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REVIEW ARTICLE

TSH-suppressive treatment in differentiated thyroid cancer. A dogma under review☆

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Abstract   TSH-suppressive therapy (ST) is part of the treatment protocol for differentiated thyroid carcinoma (DTC). There is however little evidence of its clinical effectiveness. On the other side, ST is not free from side effects related to the subclinical hyperthyroidism status induced in patients for a long time period. Because of this, widespread use of ST in all patients has recently been questioned, and individualized treatment based on the characteristics of each particular case has been proposed.

Action of thyroid hormones (THs) depends on their binding to specific nuclear receptors. However, a second pathway mediated by a membrane receptor located in integrin $\alpha_V\beta_3$ has recently been established. It has been postulated that the proliferative and angiogenic effects attributed to THs would depend on this second mechanism. It is not known whether the tumorigenic action shown in other neoplasms may have an impact on DTC.

The objective of this study was to review the relationship between ST and cancer, particularly as regards tumor evolution and occurrence of second primary neoplasms. One of the future challenges in the field of DTC will be to establish the specific role of TSH and THs in malignant thyroid cells, in order to be able to define more optimized therapeutic schemes.
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Tratamiento supresor de la TSH en el cáncer diferenciado de tiroides. Un dogma en revisión

Resumen   El tratamiento supresor (TS) de la TSH forma parte del protocolo terapéutico en el carcinoma diferenciado de tiroides (CDT). No obstante, existe poca evidencia sobre su efectividad clínica. Además, esta práctica no está exenta de efectos secundarios relacionados con el estado de hipertiroidismo subclínico a la que se somete al paciente durante un largo periodo de tiempo. Por todo ello, recientemente se ha empezado a poner en duda que la TS deba ser aplicada de forma generalizada en todos los pacientes, proponiéndose un uso individualizado en función de las características de cada caso en concreto.

La acción de las hormonas tiroideas (HT) depende de su unión a receptores nucleares específicos. Pero en los últimos años se ha establecido una segunda vía mediada por un receptor de membrana presente en la integrina $\alpha_V\beta_3$. Se ha postulado que el efecto proliferativo e inductor de angiogénesis atribuido a las HT dependería de este segundo mecanismo. Se desconoce si la acción tumorogénica demostrada en otras neoplasias pueda tener repercusión en el CDT.

El objetivo del presente trabajo es revisar la relación entre TS y cáncer, especialmente en la evolución del tumor y en la aparición de segundas neoplasias primarias. Uno de los retos de futuro en el campo del CDT será establecer el papel específico de la TSH y de las HT en la célula tiroidea malignizada para poder definir unas pautas terapéuticas más optimizadas.

Introduction

Treatment for differentiated thyroid carcinoma (DTC) is based on a triad consisting of total thyroidectomy, the ablation of thyroid remnants with ^{131}I, and treatment with high thyroxine doses. This last strategy is what is usually known as ''suppressive treatment'' (ST), and was proposed as a helpful treatment more than 75 years ago[1] when the administration of thyroid extracts was shown to improve the course of DTC metastases. TSH is the main factor in thyroid cell growth and differentiation. The trophic effect is maintained in DTC, and inhibition with high thyroxine doses therefore helps prevent the extension of residual cancer cells not killed after surgery and ablation.

However, this postulate has recently been challenged after the predominant role of TSH as a cell proliferation element, particularly in neoplastic cells, was questioned.[2,3] On the other hand, new questions have arisen about the optimal treatment for DTC as the result of advances made in the past decade in our understanding of the molecular bases governing tumorigenesis. One of these questions refers to ST and the possibility that this treatment, apart from its known side effects, may induce proliferation of either DTC itself or second tumors. The objective of this study was to review the current state of ST based on these findings.

A weak scientific basis

Since its progressive implementation, ST has been widely accepted and is part of all treatment protocols for DTC. Scientific evidence for its efficacy is however limited, and there are not many studies which support its clinical use.

In 2002, McGriff et al.[4] published the first and only meta-analysis to date on the subject. These authors only analyzed the 10 articles they considered adequate for the study, which were otherwise not free from significant methodological limitations. Thus, three of them were from the same research group, so that patients could be included several times.[5-7] The same was applied to two other studies.[8,9] On the other hand, the Young et al.[9] article only analyzed follicular carcinomas (FTC), and the one by Sanders and Rossi[7] only included hidden carcinomas, i.e. those diagnosed at the metastatic stage. Moreover, the reported series included quite old DTC cases. For example, the Wanebo et al.[10] study ended in 1976, the Cady et al.[5] study included subjects treated for DTC between 1931 and 1970, the study by Sanders and Rossi[7] analyzed a patient group monitored between 1940 and 1990, and the highly referenced series of Mazzaferri and Jhiang[8] reported cases from 1950 to 1993. It is obvious that the diagnostic and therapeutic procedures performed on those patients cannot be extrapolated to current times. Finally, the number of cases in the different series was also small. Sanders and Rossi[7] reported 92 patients, and the Pujol et al. study,[11] one of the most commonly cited to show the efficacy of ST, was based on 121 subjects. However, based on the characteristics of all of these studies, the meta-analysis by McGriff et al.[4] concluded that treatment with high thyroxine doses was effective, but that it was of little significance as regards improving the survival of patients with DTC.

Some of the studies included in the meta-analysis found ST to be effective under certain circumstances. Cooper et al.[12] suggested that TSH inhibition should only be used in patients classified as high risk. Patient selection and the recognition that the widespread use of ST should be reconsidered gained strength following the review by McGriff et al. Thus, a 2006 study by Jonklaas et al.[13] stratified the efficacy of this therapeutic approach. The authors found that in stage I, survival was not related to the extent of TSH suppression. In stage II, a direct relationship was seen in TSH levels higher than 3 mU/L. In stages III and IV, a clear correlation was found between ST and survival. Moreover, Hovens et al.[14] more recently defined a value of TSH of approximately 2 mU/L as the cut-off point for best discriminating the risk of disease relapse. All of these led to an ST algorithm which was more rational and adapted to the characteristics of each individual patient being proposed.[15] This new approach started to be seen in some guidelines and practical recommendations.[16,17]

The only randomized, prospective study conducted to date which assesses the efficacy of ST has recently been published. Sugitani and Fujimoto[18] randomized more than 400 patients undergoing surgery for DTC into two groups. The first group was treated with thyroxine to achieve TSH suppression, while patients in the second group were treated to maintain TSH within the normal range. After a mean follow-up of 7 years, the authors found no significant difference between the two groups in regard to disease-free time, relapse, time of relapse, distant metastases, overall mortality, or specific mortality.

An strategy not devoid of risk

To the weak scientific evidence concerning the actual effectiveness of ST, it should be added that it is not devoid

of side effects. There are several reports which analyze this aspect, including the excellent review by Reverter and Colomé[19] recently published in this journal. The most significant harmful effects of ST are those derived from the subclinical hyperthyroidism chronically induced in patients, which often leads to a true, symptomatic clinical hyperthyroidism.

Thyroid hormones and cancer

The existence of a direct relationship between thyroid hormones (THs) and cancer was suggested more than a century ago.[20] Different studies have found a significant association between hormone levels and the occurrence of various neoplasms, including kidney, pancreas, ovary, and breast tumors.[21] In 1984, Brinton et al.[22] reported that the risk of breast cancer increased more than 10-fold when replacement therapy with THs was started in hypothyroid women. A large scale epidemiological study conducted in Norway on more than 29,000 people monitored for nine years showed that TSH levels less than 0.5 mU/L were associated with increased cancer occurrence (hazard ratio, 1.34; confidence interval, 1.06–1.69).[23] Malignant lung and prostate tumors were most common. By contrast, levels consistent with hypothyroidism did not increase the chance of tumor occurrence.[23] In this regard, recent studies suggest that hypothyroidism may improve the effectiveness of anticancer treatments.[21] Specifically, an increased progression-free time has been reported in patients with renal cancer who experience hypothyroidism following the administration of sunitinib and sorafenib.[24,25] This has led to it being postulated that THs play some role in both tumor proliferation and angiogenesis. However, the pathophysiological basis of such effects may not be established for years.

A new paradigm in thyroid hormone action

Integrins are a group of integral membrane heterodimers able to interact with various extracellular proteins, growth factors, and certain hormones to generate intracellular responses. More than 20 different integrins, resulting from the combination of various subtypes of the two subunits (alpha and beta) that form them, have been reported to date. In 2005, Bergh et al.[26] reported that the integrin known as $\alpha_V\beta_3$ has a specific site that acts as an HT receptor. This altered the traditional concept that HTs, and specifically triiodothyronine (T3), only acted through nuclear receptors (TRs). On the other hand, various studies had already demonstrated that some TH actions were not mediated by TRs. Thus, effects due to interaction with traditional receptors were called ''genomic actions'', and all other effects, ''non-genomic actions''[27]. Studies subsequent to the Bergh et al.[26] discovery confirmed the hypothesis that non-genomic actions were due to TH interaction with their surface receptor in integrin $\alpha_V\beta_3$.[28] It should be noted that this integrin has a specific locus for T3 and another different locus for tetraiodothyronine (T4).

Integrin $\alpha_V\beta_3$ is expressed in endothelial and smooth muscle cells, but shows a particularly strong expression in the cell membrane of a great number of tumors, including breast, prostate, and liver tumors. The Bergh et al. study[26]

suggested that integrin activation by THs was responsible for the angiogenesis promoter action of THs, and that the T4-$\alpha_V\beta_3$ complex acted by activating the signaling pathway dependent upon mitogen-activated protein kinase (or MAPK pathway). Other studies have supported this hypothesis, and the relationship between cancer and THs, first suspected more than a century ago, is currently thought to be due to activation of the $\alpha_V\beta_3$ receptor.[29,30] In addition, it has recently been established that T4 plays a crucial role in this phenomenon.

Impact on thyroid cancer

As previously seen, THs may, on the one hand, play a stimulating role in cancer progression, but there is also evidence to suggest that the pathophysiological mechanism is the activation of the MAPK signaling pathway, a key pathway in cell differentiation and proliferation which has been shown to be determinant in the development of papillary thyroid carcinoma (PTC).[31] All of these data have led to the impact of ST in the treatment scheme for DTC coming under consideration and suggested a potential new, unknown adverse effect of ST: the possibility that ST is related to either DTC evolution or to the occurrence of a second tumor. Few experimental data are available in this regard.

Hoffmann et al.[32] showed in 2005 that normal thyroid tissue expresses $\alpha_V\beta_3$ and that various DTC cell lines show variable integrin expression patterns. In addition, Illario et al.[33] have shown that the T4-$\alpha_V\beta_3$ complex also activates the MAPK signaling pathway in thyroid cells. More recently, Yalcin et al.[34] reported that, in an experimental follicular carcinoma model, T4-$\alpha_V\beta_3$ blockade resulted in decreases in both angiogenic capacity and tumor mass. In an interesting article, Lin et al.[35] found that activation of T4-$\alpha_V\beta_3$, at physiological T4 levels, caused a proliferative stimulus and a decreased apoptotic capacity in PTC and FTC cell cultures. In their conclusions, the authors postulated that in some patients ST may have a stimulating action on residual tumor growth, even in the absence of TSH.

TSH suppressive therapy and second tumors

Patients with DTC are at greater risk than the general population of developing a second primary tumor (SPT). Studies reported in recent decades, including three large epidemiological studies[36–38] and a meta-analysis,[39] confirm a risk of SPT 5–31% greater than expected. One of the reasons given for this increase is the carcinogenic effect of ^{131}I ablation therapy.[40] De Vathaire et al.[41] reported that the increase in colon cancer occurrence was related to the total dose of ^{131}I administered. More recently, Fallahi et al.[42] estimated that a cumulative total dose higher than 40 GBq (1.08 Ci) was associated with a significant increase in SPTs. Ronckers et al.[37] conducted a study based on the patient cohort from the US Surveillance, Epidemiology, and End-results (SEER) program. The authors analyzed the incidence of a subgroup of tumors in tissues with a greater exposure to the radioisotope. These included tumors in the salivary glands, stomach, small bowel, and urinary bladder, as well as in leukemias. The risk of experiencing some of these tumors

was two-fold greater in patients with DTC who had received ^{131}I as compared to those given no ablation therapy.

However, other authors found no association between SPT and ^{131}I treatment. Bhattacharyya and Chien[43] compared two patient groups with DTC depending on whether or not they had received isotope treatment and found that STP occurred in 6.7% and 4.8% of untreated and treated patients respectively. Similarly, Berthe et al.[44] and Verkooijen et al.[45] found no influence of the type of treatment used. This fact, combined with the evidence that the inverse relationship is also significant[37,38,46] (patients with extrathyroid neoplasms who subsequently develop DTC), has led to other hypotheses being considered. Thus, it has been suggested that a patient may have common risk factors for the occurrence of different tumors, such as some environmental conditions or a genetic predisposition.[45,47]

No published study has assessed the potential role of ST in the risk of SPT. Although this is fully speculative, it is interesting to note that in a majority of series, the most common SPTs are breast, kidney, and prostate tumors, which are the ones most commonly involved in the association between THs and cancer.

TSH an differentiated thyroid carcinoma

The role of THs and TSH in DTC appears to be even more complex. Although, as already noted, the epidemiological Norwegian study by Hellevik et al.[23] related TSH levels less than 0.5 mU/L to a high risk of various tumors, there is some evidence that the opposite occurs in DTC, i.e. a direct relationship appears to exist between TSH values and the risk of thyroid cancer. Boelaert et al.[48] reported in 2006 that serum TSH levels were an independent predictor of malignancy. Other studies have subsequently shown that presurgical TSH levels are a risk marker for DTC in thyroid nodular disease (TND).[49,50] Jin et al.[51] found that in TND patients, TSH levels less than 0.9 mU/L were associated with a 10% chance of experiencing DTC, but that the risk increased to 65% with TSH levels higher than 5.5 mU/L. Moreover, TSH elevation is also related to DTC which is diagnosed at more advanced stages or is more aggressive.[49,52] Our group recently reported a 12% risk of malignancy in patients with TND and subclinical hyperthyroidism, which increased to 20.5% when TSH was within normal limits and to 42% in patients with subclinical hypothyroidism.[53] TSH levels were, in turn, correlated to tumor size, so that mean levels were 1.36 ± 1.62 mU/L in TND without DTC, 1.71 ± 1.52 mU/L in patients with a final diagnosis of DTC less than 1 cm in size (microcarcinoma), and 2.42 ± 2.5 mU/L in cases with bigger DTCs.

Conclusions

ST is usually part of the treatment scheme for DTC. The possibility that subclinical hyperthyroidism associated with ST could cause side effects, particularly at cardiovascular and bone level, has been considered for some time. More recently, it has been established that the proliferative and angiogenesis-promoting effects derived from THs are due to hormone interaction with integrin $\alpha_V\beta_3$. The influence of this effect on ST on both the course of DCT and the

occurrence of second tumors is currently unknown. On the other hand, low TSH levels correlate to an increased risk of extrathyroid tumors, but appear to decrease the risk of DTC in TND.

DTC has traditionally been considered as a group of TSH-dependent tumors, and TSH inhibition by ST was therefore regarded as an effective measure. However, neither the possibility that DTC was TH-dependent nor the direct effect of THs on tumor course was ever taken into consideration. In the future, we will need to identify which tumors are closer to TSH dependence and which have a predominant dependence on THs. This approach may possibly allow us to understand cases that do not respond to standard treatment, or to understand why ST has not shown a universal efficacy. The aim should be to determine the specific role of TSH and THs in DTC occurrence and development, and to individually optimize the most adequate treatment while minimizing any adverse effects.

Conflicts of interest

The author states that he has no conflicts of interest.

References

1. Dunhill TP. The surgery of the thyroid gland: the Lettsomian lectures. Trans Med Soc Lond. 1937;60:234–82.
2. Brabant G. Thyrotropin suppressive therapy in thyroid carcinoma: what are the targets? J Clin Endocrinol Metab. 2008;93:1167–9.
3. Derwahl M, Broecker M, Kraiem Z. Thyrotropin may not be the dominant growth factor in benign and malignant thyroid tumors. J Clin Endocrinol Metab. 1999;84:829–34.
4. McGriff NJ, Csako G, Gourgiotis L, Guthrie LC, Pucino F, Sarlis NJ. Effects of thyroid hormone suppression therapy on adverse clinical outcomes in thyroid cancer. Ann Med. 2002;34:554–64.
5. Cady B, Cohn KH, Rossi RL, Sedgwick CE, Meissner WA, Werber J, et al. The effect of thyroid hormone administration upon survival in patients with differentiated thyroid carcinoma. Surgery. 1983;94:978–83.
6. Rossi RL, Cady B, Silverman ML, Wool MS, ReMine SG, Hodge MB, et al. Surgically incurable well-differentiated thyroid carcinoma. Arch Surg. 1988;123:569–74.
7. Sanders LE, Rossi RL. Occult well differentiated thyroid carcinoma presenting as cervical node disease. World J Surg. 1995;19:642–7.
8. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med. 1994;97:418–28.
9. Young RL, Mazzaferri EL, Rahe AJ, Dorfman SG. Pure follicular thyroid carcinoma: impact of therapy in 214 patients. J Nucl Med. 1980;21:733–7.
10. Wanebo HJ, Andrews W, Kaiser DL. Thyroid cancer: some basic considerations. Am J Surg. 1981;142:474–9.
11. Pujol P, Daures JP, Nsakala N, Baldet L, Bringer J, Jaffiol C. Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. J Clin Endocrinol Metab. 1996;81:4318–23.
12. Cooper DS, Specker B, Ho M, Sperling M, Ladenson PW, Ross DS, et al. Thyrotropin suppression and disease progression in patients with differentiated thyroid cancer: results from the National Thyroid Cancer Treatment Cooperative Registry. Thyroid. 1998;8:737–44.

13. Jonklaas J, Sarlis NJ, Litofsky D, Ain KB, Bigos T, Brierley JD, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid. 2006;16:1229–42.

14. Hovens GC, Stokkel MP, Kievit J, Corssmit EP, Pereira AM, Romijn JA, et al. Associations of serum thyrotropin concentrations with recurrence and death in differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2007;92:2610–5.

15. Cooper DS. TSH suppressive therapy: an overview of long-term clinical consequences. Hormones. 2010;9:57–9.

16. Cooper DS, Doherty G, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19:1167–214.

17. Biondi B, Cooper DS. Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer. Thyroid. 2010;20:135–46.

18. Sugitani I, Fujimoto Y. Does postoperative thyrotropin suppression therapy truly decrease recurrence in papillary thyroid carcinoma? A randomized controlled trial. J Clin Endocrinol Metab. 2010;95:4576–83.

19. Reverter JL, Colomé E. Posibles efectos adversos del tratamiento supresor de la TSH en el carcinoma diferenciado de tiroides. Endocrinol Nutr. 2011;58:75–83.

20. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. Lancet. 1896;2:104–7.

21. Hercbergs AH, Ashur-Fabian O, Garfield D. Thyroid hormones and cancer: clinical studies of hypothyroidism in oncology. Curr Opin Endocrinol Diabetes Obes. 2010;17:432–6.

22. Brinton LA, Hoffman DA, Hoover, Fraumeni Jr JF. Relationship of thyroid disease and use of thyroid supplements to breast cancer risk. J Chronic Dis. 1984;37:877–93.

23. Hellevik A, Asvold B, Bjoro T, Romundstad P, Nilsen T, Vatten L. Thyroid function and cancer risk: a prospective population study. Cancer Epidemiol Biomarkers Prev. 2009;18:570–4.

24. Baldazzi V, Tassi R, Lapini A, Santomaggio C, Carini M, Mazzanti R. The impact of sunitinib-induced hypothyroidism on progression-free survival of metastatic renal cancer patients: a prospective single-canter study. Urol Oncol. 2010, epub ahead of print.

25. Riesenbeck LM, Bierer S, Hoffmeister I, Köpke T, Papavassilis P, Hertle T, et al. Hypothyroidism correlates with a better prognosis in metastatic renal cancer patients treated with sorafenib or sunitinib. World J Urol. 2011;29:807–13.

26. Bergh JJ, Lin HY, Lansing LL, Mohamed SN, Davis FB, Mousa S, et al. Integrin $\alpha_V\beta_3$ contains cell surface receptor site for thyroid hormone that is linked to activation of mitogen-activated protein kinase and induction of angiogenesis. Endocrinology. 2005;146:2864–71.

27. Cheng SY, Leonard JL, Davis PJ. Molecular aspects of thyroid hormone actions. Endocrine Rev. 2010;31:139–70.

28. Davis PJ, Davis FB, Lin HY, Mousa S, Zhou M, Luidens MK. Translational implications of nongenomic actions of thyroid hormone initiated at its integrin receptor. Am J Physiol Endocrinol Metab. 2009;297:E1238–46.

29. Davis PJ, Davis FB, Mousa S, Luidens MK, Lin HY. Membrane receptor for thyroid hormone: physiologic and pharmacologic implications. Annu Rev Pharmacol Toxicol. 2011;51:99–115.

30. Pinto M, Soares P, Ribatti D. Thyroid hormone as a regulator of tumor induced angiogenesis. Cancer Lett. 2011;301:119–26.

31. Zafon C, Obiols G. Vía de señalización dependiente de la proteincinasa de activación mitogénica en el carcinoma papilar de tiroides. De las bases moleculares a la práctica clínica. Endocrinol Nutr. 2009;56:176–86.

32. Hoffmann S, Maschuw K, Hassan I, Reckzeh B, Wunderlich A, Lingelbach S, et al. Differential pattern of integrin receptor expression in differentiated and anaplastic thyroid cancer cell lines. Thyroid. 2005;15:1011–20.

33. Illario M, Cavallo AL, Monaco S, Di Vito E, Mueller F, Marzano LA, et al. Fibronectin-induced proliferation in thyroid cells is mediated by $\alpha_V\beta3$ integrin through Ras/Raf-1/MEK/ERK and calcium/CaMKII signals. J Clin Endocrinol Metab. 2005;90:2865–73.

34. Yalcin M, Bharali DJ, Dyskin E, Dier E, Lansing L, Mousa SS, et al. Tetraiodothyroacetic acid and tetraiodothyroacetic acid nanoparticle effectively inhibit the growth of human follicular thyroid cell carcinoma. Thyroid. 2010;20:281–6.

35. Lin HY, Tang HY, Shih A, Keating T, Cao G, Davis PJ, et al. Thyroid hormone is a MAPK-dependent growth factor for thyroid cancer cells and is anti-apoptotic. Steroids. 2007;72:180–7.

36. Brown AP, Chen J, Hitchcock YJ, Szabo A, Shrieve DC, Tward JD. The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2008;93:504–15.

37. Ronckers CM, McCarron P, Ron E. Thyroid cancer and multiple primary tumors in the SEER cancer registries. Int J Cancer. 2005;117:281–8.

38. Sandeep TC, Strachan MWJ, Reynolds RM, Brewster DH, Scélo G, Pukkala E, et al. Second primary cancers in thyroid cancer patients: a multinational record linkage study. J Clin Endocrinol Metab. 2006;91:1819–25.

39. Subramanian S, Goldstein DP, Parlea L, Thabane L, Ezzat S, Ibrahim-Zada I, et al. Second primary malignancy risk in thyroid cancer survivors: a systematic review and meta-analysis. Thyroid. 2007;17:1277–88.

40. Sawka AM, Thabane L, Parlea L, Ibrahim-Zada I, Tsang RW, Brierley JD, et al. Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. Thyroid. 2009;19:451–7.

41. De Vathaire F, Schlumberger M, Delisle MJ, Francese C, Challeton C, De la Genardiére E, et al. Leukaemias and cancers following iodine-131 administration for thyroid cancer. Cancer. 1997;75:734–9.

42. Fallahi B, Adabi K, Majidi M, Fard-Esfahani A, Heshmat R, Larijani B, et al. Incidence of second primary malignancies during a long-term surveillance of patients with differentiated thyroid carcinoma in relation to radioiodine treatment. Clin Nucl Med. 2011;36:277–82.

43. Bhattacharyya N, Chien W. Risk of second primary malignancy after radioactive iodine treatment for differentiated thyroid carcinoma. Ann Otol Rhinol Laryngol. 2006;115:607–10.

44. Berthe E, Henry-Amar M, Michels JJ, Rame JP, Berthe P, Babin E, et al. Risk of second primary cancer following differentiated thyroid cancer. Eur J Nucl Med Mol Imaging. 2004;31:685–91.

45. Verkooijen RBT, Smit JWA, Romijn JA, Stokkel MP. The incidence of second primary tumors in thyroid cancer patients is increased, but not related to treatment of thyroid cancer. Eur J Endocrinol. 2006;155:801–6.

46. Ömür O, Özcan Z, Yazici B, Akgün A, Oral A, Özkiliç H. Multiple primary tumors in differentiated thyroid carcinoma and relationship to thyroid cancer outcome. Endocr J. 2008;55:365–72.

47. Lang BH, Lo CY, Wong IOL, Cowling BJ. Impact of second primary malignancy on outcomes of differentiated thyroid carcinoma. Surgery. 2010;148:1191–7.

48. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab. 2006;91:4295–301.

49. Haymart MR, Repplinger DJ, Leverson GE, Elson DF, Sippel RS, Jaume JC, et al. Higher serum thyroid stimulating hormone level in thyroid nodular patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. J Clin Endocrinol Metab. 2008;93:809–14.

50. Jonklaas J, Nsouli-Maktabi H, Soldin SJ. Endogenous thyrotropin and triiodothyronine concentrations in individuals with thyroid cancer. Thyroid. 2008;18:943–52.

51. Jin J, Machekano R, McHenry CR. The utility of preoperative serum thyroid-stimulating hormone level for predicting malignant nodular thyroid disease. Am J Surg. 2010;199:294–8.

52. Fiore E, Rago T, Provenzale MA, Scutari M, Ugolini C, Basolo F, et al. Lower levels of TSH are associated with a lower risk of papillary thyroid cancer in patients with thyroid nodular disease: thyroid autonomy may play a protective role. Endocr Relat Cancer. 2009;16:1251–60.

53. Zafon C, Obiols G, Baena JA, Castellvi J, Dalama B, Mesa J. Preoperative thyrotropin serum concentrations gradually increase from benign thyroid nodules to papillary thyroid microcarcinomas then to papillary thyroid cancers of larger size. J Thyroid Res. 2012;ID 530721:4.