms used for CT. A number of 62 references are selected, since 2004 (while 45 of them are published between 2015 and 2017), and 53 of them are accessible via PubMed database. The CT - PTC relationship may be described at different levels: PTC is presented more frequently than follicular thyroid cancer in relationship with iodine supplements including cases with autoimmune background; 2. CT is involved in multifocal PTC but this histological pattern may not be more aggressive than generally expected because lymph nodes are somehow blocked by the immune process and protected by lymph nodes metastasis from primary thyroid source of PTC so the risk of recurrence and aggressive profile is not higher than seen in CT-free subjects. Team approach is essential for many aspects as the detection of CT and the selection of those rare cases that need thyroidectomy. The association between CT and PTC is actually more frequent than expected, especially for micro-PTC subtype. Overall, the survival of PTC patients does not seem to be influenced by CT if surgery is correctly applied despite a risk of multifocal intra- and not extra-thyroid spreading of malignancy.*

**Keywords:** thyroidectomy, papillary thyroid cancer, chronic thyroiditis, thyroid nodules**Introduction**

Thyroid represents one of the easiest to access parenchyma organs in modern society and the indication of surgery is based on rather simple protocols of detection, assessment, and

follow-up for thyroid nodules [1-3]. Classically, the autoimmune background as found in chronic thyroiditis (CT), also known as Hashimoto's thyroiditis or autoimmune lymphocytic thyroiditis, does not represent an indication of surgery but large compressive glands or the

discovery of macro-nodules on the autoimmune context may represent a risk for thyroid cancer, thus thyroidectomy became an important tool of approach [4-6]. Environmental triggers, less or more described up to this moment, represent a contributor to higher prevalence of CT and to the shift to more frequent cases of papillary thyroid cancers (PTC) rather than follicular type, including a specific pattern of association between these two conditions (CT-PTC) [7-9]. Cervical surgery is essential to provide the tools for best prognosis in these cases but the decision and timing of thyroidectomy requires a multidisciplinary approach including the surgeon, the endocrinologist, the ultrasound and imagery specialist, etc. [9,10].

---

## Materials and methods

This is a mini-review of literature focused on the association between CT and differentiated thyroid cancer, especially PTC. The research used as key words all the mentioned synonyms used for CT. A number of 62 references are selected, since 2004 (while 45 of them are published between 2015 and 2017), and 53 of them are accessible via PubMed database.

---

## Results

### *Chronic thyroiditis: general panel of approach*

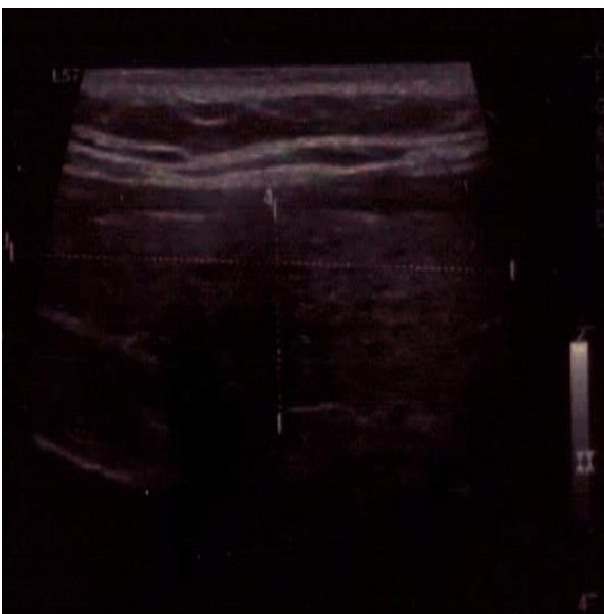
CT has an increasing prevalence due to the diagnosis based on antithyroid antibodies assays which are routinely available: antithyroperoxidase antibodies (TPOAb), respective antithyroglobulin antibodies (TgAb) [11,12]. The positive detection of at least one of them is enough for a practitioner to establish the diagnosis of CT despite the general well known aspect that only a pathological exam is certain for diagnosis [13,14]. These antibodies are relatively inexpensive and a simple blood test easily provides their value; nowadays, when thyroid function is tested (for instance, using Thyroid Stimulating Hormone or TSH), at least TPOAb are usually assessed, too [15,16]. As a screening tool, TPOAb are probably more valuable than TgAb but either of them, or both

are useful in cases of hypothyroidism (regardless of mild phenotype or mixedema); a cellular immune mechanism is consistent in association with antibodies combinations but this aspect is not accessible for every day practice of medicine [17,18]. The term of “chronic” is not pathogenically related to other forms of thyroiditis which display a completely different cause, for instance, acute type is related to bacterial infections while sub-acute form is linked to viral infections following acute upper respiratory infections [19,20]. Apart from the mentioned thyroid antibodies which are specific for CT, there is another category. Classical TRAb (TSH-Receptor Antibodies) represent the specific pathogenic loop for Basedow’s disease while another type, the TSH-Receptor blocking antibodies, are involved in severe types of hypothyroidism and atrophic mixedema but they are not routinely available for the practitioner who establishes the diagnosis of CT [17,18]. Their presence is indirectly sustained based on negative TPOAb and TgAb profile and suppressed thyroid function and/or specific ultrasound features for a chronic inflammation [21,22]. Regardless of the type of antibodies cocktail which is the main player for CT diagnosis, the echography is essential to confirm it, based on the hypoechoic, inhomogeneous highly suggestive pattern [23]. However, sometimes macro-nodules are detected on the CT background, and the cut-off of clinical significance is over 1 centimetre [24]. The presence of a thyroid nodule does not necessarily mean a thyroid cancer since their presence is largely recognised in the general population (as CT also has an increasing prevalence in general population) [25,26]. Fine needle aspiration specific features as low differentiated follicular cells or intense lymphocytic infiltrative aspects increase the risk of a malignancy, thus thyroidectomy may be necessary [27,28]. Also, compressive effects of the gland regardless of the dimensions of the nodules may indicate surgical approach [27,28]. Generally, the main therapeutically options for CT do not involve surgery unless the presence of previously mentioned aspects [29,30]. Typically, the thyroid function needs to be followed and corrected under substitution with daily oral levothyroxine [29,30]. Another aspect

to follow is the risk of a second non-thyroid autoimmune condition as seen in poly-glandular autoimmune syndromes as type II, III, etc. [31,32]. Some studies also suggested a potential correlation of CT with other endocrine tumours or malignancies as breast cancer but most probably an incidental overlap is registered rather than a common pathogenic mechanism [33-35].

### ***Thyroid cancer: general background***

Thyroid nodules represent the most frequent endocrine condition in general practice but a small percentage of them are actually malignant [36- 40]. Typically, the follicular cell degenerates into differentiated thyroid cancer (papillary or follicular, the first one with the best prognosis) or poorly differentiated/undifferentiated type (also known as anaplastic) while C para-follicular cells are associated with medullar thyroid cancer (sporadic or familial, isolated or associated with Multiple Endocrine Neoplasia type 2A Syndrome) [39,41-43]. CT may be associated with thyroid nodules like endemic goitre background for people residents in endemic areas regarding iodine deficiency or isolated macro-nodules raising the question of a malignancy [44-46] (Figure 1). Among all four classical histological types of primary thyroid cancers, the association of CT with papillary thyroid cancer (PTC) is a modern topic and seems not incidental [45,46].



**Figure 1A - thyroid nodules**



**Figure 1B - thyroid nodules**

Whether positive anti-thyroid antibodies as found in CT represent a prognostic factor for differentiated types of carcinoma is still controversial as the influence of environmental factors (for instance, iodine supplements for general population) may also be a contributor co-factor for CT-PTC association [46,47]. Except for post-operative histological report, the most important tool for practitioners is pre-operative cytological report in addition to ultrasound features [48]. Figure 1- This is a 33-year-old non-smoking female, resident of a non-endemic area, with a history of chronic thyroiditis for 3 years before when a mild elevation of TPOAb to 57UI/mL had appeared. Normal <35UI/mL with normal thyroid function was registered in association with hypoechoic pattern, and a thyroid nodule of 2.3 centimeter [cm] was detected. Fine needle aspiration cytological exam showed a follicular adenoma-like nodule with well differentiated pattern. Currently, TPOAb increased to a level above 1000UI/mL, with stationary function and hypoechoic pattern at ultrasound (Figure 1A) but the nodule of the right lobe increased to 2.53 by .54 by 1.88 cm (Figure 1B), in addition to another at the inferior right lobe of 1.4 by 1 by 1.1 cm.

### ***Chronic thyroiditis and papillary thyroid cancer [PTC]: different levels of evidence***

The CT - PTC relationship may be mainly described at three different levels: firstly, PTC is presented more frequently than follicular

thyroid cancer in relationship with iodine supplements including on autoimmune background (PTC has a better prognosis than the follicular carcinoma so this may be regarded as a positive influence); secondly, CT is involved in multifocal intra-thyroid PTC but this histological pattern may not be more aggressive than generally expected because (and this is the third aspect) lymph nodes are somehow blocked by the immune process and protected by the lymph nodes metastasis from primary thyroid source of PTC so the risk of recurrence and aggressive profile is not higher than seen in CT-free [49- 51]. Regarding all these aspects there is not a general consensus based on the current level of evidence based medicine. The most important studies are derived from the surgical experience and the post-operative confirmation of both CT and PTC. Fine-needle aspiration cytological report in patients with CT may associate false-positive results which lead to unnecessary thyroidectomy. A retrospective study published in 2017 on 3788 subjects with surgical approach identified 48 of them with pre-operative suspicion for PTC. CT prevalence was higher in this sub-group which may represent a confusion factor for inexperienced pathologists [52]. Most of the authors agree that the confirmation of CT does not seem a factor of progression after the thyroid was removed. Out of 660 patients with surgery for differentiated thyroid cancer between 2003 and 2013, 41% had histologically confirmed CT. Subjects with positive TgAb and CT infiltrate had a smaller number of lymph nodes metastasis than the patients with negative TgAb and CT histological infiltrate [53]. The theory sustaining that CT antagonizes PTC despite high risk profile [as positive BRAF mutation] was analysed in a study of 3332 PTC subjects to whom thyroidectomy was performed in addition to bilateral central neck dissection, between 2008 and 2015. BRAF mutation was rarer in PTC-CT patients while CT positive subjects have statistically significant less aggressive PTC, independent of the BRAF status [54]. Another potential prognosis marker is psammoma bodies as studied in a retrospective analysis of case-control design on 1052 patients with PTC confirmation after thyroidectomy. 30.8% of them had these micro-

calcifications. If they were found on CT background, PTC was more aggressive, becoming a particular poor prognosis marker [55]. The circulating level of TPOAb also has been found correlated with multifocal PTC in CT positive subjects. For instance, a retrospective cohort study from 2015 identified 808 cases of CT +/- PTC [56]. All of them were referred to surgeon and had a pathological confirmation after total thyroidectomy [56]. Patients with TPOAb  $\leq$  1300 IU/mL had unifocal pattern opposite to those with a level above the mentioned cut-off with multifocal type providing a clue of more aggressive profile for PTC, thus the consideration for total removal of the thyroid gland [56]. Some longitudinal observations suggested that up to 9.8% of patients with CT and indication of thyroidectomy may display a micro-PTC [57]. On the other hand, a percent of 22.7% of micro-PTC have post-operative positive CT in a retrospective series with histological reports after surgery [58]. MicroPTC is a subtype of PTC that was found in 16.3% of 2455 of subjects undergoing thyroidectomy for pre-operative benign thyroid condition, between 2008 and 2013 [58]. Micro-PTC has no specific prevalence regarding age and sex but there is a higher chance to find an association with CT elements [58]. Finally, the overall survival in patients with PTC and CT is not affected by the presence of CT [59]. Moreover, the identification of chronic lymphocytic infiltrate is correlated with PTC of lower grade based on different studies, as one retrospective cohort on 160 patients, enrolled between 2005 and 2013 with period of follow-up of 61 months (between 18 and 132 months) [59].

---

## Discussions

The thyroidectomy in patients with CT [if there are reasons to be indicated] with or without further confirmation of PTC has no specific issues and post-operative complications as cervical hematoma, lifelong hypothyroidism, vocal folds disturbances, hypocalcemia, etc are reported with a similar frequencies as seen in other conditions requiring thyroid removal while radioiodine ablative therapy is added

based on specific guidelines of thyroid cancer without particular aspects involving CT positive patients [60- 62].

## Conclusion

Team approach is essential for many aspects as the detection of CT and the selection of those rare cases that need thyroidectomy. The association between CT and PTC is actually more frequent than expected, especially for micro-PTC subtype. Overall, the survival of PTC patients does not seem to be influenced by the CT, if surgery is correctly applied despite a risk of multifocal intra- and not extra-thyroid spreading of malignancy.

## References

- [1]Burman KD, Wartofsky L. Clinical Practice. Thyroid Nodules. *N Engl J Med.* 2015 Dec 10;373[24]:2347-56. doi: 10.1056/NEJMcp1415786.
- [2]Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid.* 2016 Jan;26[1]:1-133. doi: 10.1089/thy.2015.0020.
- [3]Yoon JH, Lee HS, Kim EK, Moon HJ, Kwak JY. Malignancy Risk Stratification of Thyroid Nodules: Comparison between the Thyroid Imaging Reporting and Data System and the 2014 American Thyroid Association Management Guidelines. *Radiology.* 2016 Mar;278[3]:917-24. doi: 10.1148/radiol.2015150056.
- [4]Zhang JW, Chen ZJ, Gopinathan A. Focal Nodular Hashimoto's Thyroiditis: Comparison of Ultrasonographic Features with Malignant and Other Benign Nodules. *Ann Acad Med Singapore.* 2016 Aug;45[8]:357-63.
- [5]Lalić T, Beleslin B, Savić S, Stojković M, Cirić J, Zarković M. Challenges in interpretation of thyroid hormone test results. *Srp Arh Celok Lek.* 2016 Mar-Apr;144[3-4]:200-3.
- [6]Albu SE, Carsote M, Terzea D, Ghemigian A, Valea A, Petrova E, Vasiliu C. Thyroid autoimmune disease: between hypothyroidism and hyperthyroidism. *Archives of Balkan Medical Union [The Official Journal of the Balkan Medical Union].* 2016; 51[4]:481-485.
- [7]Gabalec F, Srbova L, Nova M, Hovorkova E, Hornychova H, Jakubikova I, Ryska A, Cap J. Impact of Hashimoto's thyroiditis, TSH levels, and anti-thyroid antibody positivity on differentiated thyroid carcinoma incidence. *Endokrynol Pol.* 2016;67[1]:48-53. doi: 10.5603/EP.a2016.0022.
- [8]Benvenga S, Antonelli A, Vita R. Thyroid nodules and thyroid autoimmunity in the context of environmental pollution. *Rev Endocr Metab Disord.* 2015 Dec;16[4]:319-40. doi: 10.1007/s11154-016-9327-6.
- [9]de Alcântara-Jones DM, de Alcântara-Nunes TF, Rocha Bde O, de Oliveira RD, Santana AC, de Alcântara FT, de Faria TM, da Silva IC, Araújo LM. Is there any association between Hashimoto's thyroiditis and thyroid cancer? A retrospective data analysis. *Radiol Bras.* 2015 May-Jun;48[3]:148-53. doi: 10.1590/0100-3984.2014.0072.
- [10]Durfee SM, Benson CB, Arthaud DM, Alexander EK, Frates MC. Sonographic appearance of thyroid cancer in patients with Hashimoto thyroiditis. *J Ultrasound Med.* 2015 Apr;34[4]:697-704. doi: 10.7863/ultra.34.4.697.
- [11]Wémeau JL. Hashimoto's thyroiditis [hypertrophic chronic lymphocytic thyroiditis]: the centennial of a discovery. *Presse Med.* 2012 Dec;41[12 P 2]:e609-10. doi: 10.1016/j.lpm.2012.10.004.
- [12]Fink H, Hintze G. Autoimmune thyroiditis [Hashimoto's thyroiditis]: current diagnostics and therapy. *Med Klin [Munich].* 2010 Jul;105[7]:485-93. doi: 10.1007/s00063-010-1082-y.
- [13]Brown RS. Autoimmune thyroid disease: unlocking a complex puzzle. *Curr Opin Pediatr.* 2009 Aug;21[4]:523-8. doi: 10.1097/MOP.0b013e32832cf824.
- [14]Duntas LH. Environmental factors and autoimmune thyroiditis. *Nat Clin Pract Endocrinol Metab.* 2008 Aug;4[8]:454-60. doi: 10.1038/ncpendmet0896.
- [15]Tozzoli R, Villalta D, Bizzaro N. Challenges in the Standardization of Autoantibody Testing: a Comprehensive Review. *Clin Rev Allergy Immunol.* 2016 Aug 8. [Epub ahead of print]
- [16]Ramos-Leví AM, Marazuela M. Pathogenesis of thyroid autoimmune disease: the role of cellular mechanisms. *Endocrinol Nutr.* 2016 Oct;63[8]:421-9. doi: 10.1016/j.endonu.2016.04.003.
- [17]Sheehan MT. Biochemical Testing of the Thyroid: TSH is the Best and, Oftentimes, Only Test Needed - A Review for Primary Care. *Clin Med Res.* 2016 Jun;14[2]:83-92. doi: 10.3121/cmr.2016.1309.
- [18]Juby AG, Hanly MG, Lukaczer D. Clinical challenges in thyroid disease: Time for a new

- approach? *Maturitas*. 2016 May;87:72-8. doi: 10.1016/j.maturitas.2016.02.001.
- [19]Ghaemi N, Sayedi J, Bagheri S. Acute suppurative thyroiditis with thyroid abscess: a case report and review of the literature. *Iran J Otorhinolaryngol*. 2014 Jan;26[74]:51-5.
- [20]Alfadda AA, Sallam RM, Elawad GE, Aldhukair H, Alyahya MM. Subacute thyroiditis: clinical presentation and long term outcome. *Int J Endocrinol*. 2014;2014:794943. doi: 10.1155/2014/794943.
- [21]Tozzoli R, Bagnasco M, Giavarina D, Bizzaro N. TSH receptor autoantibody immunoassay in patients with Graves' disease: improvement of diagnostic accuracy over different generations of methods. Systematic review and meta-analysis. *Autoimmun Rev*. 2012 Dec;12[2]:107-13. doi: 10.1016/j.autrev.2012.07.003.
- [22]Furmaniak J, Sanders J, Rees Smith B. Blocking type TSH receptor antibodies. *Auto Immun Highlights*. 2012 Mar 21;4[1]:11-26. doi: 10.1007/s13317-012-0028-1. eCollection 2013.
- [23]Shin YG, Yoo J, Kwon HJ, Hong JH, Lee HS, Yoon JH, Kim EK, Moon HJ, Han K, Kwak JY. Histogram and gray level co-occurrence matrix on gray-scale ultrasound images for diagnosing lymphocytic thyroiditis. *Comput Biol Med*. 2016 Aug 1;75:257-66. doi: 10.1016/j.combiomed.2016.06.014.
- [24]Haugen BR Md, Sawka AM, Alexander EK, Bible KC, Caturegli P Dr, Doherty G, Mandel SJ, Morris JC 3rd, Nassar A, Pacini F, Schlumberger M, Schuff KG, Sherman SI, Somerset H, Sosa JA, Steward DL, Wartofsky L, Williams MD. The ATA Guidelines on Management of Thyroid Nodules and Differentiated Thyroid Cancer Task Force Review and Recommendation on the Proposed Renaming of eFVPTC without Invasion to NIFTP. *Thyroid*. 2017 Jan 23. doi: 10.1089/thy.2016.0628.
- [25]Zantour B, Sfar MH, Alaya W, Chebbi W, Chatti K, Jerbi S. Hashimoto's thyroiditis and severe hypothyroidism, associated with a single hot nodule. *Rev Esp Med Nucl*. 2011 Sep-Oct;30[5]:317-9. doi: 10.1016/j.remna.2010.10.011.
- [26]Kim BW, Yousman W, Wong WX, Cheng C, McAninch EA. Less is More: Comparing the 2015 and 2009 American Thyroid Association Guidelines for Thyroid Nodules and Cancer. *Thyroid*. 2016 Jun;26[6]:759-64. doi: 10.1089/thy.2016.0068.
- [27]Zivaljevic VR, Bukvic Bacotic BR, Sipetic SB, Stanisavljevic DM, Maksimovic JM, Diklic AD, Paunovic IR. Quality of life improvement in patients with Hashimoto thyroiditis and other goiters after surgery: A prospective cohort study. *Int J Surg*. 2015 Sep;21:150-5. doi: 10.1016/j.ijsu.2015.08.001.
- [28]Qureshi IA, Khabaz MN, Baig M, Begum B, Abdelrehman AS, Hussain MB. Histopathological findings in goiter: A review of 624 thyroidectomies. *Neuro Endocrinol Lett*. 2015;36[1]:48-52.
- [29]Khan FA, Al-Jameil N, Khan MF, Al-Rashid M, Tabassum H. Thyroid dysfunction: an autoimmune aspect. *Int J Clin Exp Med*. 2015 May 15;8[5]:6677-81. eCollection 2015.
- [30]Topliss DJ, Eastman CJ. Diagnosis and management of hyperthyroidism and hypothyroidism. *Med J Aust*. 2004 Feb 16;180[4]:186-93.
- [31]Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune thyroid disorders. *Autoimmun Rev*. 2015 Feb;14[2]:174-80. doi: 10.1016/j.autrev.2014.10.016.
- [32]Lazúrová I, Benhatchi K, Rovenský J, Kozáková D, Wagnerová H, Tajtáková M, Shoenfeld Y, Macejova Z. Autoimmune thyroid disease and autoimmune rheumatic disorders: a two-sided analysis. *Ann N Y Acad Sci*. 2009 Sep;1173:211-6. doi: 10.1111/j.1749-6632.2009.04809.x.
- [33]Valea A, Carsote M, Ghemigian A, Dumitrache C. Pituitary macroadenoma and thyroid autoimmunity: cross-sectional observations in adult population. *Current Health Sciences Journal*. 2016; 42[S5]:50-53.
- [34]Gruia A, Dumitru A, Carsote M, Morar A, Valea A. Testicular regression syndrome and extremely elevated anti-thyroid antibodies on a patient with large unilateral polycystic renal mass. *Archives of Balkan Medical Union*. 2016; 51[4]:537-541.
- [35]Valea A, Ghervan C, Morar A, Pop DD, Carsote M, Albu SE, Georgescu CE, Chiorean A. Hashimoto's thyroiditis and breast cancer: coincidence or correlation?. *Archives of Balkan Medical Union*. 2016; 51[1]:129-132.
- [36]Huang TW, Lai JH, Wu MY, Chen SL, Wu CH, Tam KW. Systematic review of clinical practice guidelines in the diagnosis and management of thyroid nodules and cancer. *BMC Med*. 2013 Aug 29;11:191. doi: 10.1186/1741-7015-11-191.
- [37]Aspinall SR, Ong SG, Wilson MS, Lennard TW. How shall we manage the incidentally found thyroid nodule? *Surgeon*. 2013 Apr;11[2]:96-104. doi: 10.1016/j.surge.2012.11.004.
- [38]Reggio S, Grimaldi L, Vergara E, Danzi R, Pannullo M, Danzi M. The incidence of thyroid carcinoma in the nodules. A retrospective study. *Ann Ital Chir*. 2014 May-Jun;85[3]:230-6.
- [39]Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedüs L, Vitti P; AACE/AME/ETA Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European

- Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. *J Endocrinol Invest.* 2010;33[5 Suppl]:51-6.
- [40]Dumitru N, Ghemigian A, Carsote M, Albu SE, Terzea D, Valea A. Thyroid nodules after initial evaluation by primary health care practitioners: an ultrasound pictorial essay. *Archives of the Balkan Medical Union.* 2016;51[3]:434-438.
- [41]Valea A, Carsote M, Terzea D, Ghemigian A. Timing of surgical approach on patients with somatotropinoma and differentiated thyroid cancer. *Journal of Surgical Sciences.* 2016; 3[3]:148-152.
- [42]Carsote M, Albu SE, Iorgulescu R, Dumitrascu A, Terzea D, Goldstein A, Poiana C. From vasomotor symptoms to solid and insular papillary thyroid cancer with oxyphil variant areas. *Journal of Surgical Sciences.* 2015; 2[2]:87-91.
- [43]Valea A, Radu O, Morar A, Ghemigian A, Carsote M. Synchronous medullar thyroid cancer and primary hyperparathyroidism on a female within the sixth decade of life with positive family history for type 2A MEN syndrome. *Journal of Medical Practice [Practica Medicala].* 2016;4[47]-11:346-349.
- [44]Donangelo I, Walts AE, Bresee C, Braunstein GD. Lymphocytic thyroiditis is associated with increased number of benign cervical nodes and fewer central neck compartment metastatic lymph nodes in patients with differentiated thyroid cancer. *Endocr Pract.* 2016 Oct;22[10]:1192-1198.
- [45]Nam HY, Lee HY, Park GC. Impact of co-existent thyroiditis on clinical outcome in papillary thyroid carcinoma with high preoperative serum antithyroglobulin antibody: a retrospective cohort study. *Clin Otolaryngol.* 2016 Aug;41[4]:358-64. doi: 10.1111/coa.12520.
- [46]Verburg FA, Luster M, Cupini C, Chiovato L, Duntas L, Elisei R, Feldt-Rasmussen U, Rimmele H, Seregini E, Smit JW, Theimer C, Giovannella L. Implications of thyroglobulin antibody positivity in patients with differentiated thyroid cancer: a clinical position statement. *Thyroid.* 2013 Oct;23[10]:1211-25. doi: 10.1089/thy.2012.0606.
- [47]Wiersinga WM. Clinical Relevance of Environmental Factors in the Pathogenesis of Autoimmune Thyroid Disease. *Endocrinol Metab [Seoul].* 2016 Jun;31[2]:213-22. doi: 10.3803/EnM.2016.31.2.213.
- [48]Reinisch A, Malkomes P, Habbe N, Bojunga J, Grünwald F, Badenhop K, Bechstein WO, Holzer K. Guideline Compliance in Surgery for Thyroid Nodules - A Retrospective Study. *Exp Clin Endocrinol Diabetes.* 2017 Mar 2. doi: 10.1055/s-0042-113871. [Epub ahead of print]
- [49]Carvalho MS, Rosario PW, Mourão GF, Calsolari MR. Chronic lymphocytic thyroiditis does not influence the risk of recurrence in patients with papillary thyroid carcinoma and excellent response to initial therapy. *Endocrine.* 2017 Mar;55[3]:954-958. doi: 10.1007/s12020-016-1185-1.
- [50]Kim SK, Park I, Woo JW, Lee JH, Choe JH, Kim JH, Kim JS. Predictive Factors for Lymph Node Metastasis in Papillary Thyroid Microcarcinoma. *Ann Surg Oncol.* 2016 Sep;23[9]:2866-73. doi: 10.1245/s10434-016-5225-0.
- [51]Zhu Y, Zheng K, Zhang H, Chen L, Xue J, Ding M, Wu K, Wang Z, Kong L, Chen X. 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. *Tumour Biol.* 2016 Jun;37[6]:8037-45. doi: 10.1007/s13277-015-4706-2.
- [52]Yi KI, Ahn S, Park DY, Lee JC, Lee BJ, Wang SG, Cha W. False-positive cytopathology results for papillary thyroid carcinoma: A trap for thyroid surgeons. *Clin Otolaryngol.* 2017 Jan 28. doi: 10.1111/coa.12840. [Epub ahead of print]
- [53]Donangelo I, Walts AE, Bresee C, Braunstein GD. Lymphocytic thyroiditis is associated with increased number of benign cervical nodes and fewer central neck compartment metastatic lymph nodes in patients with differentiated thyroid cancer. *Endocr Pract.* 2016 Oct;22[10]:1192-1198.
- [54]Kim SK, Woo JW, Lee JH, Park I, Choe JH, Kim JH, Kim JS. Chronic lymphocytic thyroiditis and BRAF V600E in papillary thyroid carcinoma. *Endocr Relat Cancer.* 2016 Jan;23[1]:27-34. doi: 10.1530/ERC-15-0408.
- [55]Cai YF, Wang QX, Ni CJ, Guo GL, Li Q, Wang OC, Wu L, Du HY, You J, Zhang XH. The Clinical Relevance of Psammoma Body and Hashimoto Thyroiditis in Papillary Thyroid Carcinoma: A Large Case-control Study. *Medicine [Baltimore].* 2015 Nov;94[44]:e1881. doi: 10.1097/MD.0000000000001881.
- [56]Dong S, Xia Q, Wu YJ. High TPOAb Levels [ $>1300$  IU/mL] Indicate Multifocal PTC in Hashimoto's Thyroiditis Patients and Support Total Thyroidectomy. *Otolaryngol Head Neck Surg.* 2015 Jul;153[1]:20-6. doi: 10.1177/0194599815581831.
- [57]Tao L, Xi-Lin H, Xiang-Dong M. Surgical Treatment of Hashimoto's with Thyroid Microcarcinoma. *Cell Biochem Biophys.* 2015 May;72[1]:123-6. doi: 10.1007/s12013-014-0418-2.
- [58]Šlijepevc N, Zivaljevic V, Marinkovic J, Sipetic S, Diklic A, Paunovic I. Retrospective evaluation of the incidental finding of 403 papillary thyroid microcarcinomas in 2466 patients undergoing thyroid surgery for presumed benign

- thyroid disease. *BMC Cancer*. 2015 Apr 30;15:330. doi: 10.1186/s12885-015-1352-4.
- [59] Dobrinja C, Makovac P, Pastoricchio M, Cipolat Mis T, Bernardi S, Fabris B, Piscopello L, de Manzini N. Coexistence of chronic lymphocytic thyroiditis and papillary thyroid carcinoma. Impact on presentation, management, and outcome. *Int J Surg*. 2016 Apr;28 Suppl 1:S70-4. doi: 10.1016/j.ijso.2015.12.059.
- [60] Perera M, Anabell L, Page D, Harding T, Gnaneswaran N, Chan S. Risk factors for post-thyroidectomy haematoma. *J Laryngol Otol*. 2016 Jan;130 Suppl 1:S20-5. doi: 10.1017/S0022215115003199.
- [61] Ghemigian A, Carsote M, Dumitru N, Petrova EN, Bururiana A, Goldstein A, Valea A. The bone profile after surgery for differentiated thyroid carcinoma. *Current Health Sciences Journal*. 2016; 42[S5]:39-42.
- [62] Higgins TS, Gupta R, Ketcham AS, Sataloff RT, Wadsworth JT, Sinacori JT. Recurrent laryngeal nerve monitoring versus identification alone on post-thyroidectomy true vocal fold palsy: a meta-analysis. *Laryngoscope*. 2011 May;121[5]:1009-17. doi: 10.1002/lary.21578.