CLINICAL THYROIDOLOGY

Clinical Thyroidology for Patients
www.thyroid.org/patients/ct/index.html

A publication of the American Thyroid Association

EDITORS' COMMENTS

This is the 9th 2009 issue of *Clinical Thyroidology*. As you may know, each issue will be sent to you by email as a separate list of articles that can be downloaded individually or as the entire document.

CLINICAL THYROIDOLOGY STATISTICS We are happy to report that there are more than 4,300 subscribers to *Clinical Thyroidology* online. The articles in Volume 21, Issue 1 to 7 have been viewed by more than 27,000 unique times. Our subscribers include 2,502 MDs and 202 PhDs, as well as members from 196 different specialties or areas of Interest from 118 countries. We are grateful that so many are using *Clinical Thyroidology*.

We wish to thank Dr. Jerome M. Hershman, MD, MACP, for his contribution to this edition of Clinical Thyroidology. Dr. Hershman is past president of the American Thyroid Association, and past Editor-in Chief of THYROID. He is Distinguished Professor of Medicine at the David Geffen School of Medicine at UCLA. His comments on human chorionic gonadotropin (hCG) reflect his important past studies that paved the way for our understanding of this hormone in pregnant women and the clinical syndromes associated with high hCG concentrations.

SEARCH FOR PREVIOUS ISSUES OF *CLINICAL THYROIDOLOGY* A number of our readers have asked for a quick way to find articles published in this journal over the past years. Now you can access previous issues using key words, author names, and categories such as thyroid cancer, or other terms. You will find this by simply right clicking the following: http://thyroid.org/professionals/publications/clinthy/index.html.

FIGURES The articles in *Clinical Thyroidology* contain figures with the ATA logo and a CT citation with the volume and issue numbers. We encourage you to continue using these figures in your lectures, which we hope will be useful to you and your students.

WHATS NEW The last page now has a set of references to **REVIEWS & HOT ARTICLES** which contains references to important reviews and very recent articles that look especially important to the Editors.

EDITOR'S CHOICE ARTICLES are particularly important studies that we recommend you read in their entirety.

We welcome your feedback and suggestions on these changes.

CONCISE REVIEW CITATIONS can be cited by using the electronic citation at the end of each review.

Ernest L. Mazzaferri, MD, MACP
Jennifer A. Sipos, MD

How to navigate this document: The Table of Contents and the Bookmarks are linked to the articles. To navigate, move your cursor over the article title you wish to see (either in the Contents or in the Bookmarks panel) and the hand will show a pointing finger, indicating a link. Left-click the title and the article will instantly appear on your screen. To return to the Contents, move the cursor to the bottom of the page and left-click Back to Contents which appears on every page. If you would like more information about using Bookmarks please see the help feature on the menu bar of Acrobat Reader.

TSH levels are altered by the timing of levothyroxine administration

SUMMARY

BACKGROUND Levothyroxine (L-T$_4$) has a narrow therapeutic index, which is influenced by intestinal absorption. Administration with food, other medications, and even certain beverages such as coffee may result in interference with L-T$_4$ absorption. The aim of this study was to determine whether taking L-T$_4$ with breakfast or at bedtime results in significant elevations in serum thyrotropin (TSH) as compared with its traditional administration after an overnight fast, 1 hour before breakfast.

METHODS The study subjects were patients 18 to 75 years of age who had hypothyroidism for at least 2 years or had thyroid cancer with no evidence of persistent disease. The patients with hypothyroidism were required to have a stable TSH for >6 months while taking one of the two most popular brands of L-T$_4$. Those with thyroid cancer were required to have a TSH level ranging from 0.01 to 0.5 µIU/ml. Patients were excluded from the study if they were pregnant, were taking medications known to interfere with L-T$_4$ absorption or metabolism, or had a chronic illness such as heart disease, diabetes, or pulmonary, gastrointestinal, or renal disease.

At entry into the study, blood was drawn at 8 a.m. under fasting conditions to measure serum TSH, free thyroxine (T$_4$), and total triiodothyronine (T$_3$). Patients then completed three 8-week regimens defined by the timing of L-T$_4$ administration. In one 8-week block, patients were asked to take L-T$_4$ after an overnight fast at least 1 hour before breakfast (BB). In another 8-week block, patients were asked to take L-T$_4$ with breakfast (WB), and in the last 8-week block, they were asked to take L-T$_4$ as they retired for bed at least 2 hours after their last meal of the day (HS). Thyroid-function studies were repeated upon completion of each of the three regimens. Blood was separated into two aliquots, one for immediate processing for the thyroid-function studies and another for storage and processing by the General Clinical Research Center upon completion of the study. When patients were on one of the two morning regimens, L-T$_4$ administration was delayed until after the phlebotomy.

Patients were asked to keep a diary on the time L-T$_4$ was ingested and the times that foods were consumed at meals. They also were asked to take calcium supplements, ferrous sulfate, and multivitamins with a meal other than breakfast and separated from L-T$_4$ by at least 4 hours. Telephone or e-mail follow-ups were made every four weeks.

Power calculations for the study that were performed to determine the sufficient sample size found that a sample of 42 patients would be sufficient to detect a 1.0 µIU/ml difference in TSH between the regimens with 90% power. Upon completion of WB or HS regimens, a rise in the serum TSH of ≥1.0 µIU/ml above the cohort's mean TSH concentration during the fasting regimen was considered a treatment failure.

RESULTS Sixty-five patients completed the study; 42 had hypothyroidism and 23 had thyroid cancer. At the time of the baseline TSH determination, 88% of patients were taking their L-T$_4$ in the fasting state, 9% were taking L-T$_4$ at bedtime, and 3% were taking it at least an hour before breakfast.
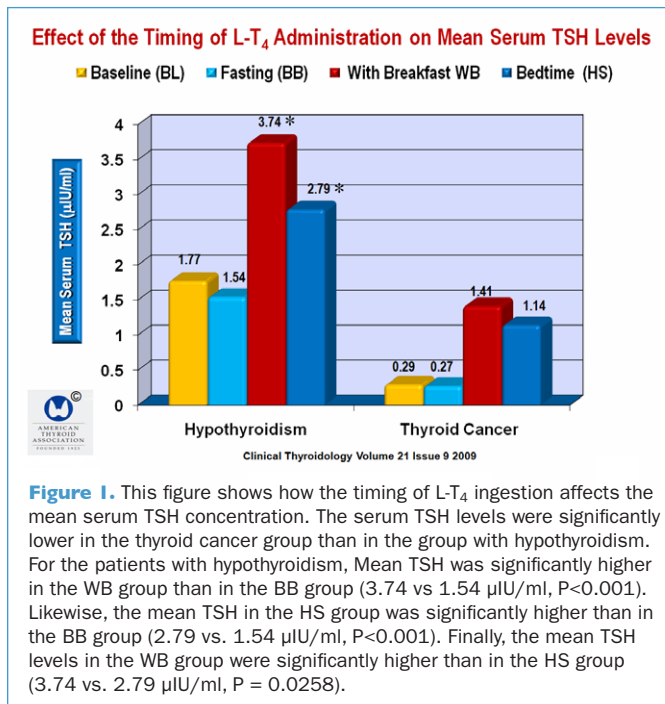
Figure 1. This figure shows how the timing of L-T$_4$ ingestion affects the mean serum TSH concentration. The serum TSH levels were significantly lower in the thyroid cancer group than in the group with hypothyroidism. For the patients with hypothyroidism, Mean TSH was significantly higher in the WB group than in the BB group (3.74 vs 1.54 µIU/ml, P<0.001). Likewise, the mean TSH in the HS group was significantly higher than in the BB group (2.79 vs. 1.54 µIU/ml, P<0.001). Finally, the mean TSH levels in the WB group were significantly higher than in the HS group (3.74 vs. 2.79 µIU/ml, P = 0.0258).
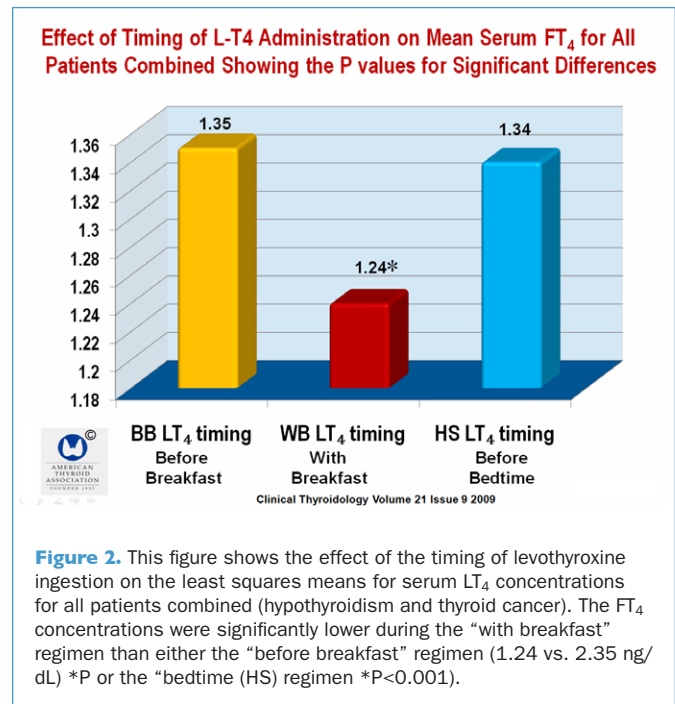
Figure 2. This figure shows the effect of the timing of levothyroxine ingestion on the least squares means for serum LT$_4$ concentrations for all patients combined (hypothyroidism and thyroid cancer). The FT$_4$ concentrations were significantly lower during the "with breakfast" regimen than either the "before breakfast" regimen (1.24 vs. 2.35 ng/dL) *P or the "bedtime (HS) regimen *P<0.001.

Figure 3. This figure shows the total T_3 levels were not significantly different across the three groups.
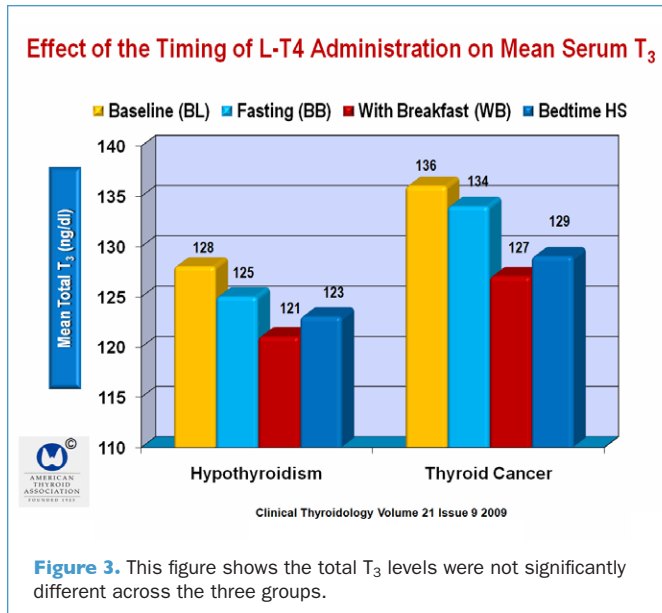
The patients who declined to enter the study and those who withdrew from the study were similar in terms of age, sex, and L-T_4 dose as compared with patients who completed the study. The majority of patients without thyroid cancer had Hashimoto's thyroiditis (73%) followed by postsurgical hypothyroidism (17%), and radioiodine-induced hypothyroidism (10%). The patients with thyroid cancer had a higher mean L-T_4 dose and a lower serum TSH at baseline than did those with hypothyroidism.

Protocol deviations were discovered at a rate of 1.2%; only 70% of patients completed the study diaries.

The cause of the thyroid failure (hypothyroid vs. thyroid cancer) had no significant effect on the differences in thyroid-function tests during the various timing regimens. Significant overlap was found between the baseline serum TSH and the mean values in the BB group (Figure 1). For the patients with hypothyroidism, the mean TSH in the WB group was significantly higher than in the BB group (3.74 vs 1.54 µIU/ml, P<0.001). Likewise, the mean TSH in the HS group was significantly higher than in the BB group (2.79 vs. 1.54 µIU/ml, P<0.001). Lastly, the mean TSH levels in the WB group were significantly higher than in the HS group (3.74 vs. 2.79 µIU/ml, P = 0.0258) (Figure 1).

The free T_4 values were significantly lower in the WB group than in the BB group (1.16 vs. 1.23 ng/dl, P<0.001) or the HS group (1.24 vs. 1.34 ng/dl, P<0.001) (Figure 2). The total T_3 levels were not significantly different across the three groups (Figure 3).

Patients in the WB regimen had the greatest interindividual variability in serum TSH values; the HS measurements showed intermediate variability. An increase in serum TSH of >1 µIU/ml occurred in 55% of patients in the WB group, as compared with the BB group. Only 35% of patients had a rise in TSH of >1 µIU/ml upon completion of the HS regimen as compared with BB values.

CONCLUSION Administration of levothyroxine with breakfast or at bedtime is associated with greater variability and higher values of serum TSH as compared with taking it in a fasting state.

COMMENTARY

Levothyroxine is a routinely prescribed medication, but ensuring proper dosing can be an intricate process. Because levothyroxine has a very narrow therapeutic index, the margin between overdosing and underdosing can be quite small. In addition, absorption of this medicine is highly variable, depending on how it is taken. It has long been recognized that absorption of L-T_4 is reduced by concurrent ingestion of food (1). Likewise, simultaneous ingestion with certain medications may reduce the absorption of L-T_4; moreover, the list of offenders continues to grow (2,3). Multiple medical conditions, including nephrotic syndrome (4), malabsorption syndromes (5), and gastric acid hyposecretion (6) may also result in increased L-T_4 requirements. Recognition of the tendency for poor enteral absorption of L-T_4 has led clinicians to recommend taking it on an empty stomach and apart from other medications. The exact length of time needed to elapse before eating or taking other medications is not known; however, it is generally recommended that patients wait at least 30 to 60 minutes. For some patients, the ideal scenario of taking L-T_4 on an empty stomach at least 30 minutes before eating breakfast or taking other medications may be difficult to accommodate, particularly when other medications require similarly restrictive timing considerations.

The study by Bach-Huynh et al. was aimed at quantifying the changes in serum TSH levels with the administration of L-T_4 at various times to determine whether rigid timing is truly warranted. In this crossover trial, each patient served as her or his own control. It was surprising neither that the serum TSH went up when patients took their L-T_4 with breakfast nor that the fluctuations in thyroid-function tests were greatest in this group. Although a similar rise in serum TSH was also seen with administration of L-T_4 at bedtime as compared with the fasting regimen, this trend was less severe than that which occurred with breakfast. The authors verified that the current recommendations of taking L-T_4 on an empty stomach at least an hour before breakfast is the optimal condition for absorption of the drug. If this is inconvenient for patients, then taking L-T_4 at bedtime is a reasonable alternative, with the caveat that the patient may require slightly higher doses of L-T_4.

Bolk et al. (7) recently studied 12 patients with hypothyroidism taking L-T_4 during two 2-month regimens, one on a stable morning regimen of L-T_4 administration and the other after switching to nighttime administration using the same dose of L-T_4. After the conclusion of each study period, patients were admitted to the hospital, where serial blood samples were obtained via an indwelling catheter at hourly intervals for 24 hours. The study found that serum TSH levels were lower when the patients were given the L-T_4 at bedtime. Although seemingly at odds with the results of the study by Bach-Huynh et al., the findings of the two studies may in fact corroborate each other. For instance, in the Bolk study (7), patients waited only 30 minutes in the morning, but this may represent a midway point between the

two morning regimens used in the two studies. Taken together, these findings suggest that waiting longer than 30 minutes to eat before taking L-T$_4$ may be necessary to avoid interference with L-T$_4$ absorption.

The results of the elegant study by Bach-Huynh et al. confirm that L-T$_4$ therapy is highly susceptible to interference of absorption in the presence of food and that TSH levels are more variable in this setting. Therefore, careful patient education regarding timing of administration with regard to food and other medications is essential before initiating levothyroxine therapy in order to achieve consistent TSH levels within the target range.

Jennifer Sipos MD

References

1.   Wenzel KW, Kirschsieper HE. Aspects of the absorption of oral L-thyroxine in normal man. Metabolism 1977;26:1-8.

2.   Sachmechi I, Reich DM, Aninyei M, et al. Effect of proton pump inhibitors on serum thyroid-stimulating hormone level in euthyroid patients treated with levothyroxine for hypothyroidism. Endocr Pract 2007;13:345-9.

3.   John-Kalarickal J, Pearlman G, Carlson HE. New medications which decrease levothyroxine absorption. Thyroid 2007;17:763-5.

4.   Collins MT, Remaley AT, Csako G, et al. Increased levothyroxine requirements presenting as "inappropriate" TSH secretion syndrome in a patient with nephrotic syndrome. J Endocrinol Invest 2000;23:383-92.

5.   Azizi F, Belur R, Albano J. Malabsorption of thyroid hormones after jejunoileal bypass for obesity. Ann Intern Med 1979;90:941-2.

6.   Centanni M, Gargano L, Canettieri G. et al. Thyroxine in goiter, Helicobacter pylori infection, and chronic gastritis. N Engl J Med 2006;354:1787-95.

7.   Bolk N, Visser TJ, Kalsbeek A, et al. Effects of evening vs morning thyroxine ingestion on serum thyroid hormone profiles in hypothyroid patients. Clin Endocrinol (Oxf) 2007;66:43-8.

At serum hCG concentrations >400,000 IU/L, TSH is consistently suppressed, and hCG concentrations >200,000 do not lead to symptoms of hyperthyroidism

SUMMARY

BACKGROUND When serum human chorionic gonadotropin (hCG) concentrations are highest in pregnancy, there is a transient suppression of serum thyrotropin (TSH) concentrations. Although serum TSH generally remains within the nonpregnant reference intervals, in some cases TSH is suppressed, raising questions about hyperthyroidism and hyperemesis gravidarum. The aims of this study were first, to determine whether there is an hCG concentration above which serum TSH levels are suppressed to <0.2 µIU/ml; second, to determine how thyroid hormone concentrations change in response to hCG concentrations; and third, to study the clinical symptoms in patients with hCG concentrations >200,000 IU/L.

METHODS This is a collaborative cohort study between Washington University, Barnes–Jewish Hospital (BJH) in St. Louis, and the University of North Carolina (UNC) Hospitals in Chapel Hill. Residual blood specimens sent to the BJH and UNC laboratories for physician-ordered hCG testing were used. The goal was to accrue at least 60 women into the study with hCG concentrations >200,000 IU/L and a specimen volume sufficient for additional measurements of TSH and free thyroxine (FT$_4$).

RESULTS A total of 15,597 physician-ordered hCG tests were performed at BJH and UNC over a 26-month period and a 13-month period, respectively. Of this group, 69 specimens (0.4%) were from 63 women with hCG concentrations >200,000 IU/L. The medical records of 63 patients revealed that 23 (37%) had hyperemesis gravidarum (HGD) and 12 (19%) had gestational trophoblastic disease (GTD), including benign and malignant hydatidiform mole as well as choriocarcinoma with or without hCG. The remaining 28 patients (44%) were pregnant women with threatened abortion (n = 10), vaginal bleeding or spotting (n = 9), abdominal pain (n = 3), but had a normal intrauterine pregnancy (n = 6). Of the total population, 6 of 63 (10%) were pregnant with twins and one had a threatened abortion (Figure 1). None of the subjects had a prior diagnosis of hyperthyroidism. Gestational ages ranged from 4 to 20 weeks. Five subjects with a serum hCG >200,000 IU/L on more
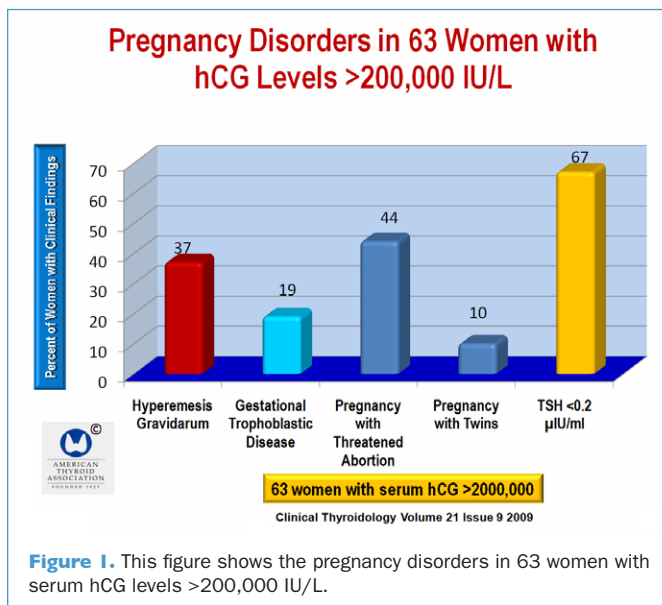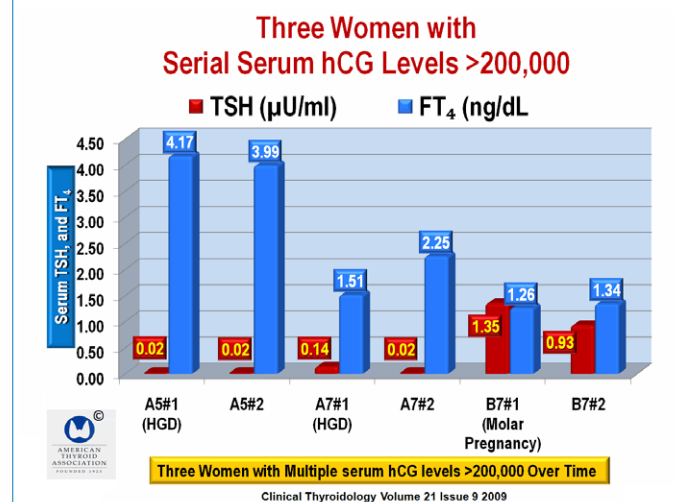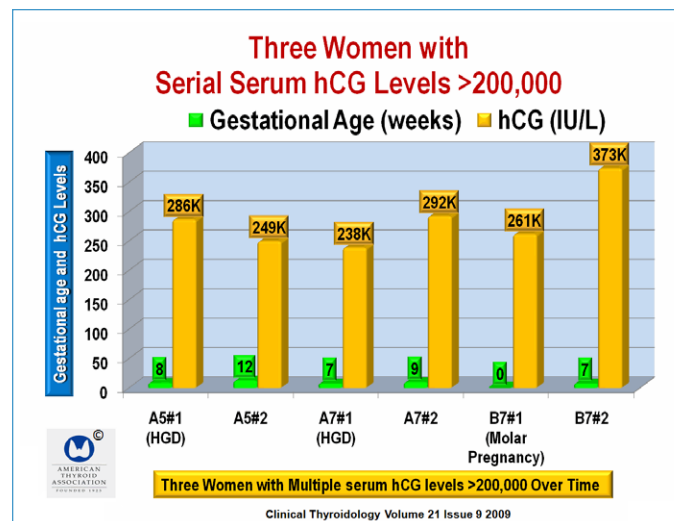

Figure 1. This figure shows the pregnancy disorders in 63 women with serum hCG levels >200,000 IU/L.

Figures 2A and 2B. These figures show serum hCG and thyroid hormone concentrations and the clinical history in three women with serial serum hCG levels >200,000 IU/L. The data for these figures are derived from Table 3 of Lockwood et al.
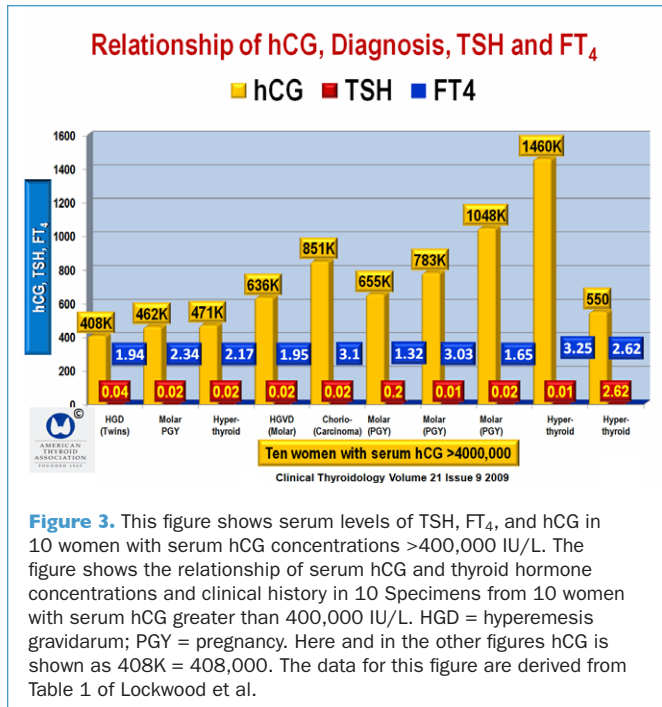
Figure 3. This figure shows serum levels of TSH, FT$_4$, and hCG in 10 women with serum hCG concentrations >400,000 IU/L. The figure shows the relationship of serum hCG and thyroid hormone concentrations and clinical history in 10 Specimens from 10 women with serum hCG greater than 400,000 IU/L. HGD = hyperemesis gravidarum; PGY = pregnancy. Here and in the other figures hCG is shown as 408K = 408,000. The data for this figure are derived from Table 1 of Lockwood et al.
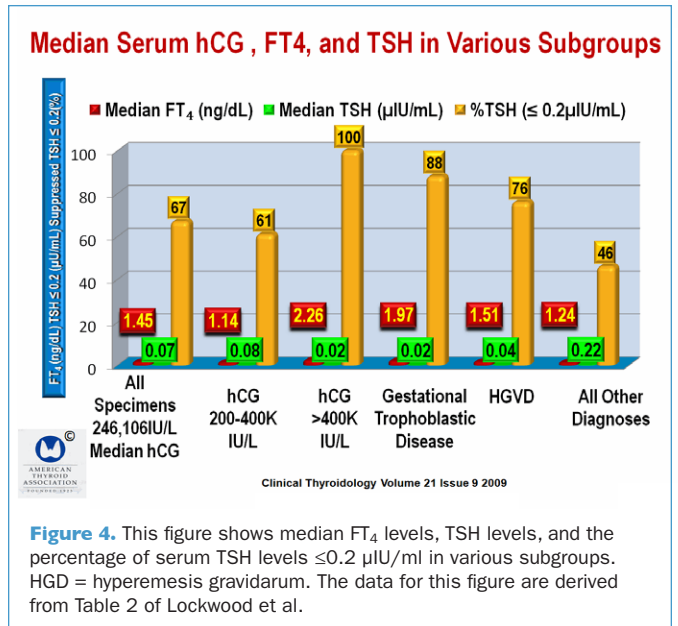

Figure 4. This figure shows median FT$_4$ levels, TSH levels, and the percentage of serum TSH levels ≤0.2 µIU/ml in various subgroups. HGD = hyperemesis gravidarum. The data for this figure are derived from Table 2 of Lockwood et al.

than one occasion, demonstrating how thyroid hormone levels change in response to changing hCG concentrations (Figure 2).

Among the 10 specimens with hCG concentrations >400,000 IU/L, 100% had serum TSH levels ≤2 µIU/ml and 90% had TSH levels <0.05 µIU/ml. Among the 10 specimens with an hCG concentration >400,000 IU/L, 7 were from women with molar pregnancies, 1 was from a woman with choriocarcinoma, and 2 were from pregnancies with HGD (Figure 3). Only 23 (33%) of the 69 specimens had FT$_4$ levels above the reference interval. Among the specimens with serum hCG concentrations >400,000 IU/L, only 8 of 10 (80%) had an FT$_4$ concentration >1.8 ng/dL, and of the 2 subjects with normal FT$_4$ concentrations, 1 had choriocarcinoma, with the greatest TSH concentration of 0.20 µIU/ml among specimens with hCG concentrations >400,000 IU/L. In another subject with a complete molar pregnancy, the FT$_4$ level was within the normal reference range, but was 1.65 ng/dl with a concurrent TSH

level suppressed to <0.02 µIU/ml. Median serum TSH and FT$_4$ concentrations for the entire study population and subgroups with serum hCG concentrations <400,000 IU/L are shown in Figure 4. Although there were differences in FT$_4$ concentrations, clinical signs and symptoms of hyperthyroidism were noted in only 4 of 63 subjects (6%) 2 of whom had hCG concentrations >400,000 IU/L.

Median serum TSH and FT$_4$ concentrations for women with GTD was half that of the hCG group and 10-fold less that of the non-GTD and non-hCG patients. Moreover, median hCG concentrations were nearly twofold those in women with GTD than the median hCG concentrations for women with hCG or other diagnoses. In all, 80% of women with GTD had suppressed TSH concentrations <0.2 µIU/ml. Of the 69 specimens, 22 (32%) had both low TSH and elevated FT$_4$ concentrations.

CONCLUSION At hCG concentrations >400,000 IU/L, TSH is consistently suppressed, serum FT$_4$ and TSH respond to changes in serum hCG levels, and most patients with hCG concentrations >200,000 do not have symptoms of hyperthyroidism.

COMMENTARY
This study is a significant contribution to the literature showing that patients with very high serum hCG levels due to trophoblastic tumors or hyperemesis gravidarum have suppressed TSH and elevated free T$_4$ concentrations. Among the 69 serum samples with hCG >200,000 IU/ml, 46 (67%) had TSH <0.2 µIU/ml and 23 (33%) had an elevated FT$_4$ level. Yet, only 4 patients had a clinical diagnosis of hyperthyroidism. The lack of clinical hyperthyroidism in many patients with trophoblastic tumors and high concentrations of hCG was reported over 30 years ago by Sidney Ingbar and his colleagues (1, 2). In contrast with these reports, Higgins et al. reported several patients with hydatidiform mole who had hyperthyroidism that was very severe both biochemically and clinically (3, 4). The serum hCG is

generally less in patients with hyperemesis gravidarum than in those with trophoblastic tumor. In 57 women with hyperemesis gravidarum, Goodwin et al. noted that 60% had subnormal serum TSH levels and 45% had increased FT$_4$ levels, but none had any clinical features of hyperthyroidism (5). Their mean serum hCG level of about 100 IU/ml was threefold higher than that of a matched control group at 10 weeks of gestation. The serum hCG correlated with increased thyroid-stimulating activity in a bioassay.

The thyroid-stimulating activity of hCG measured by bioassay was reported over 30 years ago (6). HCG has about 10^4 the activity of TSH. This thyrotropic activity depends on at least two factors: (1) the composition of hCG, which is a heterogeneous

molecule because it has variable carbohydrate composition, and (2) the TSH receptor and thyroid gland response of the host. Thirty percent of hCG is carbohydrate, more than any other glycoprotein hormone. When the sialic acid content of hCG is decreased, its thyrotropic potency is increased (7), but loss of sialic acid reduces its half-life in serum, thus decreasing its bioactivity in the host (8).

What is the potential explanation for the absence of characteristic features of hyperthyroidism in patients with high hCG and suppressed TSH? For the thyrotropic activity of hCG to have clinical consequences in these patients, the high levels of hCG must persist for several weeks, the patient must perceive symptoms, and the physician who examines the patient must do a thorough evaluation of possible features of hyperthyroidism and record them appropriately. It is not uncommon for patients with overt biochemical hyperthyroidism to deny having most of the typical symptoms and signs, even when there is some evidence that the disease has been present for several months.

Symptoms in young patients are easily perceived when the hyperthyroidism is severe, but not when it is mild.

Excessive secretion of hCG causes a spectrum of thyroid dysfunction varying from suppressed TSH with no clinical features to mild hyperthyroidism detected by very careful clinical evaluation to flagrant hyperthyroidism. The variability of the thyrotropic potency of hCG depends on its carbohydrate composition, and this cannot be determined in conventional immunoassays. The potency of the thyrotropin together with the patient's response to it determines the clinical features. The variability of these two factors may explain the apparent paradox of biochemical hyperthyroidism without the usual clinical symptoms and signs in trophoblastic thyrotoxicosis.

Jerome M. Hershman, MD, MACP
Distinguished Professor of Medicine
David Geffen School of Medicine at UCLA
VA Greater Los Angeles Healthcare System

References

1.   Galton VA, Ingbar SH, Jimenez-Fonseca J, Hershman JM. Alterations in thyroid hormone economy in patients with hydatidiform mole. J Clin Invest 1971;50:1345-54.

2.   Nagataki S, Mizuno M, Sakamoto S, et al. Thyroid function in molar pregnancy. J Clin Endocrinol Metab 1977;44:254-63.

3.   Hershman JM, Higgins HP. Hydatidiform mole—a cause of clinical hyperthyroidism: report of two cases with evidence that the molar tissue secreted a thyroid stimulator. N Engl J Med 1971;284:573-7.

4.   Higgins HP, Hershman JM, Kenimer JG, et al. The thyrotoxicosis of hydatidiform mole. Ann Intern Med 1975;83:307-11.

5.   Goodwin TM, Montoro M, Mestman JH, et al. The role of chorionic gonadotropin in transient hyperthyroidism of hyperemesis gravidarum. J Clin Endocrinol Metab 1992;75:1333-7.

6.   Kenimer JG, Hershman JM, Higgins HP. The thyrotropin in hydatidiform moles is human chorionic gonadotropin. J Clin Endocrinol Metab 1975;40:482-91.

7.   Yoshimura M, Hershman JM, Pang XP, et al. Activation of the thyrotropin (TSH) receptor by human chorionic gonadotropin and luteinizing hormone in Chinese hamster ovary cells expressing functional human TSH receptors. J Clin Endocrinol Metab 1993;77:1009-13.

8.   Talbot JA, Lambert A, Anobile CJ, et al. The nature of human chorionic gonadotrophin glycoforms in gestational thyrotoxicosis. Clin Endocrinol (Oxf) 2001;55:33-9.

The optimal time to identify residual thyroid tissue or persistent differentiated thyroid cancer on a posttreatment whole-body scan is 3 to 6 days after therapeutic radioiodine is administered

SUMMARY

BACKGROUND The optimal time for performing a posttreatment whole-body scan (RxWBS) is not entirely clear. This may be the consequence of a variety of things that might alter ^{131}I uptake, such as inadequate pretherapy preparation, lack of functioning sodium–iodine symporters, poorly differentiated thyroid cancers, advanced patient age, or improper timing of the RxWBS. The aim of this study was to identify the optimal time for performing an RxWBS.

METHODS This is a retrospective study of 239 patients with differentiated thyroid cancer who were treated from January 2006 through May 2008 in the Department of Nuclear Medicine in Chang Gung Memorial Hospital, University College of Medicine in Kaohsiung, Taiwan. All patients were treated with total thyroidectomy followed by ^{131}I therapy after patients were off levothyroxine for at least 4 weeks. The patients had three sequential whole-body scans on the 3rd to 4th day, the 5th to 6th day, and the 10th to 11th day after ^{131}I was administered. Simultaneous anterior and posterior whole-body images and spot views of the abdomen and pelvis were included in some patients to more accurately localize the ^{131}I-avid tumors, which were scored by visual assessment into three grades, as follows: grade 0 = no visible uptake, grade 1 = visible uptake, and grade 2 = clearly visible uptake. Metastatic tumors and thyroid remnants were regarded as having early ^{131}I washout when uptake was no longer visible in the third RxWBS. All scans were interpreted by two experienced specialists in nuclear medicine.

If the readings were conflicting, then a third reviewer evaluated the images.

RESULTS Of the 239 patients comprising the study cohort, 172 were women (72%) and 67 were men (28%), with a mean (±SD) age of 45.8±15.0 years. A total of 205 patients had

Figure 2. This figure shows the linear trend of decreasing ^{131}I uptake in sequential images of lymph-node metastases. †P<0.01, comparing the first and second with the third RxWBS.
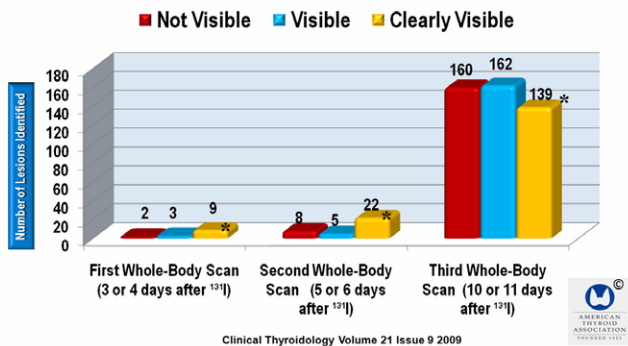
Figure 1. This figure shows a linear trend of decreasing ^{131}I uptake in sequential images of thyroid remnants. *P<0.001, comparing the first and second with the third RxWBS results. There was no statistical difference between the second and third RxWBS visualization for all of the studies, including remnant ablation and lymph-node, lung, and bone metastases. Only 9 of 170 remnants were missed on the third RxWBS (5%).

Figure 3. This figure shows the linear trend of decreasing ^{131}I uptake in sequential images of lung metastases. ‡P<0.003, comparing first and second with the third RxWBS. The third RxWBS missed 7 of 41 lung metastases (17%).

Back to Contents

papillary thyroid (86%) cancer (PTC) and 34 had follicular thyroid cancer (14%). Patients were treated with 30 to 200 mCi (1.1 to 7.4 MBq) of [131]I. The mean amount of ^{131}I administered was 108±32 mCi (4.0±1.2 GBq). There were a total of 295 images, 227 of which revealed uptake in the anterior neck (77%). This was interpreted as either intrathyroidal or extrathyroidal ^{131}I uptake, which was confirmed by physical examination, neck ultrasonography, and computed tomography scans. A total of 170 of the 227 images with thyroid-bed uptake (44%) were interpreted as thyroid remnants (75%), and 57 extrathyroid bed lesions were regarded as lymph-node metastasis (25%). In addition, there were metastases in the lung (n = 41), bone (n = 18), and mediastinum (n = 6). Serum thyroglobulin (Tg) levels were assessed in patients with visible RxWBS lesions, some of which were also found on fluorodeoxyglucose–positron-emission tomographic images. Here and elsewhere, percentages are rounded to an integer.

There was a difference in the early washout of ^{131}I in thyroid remnants and metastatic lesions (Figure 1). The third posttherapy RxWBS missed 18 of 63 lymph-node metastases (29%) (Figure 2); 7 of 41 lung metastases (17%) (Figure 3); and 3 of 18 bone metastases (17%) (Figure 4); however, only 9 of 170 thyroid remnants were missed on the third RxWBS (5%) (Figure 5). Comparisons of the first and second scans found no statistical difference between the two scans, including observations of scans on lymph-node, lung, and bone metastases (P = 0.154, P = 0.602, and P = 0.630, respectively). However, the third scans were significantly poorer as compared with the first two, detecting significantly fewer lymph-node metastases than the first (P = 0.043) and second (P<0.001) scans. Moreover, there were no significant findings in the third scan as compared with the first two scans (Figure 5). The mean serum Tg levels were significantly different between patients with lymph-node metastases and those with lung (98.5 vs. 91.1 µg/L) or bone (98.5 vs. 4.7 µg/L) metastases. There was no correlation with serum Tg concentrations among patients with and without early ^{131}I washout.

CONCLUSION The optimal time to identify residual thyroid tissue or persistent differentiated thyroid cancer metastases on DxWBS is on the 3rd to 6th day after therapeutic radioiodine has been administered.
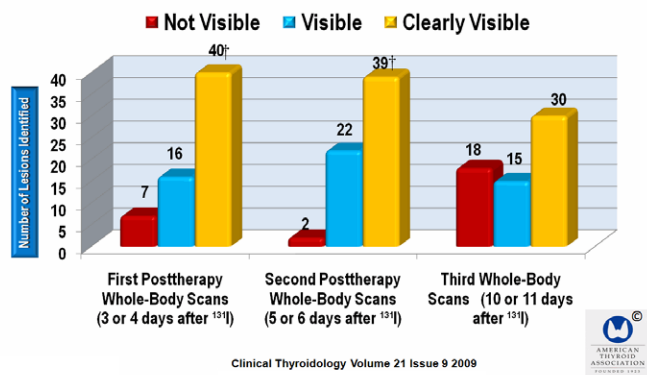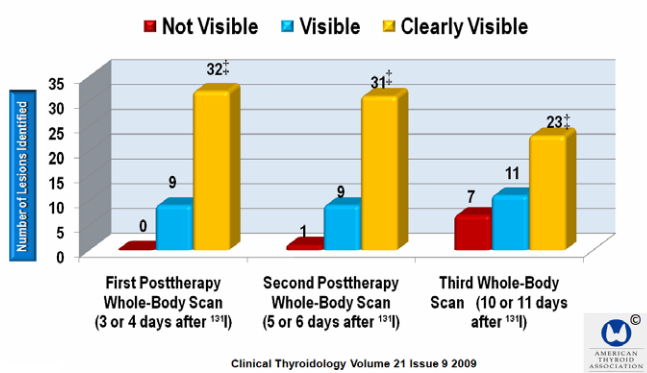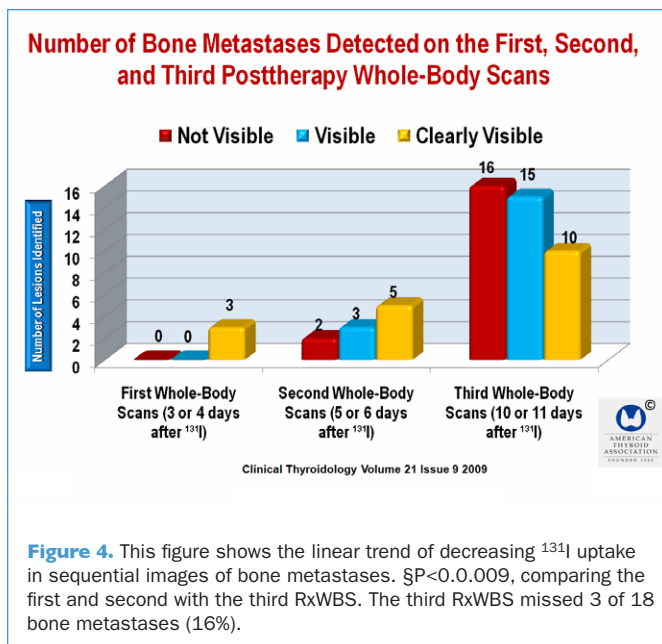

Figure 4. This figure shows the linear trend of decreasing ^{131}I uptake in sequential images of bone metastases. §P<0.0.009, comparing the first and second with the third RxWBS. The third RxWBS missed 3 of 18 bone metastases (16%).
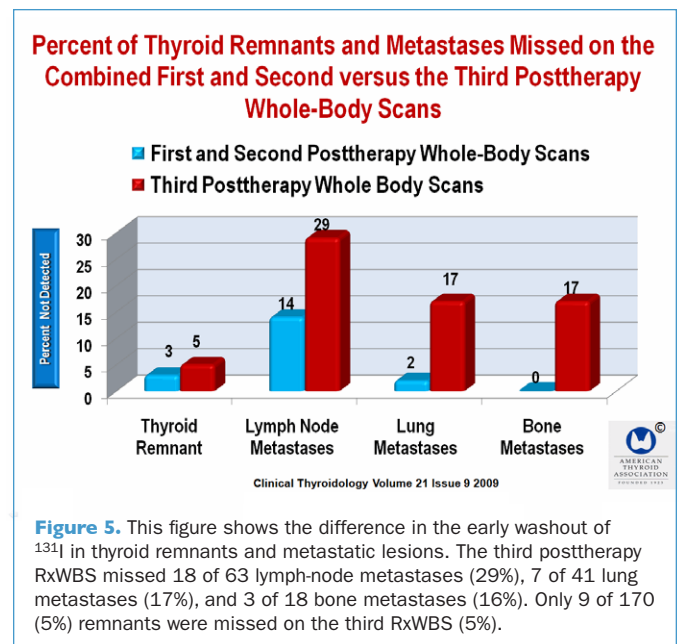
Figure 5. This figure shows the difference in the early washout of ^{131}I in thyroid remnants and metastatic lesions. The third posttherapy RxWBS missed 18 of 63 lymph-node metastases (29%), 7 of 41 lung metastases (17%), and 3 of 18 bone metastases (16%). Only 9 of 170 (5%) remnants were missed on the third RxWBS (5%).

COMMENTARY

The key question that arises after initial near-total thyroidectomy for differentiated thyroid cancer is whether or not substantial thyroid tissue—with or without lymph-node metastases—has escaped the surgeon's scalpel. Neck ultrasonography fails to immediately answer this question because of interfering postoperative cervical edema that disrupts landmarks, blocking this diagnostic path for months. Likewise, serum Tg measurements also fail to localize residual tumor.

However, among patients who are candidates for postoperative ^{131}I therapy, the RxWBS offers an effective way to promptly identify the location and extent of residual tumor. RxWBS thus becomes the lynchpin that guides subsequent clinical maneuvers, providing major clues as to tumor location and prognosis. When posttherapy ^{131}I is not administered, or when there is little or no ^{131}I uptake on the RxWBS, the next maneuver becomes problematic on several levels. There is robust evidence that a diagnostic whole-body scan (DxWBS) using 4 or 5 mCi (148 or 185 MBq) of ^{131}I fails to identify up to 80% of the residual tumor foci (1), underscoring that RxWBS is a much more potent diagnostic test than DxWBS (1;2). A false-negative RxWBS may be the result of several problems, such as inadequate preparation for ^{131}I therapy, iodine contamination from contrast material used for computed tomography, failure to adhere to a low-iodine diet, poorly differentiated non-^{131}I-avid tumor, and in some cases—the best scenario after ^{131}I therapy— is complete excision of the thyroid and lymph-node metastases. Still, the most common problem may be appropriate timing of the

RxWBS after ^{131}I therapy. In my experience, the optimal timing of an RxWBS is one of the most frequent questions posed by clinicians. Unfortunately, until now there has been almost no detailed information to properly answer this question. However, the retrospective study by Huang et al. provides important information on the timing of RxWBS.

After studying 239 patients, Huang et al. found that the identification of thyroid remnants was influenced by timing of the RxWBS, even after treating patients with an average of approximately 108 mCi of ^{131}I. The visualization of thyroid remnants was significantly more accurate when RxWBS was performed 3 to 6 days after the administration of ^{131}I, as compared with RxWBS performed 10 to 11 days after ^{131}I therapy. Still, only 9 of 170 thyroid remnants (5%) were missed on the third RxWBS (5%). The accuracy of identifying metastases is another matter. First, there was a difference in the early washout of ^{131}I in thyroid remnants and metastatic lesions. Second, there was some difference in the type of metastasis.

The third posttherapy RxWBS performed 10 or 11 days after ^{131}I therapy missed 18 of 63 lymph-node metastases (29%), 7 of 41 lung metastases (17%), and 3 of 18 bone metastases (17%). There were no statistically significant differences between the findings in the first and second RxWBS, including scans on lymph-node, lung, and bone metastases (P = 0.154, P = 0.602, and P = 0.630, respectively). Thus, the third RxWBS performed 10 or 11 days after ^{131}I was significantly poorer as compared with the first two scans performed 3 to 6 days after ^{131}I. The Huang study thus indicates that the optimal timing for RxWBS

is 3 to 6 days after ^{131}I; however, there were no data concerning day 2, and days 7 through 9 after ^{131}I.

As all of the patients in the Huang study were pretreated with thyroid hormone withdrawal (THW) before ^{131}I therapy, one might be concerned that the study findings could be different from those in patients prepared with recombinant human thyrotropin (rhTSH). In this case, intramuscular rhTSH is typically administered on days 1 and 2 (Monday and Tuesday), and ^{131}I is administered on day 3 (Wednesday), and RxWBS is performed on day 5 (Friday), which is not precisely the same timeframe used in the Huang study. The optimal timing for RxWBS might be 1 week after the administration of rhTSH (5 days after ^{131}I). However, the effective half-life of ^{131}I in follicular cells is significantly longer after rhTSH as compared with THW (3;4), which would enhance RxWBS uptake and could provide a more accurate RxWBS performed 2 days after ^{131}I (Friday). In the study by Haugen et al. (5), patients were prepared first by rhTSH and again after thyroid hormone withdrawal, and the RxWBS was obtained 48 hours after ^{131}I (i.e., on Friday) in patients pretreated with either rhTSH or THW. The RxWBS results were concordant after rhTSH and THW in 89% of the patients. Of the discordant scans, 8 (4%) had superior scans after rhTSH and 17 (8%) had superior scans after thyroid hormone withdrawal, a difference that was not statistically significant. Thus, it would seem that the Huang study could be applicable to patients pretreated with rhTSH, meaning that days 3 to 6 would be the optimal time to administer rhTSH.

Ernest L. Mazzaferri, MD, MACP

References

1. Mazzaferri EL, Robbins RJ, Spencer CA et al. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 2003;88:1433-41.

2. Mazzaferri EL, Kloos RT. Is Diagnostic Iodine-131 Scanning With Recombinant Human TSH (rhTSH) Useful in the Follow-up of Differentiated Thyroid Cancer after Thyroid Ablation? J Clin Endocrinol Metab 2002;87:1490-8.

3. Hanscheid H, Lassmann M, Luster M et al. Iodine biokinetics and dosimetry in radioiodine therapy of thyroid cancer: procedures and results of a prospective international controlled study of ablation after rhTSH or hormone withdrawal. J Nucl Med 2006;47:648-54.

4. Remy H, Borget I, Leboulleux S et al. ^{131}I Effective Half-Life and Dosimetry in Thyroid Cancer Patients. J Nucl Med 2008;49:1445-50.

5. Haugen BR, Pacini F, Reiners C et al. A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. J Clin Endocrinol Metab 1999;84:3877-85.

www.thyroid.org/patients/ct/index.html

THYROID CANCER

Higher serum TSH levels correlate with a higher incidence of differentiated thyroid cancer and extrathyroidal extension of tumor in elderly patients

SUMMARY

BACKGROUND Previous studies by Haymart and associates have shown that a higher than usual serum thyrotropin (TSH) level is associated with a greater than usual risk of differentiated thyroid cancer in patients with a thyroid nodule, and of advanced tumor stage at the time of diagnosis. It is also known that age over 45 years is also associated with more advanced disease at the time of diagnosis. The aim of this study was to determine the relationship between higher serum TSH levels in patients with advanced age and tumor stage.

METHODS This is a retrospective study of 1361 patients who had thyroid surgery at the University of Wisconsin, Madison, from May 1994 through December 2007, among whom demographic and pathological data were available in 980 patients with preoperative TSH measurements. Of this group, 26 were excluded from the study, 8 without initial surgical records and 18 with thyroid malignancy other than differentiated thyroid cancer (DTC), leaving 954 patients, 249 with DTC (26%) and 705 with benign thyroid disease (74%). The latter had symptomatic goiters, follicular adenomas, and large benign nodules, and a few had Graves' disease. Of the 954 patients, 772 were women (81%) and 182 were men (19%). Here and elsewhere, percentages are rounded to an integer.

Age was evaluated as a continuous variable within age ranges of <45 versus ≥45 years and <20 years, and categorically in ranges of 20 to 44, 45 to 59, and ≥60 years. Age 45 was used as a cutoff, as DTC of similar extent has a worse prognosis in

older patients than in younger patients; also measured were categories of age ranges <20 and ≥60 years, as the likelihood of cancer recurrence is greatest in patients younger than 20 and in those 60 years or older.

High-risk cancer such as a primary tumor >4 cm, distant metastases, and extrathyroidal extension were also analyzed in relation to TSH; however, lymph-node metastases were not included as a high-risk feature, mainly because central compartment lymph-node dissection was not routinely performed, and such an analysis would likely exclude patients with undetected lymph-node metastases. All analyses were repeated without the 118 patients taking levothyroxine (L-T$_4$) preoperatively to avoid an artificially determined TSH value.

RESULTS The incidence of DTC was 31% (118 of 383) in patients younger than 45 and 23% (131 of 571) in those 45 years or older (P = 0.04) (Figure 1). Men comprised 14% of the younger group (53 of 383) and 22% (129 of 571) of the older group. The thyroid nodule size resulting in surgery was 2.37±0.01 cm in the younger group, versus 2.74±0.01 cm in older patients (P = 0.007). Multiple thyroid nodules were detected in 46% (173 of 383) of the younger patients, versus 53% (302 of 571) of the older group (P = 0.012). The mean TSH was 2.24±0.24 µIU/ml in the younger patients, versus 1.52 ± 0.11 µIU/ml in the older patients (P = 0.108). The only demographic or pathological variable that did not differ significantly between groups was Hashimoto's thyroiditis.
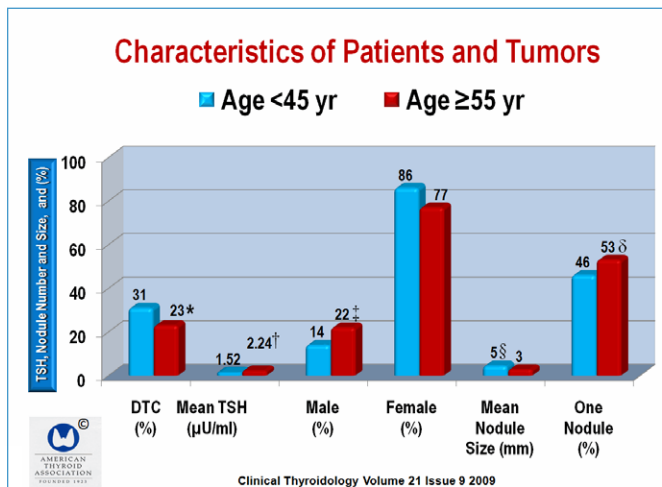
Figure 1. This figure shows the patient and tumor characteristics of the study cohort. Hashimoto's thyroiditis was present in 83 patients (21%) <45 years of age and 19% in patients ≥45 (not shown). *P = 0.004. †P = 0.018. ‡P = 0.001. §P = 0.007. ¶P = 0.012, comparing age <45 with age ≥ 45 years.
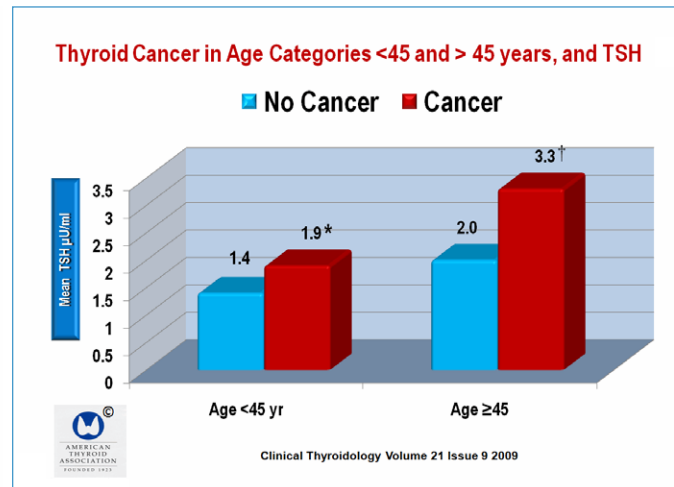
Figure 2. This figure shows the mean serum TSH and the presence or absence of thyroid cancer in patients <45 and ≥45 years. *P = 0.046 and †P = 0.027, comparing patients <45 versus ≥45 years.

TSH and Age Without Preoperative Levothyroxine

Figure 3. This figure shows the TSH levels in patients with thyroid cancer relative to patient age in the subgroups <20 to ≥60 years. *P = 0.39 for TSH in patients 20 to 44 years of age. †P = 0.35 for patients 45 to 59 years of age.

Among the two age groups younger than 45 years and 45 or older, the mean TSH in patients not taking L-T$_4$ was significantly higher in patients with thyroid cancer as compared with patients without cancer, both in patients younger than age 45 (P = 0.46) and those 45 years or older (P = 0.027) (Figure 2). When the patients were further subdivided by age categories <20, 20 to 44, 45 to 59, and 60 years or older, there was a nonsignificant trend toward a rise in mean TSH with age in the patients with benign tumors and a parallel but more rapid increase in TSH in the patients with thyroid cancer in the age categories of 20 to 44 years and 45 to 59 years (P <0.05). The difference between cancer and no cancer within each subgroup was statistically significant in those 20 to 44 (P = 0.39) and 45 to 59 (P = 0.35) years of age (Figure 3). When the 118 patients on preoperative L-T$_4$ were excluded, the same pattern of higher mean TSH levels
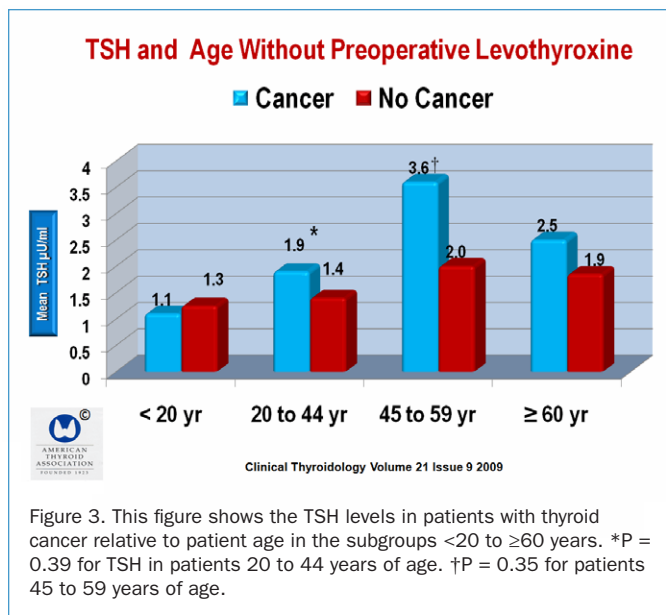
in patients with thyroid cancer versus those without cancer persisted in the age categories of 20 to 44 (P = 0.019) and 45 to 59 years (P = 027). Although the serum TSH was higher in the groups with thyroid cancer, it consistently remained in the normal range.

Statistical significance was established in the age groups with the largest number of patients: thyroid cancer was found in 14 of 48 patients (29%) in the age group <20 years; 104 of 335 (31%) in the group 20 to 44 years; 82 of 334 (25%) in the group 45 to 59 years; and 49 of 237 (21%) in the group 60 years or older.

On multivariate analysis, there was a significant association of higher TSH with the incidence of thyroid cancer. There was a trend for an association between higher TSH and advanced age when only age and cancer were compared (P = 0.01 for cancer and P = 0.124 for age). However, when patients who were taking L-T$_4$ were excluded and the analysis included sex, nodule size, nodule number, and Hashimoto's thyroiditis, only Hashimoto's thyroiditis (P = 0.001) and thyroid cancer (P = 0.39) were independently associated with higher TSH. Patients ≥45 years had a nonsignificant trend for higher mean TSH in patients with stages III and IV disease versus those with stages I and II disease (P = 0.125). When the high-risk features of age, extrathyroidal tumor extension, tumor >4 cm, and distant metastases were analyzed in relation to the mean TSH in patients with thyroid cancer, only extrathyroidal extension was associated with higher mean TSH on univariate (P = 0.04) and multivariate analysis (P = 0.002). When only patients ≥45 years were evaluated, extrathyroidal extension was the only high-risk feature associated with higher TSH (P = 0.008)

CONCLUSION Higher serum TSH levels correlate with a higher incidence of thyroid cancer and extrathyroidal extension of tumor.

COMMENTARY

Haymart et al. published an important article (1) showing that higher serum TSH levels in patients with thyroid nodules is associated with a greater risk of differentiated thyroid cancer and advanced tumor stage at the time of diagnosis. On both univariate and multivariate analyses, the risk of malignancy was found to correlate with higher TSH levels. The likelihood of malignancy was 16% when the serum TSH was <0.06 μIU/ml, versus 52% when the TSH was ≥5.0 μIU/ml (P = 0.001). When the serum TSH was 0.40 to 1.39 μIU/ml, the likelihood of malignancy was 25%, versus 35% when the TSH ranged between 1.40 and 4.99 μIU/ml. Moreover, mean (±SD) TSH was 2.1±0.2 μIU/ml in patients with stage I or II as compared with 4.9±1.5 μIU/ml in patients with stage III or IV disease (P = 0.002). The main conclusion of the study was that the likelihood of thyroid cancer increases with higher serum TSH concentration; even when TSH was within the normal range. A TSH level above the population mean was found to be associated with a significantly greater likelihood of thyroid cancer than a TSH below the mean, showing that a higher TSH level is associated with advanced DTC stage.

This study is an extension of the idea that higher serum TSH levels are significantly associated with extrathyroidal extension of tumor. However, the major thrust of the current study is that high serum TSH is the harbinger of advanced disease, whereas age, per se, is not the cause of advanced disease. This is a giant leap from our current understanding of the pathophysiology of DTC and the high risk for poor outcomes in patients 45 years or older. The younger patients in the Haymart study were more likely to have DTC, along with a smaller nodule size and a solitary nodule. Surgical patients under age 45 had a 31% incidence (118 of 383) of DTC, versus those ≥45 years, who had a 23% likelihood of DTC. Further supporting the hypothesis that there is an independent relationship between serum TSH and the incidence of thyroid cancer, multivariate analysis found that thyroid cancer was associated with the higher serum TSH concentrations, not age.

There are, however, several limitations to the current study. The authors acknowledge that all the patients had undergone thyroidectomy, and this population may not be representative of the broad population. Also, not all of the patients had

preoperative TSH levels measured. A more significant limitation is that the serum TSH was not related to patient race and ethnicity. During the past 15 years, the reported upper limit of TSH has been considered to be approximately 4.1 µIU/ml when TSH is measured by immunochemiluminometric assay (2). Moreover, recent studies have shown that the reference limits for TSH differ between races and with age and that the use of race- and age-specific reference limits decreases misclassification of patients with lowered or raised TSH in an urban practice (3). In addition, the TSH shifts to higher concentrations with age, which appears to be a continuum that extends even to people with exceptional longevity (4). TSH was found to be distributed at higher concentrations, without skew, in whites as compared with blacks (median, 1.54 µIU/ml vs. 1.18 µIU/ml; $P < 0.001$) and in old (>80 years) as compared with young (20 to 29 years) persons. These observations raise some question that TSH, per se, is responsible for the increase in thyroid cancer in thyroid nodules, regardless of patient age.

Ernest L. Mazzaferri, MD, MACP

References

1.   Haymart MR, Repplinger DJ, Leverson GE, et al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. J Clin Endocrinol Metab 2008;93:809-14.

2.   Hamilton TE, Davis S, Onstad L, et al. Thyrotropin levels in a population with no clinical, autoantibody, or ultrasonographic evidence of thyroid disease: implications for the diagnosis of subclinical hypothyroidism. J Clin Endocrinol Metab 2008;93:1224-30.

3.   Boucai L, Surks MI. Reference limits of serum TSH and free T_4 are significantly influenced by race and age in an urban outpatient medical practice. Clin Endocrinol (Oxf) 2009;70:788-93.

4.   Atzmon G, Barzilai N, Hollowell JG, et al. extreme longevity is associated with increased serum thyrotropin. J Clin Endocrinol Metab 2009;94:1251-4.

Surgery for thyroid cancer increases the survival rate and enhances the quality of life of elderly patients providing they are well enough to tolerate surgery

SUMMARY

BACKGROUND Thyroid cancer is typically more aggressive in elderly patients than in younger patients. Elderly individuals with thyroid cancer may have other chronic diseases that make thyroid surgery difficult. As a result, they may experience increased morbidity from thyroid cancer therapy and may not be able to tolerate extensive surgery and postoperative radioiodine or external-beam radiation therapy. This is a retrospective study aimed at comparing the clinical characteristics of thyroid cancer therapy in elderly and younger patients to assess how the elderly fare with surgery as compared with younger patients.

METHODS This is a retrospective study of patients treated for thyroid cancer from 1994 through 2004 in the Department of Otolaryngology in Chuo, Japan, and at the Department of Head and Neck, Cancer Institute Hospital (CIH) in Tokyo. Study patients were divided into two groups: an "elderly group" who were age 75 years or older, and a "young group" age 30 years or younger. Patients were further divided into "primary patients" who had initial surgery at CIH, and "secondary patients" who were first treated elsewhere and were referred to CIH for treatment of a recurrence. The characteristics of thyroid cancer were studied in older and younger patients to further understand the specific characteristics of thyroid cancer therapy in these two groups. Patients were classified as high or low risk according to the authors' papillary thyroid cancer risk-group classification. The study also assessed the quality of life in patients with local tumor recurrence and in those who had invasive cancer. Here and elsewhere, percentages are rounded to an integer.

RESULTS PRIMARY PATIENTS:
Comparison of the Elderly and Young

Groups Of the 685 primary patients treated at CIH during the 11-year period under study, 42 (6%) were in the elderly group, 13 of whom were men (31%) and 29 women (69%), with a mean age of 78 years (range, 75 to 89). The mean follow-up in this group was 41 months (range, 2 to 123). The young group comprised 37 patients (5%) of whom 9 (24%) were men and 28 (76%) were women, with a mean age of 25 years (range, 16 to 29). The cancer histology was papillary thyroid cancer (PTC) in 32 of 42 elderly patients (76%), follicular thyroid cancer (FTC) in 2 of 42 elderly patients (5%) and 0% in the younger group of patients, and was medullary thyroid cancer (MTC) in 7 of 42 elderly patients (2%) and 3 of 37 younger patients (8%) One or more of the following systemic disorders were present in the elderly: hypertension (n = 1), cardiopulmonary disease (n = 14), tuberculosis (n = 7), other malignant tumors (n = 13), diabetes mellitus (n= 5), cerebral infarction (n = 3), asthma (n = 2), hepatitis (n = 1), chronic respiratory failure (n = 1), and dementia (n = 1). Of the younger patients, two of the three with MTC had pheochromocytoma and one had tuberculosis. None of the elderly patients had a family history of thyroid cancer, but two of the younger group had a family history of PTC. There was no significant difference in the clinical characteristics of patients with PTC; there was no significant difference in the proportion of patients with tumor ≥4 cm between the older and younger groups. However, obvious extrathyroidal invasion of adjacent tissues, including the recurrent laryngeal nerve and the trachea, with or without esophageal invasion, was found in the
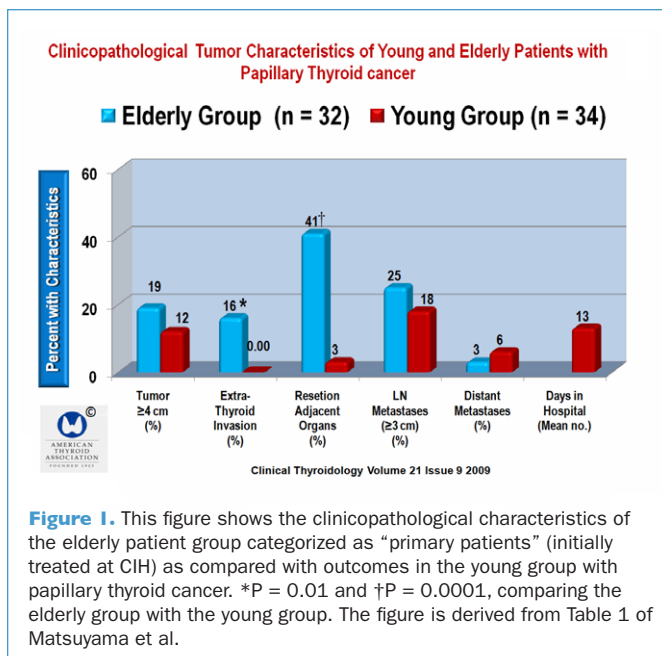
Figure 1. This figure shows the clinicopathological characteristics of the elderly patient group categorized as "primary patients" (initially treated at CIH) as compared with outcomes in the young group with papillary thyroid cancer. *P = 0.01 and †P = 0.0001, comparing the elderly group with the young group. The figure is derived from Table 1 of Matsuyama et al.
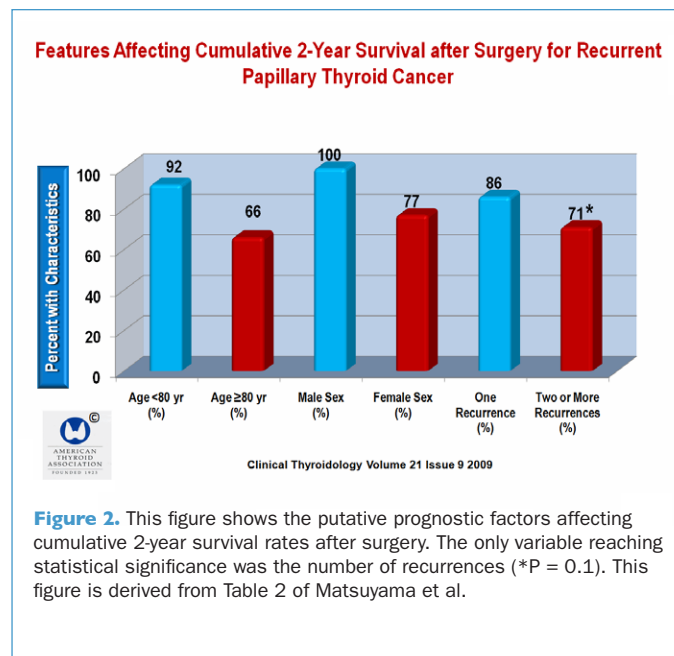
Figure 2. This figure shows the putative prognostic factors affecting cumulative 2-year survival rates after surgery. The only variable reaching statistical significance was the number of recurrences (*P = 0.1). This figure is derived from Table 2 of Matsuyama et al.

elderly patient group. As a consequence, combined resection of the thyroid tumor that involved adjacent organs was necessary significantly more often in the elderly than in the younger group and hospitalization was significantly longer in the elderly as compared with the younger patients (Figure 1).

Recurrence of PTC was found in 7 of 32 patients in the elderly group (17%), all of whom had lymph-node metastases (Figure 2). Three patients also had lung metastases and two died of other diseases. In the 34 young patients with PTC, only one had a recurrence, which was in lymph nodes (3%), and none died of thyroid cancer. In the elderly group, the 5-year disease-specific survival rate (DSS) was 100% and the cumulative survival rate (CS) was 92%, as compared with 100% DSS and 100% CS in the young group. The CS was significantly higher in the young group as compared with the older group (P = 0.03), but DSS was not significantly different in the two groups (Figure 3).

According to the authors' stage classification, tumors were categorized as high-risk in patients <50 years of age with distant metastases, and in those ≥50 years with distant metastases, extrathyroidal invasion, or lymph-node metastases ≥3 cm. In elderly patients, tumors were classified as high-risk in 16 of 32 with PTC (50%) and as low-risk in 16 of 34 (50%). In the young age group, tumors were classified as high-risk in 2 of 37 patients (5%) and as low-risk in 35 of 37 (95%) patients. The quality of life deteriorated in 2 of 32 (6%) elderly patients with extremely aggressive, advanced tumor; it was affected in none of the young patients (Figure 3)

OUTCOMES of the Elderly Patients
with Recurrent Thyroid Cancer
Of the 30 elderly patients who had surgery for recurrent thyroid cancer, 18 (60%) were primary patients who had initial surgery at CIH and 12 (40%) were secondary patients who were referred to CIH for treatment of a recurrence. Their mean age was 81 years (range, 75 to 88); 4 were men (20%) and 24 were women (80%). Of this group, 26 had PTC (87%) and 4 had FTC (13%).

After a mean follow-up of 26 months (range, 0.5 to 63 months), lymph-node recurrences were found in the lateral lymph-node compartments in 18 of the 26 patients with PTC (69%) and in the central compartment lymph-node metastases in 12 of 26 (46%), including the overlap of metastases in both neck compartments. (Figure 4). Thirteen of 26 patients (50%) required combined resection of the recurrence and adjacent tissues, which included the recurrent laryngeal nerve (n = 4), muscle layer of the esophagus (n = 3), the trachea (n = 3), neck skin (n =3), accessory nerve (n =2), larynx (n =1), and the posterior cervical muscles (n = 1), including the overlap of tumor sites. The mean number of recurrences was 1.3 (range, 1 to 4). Nine of the 26 patients (35%) died of primary cancer. After surgery, the 2-year DSS was 84% and the CS was 81% (Figure 4).

Although survival tended to be worse for secondary patients than for primary patients initially treated at CIH, the difference did not differ significantly (P = 0.08). Likewise, survival also tended to be worse for patients who had single-lymph-node resection ("berry picking") rather than a modified neck dissection but did not differ significantly (P = 0.07). Likewise, age, sex, number of tumor recurrences, extent of surgery, and duration of hospitalization did not differ significantly. Outcome also did not differ significantly after resection of adjacent tissues and patients who had simple tumor resection or between patients who had palliative versus radical surgery, although the 2-year CS after radical surgery was 91%, as compared with 65% after palliative resection (Figure 2).

OUTCOMES of Elderly Patients
Treated Nonoperatively
Among a total of 85 elderly patients with thyroid cancer, 13 (15%) were treated nonoperatively. Of 13 such patients, 12 had PTC and 1 had FTC; 4 were men (31%) and 9 were women (69%); their mean age was 81 years (range, 75 to 88). Seven had primary thyroid cancer (54%) and 6 had recurrent thyroid cancer (46%). Nonoperative management was done because general anesthesia was contraindicated because of poor general

The 5-Year Disease-Specific Survival and Cumulative Survival Rates in Young and Elderly Patients with PTC

■ Elderly Patients ■ Young Patients
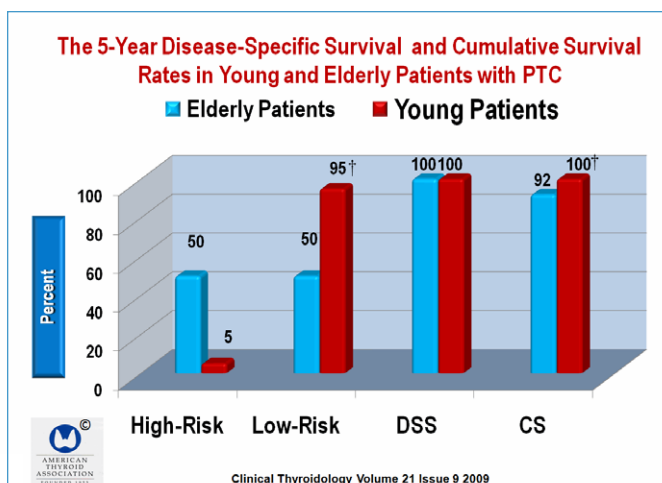
Figure 3. This figure shows the rate of high-and low-risk tumors in elderly and young patients. CS = cumulative survival; DSS = disease-specific survival; PTC = papillary thyroid carcinoma. The only significant difference between the elderly and young patients is cumulative survival (†P = 0.03). This figure is derived from data of Matsuyama et al.

Outcomes of Elderly Patients with Recurrent Papillary Thyroid Cancer

Lymph-Node Metastases

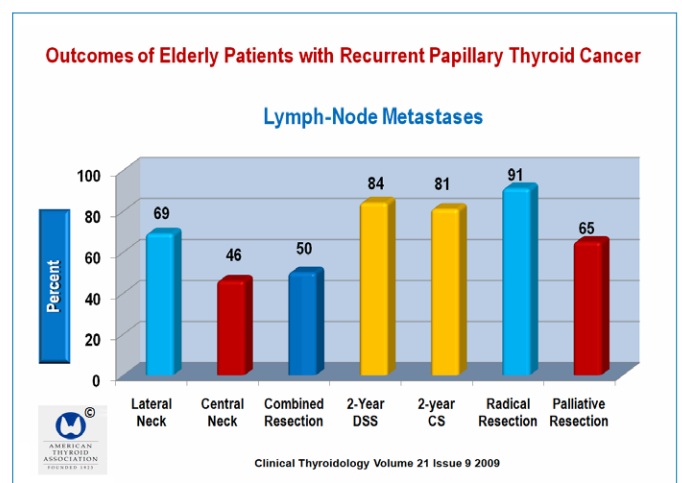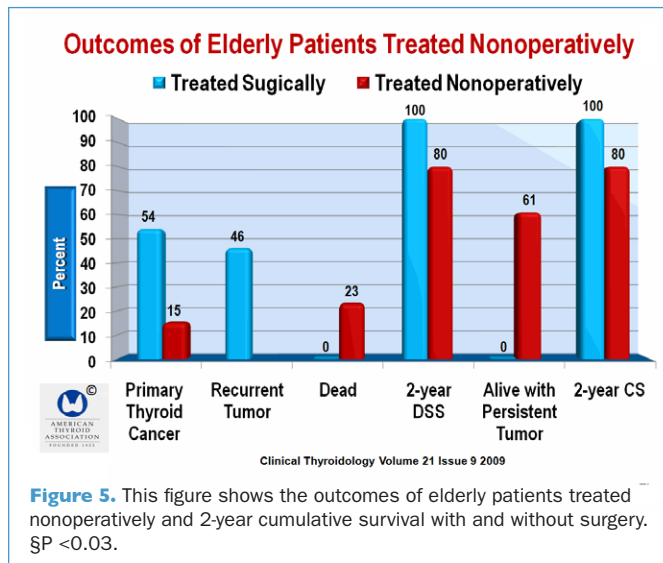**Figure 4.** This figure shows the location of and outcomes with recurrent papillary thyroid cancer. CS = cumulative survival; DSS = disease-specific survival. Combined resection is surgical excision of lymph-node metastases and surrounding neck tissues involved with invasive tumor. Radical resection is surgical removal of invasive tumor. Palliative resection is removal only of lymph-node metastases.

Figure 5. This figure shows the outcomes of elderly patients treated nonoperatively and 2-year cumulative survival with and without surgery. §P <0.03.

health, such as lung lobectomy or dementia, or because of heart failure, advanced cancer, or a patient's refusal of surgery or small tumors causing few physical complaints. Three of these patients died of primary cancer, 8 were alive with persistent tumor, and 1 was lost to follow-up. Three patients died, one was in poor general health, one had advanced tumor, and one who refused surgery died of primary cancer.

The 2-year DSS and CS were both 100% for the 16 patients treated surgically, and were both 80% for the 5 patients not treated surgically. CS was significantly higher in the patients treated surgically (P = 0.02). During follow-up, the quality of life was severely impaired in of 8 of 12 patients not treated surgically (67%) and in 2 of 32 treated surgically (6%). The latter two patients with PTC deteriorated during follow-up as a result of extremely aggressive and advanced tumors (Figure 4).

CONCLUSIONS Surgery for thyroid cancer increases the survival rate and enhances the quality of life of elderly patients providing they are well enough to tolerate the procedure.

COMMENTARY

There is little question that advanced patient age is associated with advanced tumor stage. Thyroid carcinoma in elderly patients behaves more aggressively and these patients have a less favorable prognosis as compared with younger adults. Advanced age is associated with an increased risk for locoregional and a higher incidence of distant metastases (1-3). In the study by Matsuyama et al., patients with low-risk PTC had a prognosis that was not worse in elderly patients than that in young patients. Still, many of the elderly with PTC required resection of lymph-node metastases and locoregional metastases outside the thyroid bed, which resulted in longer than usual hospitalization. Likewise, the quality of life was severely impaired by various conditions, such as dyspnea and dysphagia produced by invasive tumors. Elderly patients with recurrent PTC had no significant differences in survival, including those who had recurrences prior to a second operation, as compared with patients who had metastases at the time of initial surgery. In addition, elderly patients had one or more serious medical conditions such as hypertension, cardiopulmonary disease, tuberculosis, other malignant tumors, diabetes mellitus and stroke.

Comorbidity is known to be an important contributory factor to poor outcomes with thyroid cancer, especially in elderly patients. For example, a population-based observational study from the Netherlands (3) found that hypertension was the most frequent comorbidity with thyroid cancer (18%), followed by other serious conditions such as cardiovascular diseases (6%) and diabetes mellitus (6%). In fact, the prevalence of hypertension was twice as high as expected in all age groups, yet comorbidity was not independently associated with overall survival up to 5 years (3).

These observations are similar to those made by Matsuyama et al. in elderly patients. In their study of elderly patients with recurrent PTC, there were no statistically significant differences in survival among patients with locoregional metastases when patients had metastases found on the initial surgery or were secondarily identified as locoregional recurrences later in the course of follow-up. Although outcome tended to be worse in patients undergoing a second surgery for recurrent metastases, the difference was not statistically significant as compared with patients who had metastases at the time of initial surgery.

An interesting observation was that half of the elderly patients had tumors classified as high-risk and half had low-risk tumors and 5% of the younger patients had low-risk tumors. The 2-year survival rate in elderly patients with a high-risk tumor was significantly lower in patients treated surgically than in those not treated surgically. The authors suggest that surgery for thyroid cancer increases the survival rate and promotes the quality of life in elderly patients with persistent or recurrent thyroid cancer, providing they are well enough to tolerate surgery.

Although there are a few problems with the study, including its retrospective design and the relatively small number of patients and lack of rigorous statistical analysis, this study underscores the fact that advanced age alone is not a sound reason to forgo surgery—or any other treatment for that matter. This decision must be based on the patient's health status and willingness to undergo surgery that may be riskier than usual because of comorbidities. As usual, the patient must be the final arbiter.

Ernest L. Mazzaferri, MD, MACP

References

1.   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.

2.   Vini L, Hyer SL, Marshall J, et al. Long-term results in

elderly patients with differentiated thyroid carcinoma. Cancer 2003;97:2736-42.

3.   Kuijpens JL, Janssen-Heijnen ML, Lemmens VE, et al. Comorbidity in newly diagnosed thyroid cancer patients: a population-based study on prevalence and the impact on treatment and survival. Clin Endocrinol (Oxf) 2006;64:450-5.

Back to Contents

HOT ARTICLES

1. de RA, Vandenbroucke J, Smit J, Stokkel M, Dekkers O.Clinical outcomes after estimated versus calculated activity of radioiodine for the treatment of hyperthyroidism: systematic review and meta-analysis. Eur J Endocrinol 2009.

2. Bogazzi F, Tomisti L, Rossi G, Dell'Unto E, Pepe P, Bartalena L, Martino E.Glucocorticoids are preferable to thionamides as first-line treatent for amiodarone-induced thyrotoxicosis due to destructive thyroiditis: A matched retrospective chohort study. J Clin Endocrinol Metab 2009.

3. Haymart MR, Cayo M, Chen H.Papillary Thyroid Microcarcinomas: Big Decisions for a Small Tumor. Ann Surg Oncol 2009.

4. Sherman SI, Tielens ET, Sostre S, Wharam MD, Jr., Ladenson PW.Clinical utility of posttreatment radioiodine scans in the management of patients with thyroid carcinoma. J Clin Endocrinol Metab 1994;78:629-34.

5. Traisk F, Tallstedt L, Abraham-Nordling M, Andersson T, Berg G, Calissendorff J, Hallengren B, Hedner P, Lantz M, Nystrom E, Ponjavic V, Taube A, Torring O, Wallin G, Asman P, Lundell G.Thyroid-Associated Ophthalmopathy after Treatment for Graves' Hyperthyroidism with Antithyroid Drugs or Iodine-131. J Clin Endocrinol Metab 2009.

6. Choi SH, Kim EK, Kwak JY, Kim MJ, Son EJ.Inter/Intraobserver Variation in Ultrasound Assessment of Thyroid Nodules. Thyroid 2009.

7. Alevizaki M, Saltiki K, Voidonikola P, Mantzou E, Papamichael C, Stamatelopoulos K.Free thyroxine is an independent predictor of subcutaneous fat in euthyroid individuals. Eur J Endocrinol 2009;161:459-65.

8. Choi YJ, Yun JS, Kim DH.Clinical and ultrasound features of cytology diagnosed follicular neoplasm. Endocr J 2009;56:383-9.

9. Ribault V, Castanet M, Bertrand AM, Guibourdenche J, Vuillard E, Luton D, Polak M.Experience with Intraamniotic Thyroxine Treatment in Nonimmune Fetal Goitrous Hypothyroidism in 12 Cases. J Clin Endocrinol Metab 2009.

10. Mekel M, Stephen AE, Gaz RD, Perry ZH, Hodin RA, Parangi S.Thyroid surgery in octogenarians is associated with higher complication rates. Surgery 2009.

11. Schellhaas E, Konig C, Frank-Raue K, Buhr HJ, Hotz HG.Long-term outcome of "prophylactic therapy" for familial medullary thyroid cancer. Surgery 2009.

12. Pitoia F, Niepomniszcze H.Recombinant human TSH: the Argentinean experience. Thyroid 2009;19:799.

13. Van ND, Atkins F, Moreau S, Aiken M, Kulkarni K, Wu JS, Burman KD, Wartofsky L.Utility of the Radioiodine Whole-Body Retention at 48 Hours for Modifying Empiric Activity of 131-Iodine for the Treatment of Metastatic Well-Differentiated Thyroid Carcinoma. Thyroid 2009.

14. Zhu C, Zheng T, Kilfoy BA, Han X, Ma S, Ba Y, Bai Y, Wang R, Zhu Y, Zhang Y.A Birth Cohort Analysis of the Incidence of Papillary Thyroid Cancer in the United States, 1973-2004. Thyroid 2009.

15. Sidiropoulos N, Dumont LJ, Golding AC, Quinlisk FL, Gonzalez JL, Padmanabhan V.Quality Improvement by Standardization of Procurement and Processing of Thyroid Fine-Needle Aspirates in the Absence of On-site Cytological Evaluation. Thyroid 2009.

HOT ARTICLES continued

16. Verburg FA, Gasser M, Beissert M, Geissinger E, Luster M, Reiners C.Intratracheal growth of recurrent benign goiter. Thyroid 2009;19:1009-11.

17. Kloos RT.Protecting thyroid cancer patients from untoward effects of radioactive iodine treatment. Thyroid 2009;19:925-8.

REVIEWS

1. Golden SH, Robinson KA, Saldanha I, Anton B, Ladenson PW.Clinical review: Prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. J Clin Endocrinol Metab 2009;94:1853-78.

2. Kaptein EM, Beale E, Chan LS.Thyroid Hormone Therapy for Obesity and Nonthyroidal Illnesses: A Systematic Review. J Clin Endocrinol Metab 2009.

3. de RA, Vandenbroucke J, Smit J, Stokkel M, Dekkers O.Clinical outcomes after estimated versus calculated activity of radioiodine for the treatment of hyperthyroidism: systematic review and meta-analysis. Eur J Endocrinol 2009.

4. Sawka AM, Goldstein DP, Brierley JD, Tsang RW, Rotstein L, Ezzat S, Straus S, George SR, Abbey S, Rodin G, O'Brien MA, Gafni A, Thabane L, Goguen J, Naeem A, Magalhaes L.The impact of thyroid cancer and post-surgical radioactive iodine treatment on the lives of thyroid cancer survivors: a qualitative study. PLoS ONE 2009;4:e4191.

5. Sawka AM, Thabane L, Parlea L, Ibrahim-Zada I, Tsang RW, Brierley JD, Straus S, Ezzat S, Goldstein DP.Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. Thyroid 2009;19:451-7.

DISCLOSURE

The ATA invites you to

Join Us!

American Thyroid Association Spring 2010 Meeting

Thyroid Disorders in the Era of Personalized Medicine

MAY 13-16, 2010 • HYATT REGENCY MINNEAPOLIS, MINNESOTA

Invited Audience...

The community of endocrinologists, surgeons, scientists, other physicians and health care professionals who wish to broaden and update their knowledge of the thyroid gland and its disorders.

Program Design...

Features innovative talks on clinical topics, "meet-the-professor" workshops, interactive sessions, state of the art information and unparalleled collegiality.

American Thyroid Association

Dedicated to scientific inquiry, clinical excellence, public service, education, and collaboration.

Registration opening in late 2009/early 2010
Meeting information: www.thyroid.org

JOINTLY SPONSORED BY THE AMERICAN THYROID ASSOCIATION AND THE UNIVERSITY OF COLORADO DENVER SCHOOL OF MEDICINE

AMERICAN THYROID ASSOCIATION
FOUNDED 1923

University of Colorado Denver
SCHOOL OF MEDICINE
Advancing Science
Improving Care.