CLINICAL THYROIDOLOGY

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EDITOR'S COMMENTS

This issue of *Clinical Thyroidology* represents the first totally online platform for the journal which has several new features and a few advantages. We have more space for figures and commentaries, and the fonts are larger and easier to read. In addition, PDF files can be enlarged for easy reading or closer inspection of the tables and figures. Of course, recipients can print the issue, which looks best when printed in color.

We are introducing four new features in this issue of *Clinical Thyroidology*.

A CONCISE REVIEW will summarize important clinical issues that have a major impact on practice. The first review published in this issue is written by Dr. Elaine Ron from the Radiation Epidemiology Branch of the National Cancer Institute. An internationally recognized authority on the epidemiology of thyroid cancer, Dr. Ron reviews the subject of nonthyroidal cancers that occur in patients treated with radioiodine. She puts this problem into perspective for practitioners who must discuss it with patients undergoing radioiodine therapy.

INVITED EDITORIALS Experts in the field will provide opinions about current issues that are controversial or that address innovative ideas that are in the forefront of clinical practice. In this issue of *Clinical Thyroidology*, Dr. Martin Surks, a leading expert in the intricacies of subclinical thyroid dysfunction, writes an editorial concerning the upper reference limit for serum TSH, a controversial subject that is likely to affect millions of patients.

EDITOR'S CHOICE Each issue will highlight one or more articles that in our view offer key information for practitioners that should be carefully read.

KEY FIGURES will be provided for each article to visually summarize the data from the articles being reviewed. Hopefully, this will communicate the study findings quickly and will underscore the key points of the article.

Our thanks go to the people who have written commentaries about the articles summarized in this issue of *Clinical Thyroidology*. Our call for members of the American Thyroid Association to render comments for the articles published in this journal has been more than generously answered. In this issue, Drs Rebecca Bahn, Elizabeth Pearce, Leonard Wartofsky, and Kenneth Woeber, all of whom are experts in the field, have provided thoughtful commentaries about articles.

Ernest L. Mazzaferri, MD, MACP
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Radioiodine Treatment for Thyroid Cancer as a Risk Factor for a Second Malignancy

Over the past three decades, the incidence of thyroid cancer has been increasing rapidly in the United States and other parts of the world (1, 2). It is estimated that 37,340 thyroid cancers will be diagnosed in the United States in 2008, with about 75% of them expected to occur among women, making thyroid cancer the sixth most common female cancer today (3). Differentiated thyroid cancer, which occurs at relatively young ages, is typically treated with total or subtotal thyroidectomy with or without the postoperative administration of high-dose adjuvant radioiodine (^{131}I) to ablate residual thyroid tissue (4). Most thyroid cancers are highly treatable, and 5-year relative survival in the United States has improved from 93% in 1975–1977 to 97% in 1996–2003 (5). Early age at diagnosis coupled with excellent prognosis leads not only to a long life after treatment, but also, because of this long life, concern about the carcinogenic potential of ^{131}I therapy, especially to organs that concentrate iodine such as the salivary gland, stomach, small intestine, bladder, and red bone marrow.

Elevated risks of second primary malignancies (SPM) among thyroid cancer survivors have been observed in numerous studies conducted in the past 10 years (6–15). In a meta-analysis of 13 studies of patients with thyroid cancer, Subramanian (16) reported a 20% increase in subsequent cancer risk as compared with the general population (standardized incidence ratio [SIR] =1.20; 95% confidence interval, 1.17 to 1.24) with statistically significantly elevated risks seen for cancers of the salivary gland, stomach, colon, breast, prostate, kidney, brain and central nervous system (CNS), and adrenal gland, plus soft-tissue sarcoma, non-Hodgkin's lymphoma, and leukemia. Significant deficits of lung and cervical cancers also were observed. Ronckers et al. (12) studied the risk of SPM following thyroid cancer and the reciprocal risks of secondary thyroid cancer following any other first cancer and found reciprocal risks for all cancers combined, cancers of the salivary gland, breast, prostate, scrotum, kidney, brain and CNS, and leukemia suggesting that underlying causal factors, heightened medical surveillance, or both and better diagnosis may partly explain these associations.

The contribution of radiotherapy for a first primary thyroid cancer to the development of a subsequent cancer has not been quantified adequately, and the results from the few suitable studies are not consistent. Rubino and colleagues (13) conducted a large study, in which radiotherapy information was available from individual patients, by pooling data from three cohorts (17-19) (Table). Statistically significant positive associations between ^{131}I treatment and all solid SPM, cancers of the salivary gland, bone and soft tissue, and uterus, as well as leukemia were demonstrated and significant trends for increasing risk with greater levels of administered ^{131}I activity were reported for all solid cancers, cancer of the bone and soft tissue, colorectal cancer, and leukemia. A linear relationship between cumulative exposure and risk of solid cancers and leukemia was noted, with an excess relative risk (ERR) of 3.5% per GBq (27 mCi) of ^{131}I for solid cancers and 39% per GBq (27 mCi) for leukemia. In a recent editorial, de Vathaire (20) commented that based on these data ^{131}I therapy could increase the risk of SPM among thyroid cancer survivors by 10 to 20%. In contrast, no association was observed between ^{131}I treatment and risk of developing a SPM in two small studies that had limited statistical power (6, 15).

Four groups have analyzed data from the U.S. Surveillance, Epidemiology, and End Results (SEER) program in the past few years using slightly different statistical methods, subject inclusion criteria, and follow-up periods (7–9, 12). Despite the fact that treatment data were limited and radiation doses were not available, three studies (8, 9, 12) reported a significant association between radiation treatment and the risk of leukemia (Table). Ronckers et al. (12) and Brown and colleagues (8) also found a significantly elevated SIR for stomach cancer in patients treated with ^{131}I, which was not observed among nonirradiated patients, and Chuang et al. (9) observed a significantly increased relative risk of secondary cancer of the upper digestive system as compared with the nonirradiated group. Bhattacharya and Chien (7) evaluated only all SPM combined and, therefore, did not find an association with radiation treatment (Table).

Taken together, the data provide evidence of an increased risk of leukemia following treatment with radioiodine for thyroid cancer and some support for an elevated risk of all solid cancers combined, stomach cancer, salivary gland cancer, and cancers of the bone and soft tissue. Because leukemia and cancers of the salivary gland, bone and soft tissue are rare malignancies, the number of excess PMC attributed to radioiodine treatment is small, but even a small increase in total solid cancer incidence would result in a not insubstantial number of excess cancers. For example, based on data from the Rubino study (13), one might expect 172 cancers per 10,000 people surviving 20 years after treatment with the mean study dose of 6 GBq (163 mCi). The incidence of stomach cancer varies considerably around the world (21), and a moderate radiation-related risk would translate into an appreciable number of excess cancers in high-incidence countries such as Japan.

The current literature is limited by the short follow-up, with

most studies having a mean follow-up of less than 10 years. Data from the studies of atomic bomb survivors indicate that radiation-related risks for solid cancer peak at about 15 to 30 years but continue throughout life, and radiation-associated leukemias, which have an earlier peak, still are seen 40 years or longer after exposure (22, 23). An additional limitation of the investigations conducted to date is that they reflect the effects of earlier treatment regimens. The ^{131}I activity used to treat thyroid cancer varies; in the epidemiologic studies of SPM, cumulative mean ^{131}I activity ranged from about 4 GBq (108 mCi) (6, 17) to about 7 GBq (189 mCi) (15, 18), and activity in the pooled analysis conducted by Rubino et al. (13) ranged from ≤0.2 to ≥18.5 GBq (1 to 486 mCi). These studies included patients treated years ago and current guidelines recommend linking dose to predicted clinical outcomes such as stage, disease recurrence or mortality (4) with low-risk patients receiving smaller treatment doses. To adequately quantify risk, better estimates of organ doses are needed. Improved estimates were recently published, but they are based on 26 patients (10 female) with metastatic thyroid disease, and only a limited number of organs were studied (24). To better inform clinical decisions about appropriate treatment, the SPM risks associated with ^{131}I therapy need to be evaluated by thyroid cancer histology, stage, ^{131}I administered activity, and specific organ doses.

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Risk of Second Primary Cancers following Radiotherapy for a First Primary Thyroid Cancer.

Study and Location	Thyroid Cancer Histologies	Exclusions	Follow-up Period (Mean)	No. of Patients with Thyroid Cancer	No. of Second cancers	Mean ^{131}I Activity (GBq)	Results
Rubino et al., 2003; France, Sweden, Italy	Papillary and follicular	<2-yr survivors	1934–1997 (13 yr)	6841 total (4225 ^{131}I 1194 external beam)	576 total (301 ^{131}I 275 no ^{131}I)	6.0 (162 mCi)	A significant exposure response between ^{131}I activity and risk of solid cancer and leukemia; a significant association between ^{131}I activity and risk of cancers of the bone and soft tissue, colon and rectum, and salivary gland; no significant association between external-beam radiation and total solid cancers
Berthe et al., 2004; France	Papillary and follicular		1960–2002 (median 8 yr)	875 total (594 ^{131}I 281 surgery only)	58	4 (108 mCi) (median)	In multivariate analysis, no significant association between cumulative ^{131}I activity and total SPM; individual cancers sites not evaluated
Verkooijen et al., 2006; Netherlands	Papillary and follicular	Patients not treated with ^{131}I	1985–? (10.6 yr)	282	20	2.6 (70 mCi)	No significant increase in SPM found after ^{131}I treatment
Ronckers et al., 2005; U.S. SEER	All	<2-mo survivors	1988–2000 (7.9 yr)	17,055 total (6,745 I-131 1359 other radiation 8,951 no radiation)	683 total (236 I-131 53 other radiation 394 no radiation)	NA	Significantly elevated SIR for stomach and non-CLL leukemia following ^{131}I with no increased risks seen for these cancers among nonirradiated patients
Chuang et al., 2005; U.S. SEER	All	<6-mo survivors	1973–2000 (11.1 yr for radiated and 7.5 yr for nonirradiated)	26,639 total (9666 any radiation 16,510 no radiation)	1862 total (534 radiation 1270 no radiation 58 unknown)	NA	Significantly elevated RR of upper digestive system cancers and myeloid leukemia following any radiation compared to no radiation; and for colorectal and upper digestive system cancers following external-beam radiation; for prostate following radioactive implants; for myeloid leukemia following ^{131}I compared with no radiation
Bhattacharyya and Chien, 2006; U.S. SEER)	Papillary and follicular	None	1988–2001 (5.1 yr for ^{131}I and 4.6 for nonirradiated)	29,231 total (10,349 ^{131}I 18,882 no radiation)	1759 total (466 I-131 1293 no radiation)	NA	On univariate analysis, ^{131}I treated patients had lower risk of developing total SPM than patients not treated with radiation; on multivariate analysis there was no significant difference between the two patient groups
Brown et al., 2008; U.S. SEER	Papillary and follicular	<2-mo survivors	1973–2002 (median, 8.6 yr)	30,278 total (10,257 ^{131}I 18,029 no radiation)	2191 total (618 ^{131}I 1573 no radiation)	NA	Significantly elevated RR of all second cancers and leukemia following ^{131}I compared with no radiation; significantly elevated observed vs. expected rates for stomach cancer following ^{131}I with no increased risk seen for it among patients not treated with radiation
			1988–2002	18,060 total (8159 ^{131}I 9901 no radiation)	779 total (331 ^{131}I 448 no radiation)	NA	Significantly elevated RR of leukemia following ^{131}I compared with no radiation; significantly elevated SIR for stomach cancer following I-131 with no increased risk seen among nonirradiated patients

NA = not available; RR = relative risk; SIR = standardized incidence ratio (observed divided by expected cancer rates); SPM = second primary cancer.

There is a small risk of second primary nonthyroidal malignancies in patients with differentiated thyroid treated with radioiodine

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 cancer. J Clin Endocrinol Metab 2008;93:504-15.

SUMMARY

BACKGROUND Differentiated thyroid cancer in young and middle-aged adults is associated with 10-year cancer-specific survival rates that exceed 90%. Because many are treated with radioactive iodine, there are concerns about second malignancies. The U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, which began accruing cancer registry data in 1973, now has the largest database of thyroid cancer patients in the world, with the longest period of follow-up. This is a study of the SEER database of patients with papillary and follicular thyroid cancer treated between 1973 and 2002. The aim of the study was to identify the risk of second cancers in patients treated with radioiodine.

METHODS The study subjects were 26,517 (88%) patients with papillary cancer and 3761 (12%) with follicular cancer, 23,059 (76%) of whom were female and 7219 (24%) were male. Median age at the time of diagnosis of thyroid cancer was 43 years. The number of excess second nonthyroidal cancers was expressed as the standardized incidence ratio (SIR), which is the ratio of observed to expected cases per 10,000 patient-years (PYs) of follow-up. Risk is also reported as the absolute excess risk (AER), which is the number of additional patients in the study population in whom nonthyroidal cancer develops per 10,000 PYs minus the expected number of cancers found in the general population.

From 1973 to 1987, the SEER registries encoded external-beam radiation therapy separately, but encoded all radioisotope therapy, including both radioiodine therapy and brachytherapy, as "other therapy." Beginning in 1988, radioiodine therapy was also encoded separately. For statistical analysis, patients treated with other therapy between 1973 and 1987 were considered to have received radioisotope therapy, thus increasing the total number of patients treated with radioisotopes to 10,257 (34%). For patients treated between 1988 and 2002, two different latency periods (2 months or 36 months from initial treatment to study of second cancers) were used in the statistical analysis.

RESULTS Between 1973 and 2002, 2158 patients (7%) had 2338 nonthyroidal second malignancies of almost all types. The risk was greatest for patients aged 25 to 29 years and for a period of 5 years after diagnosis, after which it declined rapidly and remained low. The risk of a second nonthyroidal cancer during 1973 to 2002 was significantly higher for patients as compared with the general population (AER = 6.39, P<0.05). There was an excess risk for cancers of the central nervous system (AER = 4.98), female breast (AER 3.47), prostate (AER = 2.32), kidney–renal pelvis (AER = 2.07), and salivary glands (AER = 0.29) and for Hodgkin lymphoma (AER = 0.22), leukemia (AER 0.64), and myeloma (AER = 0.48) (all P<0.05). Risk was low for urinary bladder (AER = –0.6) and lung and mediastinal tumors (AER = –1.39) (all P<0.05) and was not affected by gender.

Between 1973 and 2002, the radioisotope-treated group was at significantly (P<0.05) greater risk for second primary malignancies as compared with the general population (AER = 13.3), as was the nonirradiated group (AER = 3.53); however, the risk was significantly greater in the radiated group (P<0.002) than the nonirradiated group, which had a cancer rate close to the endemic rate.

When the analysis was performed for the data between 1988 and 2002, using a 36-month latency exclusion, the risk of second primary malignancies was significantly greater in the radioisotope-treated group than in the general population (AER = 15.69) and was over fivefold that of the nonirradiated group (AER = 2.81) (Figure 1).

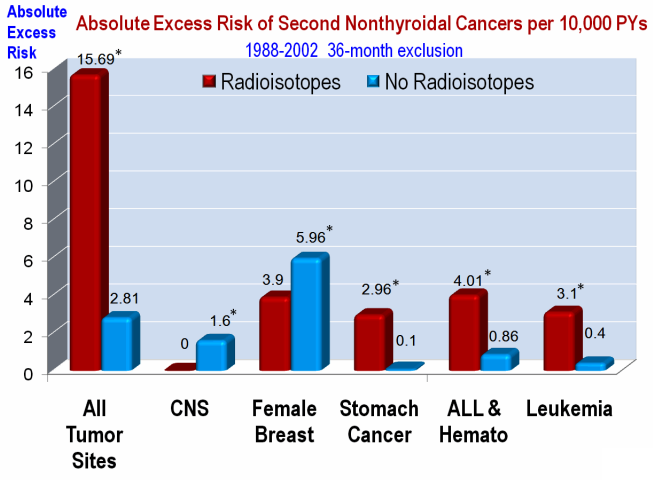

Figure 1. Data using 36-month exclusion (the time lapse before which second primary malignancies were included in the study. The absolute excess risk of second nonthyroidal cancers in 9901 patients who did and 8159 who did not receive radiotherapy. ALL & Hemo denotes all lymphatic and hematopoietic diseases, including myeloma, Hodgkin lymphoma, and leukemia; CNS central nervous system; Leuk leukemia; and PYs patient-years of follow-up. *P<0.05. Figures 1 and 2 are drawn from the data of Brown et al.

When the analysis was confined to patients whose thyroid cancer was diagnosed between 1988 and 2002, using a 2-month latency exclusion period, the risk of second nonthyroidal primary malignancies was higher than that in the general population in both the radioisotope-treated group (AER = 12.01) and the nonirradiated group (AER = 7.86); however, the difference between the two groups was not statistically significant (Figure 2).

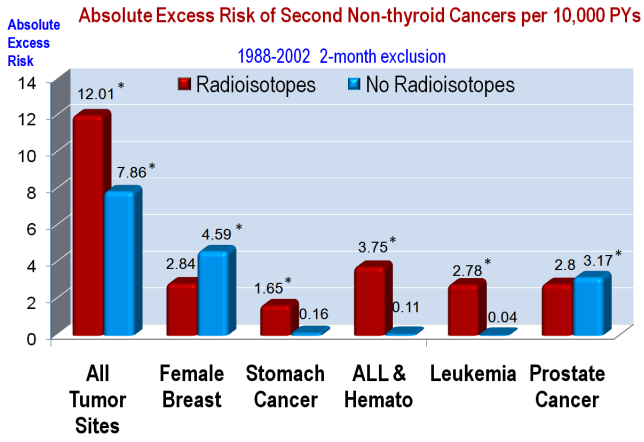

Figure 2. Data using 2-month exclusion. The absolute excess risk of second nonthyroidal malignancies in 4284 patients treated with radioiodine and 5413 patients not treated. See Figure 1 for abbreviations and symbols.

Even with analysis of the 1973 to 2002 cohort with a 36 month latency exclusion, the risk of second non-thyroid malignancies in the radioisotope-treated patients was significantly greater than that in the general population (AER = 14.89) but was not significantly elevated in the nonirradiated cohort (AER = 1.97). Hematological malignancies were elevated in the radioisotope-treated group (AER = 3.75), P< 0.05) but not the non-nonirradiated group (AER = 0.11).

CONCLUSION There is a small risk of second primary non-thyroidal malignancies in patients with differentiated thyroid carcinoma that varies by age at diagnosis, radioiodine therapy, and latency period from initial thyroid cancer treatment to appearance of second non-thyroid tumors.

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COMMENTARY

The Concise Review in this issue of Clinical Thyroidology by Dr. Elaine Ron from the National Institutes of Health gives the perspective of an expert who has long been involved with this problem and has published earlier observations on the SEER database concerning the excess risk of nonthyroidal cancers in patients with thyroid cancer treated with radioiodine. Physicians and patients alike must be aware of these risks, which are carefully summarized in her review.

It is important to emphasize that during the entire study period from 1973 to 2002, when 131I therapy was not always recorded as such but was simply categorized as radioisotope therapy, patients were at increased risk for nonthyroidal second primary cancers (AER = 13.3) over that in the general population; however, the nonirradiated survivors also had an increased risk for developing nonthyroidal tumors (AER = 3.53), a risk more closely aligned to that in the general population. Still, the risk of developing a second nonthyroidal tumor was significantly greater for the irradiated patients than for the nonirradiated patients (RR = 1.16; P<0.002). When the period of analysis was restricted to patients treated from 1988 to 2002, when 131I therapy was recorded as such in the SEER database, an increased risk of second nonthyroidal cancers was observed for both the isotope-irradiated (AER = 12.01) and nonirradiated (AER = 7.86) cohorts, but the risk in the two groups was statistically indistinguishable (P = 0.31).

When the analysis was done using a latency exclusion period for secondary cancers of 36 months as opposed to 2 months, the risk of developing nonthyroidal second primary cancers was elevated over that of the general population for those receiving radioisotope therapy (AER = 14.9), while the nonirradiated cohort had a risk similar to that in the general population (AER = 1.97). The risk of hematological malignancies was significantly elevated in the radioisotope cohort (AER = 3.75) but not in the nonirradiated cohort (AER = 0.11). During this period, there was a significantly elevated risk for stomach cancer following 131I therapy with no increased risk among nonirradiated patients. Dr. Ron makes several important caveats. From the study by Rubino et al., (1) one can anticipate 172 cancers per 10,000 people surviving 20 years after a mean treatment dose of 6 GBq (163 mCi). Dr. Ron also summarizes the limitations in the studies of this subject.

Lastly, it is important to know that an important study by Links et al. (2) which investigated life expectancy in patients with thyroid cancer found that patients who were free of disease had a normal residual life span after being cured, whereas median life expectancy was reduced to 60% in patients with residual disease. The authors concluded that treatment, including radioiodine, is safe and did not affect life expectancy.

Ernest L. Mazzaferri, MD, MACP

CLINICAL THYROIDOLOGY

EDITORIAL New evidence against lowering the thyrotropin reference limits

The diagnosis of hypothyroidism is based on negative feedback between serum thyroid hormones and serum thyrotropin (TSH). When serum TSH is raised and free T_4 decreased, the diagnosis is primary hypothyroidism, and when free T_4 remains within its reference limits, the diagnosis is subclinical hypothyroidism. Given the high prevalence of raised TSH, particularly among older patients, designation of the upper reference limit is critical.

During the past 15 years, the reported upper limit has been considered to be about 4.0 to 5.5 mIU/L, and similar limits are provided by several national reference laboratories and manufacturers of TSH assay kits. Analysis of TSH distribution among the U.S. population in the National Health and Nutrition Examination Survey III (NHANES III) (1) suggested an upper limit of 4.12 mIU/L for a large thyroid disease–free population, representative of the U.S. population with regard to age, sex, race, and geographic distribution. In that group, subjects with a history of thyroid disease or taking thyroid medications or other medications that might affect thyroid measurements and those who had antithyroid antibodies were excluded.

TSH reference limits are determined by analyzing TSH distribution after log transformation, which generally shows a skew toward higher TSH concentrations. The National Academy of Clinical Biochemistry suggested that the upper reference limit of rigorously screened individuals without thyroid disease would likely be 2.5 mIU/L (2), and some authorities and professional societies have recommended a decrease in the upper limit to 2.5 to 3.0 mIU/L (3) for a comparable population, also excluding those with thyroid ultrasound abnormalities. This recommendation is controversial (4). Such a change would have enormous public health consequences, since TSH exceeds 2.5 mIU/L in 10 to 20% of individuals of all ages and 35% of people >70 years of age. Such individuals could be designated hypothyroid and possibly treated with levothyroxine, unnecessarily, for the duration of their life (4).

The study of Hamilton and colleagues of a mainly Caucasian population (97.4%) showed that TSH distribution in a population without thyroid disease, as defined above, was skewed toward higher values. However, after log transformation, the distribution curve appeared mainly Gaussian, allowing calculation of the 2.5 and 97.5 percentiles. A similar 97.5 percentile was obtained whether or not those with thyroid ultrasound abnormalities were excluded. TSH was determined with an older enzyme-linked immunoassay (ELISA) method, which when corrected to a current method resulted in a 97.5 percentile of 4.1 mIU/L, identical to the 97.5 percentile from NHANES III, 4.12 mIU/L (1). These findings extend, to an iodine-sufficient population, observations from Germany that excluding people with antithyroid antibodies or ultrasound abnormalities did not significantly influence the 97.5 percentile (5).

The 97.5 percentile reported by Hamilton and colleagues is for a population without thyroid disease. However, the 20-year follow-up of the Whickham study did show increased progression to hypothyroidism when TSH was >3.0 mIU/L. Further analysis shows that progression to hypothyroidism occurred in <10% of 20- to 40-year-olds and in 5 to15% of individuals 50 to 70 years of age (4). The prevalence increases further in those who have antithyroid antibodies. Since nearly 80% of subjects with TSH levels between 3.0 and 5.0 mIU/L do not have antithyroid antibodies (4), it is likely that the large majority of people with TSH in that range have little risk for the development of hypothyroidism. Moreover, the data reported by Hamilton et al. reflect a Caucasian population, and are a composite for people of all ages. In the future, it is possible that age-specific and race/ethnic-specific limits for TSH will be used (6, 7).

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Lowering the thyrotropin reference limit to 2.5 µIU/ml may result in inappropriate therapy for many euthyroid individuals

Hamilton TE, Davis S, Onstad L, Kopecky KJ. 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.

SUMMARY

BACKGROUND There is considerable debate concerning the upper limit of the reference range for serum thyrotropin (TSH), which some have suggested should be lowered to 2.5 µIU/ml. This has major implications regarding the diagnosis and treatment of subclinical hypothyroidism that could result in millions of people worldwide being unnecessarily treated with levothyroxine. The uncertainty is exacerbated by differing reference ranges among some hospital laboratories, further confusing physicians.

METHODS The population evaluated in this study was a subset of the Hanford Thyroid Disease Study (HTDS) cohort born in the state of Washington between January 1940 and December 31, 1946. During the 1940s and 1950s, this group was exposed as children to 1311 emissions from the Hanford nuclear facility and was considered to be at increased risk for thyroid disease. Among 5199 persons randomly selected using birth certificates, 3440 (66%) were located and agreed to undergo a full clinical evaluation for thyroid disease, including thyroid ultrasound abnormalities. Their median age at the time of examination was 51 years (range, 45 to 57) and a large majority (97.5%) described themselves as white or Caucasian. Serum samples for TSH, the free thyroxine (T_4) index, and thyroid antibodies were obtained from 3431 of the 3440 individuals (99.7%). The authors of the HTDS previously reported that no significant radiation-dose relationship was found between TSH and 1311 exposure from Hanford or to any thyroid disease diagnosis or ultrasound abnormalities.

The present study was restricted to 1861 individuals with TSH measured by enzyme-linked immunoassay (ELISA) because the methods used to measure TSH and thyroid antibodies had changed over the course of the HTDS. Blood samples were typically drawn between approximately 800 hours and 1800 hours, half of which were drawn before 1200 hours. Because TSH results were based on an ELISA that was no longer in use, the frozen sera of 50 participants with a wide range of TSH values were tested with the IMX Ultrasensitive human TSH II assay to determine whether the results were comparable to those of a contemporary assay and to verify that the frozen TSH samples had not degraded over time. The ELISA results were compared with those from a contemporary third-generation TSH immunochemiluminometric assay (ICMA) with an analytical sensitivity of 0.004 µIU/ml (reference range, 0.350 to 5.500).

Patients were divided into three normal reference groups (NRG). NRG-1 (n = 1448) excluded anyone with thyroid dysfunction, palpable thyroid nodules, or ultrasound abnormalities with palpable nodules, as well as those taking lithium, phenytoin, glucocorticoids, or amiodarone. NRG-2 (n = 1186) excluded further those with positive antithyroid peroxidase antibodies (anti-TPOAb) and/or thyroglobulin antibody. NRG-3 (n = 766) excluded further those with an abnormal thyroid ultrasound. TSH levels in individuals from the three groups with increasingly more strict definitions were considered to represent a normal range in an unselected population. The distribution of the ELISA TSH level is shown in Figure 1 for the entire cohort and for men and women in Figures 1 and 2.

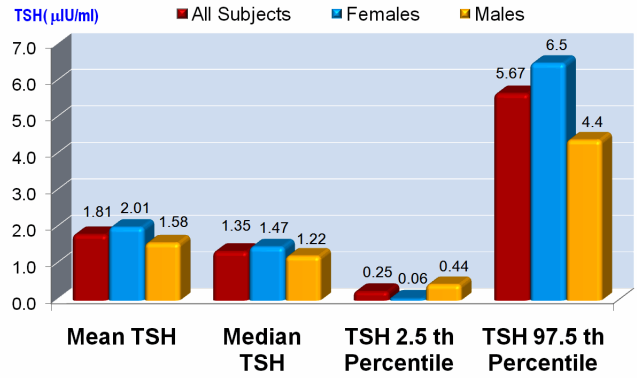

Figure 1. The mean, median, 2.5th and 97.5th percentile TSH distribution is shown using the ELISA assay for the entire cohort and for men and women alone. The figure is drawn from the data in Table 1 by Hamilton et al.

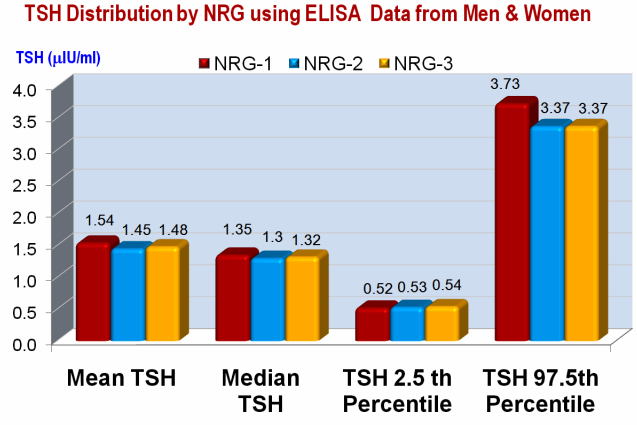

Figure 2. The mean, median, and 2.5th and 97.5th percentile mean, median, and 2.5th and 97.5th percentile TSH distributions in men and women using the ELISA assay by the normal reference groups (NRGs). The figure is drawn from the data in Table 1 by Hamilton et al.

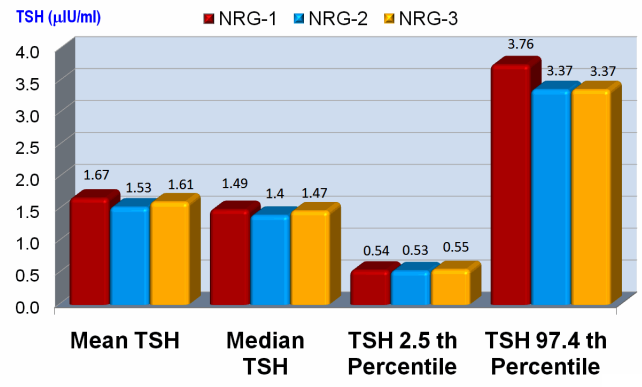

Figure 3. The mean and median TSH and 2.5th and 95.5th percentile TSH distributions according to the three NRG groups are shown using ELISA TSH data only from women.

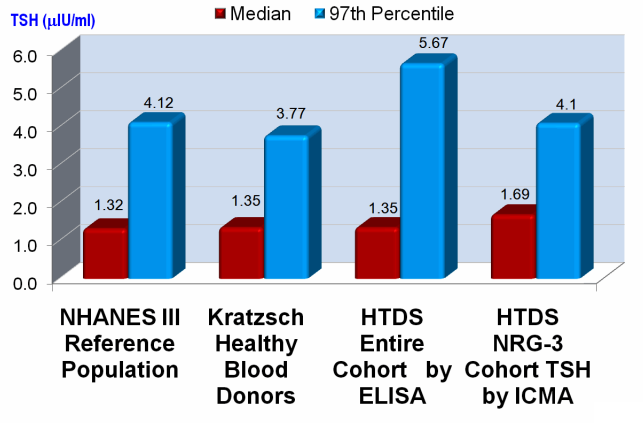

Figure 4. Median and 97.5th percentile of the TSH distributions is shown for three population samples, The NHANES (Health and Nutrition Examination Survey, 1999-2002) (1), the study by Kratzsch et al. (2), and that by Hamilton et al.

RESULTS TSH did not differ significantly between those with blood drawn before or after 1200 hours ($P<0.001$) and were thus combined in the analyses. The HTDS ELISA TSH values were concordant with those measured with the IMX assay. Similarly, there was a high degree of correlation between the original HTDS ELISA TSH values and the ICMA values. The prevalence of anti-TPOAb increased significantly ($P<0.001$), from 5% in those with a TSH of less than 0.5 µIU/ml to 16% among those with a TSH of 2.0 to 2.49 µIU/ml.

The mean serum TSH in the original HTDS ELISA study for the entire cohort (n = 1861) was 1.81 µIU/ml (men, 1.58; women, 2.01), and the 97.5th percentile was 5.67 µIU/ml (men, 4.40; women, 6.50; Figure 1). The TSH distribution was right-skewed in the entire HTDS cohort; however, after log transformation, the distribution curve mainly followed a Gaussian distribution, allowing calculation of the 2.5 and 97.5th percentiles with 15% of the individuals having a TSH by ELISA >2.5 µIU/ml, which is consistent with prior studies (Figure 3). On average, the 97.5th percentile TSH ELISA of 3.4 µIU/ml corresponded with an NRG-3 ICMA value of 4.1 µIU/ml (Figure 4). Similarly, an ICMA value of 2.5 µIU/ml corresponded to an ELISA value of 2.0 µIU/ml, which was in the 80th percentile for NRG-3. For NRG-3, the percentage of individuals with an ELISA TSH value >2.5 µIU/ml was 9.7%; moreover, the proportion of TSH values <2.5 µIU/L was estimated to be only 80%, which is significantly different from prior assertions that more than 95% of euthyroid individuals have TSH levels less than 2.5 µIU/ml.

CONCLUSION The upper reference limit for the most rigorously screened thyroid disease-free group was 4.1 µIU/ml. Lowering the TSH reference limit to 2.5 µIU/mL may result in inappropriate therapy for many euthyroid individuals

COMMENTARY

The upper reference range for serum TSH has been debated for several years and continues to be a major issue that potentially affects millions of people. The crux of the debate is whether the majority of patients without evidence of thyroid disease have an upper TSH reference limit of 2.5 µIU/ml. In an editorial in this issue of *Clinical Thyroidology*, Dr. Martin Surks summarizes the origins of the current controversy and briefly reviews the considerable evidence that the upper TSH reference range should not be lowered to 2.5 µIU/ml for the reasons stated by Hamilton et al. and previously by Surks et al., and that doing so will expose many euthyroid people to unnecessary levothyroxine therapy. Surks offers the interesting opinion that in the future, it is possible that age-specific and race/ethnic-specific limits for TSH will be used to make clinical decisions on this matter.

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Autoimmune atrophic gastritis affects intestinal absorption of levothyroxine that can be predicted by the level of serum parietal cell antibodies

Checchi S, Montanaro A, Pasqui L, Ciuoli C, De Palo V, Chiappetta MC, Pacini F. L-thyroxine requirement in patients with autoimmune hypothyroidism and parietal cell antibodies. J Clin Endocrinol Metab 2008;93:465-9.

SUMMARY

BACKGROUND Many things interfere with levothyroxine ($L\text{-}T_4$) therapy, including compliance, reduced absorption from gastrointestinal disorders such as *H. pylori* infection, malabsorption, obstructive liver disease, cirrhosis, medications such as iron supplements, antacids, proton-pump inhibitors, resins, lovastatin, sucralfate, calcium carbonate, soybeans, coffee, high-fiber diet, atrophic gastritis, and impaired gastric secretion. Based on the frequent association of parietal-cell antibodies (PCAs) with atrophic gastritis and autoimmune thyroid disease, the authors of this study hypothesized that PCA-positive patients may require higher than usual doses of $L\text{-}T_4$ and that this may be another cause for increased daily $L\text{-}T_4$ requirements.

METHODS A total of 391 study subjects (56%) were selected from a cohort of 697 consecutive patients with clinical or subclinical hypothyroidism caused by autoimmune thyroiditis. For entry into the study, subjects were required to have serum thyrotropin (TSH) levels within the normal range (0.3 to 3.0 µIU/ml) on $L\text{-}T_4$ replacement therapy with no history of taking drugs that interfere with gastric function or previous therapy for *Helicobacter pylori* infection, major chronic diseases, or a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) higher than 30. The study subjects were screened for PCA, which correlated with the daily $L\text{-}T_4$ doses required to maintain the serum TSH at the target concentration. In addition, 60 patients who had previously undergone a total thyroidectomy for Graves' disease or multinodular goiter and were on $L\text{-}T_4$ replacement therapy were selected for study after satisfying the same criteria as the subjects with autoimmune hypothyroidism. Study of the thyroidectomy group was intended to give further information on PCA interference of the $L\text{-}T_4$ target level by eliminating the variable of residual thyroid tissue. A subgroup of 73 of 155 patients (47%) with autoimmune thyroiditis agreed to undergo gastric endoscopy and biopsy to be examined for atrophic gastritis. The tissue was examined in a blinded manner by a pathologist grading gastric atrophy on a three-level scale that has been shown to reduce observer bias.

RESULTS Serum PCA was positive in 155 of 391 patients (39.6%) and negative in 236 of 391 patients (60.4%). Before the start of $L\text{-}T_4$ therapy, those with and without PCA had mean (±SD) serum TSH levels of 17.9±22.9 and 21.7±35 µIU/ml, respectively, (P = 0.8). After starting $L\text{-}T_4$ therapy, the two groups took $L\text{-}T_4$ for approximately the same amount of time, 93.1±82.1 and 90.6±67.1 months, respectively, (P>0.5). Daily $L\text{-}T_4$ requirements were significantly greater in PCA-positive patients (1.24±0.4 µg/kg/day) than in the PCA-negative patients (1.06±0.36) (P<0.002; Figure 1). After excluding the confounding factor of *H. pylori* infection, the significantly higher $L\text{-}T_4$ dosage required to maintain serum TSH within the target range remained significantly higher. The daily $L\text{-}T_4$ requirements were even higher in 47 patients with biopsy-proven gastric atrophy (1.52±0.4 µg/kg/day) compared with the $L\text{-}T_4$ requirements in 26 patients with normal gastric mucosa (1.15±0.3) (P<0.0001; Figure 1).

The $L\text{-}T_4$ requirements were also related to the degree of gastric atrophy. The daily free T_4 requirements for patients with mild, moderate, and severe gastritis were 1.18±0.41, 1.49±0.29, and 1.83±0.29 µg/kg/day, respectively (P<0.006 for moderate vs. severe, P<0.02 for mild vs. moderate; Figure 1). For the entire group of 155 PCA-positive patients, there was a significant correlation between the daily $L\text{-}T_4$ requirements and the serum levels of PCA (r = 0.55; P<0.0001). This was even more apparent when the analysis was limited to the PCA-positive patients with biopsy-documented gastric atrophy.

The daily $L\text{-}T_4$ dose required to maintain the target TSH level was significantly higher in patients who had undergone

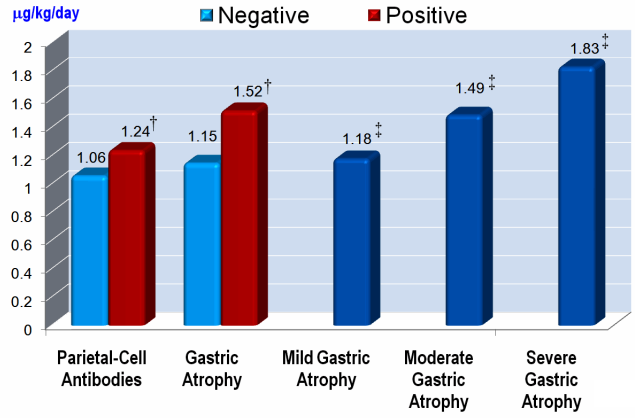

Figure 1. The daily $L\text{-}T_4$ requirements increased in patients with parietal-cell antibodies as compared with those without parietal-cell antibodies, †P<0.002, and in patients with increasingly worse gastric atrophy, ‡P = 0.006 to 0.002.

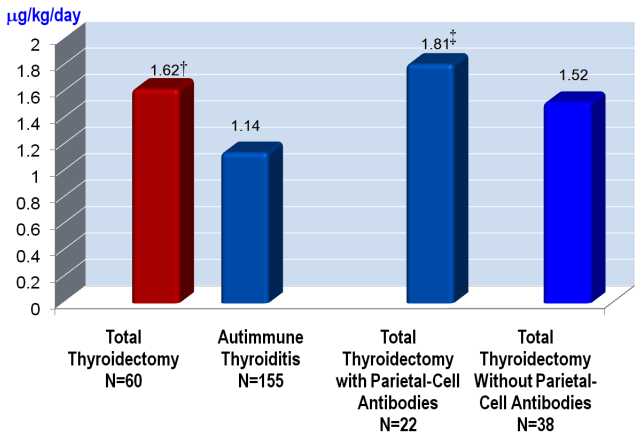

Figure 2. The daily L-T_4 requirements increased for patients with total thyroidectomy as compared with patients afflicted with autoimmune thyroiditis †P<0.001, and for patients with total thyroidectomy with parietal-cell antibodies as compared with patients who had total thyroidectomy without parietal-cell antibodies. ‡P<0.003 to 0.002.

total thyroidectomy as compared with the autoimmune hypothyroid group (1.62±0.29 vs. 1.14±0.41 µg/kg/day, P<0.001, Figure 2). The dose of L-T_4 was significantly greater in 22 patients who had undergone thyroidectomy and were PCA-positive (1.81±0.27 µg/kg/day) compared with PCA-negative patients who had undergone surgery (1.52±0.25 µg/kg/day, P<0.0003, Figure 2). Multivariate analysis found that PCA and basal TSH levels were the most significant independent variables predicting the daily L-T_4 requirement.

CONCLUSION Autoimmune atrophic gastritis affects levothyroxine absorption that can be predicted by the serum level of parietal-cell antibodies.

COMMENTARY

Oral thyroid hormone is absorbed through the intestinal mucosa at the level of the jejunum and ileum (1, 2), but normal gastric acid secretion appears to be necessary for this to occur. Normally, the absorption of thyroxine ranges from 62 to 82% (2) and peaks 3 to 4 hours after the drug has been ingested. Several factors impair intestinal absorption of thyroxine, including the age of the patient (2), dietary habits, malabsorption, and drug interference. For instance, omeprazole, lansoprazole, and other medications that reduce gastric acid secretion may interfere with intestinal absorption of thyroid hormone, and patients with impaired acid secretion require a significantly increased dose of L-T_4, further suggesting that normal gastric acid secretion is necessary for effective absorption of oral L-T_4 (3). Centanni et al. found that the daily requirement of thyroxine was, 22 to 34% greater in patients with *H. pylori*–related gastritis, atrophic gastritis, or both conditions together than in the reference group (3). Prospective studies found that *H. pylori* infection led to an increased serum TSH (P = 0.002), which was nearly reversed when the *H. pylori* infection was eradicated. Omeprazole therapy was associated with an increase in the serum TSH level in all patients treated with thyroxine, an effect that was reversed by an increase in the thyroxine dose by 37%.

Checchi et al. found that the increase in daily thyroxine requirements correlated closely with parietal-cell antibody levels. For example, daily thyroxine requirements increased by 17% when parietal-cell antibodies were present as compared with when the antibodies were not present. The levothyroxine requirements were increased by 26% when gastric atrophy increased from mild to moderate, and the L-T_4 dosage requirement increased by 55% when gastric atrophy went from mild to severe. The observations in this study suggest that serum parietal-cell antibody levels might be measured when the response to thyroxine therapy fails to achieve the expected goals.

Ernest L. Mazzaferri, MD, M.A.C.P

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Autoimmune thyroid failure is higher than usual among thyroid antibody-positive individuals on a more than adequate or excessive iodine diet

Li Y, Teng D, Shan Z, Teng X, Guan H, Yu X, Fan C, Chong W, Yang F, Dai H, Gu X, Yu Y, Mao J, Zhao D, Li J, Chen Y, Yang R, Li C, Teng W. Antithyroperoxidase and antithyroglobulin antibodies in a five-year follow-up survey of populations with different iodine intakes. J Clin Endocrinol Metab 2008;93:1751-7.

SUMMARY

BACKGROUND This study explores the prevalence, incidence, and natural course of antithyroid antibodies and hypothyroidism in three rural communities in China with differing iodine adequacy.

METHODS Baseline and follow-up studies were performed in Panshan, Zhangwu, and Huanghua, China, which are, respectively, areas of mildly deficient, adequate, and excessive iodine intake, with median urinary iodine concentrations (MUI) of 83.5, 242.9, and 650.9 µg/L, respectively. After making home visits in 1999 to 16,287 individuals older than 13 years, 3761 (23%) enrolled in the baseline study, comprising 934 (25%) men and 2827 (75%) women. Specimens were collected for urine iodine levels, serum thyrotropin (TSH), serum thyroid peroxidase antibody (TPOAb), and serum antithyroglobulin antibody (TgAb) levels. All underwent neck palpation and thyroid ultrasound examinations. Of this group, 1103 (29.3%) lived in Panshan, 1584 (42.1%) in Zhangwa, and 1074 (28.6%) in Huanghua. In 2004, a total of 3018 (80.2%) of this group underwent follow-up studies using the same protocol. The serum TSH reference range of 0.3 to 4.8 mIU/L was derived from the 2.5th to 97th percentiles on log-transformed values from 2434 carefully screened euthyroid subjects.

RESULTS OF BASELINE STUDY At the beginning of the survey, most subjects were euthyroid but a few were TPOAb-positive (9.8%) or TgAb-positive (9.1%). The prevalence of antithyroid antibodies was the same in the three study areas but was significantly greater among women than among men (P<0.001) and increased with age, especially in women. However, in subjects aged 45 years or older, TgAb was more common in Huanghua (16.3%) as compared with both Panshan (9.5%, P = 0.016) and Zhangwu (11.1%, P = 0.03, Figure 1). Median baseline serum TSH levels were lowest (1.42 µIU/ml) in subjects without serum antithyroid antibodies, were highest (2.0, P<0.001) in subjects with both TPOAb and TgAb and were intermediate (1.65 and 1.63, P<0.05 for both) in subjects with either TPOAb or TgAb alone, as compared with serum TSH levels in patients without antithyroid antibodies. Still, there were no significant differences in baseline serum TSH levels among the three study populations.

RESULTS AFTER A 5-YEAR FOLLOW-UP STUDY Among 3047 subjects without TPOAb or TgAb, 2381 (78%) participated in the follow-up study. After 5 years, the cumulative incidence of antibody-positive subjects was 2.8% for TPOAb and 3.8% for TgAb. The TgAb incidence rates were significantly higher in females than in males (4.41 vs. 2.21, P = 0.014). The 5-year cumulative incidence of positive TgAb was 2.91%, 3.64%, and 5.07%, in Panshan, Zhangwu, and Huanghua, respectively, while the incidence of TPOAb was 2.08, 3.84 and 2.84% in the three areas, respectively. The rate was significantly higher in Huanghua, especially in women, where iodine intake was excessive as compared with mildly iodine-deficient Panshan (P<0.039; Figure 2). Among women, the incidence of TgAb was significantly higher than that of TPOAb (P<0.019), and was also greater in Huanghua (P<0.019). Among men, the

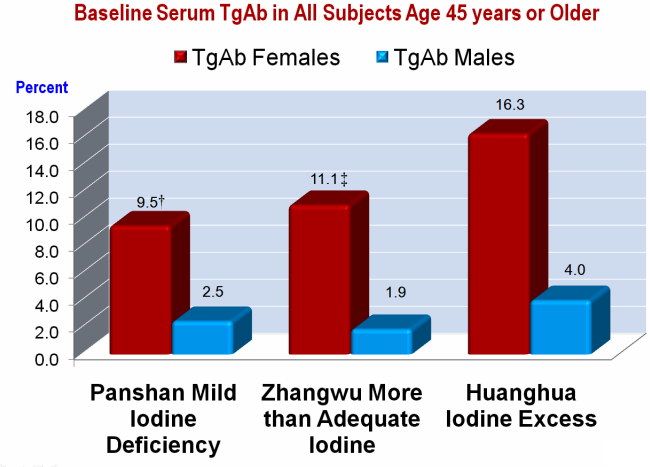

Figure 1. The baseline prevalence of antithyroglobulin antibodies (TgAb) among women and men ≤45 years old is significantly greater comparing Huanghua with both Panshan (†P = 0.03) and Zhangwu (‡P = 0.02).

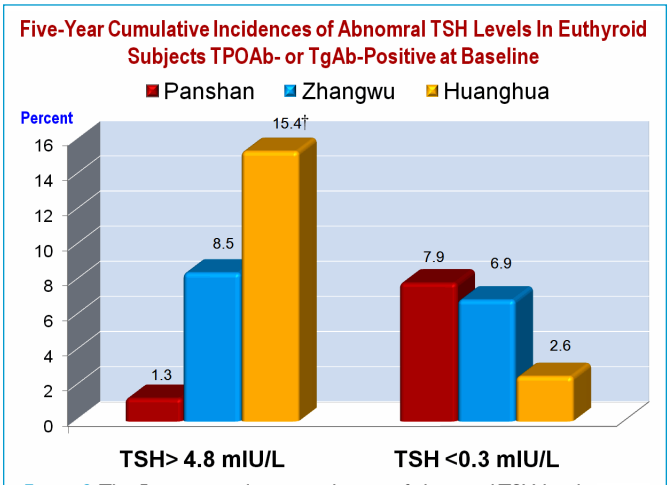

Figure 2. The 5-year cumulative incidences of abnormal TSH levels in euthyroid subjects who had serum TPOAb or TgAb at baseline was greatest in individuals living in Huanghua (†P<0.001).

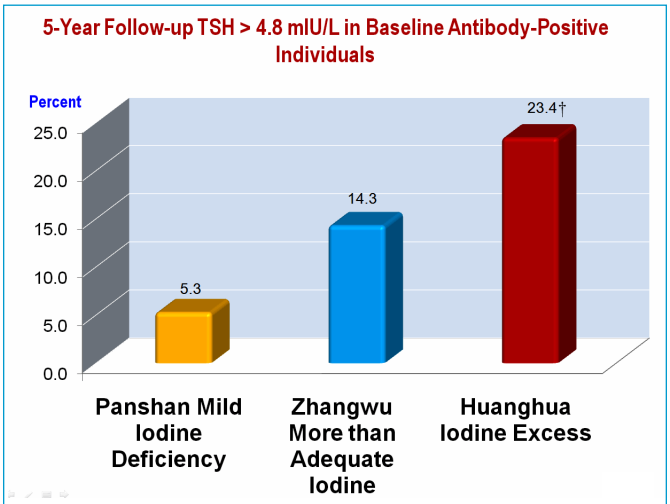

Figure 4. The 5-year incidence of elevated serum TSH levels (> 4.8 mIU/L) was significantly higher in Huanghua compared with Panshan and Zhangwu (†P = 0.001).

incidence of TPOAb-positivity was greater in Zhangwu than in Panshan (P<0.029). The incidence of serum TSH levels >4.8 or <0.3 mIU/L was significantly greater (15%) in antibody-positive than antibody-negative individuals at baseline (3%, P<0.001, Figure 2). The rate of subjects with elevated TSH levels (>4.8 mIU/L) who tested positive for either TPOAb or TgAb was 5.3% in Panshan, 14.3% in Huanghua, and 23.4% in Huanghua (P<0.001; Figure 3). Logistic regression revealed that after 5 years, euthyroid individuals with serum TPOAb concentrations in the high-normal range were at significant risk for high serum TPOAb levels (odds ratio [OR], 4.3; P<0.001) and females with serum TPOAb and TgAb levels in the high-normal range were at increased risk for becoming TgAb-positive (OR, 1.9; P = 0.03).

CONCLUSION Thyroid dysfunction develops more frequently in individuals with high-normal serum TPOAb or TgAb levels as compared with seronegative subjects. High iodine intake increases the risk for TgAb and hypothyroidism.

COMMENTARY

How do the findings of Li et al. inform clinical practice? These results confirm and add to those of the earlier Whickham Survey (1), which also examined the natural history of individuals with baseline thyroid autoimmunity. On the basis of these data, it seems clear that thyroid antibodies, once present, are likely to persist. In addition, a high-normal TPOAb titer at baseline increases the risk for progression to TPOAb positivity. Thyroid autoimmunity, in turn, increases the risk for hypothyroidism; 8% of euthyroid individuals with positive antibodies at baseline had a TSH level >5 mIU/L after 5 years of follow-up, similar to the incidence of about 2% per year noted by the Whickham investigators. It remains to be determined whether TPOAbs are a cause of or simply a marker for autoimmune thyroid dysfunction.

How should the findings of Li et al. affect public health policy? Dietary iodine intake has been quite different in the three regions studied (2, 3). In Panshan, residents have historically consumed locally produced salt with an iodine content of <3.4 mg/kg of body weight, resulting in long-term mild iodine deficiency. Drinking water in the Huanghua region has high iodine content, and therefore residents' iodine intake has been excessive for at least 20 years. Residents of Zhangwu were mildly iodine-deficient until mandatory salt iodization was carried out in 1996; iodine intake there has subsequently become more than adequate. At baseline, Li et al. noted an association between excessive iodine intake and thyroid autoimmunity among older individuals. Over the study's follow-up period, autoimmune thyroid failure was more likely to develop among thyroid antibody–positive individuals with more than adequate or excessive iodine intake than among those with mildly deficient iodine intake.

Iodine deficiency affects over 2.2 billion individuals worldwide (38% of the world's population). Its effects are devastating; iodine deficiency remains the leading cause of preventable mental retardation worldwide (4). Iodine supplementation, typically achieved by salt iodization programs, is essential in many parts of the world for the prevention of iodine deficiency disorders. However, these results underscore the importance of close monitoring both of the salt iodization process and of population median urinary iodine levels, since the overcorrection of iodine deficiency, as has occurred in Zhangwu, may lead to increased thyroid autoimmunity and autoimmune thyroid dysfunction.

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Aggressive thyroid cancers may be missed in patients with multinodular goiter not undergoing periodic follow-up with neck ultrasonography

Winbladh A, Järhult J. Fate of the non-operated, non-toxic goitre in a defined population. Br J Surg 2008;95:338-43.

SUMMARY

BACKGROUND There is no consensus in Europe or the United States regarding the management of benign nodular goiter. This is a study of the long-term results in a group of patients who were advised not to have surgery for clinically and cytologically benign nodular goiter.

METHODS The study patients were 261 of 587 patients (44%) referred in 1985 to 1999 to a Hospital Surgical Department in Esjö, Sweden, for consultation regarding nontoxic goiter, which is not endemic in this area. On the initial evaluation, 522 (89%) of the 587 patients had fine-needle aspiration biopsy (FNAB), but none had a neck ultrasound examination. Surgery was performed in 326 (55.5%) of the 587 patients, in 96 because malignancy could not be excluded on the basis of clinical grounds in 18 (19%) and on the basis of FNAB results in 78 (81%). The remaining 230 (71%) patients had surgery for local symptoms, because of patient preference, or both; 4 of them were found to have thyroid cancer. The remaining 261 comprise the study subjects who underwent a prospective follow-up of watchful waiting during which hospital records were reviewed and the subjects were interviewed by telephone. Of this group, 229 (88%) were women and the median age was 56 (14 to 88) years; 96 (37%) had solitary thyroid nodules and 165 (63%) had multinodular goiter. The median duration of follow-up from the first diagnosis to telephone interview in 199 patients was 130 months (range, 9 to 253). Among the remaining 62 subjects, 3 were lost to follow-up and 59 died. None had a neck ultrasound examination initially or during follow-up.

RESULTS During follow-up, 119 of 261 (46%) subjects were referred to the same hospital on a second occasion, mainly because of goiter enlargement, local symptoms, or recurrence of a thyroid cyst for which 57 (48%) had surgery. The main indications (72%) for surgery were goiter growth or local symptoms or both, and the fear or possibility of malignancy (Figure 1). The most common operation was hemithyroidectomy (54%) (Figure 2) and the most common diagnosis was benign nodular goiter (77%); 12% had follicular adenoma, 5% had thyroid cancer, 3.5% had goiter and occult thyroid cancer, and 2% had Hashimoto's thyroiditis (Figure 3). None had surgically induced recurrent laryngeal nerve injury or hypoparathyroidism. Of the five patients (2%) in whom thyroid cancer developed during follow-up, two were women aged 73 and 80 years with long-standing multinodular goiter in whom anaplastic thyroid

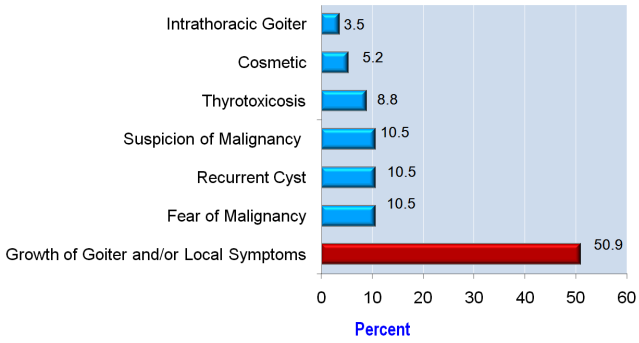

Figure 1. The main indications for surgery after the second referral were goiter growth and the fear or possibility of malignancy, which accounted for 72% of the operations.

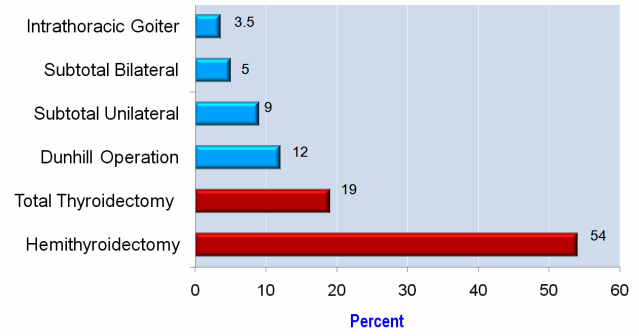

Figure 2. The most common surgical procedure after the second referral was hemithyroidectomy.

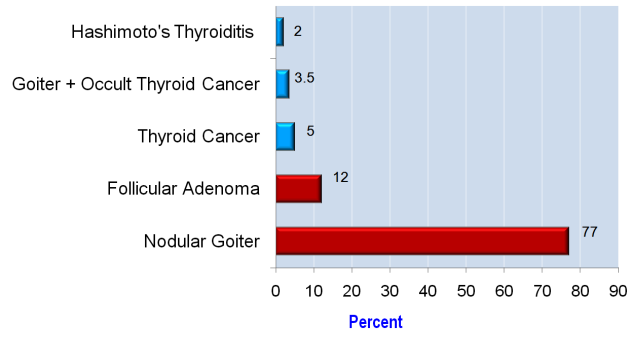

Figure 3. The most common surgical histologic diagnosis was benign nodular goiter; however, 8.5% had thyroid cancer, 5% of which were carcinomas larger than 1 cm. Three patients had serious thyroid cancers, two with anaplastic thyroid cancer and another with papillary thyroid cancer brain metastases. Also 12% of patients had follicular adenomas, a diagnosis that cannot be verified without surgical removal of the tumor in patients with a normal TSH level.

cancer developed 8 months and 12 years, respectively, after inclusion in the study. Another 82-year-old woman had an aggressive papillary thyroid cancer with brain metastases 7 years after a right-sided goiter had been diagnosed as benign. Two other middle-aged women with large nodular goiters were found to have papillary microcarcinoma, one of which was bilateral (8 mm) and the other unilateral (2 mm). Both patients, respectively, were free of tumor 8 and 9 years after surgery.

CONCLUSION There is a small but very important risk of missing aggressive thyroid cancer in patients with multinodular goiter when periodic follow-up with neck ultrasonography is not performed.

COMMENTARY

Surgical management of benign euthyroid multinodular goiter varies considerably in the United States and Europe, mainly because there are no explicit guidelines to assist physicians in the long-term clinical management of this disorder. Still, it is widely acknowledged that the risk of thyroid cancer is about the same in patients with solitary nodules and those with multinodular euthyroid goiters. Winbladh and Järhult report clinical outcomes in a highly selected group of patients. Almost 90% of the patients had undergone FNAB on the initial evaluation and over half had surgery, while the remaining patients became the study group. Neither the initial group nor the follow-up group had undergone neck ultrasound examinations; follow-up in the study group was done by chart reviews and telephone interviews. The approach to watchful waiting was thus dependent on the development of worrisome symptoms or signs of nodule growth or compression. After a follow-up of almost 11 years, aggressive thyroid cancers developed in about 1% of the patients, resulting in death. The authors opine that patients with benign goiter can undergo conservative follow-up of watchful waiting with good results. Still, three patients died of aggressive thyroid cancers following this paradigm. An evidence-based systematic review by Moalem et al. (1) of the prevention and management of multinodular goiter found that the definitive management and prevention of recurrence of benign nodular goiter is primarily surgical, which thus should be the procedure of choice for benign multinodular goiter whenever possible, considering that reoperations for goiter are significantly more morbid than any initial operation. Another evidence-based systematic review of the literature by Phitayakorn et al. (2) concerning the postoperative follow-up of patients who have had surgery for benign nodular thyroid disease found, on the basis of the available data, that patients undergoing thyroid lobectomy for benign nodular thyroid disease should be followed with an annual physical examination, neck ultrasonography, and serum thyrotropin measurements. Lastly, the American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Carcinoma recommended that benign thyroid nodules be followed with serial ultrasound examinations 6 to 18 months after initial FNAB (3). These comments underscore that even with careful analysis of the existing literature, opinions vary. Still, there can be little doubt that patients with multinodular goiters require ultrasound-guided FNAB of all nodules larger than 1 cm and careful follow-up with neck ultrasound examinations and repeat FNAB when a nodule grows more than 50% or develops during follow-up.

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The likelihood of a radiation-induced nodule being malignant depends neither on its size nor on the presence of other thyroid nodules and biopsying only the largest nodule can miss as many as half the thyroid cancers

Mihailescu DV, Schneider AB. Size, number, and distribution of thyroid nodules and the risk of malignancy in radiation-exposed patients who underwent surgery. J Clin Endocrinol Metab 2008;93:2188-93.

SUMMARY

BACKGROUND Guidelines for the management of thyroid nodules suggest that fine-needle aspiration biopsy (FNAB) should be performed on all thyroid nodules >10 mm and on smaller nodules with suspicious ultrasound characteristics, especially in patients exposed to radiation (1). The goal of this retrospective study was to evaluate how nodule size and number influence the risk of malignancy in patients exposed to radiation as children.

METHODS The study subjects were 1059 patients selected from a cohort of 4292 patients who had been exposed to irradiation before the age of 16 years for a number of benign conditions of the head and neck and subsequently had surgery for nodular thyroid disease. Because most of the surgeries (96.1%) were done before 1993, they were performed on the basis of physical examination that disclosed a palpable nodule, an abnormal thyroid on scintigraphy, or both. The size and location of the thyroid nodules were determined from the pathology report, from which the thyroid nodules were classified as benign or malignant. For studying the relationship between malignancy and nodule size, only nodules of known size were included in the study, leaving 1998 nodules, 399 (20%) of which were malignant, in 1059 patients.

For patients with thyroid cancer, the rank order of the largest malignant nodule was determined in comparison with the rest of the patient's nodules, including benign nodules of unknown size that the pathologist indicated were smaller or larger than the patient's largest malignant nodule. This was used to calculate how many cancers would have been missed if the nodule size were the only factor used to determine the need for FNAB. To determine how the number of thyroid nodules influenced the risk of cancer, patients were divided into those with solitary nodules and those with multiple nodules, and the prevalence of thyroid cancer was determined in the two groups.

RESULTS There were 612 malignant nodules in 358 patients (34%) and 2037 benign nodules in 930 (88%). Among 1709 nodules that were ≥0.5 cm, there was no increase in the risk of malignancy with increasing nodule size (odds ratio [OR], 0.91/cm, P = 0.11). Thyroid cancer was found in 149 of 166 micronodules (90%) and in 399 of 1998 macronodules >10 mm (20%). Of 1026 patients with thyroid nodules, 727 (71%) had multiple nodules and 299 (29%) had single nodules (Figure 1). The risk of malignancy in a nodule was similar with solitary (18.8%) and multiple (17.3%) nodules (risk ratio [RR], 1.64 [range, 1.27 to 2.13]). However, the probability of a patient having thyroid cancer was affected by the number of thyroid nodules: thyroid cancer was found in 56 patients (19%) with solitary nodules and 223 patients (31%) with multiple nodules (RR, 1.64; P<0.001 for single vs. multiple nodules, Figure 1), and the risk of thyroid cancer increased as the number (of nodules increased (OR, 1.35 per nodule). The results were about the same if microcarcinomas were also included. When the exact locations of thyroid nodules were known, both lobes were involved in 84 (55%) of the patients. In contrast, multifocality did not increase the

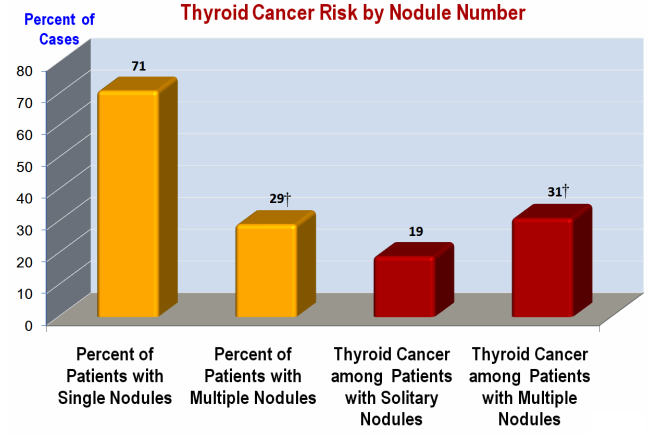

Figure 1. Thyroid cancer risk is greater in patients with multiple thyroid nodules (percent rounded to nearest integer) This and other figures drawn from the data of Mihailescu et al. †P<0.001 by •2 analysis for single vs. multiple nodules.

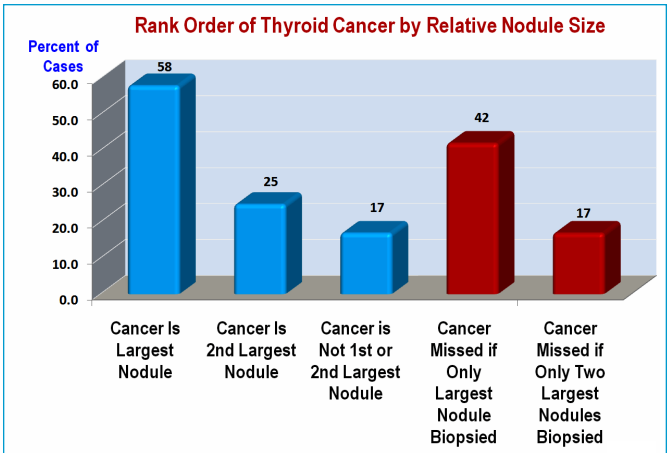

Figure 2. The rank order of thyroid cancer according to relative nodule size is shown. Performing FNAB on only the largest nodule would have resulted in missing almost half (42%) of the cancers, and biopsying only the two largest nodules would have missed 17% of the thyroid cancers.

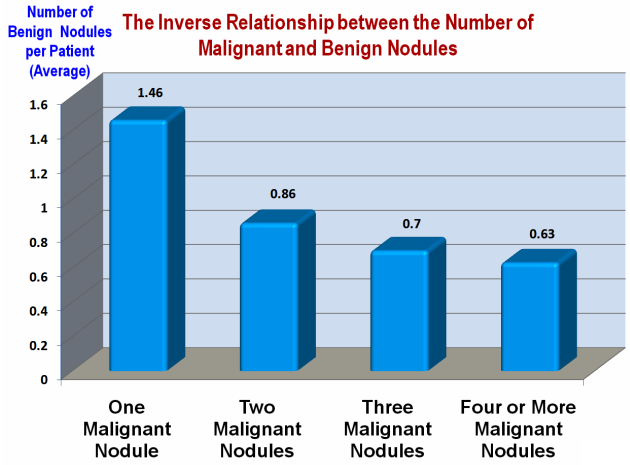

Figure 3. There is an inverse relationship between the number of malignant and benign thyroid nodules.

likelihood of malignancy in a thyroid nodule: malignancy was found in 56 of 299 (19%) solitary nodules and 368 of 2126 (17.3%) multifocal nodules. When the analysis was limited to nodules ≥5 mm, 324 of 1709 nodules (19%) were malignant and there was no relationship between nodule size and the rate of malignancy (P = 0.10). Thyroid cancer was the largest nodule in 153 of 264 (58%) patients, it was the second largest nodule in 66 (25%) patients, and the third largest nodule in 45 (17%) of the patients (Figure 2). Performing FNAB on only the largest nodules would have missed 111 of 264 thyroid cancers (42%), including 25 that were 10 mm or larger. If only the two largest nodules had been biopsied, 45 cases of thyroid cancer (17%) would have been missed, although none were 10 mm or larger (Figure 2). There was an inverse relationship between the number of benign nodules and the number of malignant nodules: as the number of benign nodules per patient decreased from 1.6 to 1.46, 0.86, 0.70, and 0.63, the number of malignant nodules increased from 1, 2, 3, and ≥4 cancer foci per patient, respectively (Figure 3).

CONCLUSION In radiation-exposed patients, the likelihood of malignancy in a thyroid nodule is independent of nodule number and size. Biopsying only the largest nodule would have resulted in missing almost half the cancers, and biopsying only the two largest nodules would have missed 20% of the thyroid cancers.

COMMENTARY

This study has five main points of considerable importance:

1. The likelihood of a radiation-induced nodule being malignant depends neither on its size nor on the presence of other nodules in the thyroid. This is different from the usual finding that the risk of malignancy is generally greater with larger nodules (2). This appears not to be the case in radiation-induced tumors. A study of 2637 atomic-bomb survivors by Imaizumi et al. (3) found that radiation dose, nodule volume, and increase in nodule volume did not predict thyroid cancer, supporting the findings of Mihailescu and Schneider. The ATA guidelines that recommend FNAB for thyroid nodules <10 mm in patients with a history of radiation exposure are in general agreement with these observations.
2. The likelihood of thyroid cancer increases when radiation-exposed patients have more than one thyroid nodule, which is in accord with other recent studies. A study of 2884 patients with 3274 thyroid nodules, on which FNAB was performed, found that the malignancy rate was 39% in patients with single nodules, 41% with two nodules, and 21% with three nodules (4). However, a study of 1985 patients by Frates et al. (5) showed that a solitary nodule had a higher likelihood of malignancy than a non-solitary nodule, but less than 1% of patients in their study had a reported exposure to childhood radiation.
3. Performing FNAB on only the largest or two nodules in patients with multiple nodules would have resulted in a significant rate of false negative FNAB findings, which is in agreement with the findings reported by Frates et al. (5).
4. Over half of the patients with thyroid cancer had multifocal tumors, and in over half of them (55%) had tumor in both thyroid lobes, which is in the range (44%) reported by Pacinia et al. in patients undergoing completion thyroidectomy (6).
5. There is an inverse relationship between the number of malignant and benign nodules, but why this occurs is uncertain.

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Preoperative neck ultrasound accurately identifies most malignant nodules when fine-needle aspiration cytology results are suspicious for malignancy

Kwak JY, Kim EK, Kim MJ, Hong SW, Choi SH, Son EJ, Oh KK, Park CS, Chung WY, Kim KW. The role of ultrasound in thyroid nodules with a cytology reading of "suspicious for papillary thyroid carcinoma." Thyroid 2008;18:517-22.

SUMMARY

BACKGROUND Malignancy is found in up to 80% of fine-needle aspiration biopsy (FNAB) cytology specimens interpreted as suspicious for papillary thyroid cancer. Current guidelines suggest that patients with this finding should undergo surgery; however, it is possible that neck ultrasound might identify the few patients with benign tumors, thus avoiding unnecessary surgery. The aim of this study was to investigate the role of ultrasound in nodules that yield suspicious cytology on FNAB.

METHODS This was a retrospective observational study of 10,497 thyroid nodules on which FNAB was performed from August 2002 to May 2006, during which FNAB cytology results were prospectively collected and maintained in a computerized database. The cytology specimens in 394 of 10,487 thyroid nodules (3.8%) were interpreted as being "suspicious for papillary thyroid cancer." Ultrasound images were performed by three radiologists with extensive thyroid ultrasound experience who were aware of the cytologic diagnosis. The ultrasound interpretations were prospectively entered into a computer database for clinical study. The sonographic features of each thyroid nodule were described, including internal features of the nodule, echogenicity features of the nodule margin, calcifications, and nodule shape. The internal features of the nodule were described as solid, mixed, or cystic. Malignant sonographic features were marked as hypogenicity, microlobulated or irregular margin, microcalcifications, and a nodule that is longer than wider shape. Any one of these findings qualified the nodule as suspicious for malignancy and if the features were absent, the nodule was considered probably benign. After the ultrasound evaluations were completed, the same radiologist performed ultrasound-guided FNAB on the nodules with suspicious ultrasound features, or the largest thyroid nodules without suspicious features when multiple thyroid nodules were present. The cytopathologists were unaware of the ultrasound diagnosis. A cytology diagnosis of suspicious for papillary thyroid cancer was based on nuclear membrane irregularity, nucleolar abnormalities, and abnormal nucleus-to-cytoplasm ratios but did not fulfill the full diagnostic criteria for papillary thyroid carcinoma.

RESULTS The study subjects comprised 303 patients (77%) with cytology findings suspicious of papillary thyroid cancer, of which 208 (94%) were female and 19 (6%) were male, all of whom had lobectomy or thyroidectomy for their suspicious nodule. The 91 remaining patients (24%) either refused surgery or had other reasons for not undergoing surgery. The mean (±SD) nodule size was 11.3±8 mm, of which 47 (15.5%) were benign and 256 (84.5%) were malignant. Of the 51 (16.8%) ultrasound nodules considered to be benign, 38 (74.5%) were histopathologically benign and 13 (25.5%) were malignant (Figure 1). Of 252 (83.2%) suspicious for malignancy, 243 (96.4%) were histopathologically malignant and 9 (3.6%) were benign (Figure 1). The final tumor diagnosis and nodule size are shown in Figure 2. The diagnostic sensitivity of neck

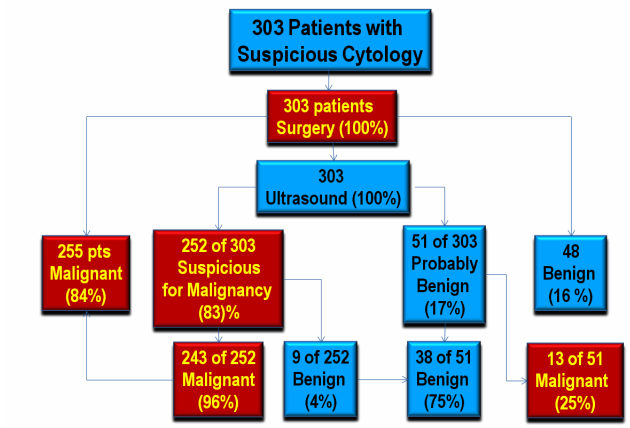

Figure 1. Ultrasound diagnoses and pathology results in 303 patients with suspicious thyroid nodules who underwent surgery. Of 252 (83%) ultrasound findings that were suspicious for malignancy, all but 9 (4%) were correct. Of 51 ultrasound findings that were considered probably benign, 13 (25%) were incorrect. The percentages are rounded to the nearest integer. Data for all the drawings are from the article by Kwak et al.

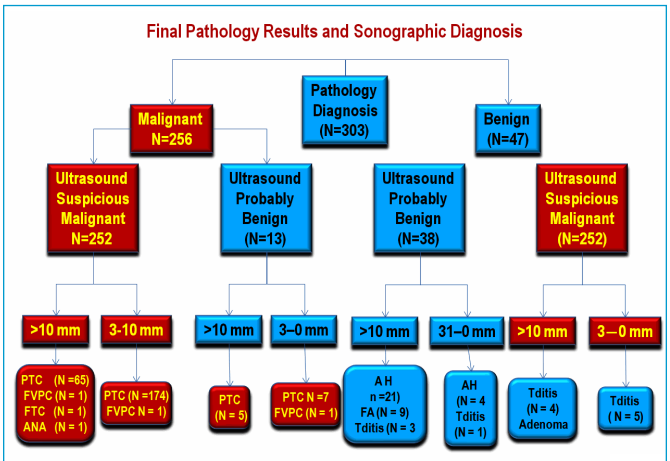

Figure 2. Final pathology results and ultrasound diagnoses. Of the 256 patients with suspicious ultrasound findings of malignancy, 9 had benign histologic findings. AH denotes adenomatous hyperplasia, ANA anaplastic thyroid cancer, FA follicular adenoma, FTC follicular thyroid carcinoma, FVPC follicular variant papillary thyroid cancer, PTC papillary thyroid cancer, and Tditis thyroiditis (Hashimoto's or subacute).

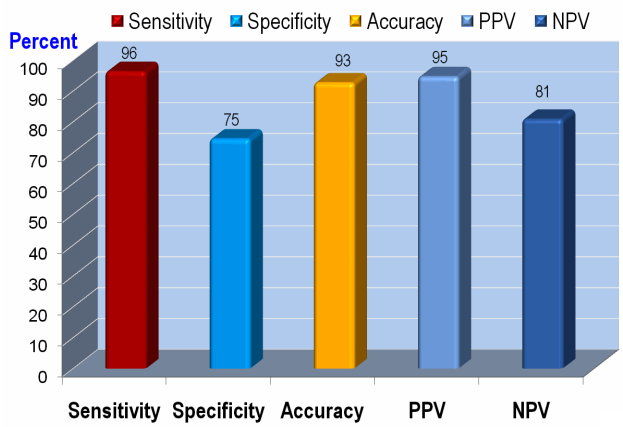

Figure 3. Accuracy of the neck ultrasound interpretation in patients who underwent surgery for cytologically suspicious thyroid nodules. PPV positive predictive value, and NPV negative predictive value.

ultrasound interpretation was 96% and the specificity was 75% (Figure 3).

CONCLUSION A preoperative neck ultrasound examination accurately identifies most malignant nodules in patients with FNAB cytology results that are suspicious for malignancy.

COMMENTARY

A few retrospective studies have reported that approximately 80% of nodules yielding cytology that is suspicious for papillary thyroid carcinoma are found at surgery to be papillary thyroid cancers; however, the studies are relatively small and frequently designate the cytology findings as indeterminate, including specimens from follicular and Hürthle-cell tumors and tumors suspicious for papillary thyroid carcinoma (1, 2). This is a problem because the cytology reports often fail to clearly separate the various types of cytology findings that are suspicious for malignancy and often do not clearly communicate the cytology findings to clinicians in a manner that enables clinicians to translate the findings into a clinically reasonable management plan (3). Moreover, few studies integrate neck ultrasound findings with cytology findings that are suspicious for papillary thyroid cancer.

Kwak et al. report their findings in a large cohort of 303 patients who had surgery for cytology diagnoses that were suspicious for papillary thyroid carcinoma. Of this group, 47 (15.5%) had histologically benign nodules and 256 (84.5%) had malignant nodules. A careful analysis of the ultrasound and cytology findings disclosed a high degree of diagnostic agreement between the two tests. When the ultrasound diagnosis was suspicious for malignancy, only 9 patients were found at surgery to have benign tumors. However, when the ultrasound diagnosis was "probably benign," which was the case in 51 of 303 patients (17%), 13 (25%) had malignant tumors, which in all but two cases were classic papillary thyroid cancer or follicular variant papillary thyroid cancer but in one case each was a follicular variant papillary cancer and anaplastic thyroid cancer. An ultrasound diagnosis suggesting a benign nodule was correct in 38 of 51 cases (75%). Still, the histologic diagnosis in this group was adenomatous hyperplasia in 25 cases, follicular adenoma in 9., and thyroiditis in 4. It is difficult to understand how nodules with adenomatous hyperplasia and follicular adenomas were regarded as ultrasonographically benign. The accuracy of neck ultrasound examinations in this study was high, with a positive predictive value of 95% and a negative predictive value of 81% (Figure 3).

The main caveat concerning this study is that the ultrasound examinations were done by three very experienced radiologists who performed the ultrasound-guided FNAB after the ultrasound diagnosis had been established, which probably played a role in the accuracy of the cytology findings (4). It is likely that an ultrasound examination in the hands of less experienced ultrasonographers would yield considerably less accurate information.

Recommendation 10 of the American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Carcinoma advises the following: If the cytology reading is "suspicious for papillary carcinoma or Hürthle-cell neoplasm," a radionuclide scan is not needed, and either lobectomy or total thyroidectomy is recommended. I believe this will still be the best approach for most clinicians unless they are highly adept at ultrasonography and the patient will accept a small risk of missing the diagnosis of thyroid cancer.

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Patients with little evidence of Graves' ophthalmopathy may have transient small increases in exophthalmometer readings after radioiodine therapy that spontaneously disappear within 1 year

Sisson JC, Schipper MJ, Nelson CC, Freitas JE, Frueh BR. Radioiodine therapy and Graves' ophthalmopathy. J Nucl Med 2008;49:923-30.

SUMMARY

BACKGROUND The available randomized, controlled trials on the effects of radioiodine (^{131}I) therapy on Graves' ophthalmopathy (GO), which have been done mainly in Europe, show that about 15% of patients have new eye disease or progression of preexisting GO within 6 months after the administration of radioiodine. This prospective, observational study of unselected patients with Graves' disease assesses the manifestations of GO in a group of American patients treated with ^{131}I in the nuclear medicine department.

METHODS The study subjects were 76 patients with Graves' disease, ranging in age from 10.6 to 72 years, of whom 61 (85%) were female. Entry criteria were a serum thyrotropin (TSH) <0.01 mIU/L and elevated concentrations of free triiodothyronine (FT_3) and free thyroxine in patients who met the following criteria: diffusely enlarged thyroid without palpable nodularity and an increased thyroidal uptake of radioiodine. Measurement of thyroid-stimulating immunoglobulin (TSI) was not a criterion for entry into the study. Exclusion criteria were previous surgical therapy for GO and recent treatment with corticosteroids in some but not all patients. No patients manifested clinical evidence of GO, based on the fact that none had been referred to specialists for management of this feature of Graves' disease. From a total of 611 patients treated with ^{131}I for hyperthyroidism, 127 (21%) were enrolled in the study, 51 (40%) of whom failed to complete the study, resulting in a total of 76 study patients. Some had been treated with methimazole or propylthiouracil that was discontinued at least 3 days before ^{131}I therapy. Patients were treated with 0.2 mCi (7.4 MBq) per millimeter estimated volume of the thyroid, determined by palpation, and the percent thyroidal uptake of a tracer amount of ^{131}I. Follow-up evaluations were performed at 2, 6, and 12 to 14 months after therapy (designated as 1 year), at which time thyroid-function tests, TSH measurements, and data from ophthalmologists and ophthalmic technicians were obtained to fulfill the 10 items of the clinical activity score (CAS). Additional information was collected about smoking, the use of antithyroid drugs before treatment, and in some cases TSI and the duration of thyrotoxicosis or hypothyroidism. Also, a quality-of-life (QOL) assessment was made after study patients were treated with ^{131}I.

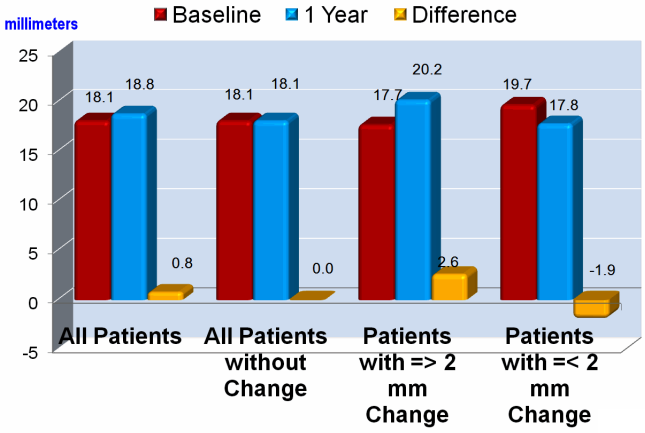

Figure 1. Mean exophthalmometer readings, which are shown for the right eye, may increase 2 mm or more but the changes are not statistically significant and spontaneously return to normal 1 year after ^{131}I therapy. Data for the left eye are essentially the same.

RESULTS Assessed according to the combined CAS scores among patients, eye pain, redness, and swelling showed a net decrease at 2 and 6 months and at 1 year, but during this time there was a small net increase in exophthalmometer readings (Figure 1). Compared with the baseline measurements, 30 patients (39%) had increases of 2 mm or more in exophthalmometer readings at 1 year. For the combined CAS items, the total number of points attributed to all 76 patients increased from 48 at 2 months to 63 at 1 year, which was related to the greater number of patients with exophthalmometer readings that increased by 2 mm or more at 1 year (Figure 1). The large number of patients with a CAS score of 2 points or more was attributed to the appearance of new proptosis. Still, the mean CAS points for all patients did not change significantly ($P = 0.17$). In all, there were 16 patients (21%) with minimal exophthalmos at baseline; minimal changes developed after treatment in 8 others (10.5%). Compared with the baseline measurements, exophthalmometer readings increased by 2 mm or more in either eye in 18 (24%) and 16 (21%) patients at 2 and 6 mo, respectively, and in 30 (39%) at 1 year but the trend between 2 mo and 1 year was not statistically significant. On the other hand, 10 (13%) exhibited a decrease of 2 mm or more in exophthalmometer readings, the largest of which was 6 mm. After 1 year, the exophthalmometer readings increased by 2 mm or more in 30 (39%), decreased by 2

mm or more in 10 (13%) and remained stable in 36 (47%). Of the 15 patients with diplopia at baseline, 10 (66%) did not exhibit it at 1 year. A CAS that increased 2 or more points at 1 year was associated with hyperthyroidism that lasted at least 6 months (P = 0.04). The QOL questionnaire that was completed by all but one patient showed no statistically significant changes.

CONCLUSION After ^{131}I therapy for Graves' disease, patients with little or no evidence of baseline ophthalmopathy may have a transient increase in exophthalmometer readings of 2 mm or more 2 to 6 months after treatment, which spontaneously disappears within 1 year of follow-up.

COMMENTARY

The few randomized, prospective studies examining the potential impact of radioiodine therapy (RAI) on GO showed that approximately 15% of European patients have new eye disease or experience progression related to the treatment within 6 months. However, the progression is mild and persists at 1 year in only 5%. The risk is highest in patients with active GO and is almost eliminated by giving a short course of oral glucocorticoids and avoiding posttreatment hypothyroidism (1).

The topic was reexamined in this prospective, observational study of an unselected U.S. population with Graves' disease treated with ^{131}I. Progression of GO was assessed using a 10-component CAS, which includes pain on or behind the globe, pain with eye motion, eyelid redness, diffuse conjunctival redness, change in proptosis measurements, and five other clinical signs and symptoms (2). The number of patients manifesting a change (appearance or disappearance) in each CAS component was counted at 2, 6, and 12 months following ^{131}I and the "net change" (appearances minus disappearances) in each item tabulated. This is an unusual use of the CAS, which was developed to aid in the treatment of individual patients with GO. Several studies have validated this clinical tool and shown that a patient having a constellation of ≥3 of 7 or 4 of 10 of these components has active disease and a high likelihood of benefiting from immunosuppressive treatment. To separate these clustered clinical signs and symptoms from the patients and consider them as unique disease measures, as was done in this study, runs counter to the sage clinical advice to "treat the patient, not the symptoms" and doesn't allow assessment of the true impact of the treatment on the patients.

It is difficult to ascertain exactly how many of the patients had evidence of GO at baseline, and whether their disease was active. That said, Table 2 of the article does indicate that only 10 of 76 patients exhibited ≥2 of 10 CAS components at 2 months. This suggests that few, if any, of the patients in the study had active GO at baseline, and that likely most lacked any clinical evidence of GO. The study population was therefore at very low risk for ocular deterioration following RAI, making the overall stability in CAS items predictable. The finding that 39% of patients experienced a modest increase in exophthalmometer readings at 1 year is difficult to understand, especially when no other feature of the disease deteriorated and no control group is provided. This result may be attributable to the known lack of reproducibility in exophthalmometer readings, especially when three different ophthalmologists are involved. That yet another 13% of patients experienced modest improvement in these readings supports this contention.

The authors conclude that the observed changes do not warrant prophylactic treatment of patients with steroids. While this is true on the face of it, they fail to point out that they studied an unselected population of patients undergoing ^{131}I therapy, the majority of whom either had no clinical evidence of GO or only mild, inactive GO. I would put forward that each patient undergoing ^{131}I therapy should be individually assessed as to the presence of clinical signs and symptoms of GO and risk factors for progression, such as smoking, high FT_3 values and recent ocular deterioration. If they are found to have active GO or are at high risk, corticosteroid prophylaxis should be considered. While this will not apply to the majority of patients undergoing RAI, it will be important in the select few to prevent deterioration of their eye disease.

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Nearly half the relapses of Graves' hyperthyroidism after antithyroid drug withdrawal are transient and require no further therapy

Kubota S, Takata K, Arishima T, Ohye H, Nishihara E, Kudo T, Ito M, Fukata S, Amino N, Miyauchi A. The prevalence of transient thyrotoxicosis after antithyroid drug therapy in patients with Graves' disease. Thyroid 2008;18:63-6.

SUMMARY

BACKGROUND Transient thyrotoxicosis sometimes occurs in patients with Graves' disease after withdrawal of antithyroid drugs, but the prevalence of this phenomenon is unknown. However, when it occurs, patients may receive unnecessary therapy. This study investigates the prevalence of transient thyrotoxicosis in patients with Graves' disease after the withdrawal of antithyroid drugs.

METHODS Study subjects were 110 patients with Graves' disease whose antithyroid drug therapy was stopped after their thyrotoxicosis went into remission. Of the study subjects, 94 (85%) were female, and the mean (±SD) age was 38.15±12.28 years. Patients were treated with antithyroid drugs for an average of 42.80±29.47 months. Initially, 93 (85%) were treated daily with 15 to 30 mg of methimazole (MIMI) and the others were treated with 300 mg of propylthiouracil (PTU). Antithyroid drugs were discontinued when the following were observed: small goiter, low levels (<30%) of thyroid-binding immunoglobulin inhibitor (TBII) and a serum thyrotropin (TSH) of 0.3 to 5.0 mIU/L and serum free thyroxine (FT_4) of 0.7 to 1.6 ng/dl for more than 6 months with the lowest doses of antithyroid drugs (2.5 mg/day of MMI or 25 mg/day of PTU). Thereafter, thyroid-function tests were performed at 3, 6, and 12 months, after which patients were advised to have their thyroid function examined every 6 months. Abnormal tests were repeated at monthly intervals. Patients with mild thyrotoxicosis (serum FT_4, <3.0 ng/dl) underwent follow-up for an additional month without therapy unless they had serious symptoms or complications of thyrotoxicosis. Patients were regarded as having a permanent recurrence of Graves' hyperthyroidism if their serum FT_4 level increased after 1 month or unbearable symptoms developed, or if their FT_4 levels transiently decreased after 1 month then increased to >3.0 ng/dl. Patients were regarded as having transient thyrotoxicosis when, after antithyroid drug withdrawal, they exhibited either overt thyrotoxicosis (TSH, <0.3 mIU/L; FT_4, >1.6 ng/dl) or subclinical thyrotoxicosis (TSH, <0.3 mIU/L; FT_4, 0.7 to 1.6 ng/dl) that spontaneously improved and they became euthyroid without antithyroid drugs. Permanent remission of Graves' disease was defined as euthyroidism for more than 1 year without antithyroid drugs or after transient thyrotoxicosis without antithyroid drugs.

RESULTS Of 110 study patients, 68 (62%) had a remission, 27 (24.5%) had a relapse, and 12 (11%) dropped out of the study. The status was indeterminate in 2 patients (2%) and 1 patient (1.0%) was excluded because of pregnancy. In all, 28 of 68 patients (41%) had transient thyrotoxicosis and 40 (59%) achieved remission without thyrotoxicosis (Figure 1). Twenty-eight patients became euthyroid after transient thyrotoxicosis, and 8 of 28 patients showed overt thyrotoxicosis while the rest had subclinical thyrotoxicosis. The observation period in the remission group ranged from 12 to >36 months (Figure 2.). Eight of the 28 patients (29%) with transient thyrotoxicosis first had a period of overt thyrotoxicosis and 71% had subclinical thyrotoxicosis.

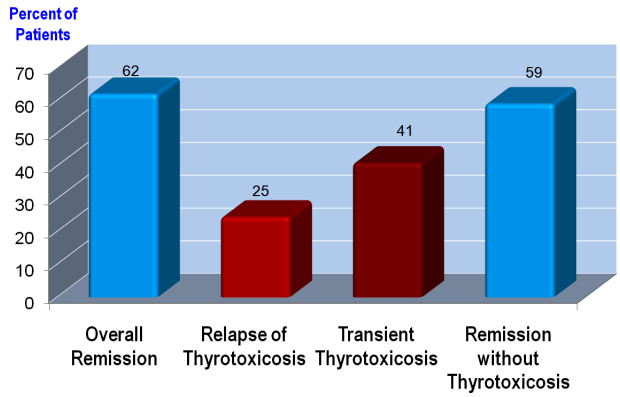

Figure 1. The overall remission rate was 62% after the withdrawal of antithyroid drugs. Overt thyrotoxicosis relapsed in 25% and transient thyrotoxicosis occurred in 41%, while 59% had remission without transient thyrotoxicosis. This and other figures are drawn from the data of Kubota et al.

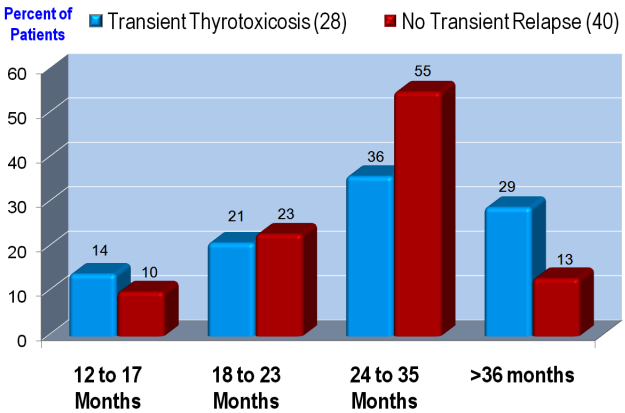

Figure 2. Follow-up period of patients who achieved remission with and without transient thyrotoxicosis.

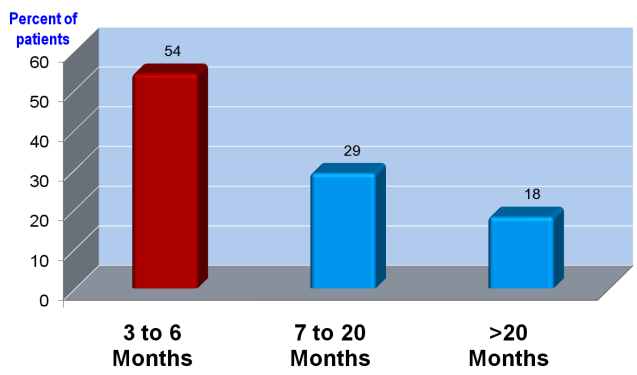

Figure 3. Time from withdrawal of antithyroid drugs (ATDs) to the development of transient thyrotoxicosis.

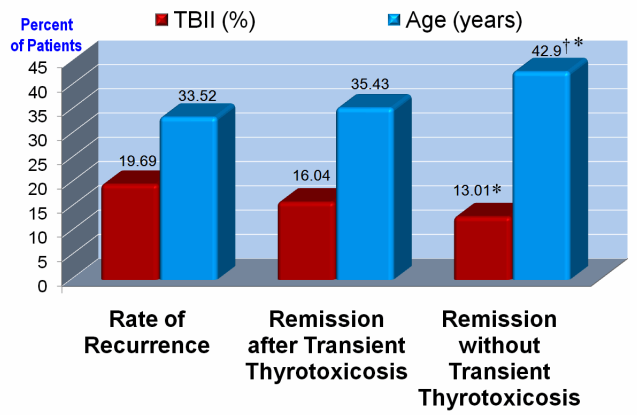

Figure 4. Remission of thyrotoxicosis after antithyroid drug withdrawal was significantly more likely in patients aged 42.9±13.98 years (*P<0.05) and was significantly less likely to be associated with transient thyrotoxicosis (†P<0.01). The mean level of thyroid-binding immunoglobulin inhibitor (TBII) was lower in the remission group without transient thyrotoxicosis than that in the recurrence group (*P<0.05); however, the difference was not significant between the remission group and the transiently thyrotoxic group.

Measured in 16 patients, TBII was positive when transient thyrotoxicosis developed. Transient thyrotoxicosis occurred 3 to 6 months after antithyroid drug withdrawal in 15 of 28 (54%) patients, and its duration was 7.02±8.02 months (Figure 3). The patients in whom transient thyrotoxicosis did not develop were significantly older than those in whom it did develop, and TBII was significantly lower in the group without transient thyrotoxicosis as compared with the group with transient recurrence (Figure 4).

CONCLUSION After antithyroid drug withdrawal, nearly half the relapses of Graves' disease hyperthyroidism are transient and require no further therapy. The majority of transient relapses occurs 3 to 6 months after the withdrawal of antithyroid drugs and persists for an average of 7 months but can last longer.

COMMENTARY

The relapse rate of hyperthyroidism following the withdrawal of antithyroid drugs in patients with Graves' disease is generally about 30% to 50% but is even higher in some studies, depending on the patient population (1–3). Still, no laboratory tests or clinical features, including longer duration of antithyroid drug therapy or addition of levothyroxine to the drug regimen accurately predict permanent remission of hyperthyroidism (1–3). As a result, most authorities simply suggest withdrawing the drug after 12 to 18 months of therapy. In the Kubota study, the relapse rate was approximately 40% even after carefully selecting patients for drug withdrawal. The surprising aspect of the study was that 41% of the 68 patients who initially appeared to be in remission had a transient relapse of thyrotoxicosis that peaked 3 to 6 months after withdrawal, although in a few cases it appeared as late as 20 to 30 months after the drug was withdrawn. Eight of the 28 (29%) patients with transient thyrotoxicosis first had a period of overt thyrotoxicosis and 71% had subclinical thyrotoxicosis. On average, it persisted for 7 months but lasted even longer in a few individuals. The main concern is that the transient nature of the thyrotoxicosis will be missed and thus unnecessarily treated. This is highly probable because neither clinical features nor laboratory tests reliably identify the recurrence as transient in nature. The only tangible clue is that it occurs more commonly in younger patients with Graves' disease.

The authors propose that patients with serum FT_4 levels <3.0 ng/dl after the withdrawal of antithyroid drugs undergo clinical follow-up for 1 month without medication unless they have serious symptoms or complications of thyrotoxicosis. On the other hand, if the serum FT_4 levels begin to decline, they suggest that it is quite likely that the thyrotoxicosis will be transient and self-limited. This paradigm seems especially applicable to patients younger than 50 years, but is not likely to be of much help in older patients, in whom complications might develop even with transient subclinical thyrotoxicosis, especially if it persists for many months. Patients who were in remission after transient thyrotoxicosis remained so during long-term follow-up lasting from 1 to 3 years.

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Recurrence rates for papillary microcarcinoma are higher in older patients without thyroid autoimmunity and with invasive or metastatic disease or tumors larger than 5 mm

Noguchi S, Yamashita H, Uchino S, Watanabe S. Papillary microcarcinoma. World J Surg 2008;32-747-53.

SUMMARY

BACKGROUND Although papillary thyroid microcarcinomas, tumors 1 cm or smaller, comprise almost half of the thyroid cancers diagnosed in the United States and Europe, there is debate regarding their management. The aim of this large retrospective study was to better understand the management of these small tumors.

METHODS The study subjects were 2070 patients with papillary microcarcinoma among 4840 patients (43%) with papillary thyroid cancer who were treated with total or near-total thyroidectomy in the authors' clinic. The median age of the patients at the time of surgery was 47 years (range, 11 to 83), and the male-to-female ratio was 1:8.9. Of the study group, 188 (9%) had Hashimoto's thyroiditis and 824 (40%) had Graves' disease. The tumor was 1 to 5 mm in 60% of the patients and 6 to 10 mm in 40%. The median follow-up time was 15.1 years and was as long as 35 years in some patients.

RESULTS In all, 255 of 2070 (12%) patients underwent central compartment node dissection, and about half of them were found to have 1 to 14 malignant lymph nodes. In all, 73 patients (3.5%) experienced a recurrence after a median of 10.3 years, (mean [±SD], 10.8±6.51) but the 30-year recurrence rate was 40% in patients older than 55 years. Cox proportional-hazards analysis found that four variables significantly predicted recurrence: (1) absence of autoimmune thyroid disease, (2) gross lymph-node metastases, (3) tumor size >5 to 10 mm, and (4) esophageal tumor invasion (Figure 1). Recurrence rates at 35 years of follow-up were 3% and 14% for tumors 1 to 5 mm and 6 to 10 mm, respectively (P<0.001); the rates were 2% and 13% for patients with and without autoimmune thyroid disease (P<0.001); 20% and 5%, for patients with and without gross lymph-node metastases (P<0.001); and 40% and 6%, for patients with and without esophageal tumor invasion (P<0.001). The number of grossly enlarged lymph nodes was inversely related to recurrence-free survival. The 30-year recurrence rates were less than 10% and 40%, respectively, for patients who were younger than 55 years and 55 years and older. However, this was not statistically significant by Cox analysis.

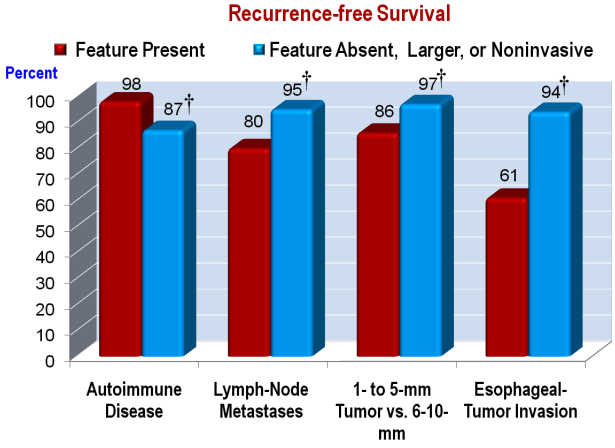

Figure 1. Recurrence-free survival is shown with the variables found to be statistically significant. †P<0.01. *P<0.05. This figure and figure 2 are drawn from the data of Noguchi et al.

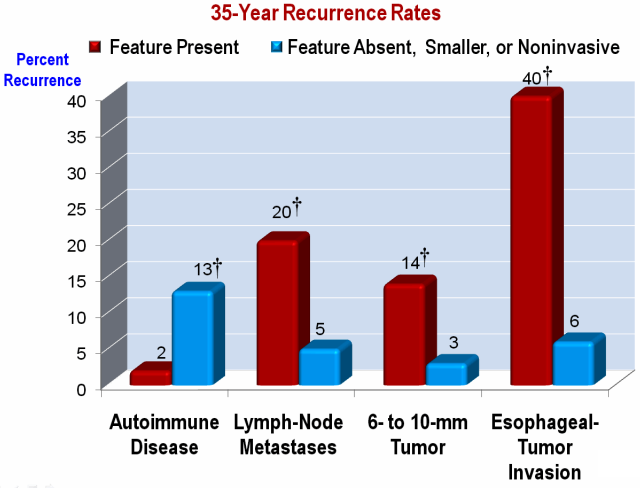

Figure 2. The 35-year recurrence rates were significantly lower in patients with than without autoimmune disease †P<0.01, and were higher with lymph-node metastases †P<0.01, and with 6- to 10-mm tumors †P<0.01, compared with tumors < 6 mm and, with esophageal tumor invasion †P<0.01.

CONCLUSION Papillary microcarcinomas larger than 5 mm that are invasive and metastatic have a high recurrence rate, especially among patients without thyroid autoimmune disease.

COMMENTARY

This is the largest study ever published on papillary microcarcinoma and to describe the course of the disease over a 35-year period. Overall, the recurrence rate was only 3.4%, within the range found in smaller studies (1, 2), However, the cumulative 35-year recurrence rates ranged from 2% to 40%, depending on patient and tumor characteristics. Among the recurrences, 91% were in the thyroid bed, cervical lymph nodes, or both, and the others were in the lung (5%), bone (5%), mediastinum (1%) and elsewhere (1%). Only 12 patients (0.6%) died of thyroid cancer, although a few had multiple recurrences.

Most studies find that age is an important risk factor for thyroid cancer recurrence but in this study it was not found to be significant in the Cox analysis. The authors opine that the reason for this is that patients 55 years of age or older at the time of surgery would have been 81 years or older after 25 years of follow-up. This does not detract from the reported findings, since there is little question that age is important in predicting outcome.

The study found that lymph-node metastases and deep tumor invasion into the esophagus or recurrent laryngeal nerve seriously affected prognosis, suggesting that subgroups of patients with metastatic or invasive disease require extended follow-up. On the other hand, patients with Hashimoto's disease had a 35-year recurrence-free survival that was better than usual, suggesting that this group requires less intense follow-up.

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Faculty of the American Thyroid Association Frontiers in Thyroid Cancer conference held in Boston July 11–12. Nearly 300 physicians from around the world attended this 2 day conference.

Thyroid cancer recurrence rates are similar when thyroid remnant ablation is performed after thyroid hormone withdrawal or recombinant human TSH stimulation

Tuttle RM, Brokhin M, Omry G, Martorella AJ, Larson SM, Grewal RK, Fleisher M, Robbins RJ. Recombinant human TSH-assisted radioactive iodine remnant ablation achieves short-term clinical recurrence rates similar to those of traditional thyroid hormone withdrawal. J Nucl Med 2008;49:764-70.

SUMMARY

BACKGROUND Recombinant human TSH (rhTSH) has been approved both in the United States and in Europe for preparing patients for thyroid radioiodine (^{131}I) remnant ablation after it was shown to be comparable to thyroid hormone withdrawal (THW) as judged by the results of posttherapy diagnostic whole-body ^{131}I scans and by a decrease in serum thyroglobulin (Tg) levels. However, there are no published studies of the efficacy of rhTSH for thyroid remnant ablation using tumor recurrence rates as a therapeutic end point. This retrospective study compares tumor recurrence in patients prepared for thyroid remnant ablation with either rhTSH or THW.

METHODS Study subjects comprised 394 consecutive patients with differentiated thyroid carcinoma who had been treated between 1997 and 2005 with total or near-total thyroidectomy and ^{131}I remnant ablation using either rhTSH or THW according to the choice of the patient and treating physician. To increase the endogenous thyrotropin (TSH) level to at least 25 mIU/L in 6 weeks, patients in group 1 (THW) were given liothyronine (T_3) for 4 weeks as a substitute for levothyroxine, which was discontinued in the last 2 weeks during which patients ingested a low-iodine diet. Patients in group 2 (rhTSH) continued to take levothyroxine and were prepared with a low-iodine diet followed by a 0.9-mg intramuscular rhTSH injection on two consecutive days. After preparation, both groups had diagnostic whole-body ^{131}I scans using 74 to 148 MBq (2 to 4 mCi). For remnant ablation, most patients received 2775 to 3700 MBq (75 to 100 mCi) of ^{131}I for intrathyroidal papillary thyroid cancers, 3700 to 5550 MBq (100 to 150 mCi) if cervical lymph nodes were involved with tumor, and more than 5500 MBq (150 mCi) if tumor was locally aggressive or metastatic to distant sites. Thereafter, patients were treated with sufficient levothyroxine to keep the TSH level at 0.1 to 0.4 mIU/L. At the 6-month follow-up, patients were examined and TSH, free thyroxine, and serum Tg levels were measured during TSH suppression. At the 12- to 18-month evaluation, the same tests were obtained in addition to an rhTSH-stimulated 185 MBq (5 mCi) diagnostic whole-body ^{131}I scan and neck ultrasonography and ^{18}fluorodeoxyglucose–positron-emission tomography (FDG-PET) scan as necessary.

For comparison purposes, treatment outcomes were categorized as no clinical evidence of disease based on a negative rhTSH-diagnostic whole-body ^{123}I scan and TSH-suppressed serum Tg levels <1 ng/ml and rhTSH-stimulated Tg levels <2 ng/ml.

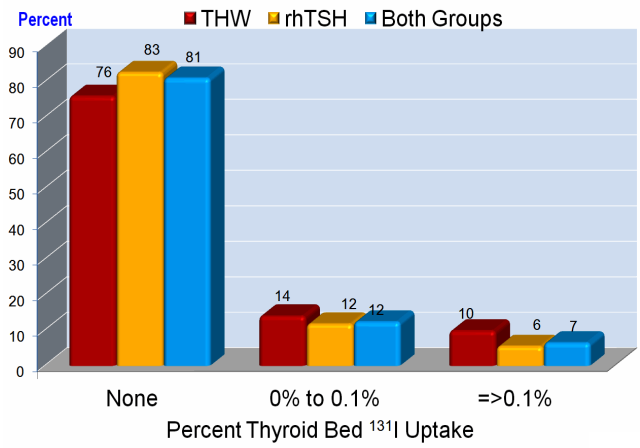

Figure 1. There is no significant difference in posttherapy thyroid bed ^{131}I uptake in patients prepared with rhTSH as compared with THW (P = 0.35,). Figures in all graphs are drawn from the data of Tuttle et al.

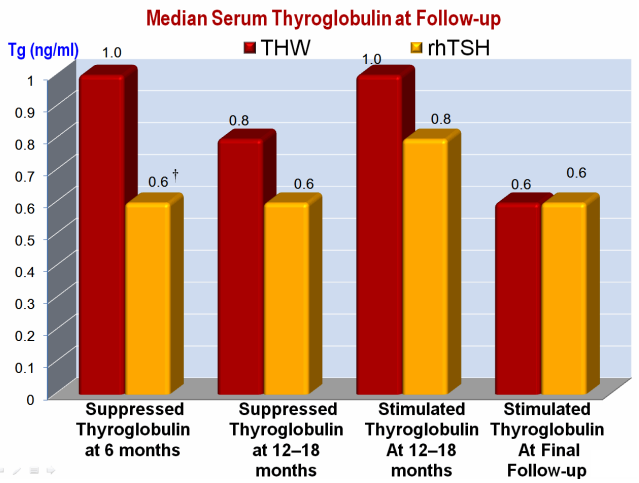

Figure 2. Serum Tg levels at the 6-month follow-up period were significantly lower in the rhTSH than in the THW group (median, 1.0 vs. 0.6 ng/ml; P<0.003) but were not significantly different thereafter.

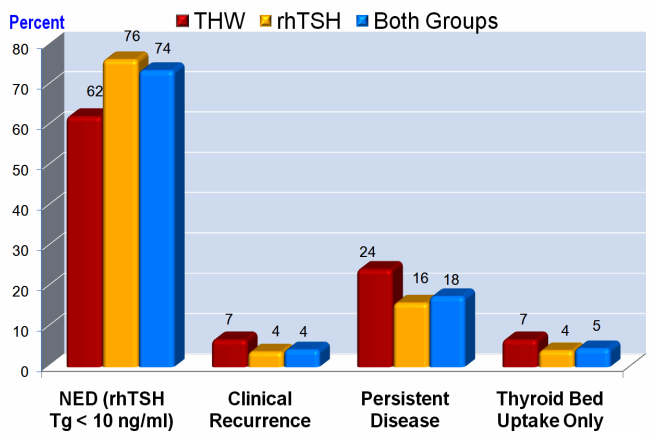

Figure 3. In the first analysis of outcomes using Tg cutoffs of <2 ng/ml during TSH suppression and <10 ng/ml after rhTSH stimulation, the rhTSH group was slightly more likely than the THW group to have no evidence of disease (76% vs. 62%, P = 0.1) and was less likely to have persistent disease (16% vs. 24%, P = 0.1)

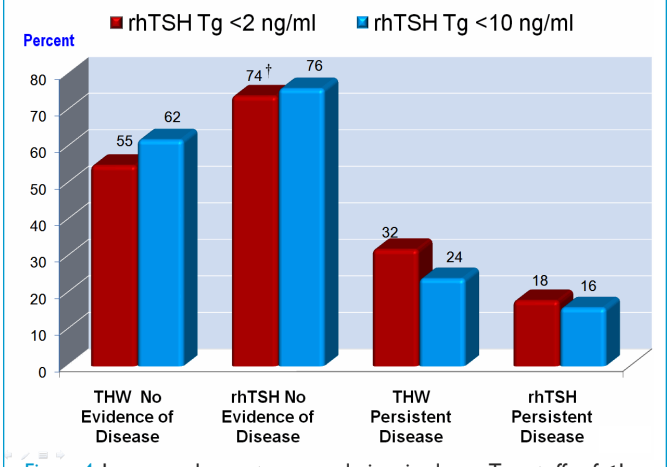

Figure 4. In a secondary outcome analysis using lower Tg cutoffs of <1 ng/ml during TSH suppression and <2 ng/ml after rhTSH stimulation, fewer patients were classified as having no clinical evidence of disease (55% vs. 62% of the THW group, and 74% vs. 76% of the rhTSH group), and more were classified as having persistent disease (32% vs. 24% of the THW group, and 18% vs. 16% of the rhTSH group). Patients in the rhTSH group were significantly more likely than those in the THW group to have no evidence of disease (74% vs. 55% †P = 0.02) and were less likely to have persistent disease (19% vs. 32%)

RESULTS Of the 394 study subjects, 74 (19%) were in the THW group and 320 (81%) were in the rhTSH group. Median patient age was higher in the rhTSH group (46.5 years; range, 18 to 83) than in the THW group (44.0; range, 6 to 81) (P = 0.03). There were no important differences in the two groups between gender, cancer histology, tumor size, lymph-node involvement and frequency of distant metastases or the overall American Joint Committee on Cancer 6th edition (AJCC) stage of disease. Slightly more ^{131}I was given to the rhTSH than to the THW group for remnant ablation (median, 4033 vs. 3811 MBq [109 vs. 103 vs mCi]; P = 0.01. Mean (±SD) follow-up time was significantly longer for the THW group than for the rhTSH group (47±24 vs. 31±15 months, P<0.001) but the time to recurrence was similar in both groups (19.6±15.8 vs. 18.5±8.9 months, P = 0.86). However, nearly all the recurrences were detected within the first 40 months. There was no significant difference in posttherapy thyroid bed ^{131}I uptake in the two groups (P = 0.35, Figure 1). Serum Tg levels at the 6-month follow-up period were significantly lower in the rhTSH than in the THW group (median, 1.0 vs. 0.6 ng/ml; P<0.003) but were not significantly different thereafter (Figure 2).

Clinical outcomes were assessed a median of 29 months after thyroid remnant ablation. A total of 17 patients had clinical evidence of tumor recurrence, 5 of 74 (6.8%) in the THW group and 12 of 320 (3.8%) in the rhTSH group. There were no significant differences in patient age at the time of initial treatment, gender, the amount of ^{131}I given for treatment, tumor multifocality, AJCC stage, and primary tumor histology. Cervical lymph nodes, which were the most common site of recurrence in both the THW group (4 of 5; 80%) and the rhTSH group (10 of 12; 83%), and new lung metastases were found in 1 of 5 (20%) patients in the THW group and 1 of 12 (8.3%) in the rhTSH group.

In the first analysis of outcomes using Tg cutoffs of <2 ng/ml during TSH suppression and <10 ng/ml after rhTSH stimulation, the rhTSH group was slightly more likely than the THW group to have no evidence of disease (76% vs. 62%, P = 0.1) and was less likely to have persistent disease (16% vs. 24%, P = 0.1; Figure 3)

In a secondary outcome analysis using lower Tg cutoffs of <1 ng/ml during TSH suppression and <2 ng/ml after rhTSH stimulation, fewer patients were classified as having no clinical evidence of disease (55% vs. 62% of the THW group, and 74% vs. 76% of the rhTSH group), and more were classified as having persistent disease (32% vs. 24% of the THW group, and 18% vs. 16% of the rhTSH group). Patients in the rhTSH group were significantly more likely than those in the THW group to have no evidence of disease (74% vs. 55% P = 0.02) and were less likely to have persistent disease (19% vs. 32%, P = 0.02; Figure 4).

CONCLUSION Thyroid cancer recurrence rates are similar in patients prepared by thyroid hormone withdrawal or recombinant human TSH stimulation for thyroid remnant ablation.

COMMENTARY

After recombinant human TSH-α was approved by the Food and Drug Administration (FDA) for clinical diagnostic use, it gradually became widely used by physicians to evaluate low-risk patients for persistent or recurrent disease. The drug was approved for thyroid remnant ablation in 2005 by the European Medicines Agency and in 2008 by the FDA after it was shown by a large prospective, randomized, multicenter international clinical trial (1) to be comparable to THW for this indication. The study, which was performed using 3700 MBq (100 mCi), found that euthyroid patients prepared for remnant ablation with rhTSH received 33% less total-body radiation as compared with hypothyroid patients (1). Moreover, Pilli et al. (2) recently found that successful ablation (no visible uptake in the diagnostic whole-body scan after rhTSH stimulation) could be achieved in almost 90% of the patients treated with 1850 MBq (50 mCi) and 3700 MBq (100 mCi), thus further reducing total body radiation in low-risk patients. A comparison of the ^{131}I kinetics in euthyroid and hypothyroid patients by Luster et al. (3) shows major differences in the radiation doses to the thyroid remnant and in residence times and radiation exposure to the blood that accounts for this difference in total-body radiation between rhTSH and THW. It also accounts for the shorter length of hospitalization that has been reported (4) and the reduced length and cost of sick leave by over a week (5) in patients treated with ^{131}I after rhTSH preparation. Short-term hypothyroidism after levothyroxine withdrawal is associated with a significant decline in quality of life that is abrogated by rhTSH (6).

Still, the efficacy of rhTSH for remnant ablation has been judged solely on the basis of posttherapy diagnostic whole-body ^{131}I scans and declining serum Tg levels. These are surrogate tumor markers that leave some concern among clinicians about the efficacy of rhTSH-stimulated remnant ablation to destroy small tumors that are inapparent prior to ^{131}I treatment.

This retrospective study by Tuttle et al. provides good evidence that rhTSH-assisted remnant ablation in everyday practice is comparable in efficacy with that of THW and that clinical recurrence rates are similar with the two modes of preparation. Like most retrospective studies, there is a possibility of selection bias, and the short period of follow-up may minimize the long-term outcome. Nonetheless, the study demonstrates that rhTSH-assisted remnant ablation is associated with rates of clinically evident recurrent tumor and persistent disease that are similar to those that occur with THW.

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Erratum

Issue volume 20, Issue 1, page 2: Commentary, tumor recurs in about 20% not 80% as stated; and page 3: Methods: TgAb (not TSH) was measured by two different methods.

Disclosure

Dr. Mazzaferri receives honoraria from Genzyme for providing lectures.

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