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EDITORS' COMMENTS

This is the third 2010 issue of *Clinical Thyroidology*.

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

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

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

WHATS NEW On the last page of the journal, in addition to the section HOT ARTICLES AND REVIEWS, we have added CURRENT GUIDELINES that have relevance to thyroidologists, endocrinologists, surgeons, oncologists, students, and others who read this journal. We hope you will find this useful.

We welcome your feedback and suggestions.

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

Back to Contents

Lymph-node metastases at the time of initial surgery predict recurrent lymph-node metastases

Baek SK, Jung KY, Kang SM, Kwon SY, Woo JS, Cho SH, Chung EJ. Clinical risk factors associated with cervical lymph node recurrence in papillary thyroid carcinoma. Thyroid 2010;20:147-52.

SUMMARY

BACKGROUND

Papillary thyroid cancer (PTC), which comprises 85% of all thyroid cancers, has a relatively low 10-year cancer-specific mortality rate of approximately 7%, yet despite this favorable survival rate, the incidence of PTC lymph-node metastases is high, varying from 15% to 50%, depending on the extent of lymph-node surgery. There is considerable controversy about routine central and lateral lymph-node compartments when preoperative studies fail to identify cervical-lymph-node metastases. There also are conflicting views about whether lymph-node surgery has a long-term impact on disease-free survival. The aim of this retrospective study was to assess the risk factors that are associated with recurrence of regional lymph-node metastases.

METHODS

The study cohort comprised 189 patients with PTC who were treated with thyroidectomy from 1992 through 2003 and had medical records sufficient for analysis and follow-up for periods longer than 2 years. Hemithyroidectomy was performed in 11 patients (6%), and the other 178 (94%) had total thyroidectomy. Central level VI lymph-node compartment dissection (CLND) was performed if metastases were suspected intraoperatively. Lateral lymph-node compartment dissection (LND) was performed if preoperative ultrasound-guided fine-needle aspiration biopsy revealed lateral-compartment lymph-node metastases. The study subjects were 33 patients (17%) with regional lymph-node recurrence and 156 (83%) who did not have cervical-lymph-node recurrence.

The mean follow-up was 81±44 months (range, 48 to 386). Patients who were treated with hemithyroidectomy were followed with serial serum thyroglobulin (Tg) levels and neck ultrasonography. The remaining patients who had total thyroidectomy and ^{131}I remnant ablation (RRA) had follow-up with serial serum Tg levels with or without thyroid-hormone suppression of thyrotropin (TSH) and had neck ultrasonography and whole-body ^{131}I scans (WBS) performed every 3 to 6 months.

Regional lymph-node recurrence was defined as positive if any of the following were present: uptake of ^{131}I on WBS, positive ultrasonography, or an increase of serial serum Tg levels with or without thyroid-hormone suppression. When these findings were positive, patients had computed tomography (CT) and preoperative ultrasonographically guided fine-needle aspiration biopsy.

RESULTS

Recurrence According to Patient Risk Factors (Figure 1)

The study group comprised 189 patients, 44.7 years of age (range, 9 to 80). Of this group, 151 were women (80%; mean age, 45.3 years; range, 9 to 80) and 38 men (20%; mean age, 45.3 years; range, 9 to 80). Regional lymph-node metastases were found in 27 of the 151 women (18%) and in 6 of the 38 men (16%). The difference in regional lymph-node metastases was not significantly different between men and women (P>0.05).

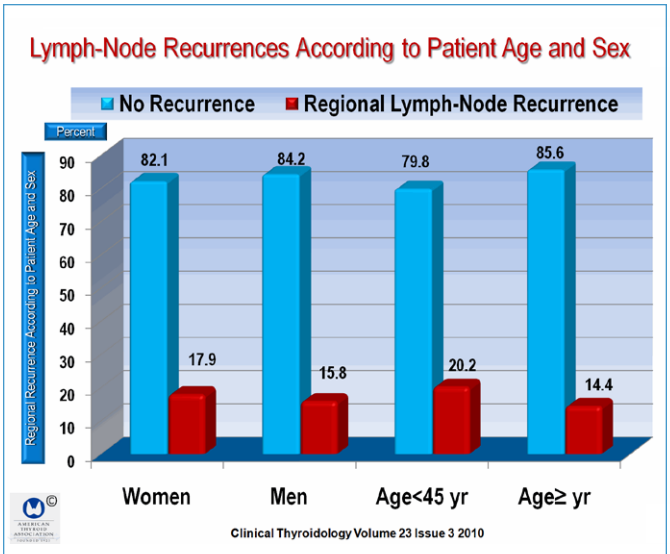

Figure 1. This figure shows the result of univariate analysis comparing recurrence of regional lymph-node metastases according to sex and age (<45 vs. ≥45 yr). There are no significant differences in patient risk factors that influence recurrence of lymph-node metastases. *P = 0.817. †P = 0.341.

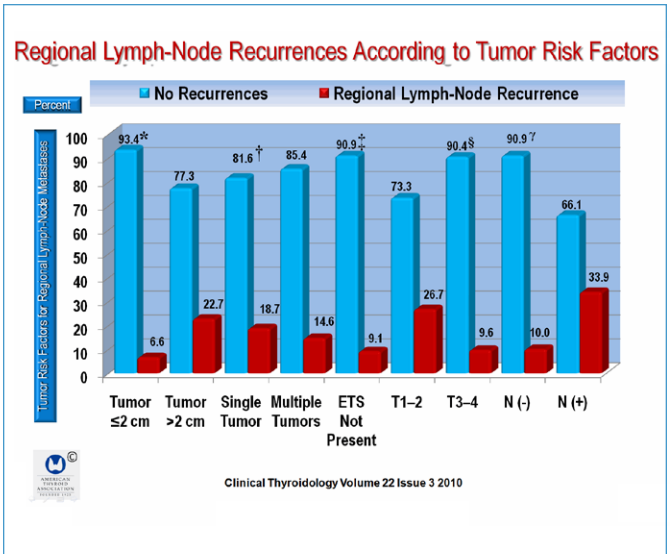

Figure 2. This figure shows the effect of tumor features on regional lymph-node recurrence. *P = 0.007 comparing <2 with ≥2 cm. †P = 0.662, comparing solitary with multiple primary tumors. ‡P = 0.002, comparing ETS with no ETS. §P = 0.007, comparing T1 to T2 with T3to T4. ɣP<0.001, comparing N stage (–) vs. N stage (+).

Likewise, there was no significant difference in age when this variable was stratified into <45 versus ≥45 years (Figure 1).

Recurrence According to Tumor Risk Factors (Figure 2)

The following were found to be risk factors for regional lymph-node metastases: tumor ≤2 cm versus >2 cm (P = 0.007); multifocality versus single tumor (P = 0.662); extrathyroidal spread of tumor (ETS) versus no ETS, (P = 0.002); higher tumor (T) stage (T1 to T2 vs. T3 to T4) (P = 0.007); and lymph-node (N) stage with (+) and without (–) lymph-node metastases (P<0.001); all of these were significantly associated with regional lymph-node recurrence (Figure 2).

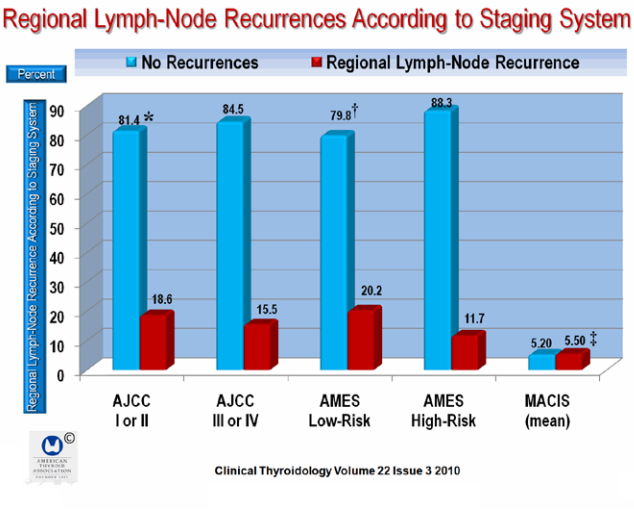

Figure 3. This figure shows that prognostic scoring systems (see text) do not predict lymph-node recurrence.*P = 0.693, comparing AJCC stage I or II with III or IV. †P = 0.261, comparing AMES low-risk with high-risk. ‡P = 0.624, as compared with MACIS mean ±SD; all comparisons refer to recurrence of lymph-node metastases.

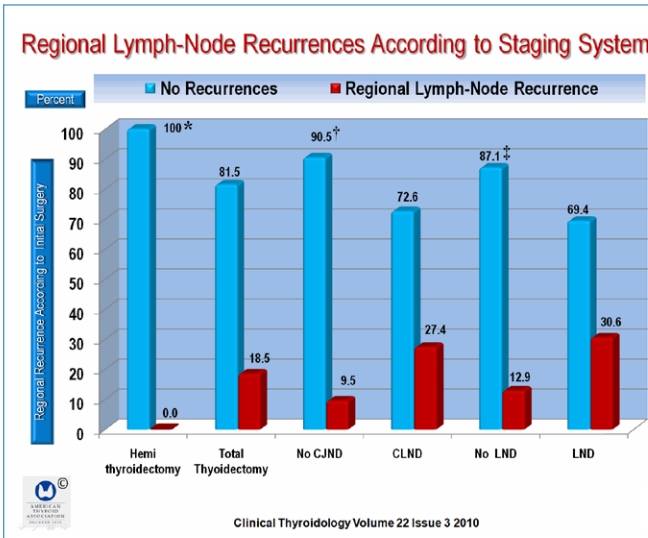

Figure 4. This figure shows the effect of initial surgical treatment on recurrent lymph-node metastases *P = 0.217, comparing total thyroidectomy with hemithyroidectomy. †P = 0.002, comparing CLND (central compartment lymph-node dissection) with no CLND. ‡P = 0.008, comparing patients with and without lateral neck-compartment dissection (LND).

Recurrence According to Prognostic Scoring Systems (Figure 3)

There were no significant differences in recurrence when risk was defined according to the American Joint Committee on Cancer (AJCC) staging system (P = 0.693), the AMES (age, distant metastases, extent, and size)scoring system (which includes patient age, distant metastases, and extent and primary tumor size) (P = 0.216, comparing low-risk vs high-risk group); and the MACIS system (which includes distant metastases, patient age, completeness of resection, local invasion, and tumor size, (P = 0.624). Thus, none of the staging systems predicted recurrence of lymph-node metastases (Figure 2).

Recurrence According to Surgical Treatment (Figure 4)

Of the 11 patients treated with hemithyroidectomy, none had regional lymph-node recurrences; however, of the 178 patients treated with total thyroidectomy, 33 of 178 (18.5%) had regional lymph-node recurrence. Still, the extent of thyroidectomy was not associated with regional lymph-node recurrence (Figure 4). A total of 84 patients had CLND and 49 had LND. The rate of regional lymph-node metastases were significantly greater in patients who had CLND as compared with LND (P<0.05).

Multivariate Analysis of the Relationship between Regional Recurrence and N Stage (Figure 5)

Multivariate analysis found that N stage was the only statistically significant variable that identified lymph-node recurrence (P<0.05). Neither CLND nor LND had an impact on regional lymph-node recurrence (Figure 5).

Multivariate Analysis of Regional Recurrence and Clinical Factors (Figure 6)

Multivariate analysis of sex, age, tumor size, T stage, N stage, and ETS, found that only N stage significantly increased the probability of regional lymph-node recurrence, by 3.474-fold (Figure 6).

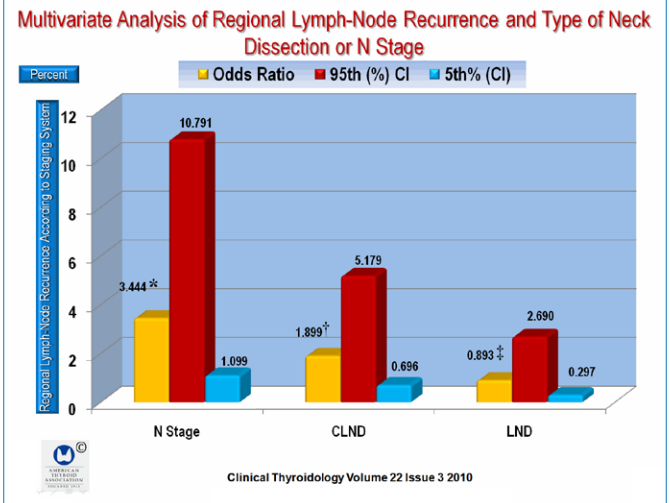

Figure 5. This figure shows the odds ratio and confidence intervals (CIs) for multivariate analysis in which only N stage significantly increased the risk for recurrence of lymph-node metastases. *P = 0.034. †P = 0.210, comparing surgery with and without CLND (central compartment lymph-node dissection). ‡P = 0.841, comparing surgery with and without LND (lateral neck-compartment dissection). Multivariate analysis found that only N stage was an independent factor in increasing the risk for lymph-node metastases.

Relationship between Disease-free Survival and Clinical Factors (Figure 7)

Univariate analysis found that disease-free survival was significantly associated with tumor >2 cm, higher T stage, lymph-node metastases, and ETS (P<0.05).

Multivariate analysis found that patients with lymph-node metastases had a 3.3-fold shorter disease-free survival period than those without lymph-node metastases (P<0.05). The 10-year disease-free survival rates were 77.8% in patients without and 57.9% in those with lymph-node metastases (P<0.05) (Figure 7).

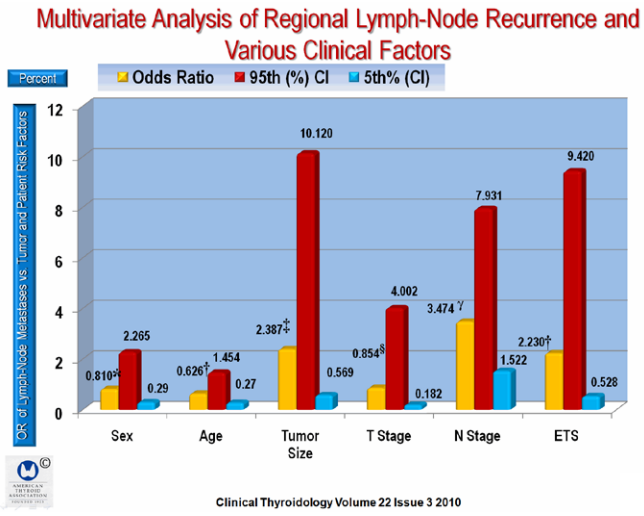

Figure 6. This figure shows the likelihood of various clinical factors increasing the risk for recurrent lymph-node metastases. The odds ratio (OR) and 95% and 5% confidence intervals (CIs) are shown. Only N stage was found to be a significant variable that was independently predictive of recurrent lymph-node metastases. *P = 0.0687, comparing women with men. †P = 0.274, comparing young with older patients. ǂP = 0.234, comparing smaller with larger primary tumors. §P = 0.841, comparing different T stages. ɣP = 0.003. ǁP = 0.275, comparing different N stages. Only N stage was an independent factor significantly increasing the risk for recurrent lymph-node metastases. ETS = extrathyroidal spread of tumor.

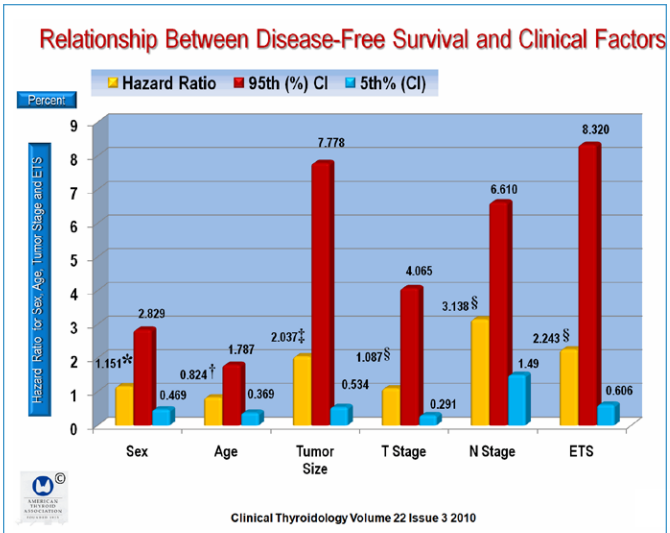

Figure 7. This figure shows the relationship between clinical factors and disease-free survival. *P = 0.739, comparing men with women. †P = 0.426, comparing young with older patients. ǂP = 0.004, comparing small and larger tumors, §P<0.001 for T stage, N stage, and extrathyroidal spread of tumor (ETS).

Clinical Characteristics of Lymph-Node Metastases (Figures 8 and 9)

Of 130 patients without lymph-node metastases at the time of initial surgery, 13 had ipsilateral neck recurrence, 1 had contralateral recurrence, and 2 had bilateral neck recurrence. Regional neck recurrence was frequent in ipsilateral neck levels II, III, and IV (Figure 8). Among 59 patients with lymph-node metastases at the time of initial surgery, 20 (33.9%) had regional recurrences. Among these patients, 14 had ipsilateral and 10 had contralateral regional neck recurrences. In the

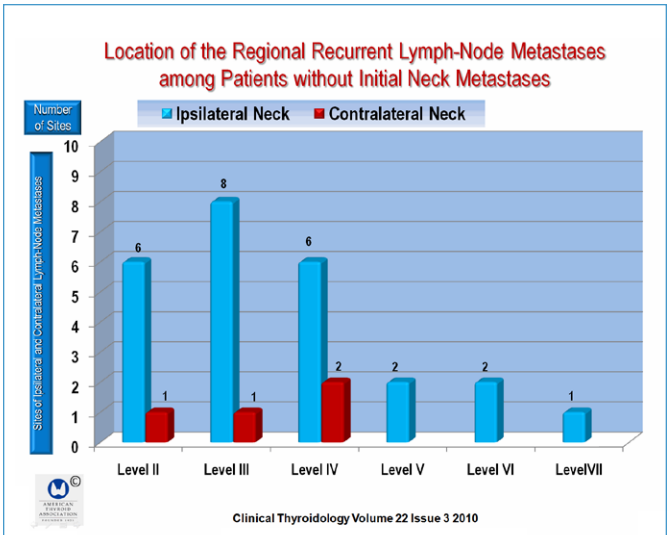

Figure 8. This figure shows the location of regional lymph-node recurrences according to ipsilateral and contralateral recurrent lymph-node metastases in patients without neck metastases at initial surgery.

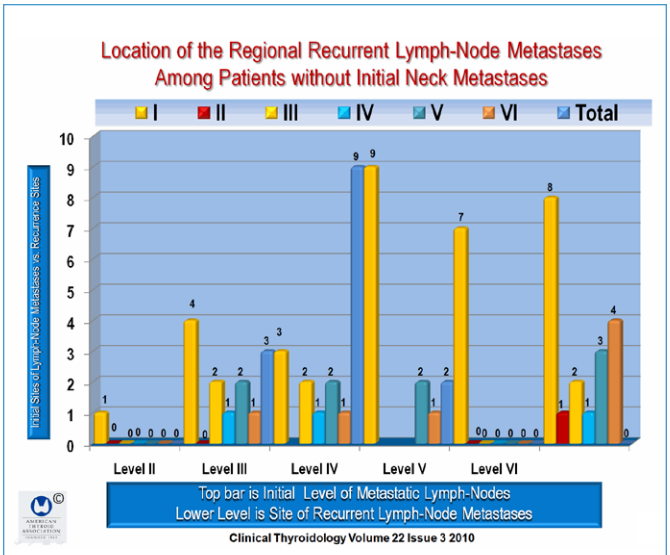

Figure 9. Regional lymph-node metastases were commonly found in ipsilateral levels II, III, and IV (Figure 8), and ipsilateral lymph-node recurrences were more frequent in levels II, III, and VI.

ipsilateral regional recurrence group, lymph-node metastases were frequently found in neck levels II, III, and VI at the initial surgery, and the regions with frequent lymph-node recurrences were in levels IV, V and VI (Figure 9).

In the contralateral regional recurrence group, the levels of lymph-node metastases in the initial surgery were in levels II, III, and VI. In the contralateral regional recurrence group, the initial levels of lymph-node metastases were in levels III, and VI, and recurrent lymph-node metastases were most common in level II. For surgical treatment of recurrent lymph-node metastases, selective neck dissection in levels II to IV and VI was performed in 18 patients and in levels I or II to V in 12 cases, and lymph-node excision in 3 cases. No patients with metastatic lymph-node recurrence died of the disease.

CONCLUSION

This study found that lymph-node metastases at the time of initial surgery were the most predictable clinical factor for disease-free survival. The authors concluded that routine prophylactic lymph-node compartment surgery in all patients is questionable, considering the low incidence (10%) of recurrent regional lymph-node metastases among patients who did not have lymph-node metastases at the time of initial surgery—the majority (79%) of patients having initial surgery.

COMMENTARY

There is considerable disagreement concerning the efficacy of routine prophylactic CLND. The foundation of this disagreement rests on the fact that relatively few studies have found that lymph-node metastases impair long-term survival (01;2;3), whereas others find no effect of lymph-node metastases on cancer-specific survival rates (4). This is not surprising considering the highly variable study subjects, the length of follow-up, and the standards that identify patients who are disease-free. Moreover, there are no prospective, randomized studies concerning the efficacy of prophylactic CLND or LND (5). Yet there are advocates who find sufficient evidence-based data to support CLND for PTC in patients under the care of experienced endocrine surgeons (5). The notion that prophylactic lymph-node dissection should be approached with caution is in accord with the American Thyroid Association guidelines (6). Therapeutic central-compartment (level VI) neck dissection for patients with clinically involved central- or lateral-neck lymph-node metastases should accompany total thyroidectomy to provide clearance of disease from the central neck (Recommendation rating: B). (b) Prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with PTC with clinically uninvolved central-neck lymph nodes, especially for advanced primary tumors (T_3 or T_4) (Recommendation rating: C).

(c) Near-total or total thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T2), noninvasive, clinically node-negative PTCs and most follicular cancers (Recommendation rating: C).

However, contrary to the Baek study, some have identified risk factors for cervical-lymph-node recurrence. For example, Leboulleux et al. (7) studied 148 consecutive patients with PTC who had lymph-node metastases, with or without extrathyroidal tumor extension at the time of diagnosis. After a mean follow-up of 8 years, eight patients (7%) with a normal postablation whole-body diagnostic ^{131}I scan experienced tumor recurrence. They found that significant risk factors for persistent disease were the number of lymph-node metastases (>10), the number of lymph-node metastases with ETS (>3), primary tumor size (>4 cm), and central lymph-node metastases. Likewise, for recurrent disease, the significant risk factors were number of lymph-node metastases (>10), ETS (>3), and elevated serum Tg levels after levothyroxine withdrawal 6 to 12 months after initial treatment. Leboulleux et al. found that the number of lymph-node metastases, ETS lymph-node metastases, tumor location, tumor size, and serum Tg concentrations were important prognostic risk factors for recurrence.

Baek et al. also found on univariate analysis that clinical risk factors such as tumor size, ETS, T stage, and N stage at the time of initial surgery were associated with regional lymph-node recurrence, in accord with several other studies (7;9). However, multivariate analysis found that only lymph-node metastasis at presentation was associated with a significant difference in regional recurrence, and it was the most predictable clinical factor for disease-free survival. Part of this result might be attributable to the fact that CLND was performed only in patients with preoperative or intraoperatively identified lymph-node metastases. This is a considerably different scenario as compared with prophylactic CLND or LND.

An additional concern about the therapeutic efficacy of prophylactic CLND is the complications of this surgical procedure, which have been summarized by Doherty, Steward, and Mazzaferri (8). Still, prophylactic CLND and level III LND identifies tumors that are not easily detected preoperatively by ultrasonography-guided fine-needle aspiration biopsy or during initial surgery. Leaving occult lymph-node metastases after surgery are in turn related to the use of postsurgical ^{131}I remnant ablation.

Radioiodine ablation is not generally recommended for tumors <10 mm, and its use depends on various factors for tumors between 10 and 20 mm, such as lymph-node metastases, which must be taken in the context of risk stratification.

The ATA guidelines define low-risk patients as having the following characteristics: (1) no local or distant metastases; (2) all macroscopic tumor has been resected; (3) there is no tumor invasion of locoregional tissues or structures; (4) the tumor does not have aggressive histology (e.g., tall-cell, insular, or columnar-cell carcinoma) or vascular invasion; and (5) if ^{131}I is given, there is no ^{131}I uptake outside the thyroid bed on the first posttreatment whole-body ^{131}I scan. Intermediate-risk patients have any of the following: (1) microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery; (2) cervical-lymph-node metastases or ^{131}I uptake outside the thyroid bed on the therapeutic whole-

body scan done after thyroid remnant ablation; or (3) tumor with aggressive histology or vascular invasion. High-risk patients have: (1) macroscopic tumor invasion; (2) incomplete tumor resection; (3) distant metastases; and possibly (4) Tg levels out of proportion to what is seen on the posttreatment scan. The problem is that central-neck-compartment metastases are generally not identified preoperatively or intraoperatively, and as many as high as 50% (Scheumann et al. 559-67;White, Gauger, and Doherty 895-904).

A retrospective study by Bonnet et al.(9) that was aimed at determining the effect of lymph-node staging on the indication for radioiodine treatment found that among 115 patients with PTC <2 cm without ultrasonographically detectable cervical-lymph-node metastases were treated with total thyroidectomy and complete selective dissection of the CLND and LND compartments. Radioiodine treatment was based on definitive histopathology, and follow-up was based on neck ultrasound and Tg levels. Lymph-node metastases were found for 42% of the patients. Radioiodine was not given to 42% of the patients with tumors <20 mm and no metastatic lymph-node metastases.

On the other hand, 58% of the patients were treated with radioiodine for lymph-node metastasis, extracapsular thyroid invasion, or unfavorable histologic subtype. The status of lymph-node metastases affected the indication for radioiodine in 30.5% of cases classified as T1: 12 patients with tumors <10 mm but with lymph-node metastases (who received radioiodine) and 13 patients with tumors between 10 and 20 mm but without lymph-node metastases (who did not receive radioiodine). Vocal-fold paralysis and hypoparathyroidism each occurred in 0.9% of cases. After 1 year of follow-up , neck ultrasonography was normal in all the patients, and recombinant human TSH-stimulated Tg was undetectable for 97% of the patients. The authors concluded that precise lymph-node staging by prophylactic neck dissection for tumors initially staged T1N0 modified the indication for radioiodine ablation for 30% of patients.

Prophylactic lymph-node compartment dissection remains a complex issue that will require further study, hopefully by prospective, randomized trials. The goal is to render patients free of disease with targeted therapy.

— Ernest L. Mazzaferri, MD, MACP

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Reanalysis of the Whickham Survey shows an association of subclinical hypothyroidism and ischemic heart disease

Razvi S, Weaver JU, Vanderpump MP, Pearce SH. The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the Whickham Survey cohort. J Clin Endocrinol Metab [Epub ahead of print February 11, 2010; doi:10.1210/jc.2009-1749]

SUMMARY

BACKGROUND

It is widely known that over a 20-year period the Whickham Survey has not found an association between ischemic heart disease (IHD) and autoimmune thyroid disease in community-dwelling subjects with positive antibodies or those using levothyroxine, which appears to be at odds with other studies. As a result, the authors performed this study to evaluate the incident rate of IHD and mortality in participants of the Whickham study in relation to their thyroid status.

METHODS

The Whickham Survey is a population-based cross-sectional study of community-dwelling adults in an urban area in northern England. The study cohort comprised a randomly selected group of 2779 individuals who were first studied from 1972 through 1973, during which a history of medical conditions was elicited, a physical examination was performed, and an electrocardiograph (ECG) and blood samples for lipids, thyroid function, and thyroid antimicrosomal antibodies were obtained. At a 20-year follow-up study, the causes of death were ascertained and further examination of survivors was performed. Excluded from the analysis were participants who had thyroid disease at baseline or were on medications that could affect thyroid function (n = 60) or who had IHD (n = 243) or a serum thyrotropin (TSH) >15 mIU/L (n = 13) and those in whom the cause of death or the cause of medical conditions could not be ascertained (n = 52). Thus, the total cohort who had follow-up for up to 20 years was 2376 individuals.

At baseline, subclinical hypothyroidism (SCH) was defined as a serum TSH of 6.0 to 15.0 mIU/L, with a serum total thyroxine (T_4) of 46 to 174 nmol/L. A first-generation TSH assay was used for the baseline survey, thus making the upper reference limit of TSH 6.0 mIU/L (the 97.5th centile) with negative thyroid antibodies and not on medication affecting thyroid function, rather than 4.5 mIU/L as it is now using sensitive assays. To make the TSH levels comparable to current ranges, the authors used a range of 6.0 to 15.0 mIU/L in the reanalysis. A TSH between 0.3 to 5.9 mIU/L was classified as the euthyroid reference limit. Total serum T_4 levels were not used for this definition because they might be elevated because of some medications such as estrogens. Positive thyroid antibodies were defined as an increase in antimicrosomal antibodies.

At the end of the 20-year follow-up, IHD events were defined by Rose angina questionnaires, ECG changes per the Minnesota code, or hospital admission for IHD, confirmed by ECG or serial cardiac enzymes. Causes of death were ascertained from death certificates.

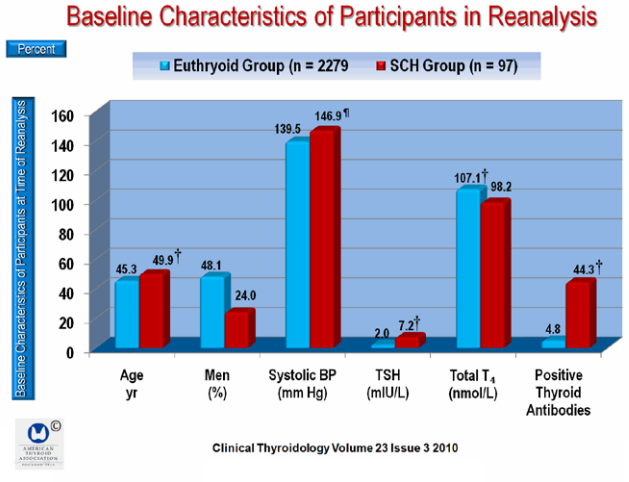

Figure 1. This figure shows the baseline characteristics of participants included in the reanalysis. Some variables may not add up to the total because of missing data. a = reference value (HR = 1.0) for Cox proportional-hazards analysis; significant results are shown in bold type: †P = 0.01, comparing treated with untreated patients in the euthyroid with subclinical hypothyroidism (SCH) group. ¶P = 0.02.

RESULTS

Baseline Characteristics of Participants in the Reanalysis (Figure 1)

In the reanalysis, at baseline the majority of participants were euthyroid (95.9%; mean age, 45.3 years; range, 18 to 92). The prevalence of SCH was 4.1% (mean age, 49.9 years; range, 18 to 87) and was higher in women, older individuals, nonsmokers, and those with positive thyroid antibodies (Figure 1). Serum TSH levels were higher in the SCH group as compared with euthyroid individuals. Over the 20-year follow-up period, 45 participants (3 men and 42 women, 25 euthyroid and 20 with SCH at baseline) had been treated with levothyroxine.

Association between Thyroid Status and IHD Risk Factors at Baseline (Figure 1)

Systolic and diastolic blood pressure and total cholesterol levels were higher in the SCH group as compared with the euthyroid group (P<0.001 for blood pressure and P = 0.02 for cholesterol). Multiple-linear-regression analysis, after adjusting for other IHD risk factors including age, sex, weight, smoking, and relevant medications, showed that SCH was significantly associated only with higher systolic blood pressure (r2 = 0.38, P = 0.03), but not for diastolic blood pressure or serum cholesterol.

Association of Baseline Thyroid Status with Incident IHD Events and Mortality (Figures 2 and 3)

There were 419 IHD fatal and nonfatal events during the follow-up period. There was a positive association between baseline SCH and incident IHD, with an adjusted hazard ratio (HR) of 1.76 (95% confidence interval [CI], 1.15 to 2.71; P = 0.01) after multivariate adjustment (full model). Excluding the use of thyroid hormone during follow-up from the multivariate model (Model B), showed a reduction in the association between SCH and IHD events (HR, 1.53; 95% CI, 0.97 to 2.45; P = 0.07).°

Over the 20-years of follow-up, there were 165 deaths due to IHD. The mortality rate of IHD was higher in the SCH participants than in the euthyroid individuals, with an adjusted HR of 1.79 (95% CI, 1.02 to 3.56; P = 0.05) in the full model (Figures 2 and 3). However, when thyroid hormone use was excluded from the multivariate analysis (Model B), there was a reduction in the association between SCH and IHD (HR, 1.45; 95% CI, 0.73 to 2.89; P = 0.28) (Figures 2 and 3).

There were a total of 595 deaths in the entire cohort, and all-cause mortality was not significantly different in the SCH and euthyroid groups, with an adjusted HR of 1.29 (95% CI, 0.87 to 1.92) (full model). Thus, withdrawal of thyroid-hormone use did not change the results. Adding thyroid antibody status to the full multivariate model (Model C) did not significantly change the results (Figure 2).

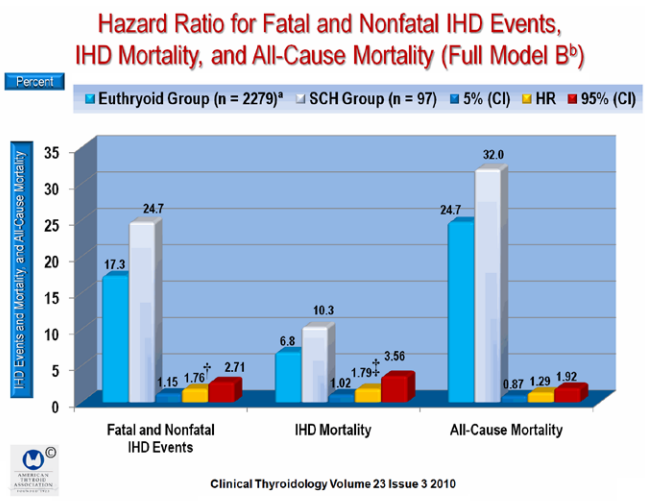

Figure 2. This figure shows the frequency and hazard ratios (HRs) for ischemic heart disease (IHD) events and mortality in participants who are euthyroid as compared with participants with IHD. Reference value (HR = 1.0) for Cox proportional-hazards analysis; significant results are shown in bold type. †P = 0.01. ¶P = 0.02. §P= 0.04. ǂP = 0.05. γP = 0.06. Full Modelb = full model with baseline age, sex, social class, body weight, history of cerebrovascular disease, diabetes mellitus, smoking, systolic and diastolic blood pressure, serum cholesterol levels, and levothyroxine use during follow-up as a covariate. Model Bc = Model B; as full model, without levothyroxine use during follow-up as a covariate. Model Cd = Model C; as full model, but with the addition of thyroid antibody status at baseline as a covariate.

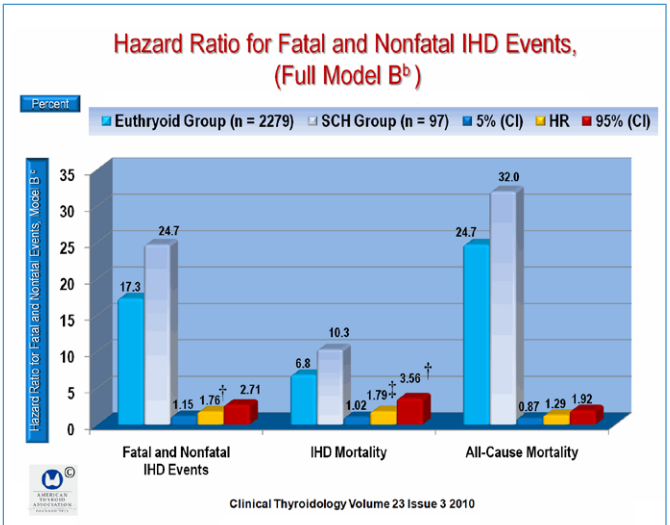

Figure 3. Frequency and hazard ratios for IHD events and mortality in treated and untreated participants with SCH over 20 years of follow-up. (See Figure 2 for explanations of symbols.)

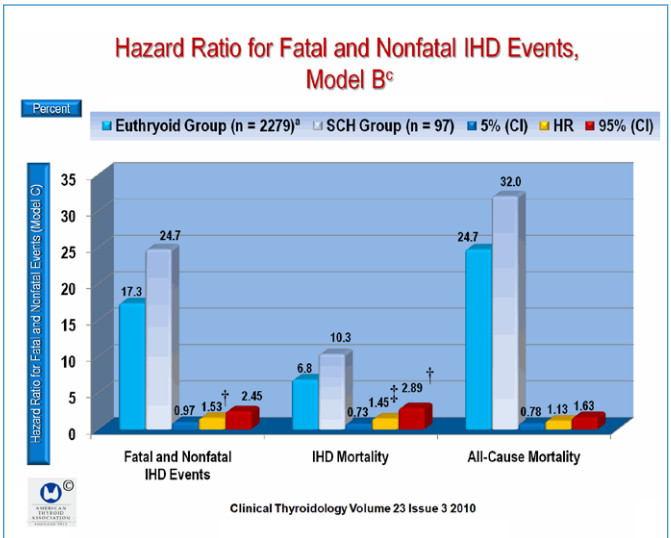

Figure 4. Hazard ratio for fatal and nonfatal IHD events (Model B^C, see Figure 2 legend for P values.)

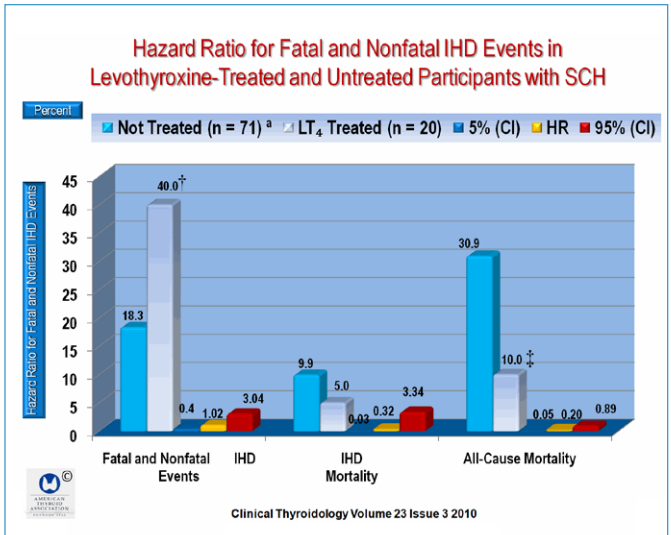

Figure 5. Hazard ratio comparing patients treated with levothyroxine (LT_4) with the untreated group. Age, sex, and total serum cholesterol adjusted. Model further adjusted for baseline social class, body weight, history of cerebrovascular disease, diabetes mellitus, smoking, and systolic and diastolic blood pressure as covariates. (See Figure 2 for P values.)

Association of Mortality and IHD Events in SCH Participants Stratified by Thyroid Hormone Therapy (Figures 3 to 6)

During the 20-year follow-up, levothyroxine therapy was started in 20 of the 91 individuals with SCH at baseline. At follow-up there were 24 deaths in the SCH group. All-cause mortality was significantly lower in the SCH group treated with levothyroxine as compared with untreated individuals with SCH (HR, 0.20; 95% CI, 0.05 to 0.89; P = 0.03) after adjusting for age, sex, and cholesterol levels, and further adjustment for other IHD risk factors did not change the results (HR, 0.22; 95% CI, 0.06 to 0.91; P = 0.02) (Figure 3). Also, IHD mortality and IHD events were not significantly different in the treated groups as compared with the untreated group (HR, 0.32; 95% CI, 0.03 to 3.34; and HR, 1.02; 95% CI, 0.40 to 3.05, respectively).

CONCLUSION

The initial report of the 20-year follow-up of the Whickham Survey cohort did not find an association between IHD events and a composite of people with either SCH or positive thyroid antibody levels or individuals taking levothyroxine, regardless of their TSH levels. The current analysis shows an association of IHD and IHD-related mortality in people with SCH.

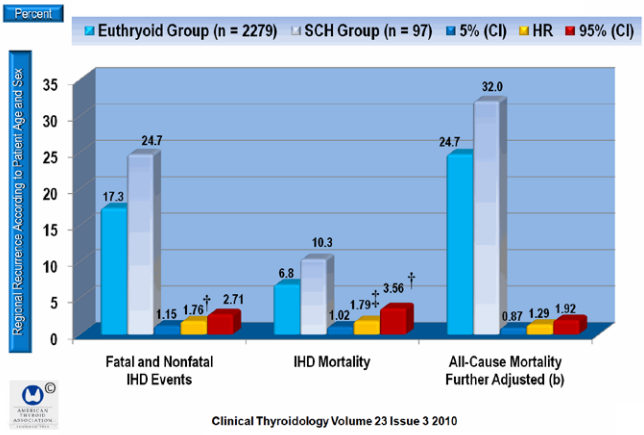

Figure 6. Frequency and hazard ratios for IHD events and mortality in treated and untreated SCH. ¶P = 0.03. b Model further adjusted for baseline social class, body weight, history of cerebrovascular disease, diabetes mellitus, smoking, and systolic and diastolic blood pressure as covariates.

COMMENTARY

Subclinical hypothyroidism (SCH) is defined as serum free T_4 and free triiodothyronine (T_3) levels within their respective reference ranges in the presence of abnormal serum TSH levels. SCH is being diagnosed more frequently in clinical practice in young and middle-aged people as well as in the elderly; still, the incidence of SCH varies widely, from 4 to 10%, largely because of the variability in TSH cutoffs used to diagnose SCH (1). Moreover, the clinical relevance of SCH continues to be debated, although it can have effects on the cardiovascular system and bone and other organs and systems (1). The treatment of SCH and population screening are even more controversial, despite the potential risk of progression to overt disease, as there is no consensus on the upper TSH reference range and at what TSH cutoff, if any, treatment should be contemplated. Thus, whether SCH plays a major role in IHD remains a matter of debate, with some finding that SCH is an independent risk factor for atherosclerosis and myocardial infarction in elderly patients (2-5), while others do not find this association.

The current reanalysis of the Whickham Survey found an association between subclinical hypothyroidism and ischemic heart disease. In addition to the main findings that link SCH with IHD and IHD-related mortality, a subgroup analysis also suggests improvement in mortality among individuals with SCH who were treated with levothyroxine over an extended period as compared with those with SCH who were not treated. Moreover, this reanalysis found that the risk for IHD events was not related to baseline antibody status. The authors of the study opine that one obvious explanation for the apparent discord between this and the previous analysis was the inclusion of individuals with hypothyroidism who were treated with levothyroxine, which may have diluted the observed risk for IHD events.

Several, but not all, studies have found that older adults with serum TSH levels ≥10.0 mIU/L have a moderately increased risk of heart failure and alterations in cardiac function that do not occur in older adults with TSH levels <10.0 mIU/L, suggesting that levothyroxine therapy might ameliorate the adverse effects in patients with SCH who had TSH levels >10 mIU/L (3,4).

Razvi et al. mention several limitations of their study; all individuals were classified as either euthyroid or as having SCH on the basis of a single blood test, which if anything, may have diluted the evidence for an association between SCH and IHD by including some euthyroid individuals with transient TSH elevations in the SCH group. Moreover, some individuals with SCH may have been progressed to overt hypothyroidism by their primary physicians or at the 20-year follow-up survey, thus increasing their vascular risk during the period without levothyroxine therapy. Also the lower TSH reference limit of 0.6 mIU/L may not be identical to the reference ranges in current sensitive TSH assays. Although the finding that levothyroxine reduced mortality rates of IHD, the authors suggest that the total number of events is small and should thus be interpreted with caution until a randomized, controlled trial is available. Of these concerns, perhaps the most important is that the diagnosis of subclinical hypothyroidism is severely limited by a single set of thyroid-function tests and the biologic variation in thyroid testing from visit to visit (6).

— Ernest L. Mazzaferri, MD, MACP

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Doses of recombinant human TSH less than 0.3 mg are likely to cause fewer adverse events when given to patients with nontoxic multinodular goiter

Fast S, Nielsen VE, Bonnema SJ, Hegedüs L. Dose-dependent acute effects of recombinant human TSH (rhTSH) on thyroid size and function: comparison of 0.1, 0.3 and 0.9 mg of rhTSH. Clin Endocrinol (Oxf) 2010;72:411-6.

SUMMARY

BACKGROUND

Recombinant human thyrotropin α (rhTSH) is used to increase the effect of radioiodine (^{131}I) therapy for nontoxic multinodular goiter. However, acute thyroid swelling and the induction of hyperthyroidism has been reported with this use of the drug. The object of this study was to determine the effects of various doses of rhTSH on thyroid size and function.

METHODS

Nine healthy men with a mean age of 33 years (range, 22 to 50) volunteered for this study; none of them took drugs known to affect thyroid size or function, and all of them had normal thyroid function without antithyroglobulin antibodies (TgAb), thyroid peroxidase (TPOAb), or TSH receptor antibodies (TSHRAb). The study compared the effects of placebo with 0.01, 0.03, and 0.9 mg of rhTSH in a paired design including four consecutive study rounds. The main outcome measurements were evaluated at baseline; 24, 48, and 96 hours; and 7 and 28 days after injection of rhTSH or placebo. During this time, thyroid volume (TV) was estimated by ultrasound and thyroid function was determined by measurements of serum (TS), free triiodothyronine (FT_3), free thyroxine (FT_4), and serum thyroglobulin (Tg). Thyroid size (range, 10 to 22 ml) and morphology was normal in all volunteers, and all had normal neck ultrasound examinations.

RESULTS

The Effects of rhTSH on Thyroid Volume (Figures 1 to 4)

Ultrasound TV did not change significantly from baseline during the 28-day follow-up. In the 0.3-mg-rhTSH round, the mean (±SEM) TV increased by 37±12.3% (P = 0.03) and 45.3±16.1% (P = 0.05) at 24 and 48 hours, respectively. In the 0.9-mg-rhTSH round, the mean TV increased by 23.3±5.8% (P = 0.008) and 35.5±18.4% (P = 0.02) at 24 and 48 hours. On day 7, the mean TV had returned to the baseline level in all study rounds (Figure 1).

The maximum thyroid enlargement in each study subject occurred between day 1 and day 4, with a significant difference among the four study rounds (P = 0.03) (Figure 2). The mean maximum TV increase was not significantly different in the placebo and 0.1-mg-rhTSH groups as compared with baseline (P = 0.12 and 0.08, respectively), and there were no differences between these two series (P = 0.40). In contrast, the maximum TV increased by 52.7±14.7% (P = 0.01), and 41.5±17.4% (P = 0.008) in the 0.3- and 0.9-mg-rhTSH rounds, respectively (Figure 3). The maximum TV increases after 0.3 and 0.9 mg rhTSH were comparable (P = 0.02 and P = 0.03). However, there was considerable interindividual variation in the maximum relative TV increase from baseline variation, indicating that some of the study subjects were more prone to thyroid enlargement than others (Figure 4). The TV in one of the study subjects increased from 21 to 90 ml 30 hours after rhTSH, which promptly responded to a nonsteroidal antiinflammatory drug.

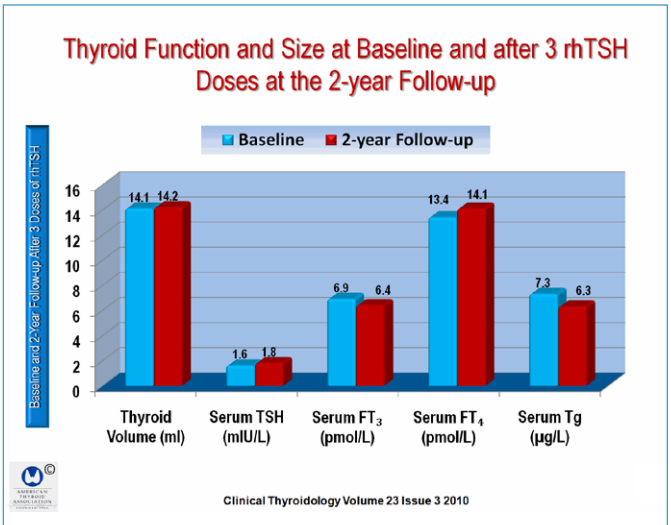

Figure 1. This figure shows differences in the baseline thyroid volume, and serum TSH, FT_3, FT_4, and serum thyroglobulin levels 2 years after three doses of rhTSH. *P = 0.093, †P = 0.77, ‡P = 0.9, ¶P = 0.21, and §P = 0.53, comparing thyroid volume change at baseline with thyroid volume at 2-year follow-up.

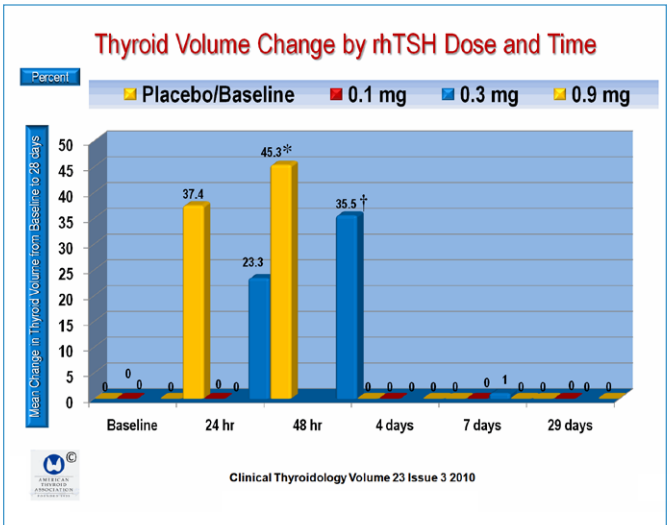

Figure 2. This figure shows the change in thyroid volume size after placebo and after 0.1, 0.3 and 0.9 mg of rhTSH and placebo. *P = 0.05, comparing changes after 0.3 mg rhTSH at 24 hours with those at 48 hours. †P = 0.02, comparing changes after 0.9 mg rhTSH at 24 and 48 hours.

Thyroid Function and Serum Thyroglobulin Response (Figure 5)

Serum TSH, FT_4, FT_3, and Tg did not change significantly from baseline after placebo injection (Figure 5). However, the 24-hour serum TSH showed a positive dose response in all four rounds (P<0.001) (Figure 5). After 24 hours, the serum TSH level showed a positive dose response that was found in all four rounds (P<0.001). The mean (±SD) TSH level was higher following 0.03 mg rhTSH (26.5±7.9 mIU/L) as compared with the response to 0.1 mg rhTSH (7.4±2.1 mIU/L) (P = 0.02); it was higher following 0.9 mg rhTSH (75.2±28.4 mIU/L), as compared with 0.3 mg rhTSH (P = 0.008).

There was an increased response in FT_3 (Figure 7) and FT_4 (Figure 8), and Tg also showed a positive dose response that peaked at 24 to 48 hours for all three variables (Figure 6). There was a highly significant difference in the area under the curve (AUC) from day 0 to day 7 among the four rhTSH placebo doses, which gradually increased with higher doses of rhTSH. The AUC was greater with 0.3 mg as compared with 0.1 mg (P = 0.02) and with 0.9 mg as compared with 0.3 mg (P = 0.02) (Figure 6). After 0.1 mg rhTSH, the AUC for FT_3 and Tg was not statistically different from that for placebo (P = 0.06 and 0.24, respectively), but the AUC for FT_4 was significantly greater than that for placebo (P = 0.02). With each rhTSH dose, the Tg response showed considerable individual variation (Figure 6).

The individual who had the greatest thyroid enlargement after 0.9 mg rhTSH had the highest Tg concentration (1560 µg/L at 48 hours, vs. 13.20 µg/L, which was the highest level among the other eight subjects in the study round. After 0.03 mg

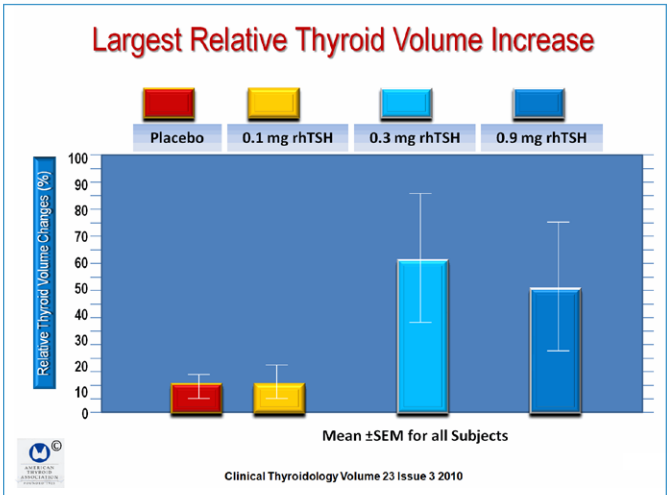

Figure 3. This figure shows the largest relative thyroid volume increases in all subjects, after receiving placebo and 0.1, 0.3, and 0.9 mg of rhTSH. This figure and Figure 4 are drawn from the data in Figure 2 of Fast et al.

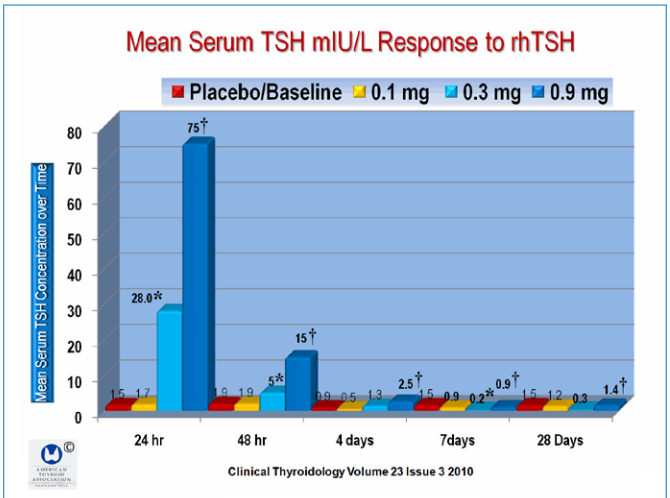

Figure 5. This figure shows the mean serum TSH (mIU/L) concentrations after placebo and 0.1, 0.3, and 0.9 mg of rhTSH. The mean serum TSH was higher following 0.3 mg as compared with 0.1 mg of rhTSH. *P<0.001 comparing all four rounds of placebo and 0.1, 0.3, and 0.9 mg rhTSH. *P<0.001 (the bold figures here and elsewhere are statistically significant changes).

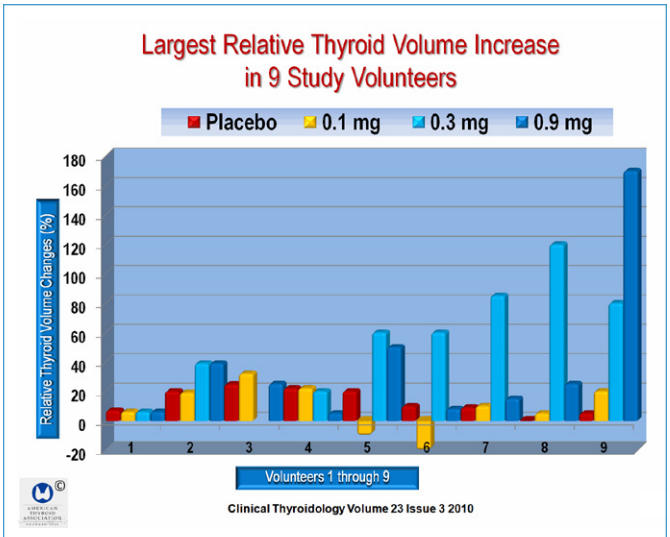

Figure 4. This figure shows the largest relative thyroid volume increase in the 9 study volunteers, which is significantly different from that among the 9 volunteers after injections with placebo and 0.1, 0.3, and 0.9 rhTSH.

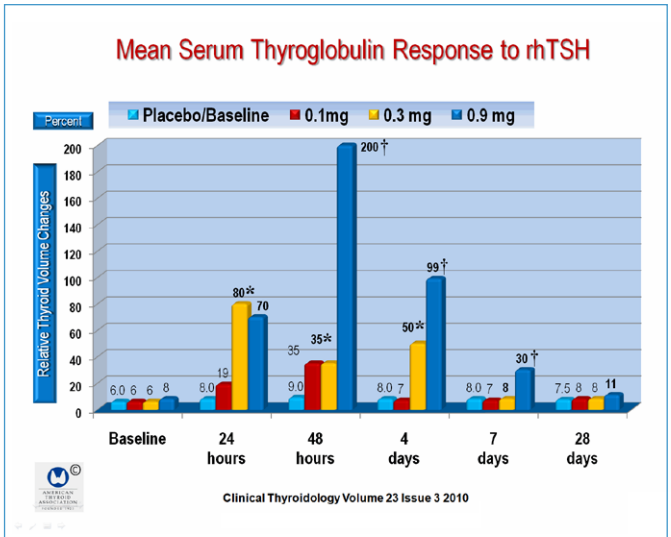

Figure 6. This figure shows the mean serum Tg response to rhTSH. The increase was greater following 0.3 mg rhTSH as compared with 0.1 mg (*P = 0.02) and even higher after 0.9 mg as compared with 0.3 mg (†P = 0.002).

rhTSH, the same individual again reached the highest Tg level (470 µg/L at 24 hours); the second highest level was 58 µg/L at 4 days in the same individual as in the 0.9-mg–rhTSH round

ADVERSE EFFECTS

In addition to the subject who had remarkable thyroid swelling, rhTSH caused various effects related to thyroid hyperfunction, including tachycardia, increased appetite, restlessness, perspiration, headache, nausea, and myalgia or visible thyroid enlargement, thyroid tenderness, or pain. At least one of these symptoms or signs appeared in seven individuals, as compared with five individuals after 0.3 mg rhTSH. Symptoms with or without signs were of short duration and self-limiting and occurred between 4 and 48 hours after rhTSH injection. Only one subject reported restlessness after 0.01 mg rhTSH between 24 and 48 hours after administration. At the end of the 2-year study period, thyroid function and size were unchanged as compared with those at study entry. Neither TSHRAb nor TPOAb developed in any of the subjects.

CONCLUSION

Doses of recombinant human TSH less than 0.1 mg are likely to cause fewer adverse events when given to patients with goiter. The symptoms are usually of short duration and self-limited.

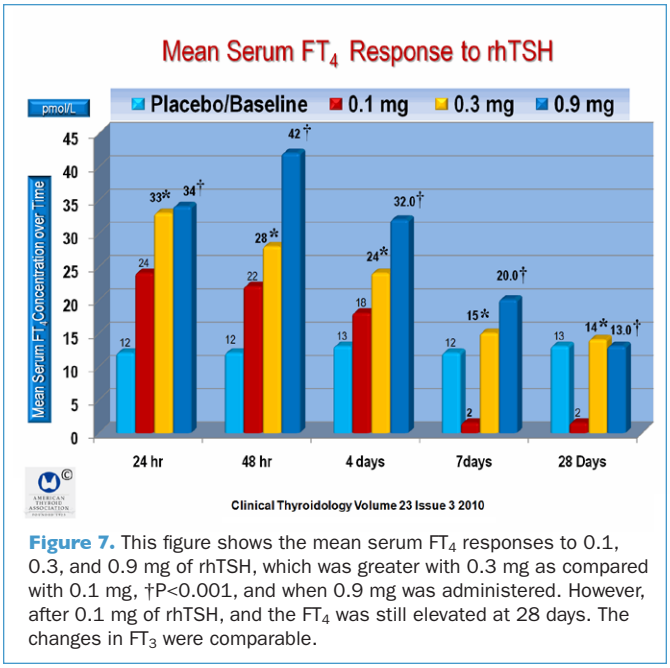

Figure 7. This figure shows the mean serum FT_4 responses to 0.1, 0.3, and 0.9 mg of rhTSH, which was greater with 0.3 mg as compared with 0.1 mg, †P<0.001, and when 0.9 mg was administered. However, after 0.1 mg of rhTSH, and the FT_4 was still elevated at 28 days. The changes in FT_3 were comparable.

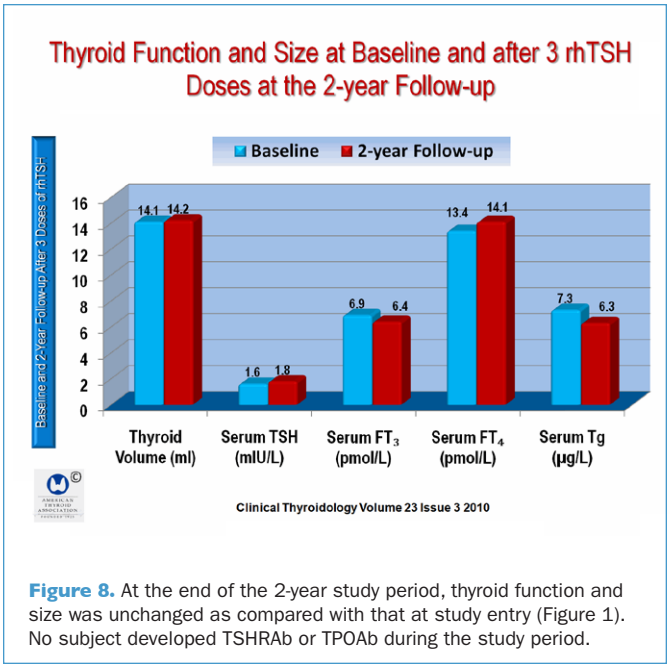

Figure 8. At the end of the 2-year study period, thyroid function and size was unchanged as compared with that at study entry (Figure 1). No subject developed TSHRAb or TPOAb during the study period.

COMMENTARY

This study demonstrates that acute thyroid swelling was induced by rhTSH, which was partly dose- dependent. The authors concluded that the swelling was most likely triggered above a certain threshold that varies among individuals. Thyroid enlargement of 35 to 45% was noted when either 0.3 or 0.9 mg of rhTSH was administered, which was not observed after 0.1 mg of rhTSH. Serum rhTSH-stimulated Tg concentrations were also dose-dependent and varied considerably among study subjects. The peak serum Tg level correlated with the extent of thyroid enlargement, and the same individuals had an increase in both Tg and thyroid volume, suggesting individual differences in sensitivity to rhTSH. The authors offer the caveat that the extent to which these findings can be extrapolated to patients with multinodular goiter (MNG) is not clear.

Over the past decade, the therapeutic use of rhTSH-stimulated radioiodine (^{131}I) has been carefully explored in patients with benign nontoxic MNG. In 2000 to 2004, several studies (1-4) investigating the doses of rhTSH for this indication used approximately 0.01 to 0.9 mg of rhTSH. Still, a single low dose of rhTSH was found to significantly enhance thyroid ^{131}I uptake in patients with MNG. Nevertheless, rhTSH doses of 0.01 mg increased the serum TSH about threefold, and serum T_3 and T_4 concentrations likewise increased significantly. A 2004 study (5) of the long-term effects of ^{131}I given at a median activity of approximately 5 to 15mCi found after a 36-month follow-up that goiter volume was reduced significantly, and after 3 years, goiter was no longer present in 76% of the patients. Nonetheless, some patients had symptoms of hyperthyroidism with or without cervical compression after rhTSH therapy, as opposed to only one patient during placebo treatment (5).

The authors of the present study have made a number of important contributions concerning the use of rhTSH-stimulated ^{131}I for the nonsurgical treatment of benign nontoxic MNG. In 2004, Nielson and associates (6) first studied the effect of rhTSH on thyroid function and ultrasonographically determined thyroid volume in healthy male volunteers. The use of 0.9 mg of rhTSH was found to profoundly stimulate thyroid size and function 1 to 14 days after the rhTSH injection. Serum TSH increased from 2.03 mIU/L (range, 0.99 to 3.07) to more than 200 mIU/L (range, 78.9 to >200), which rapidly declined

4 hours later. Mean serum FT_4 and FT_3 peaked at 48 hours, with levels approximately 30% above baseline (P<0.001). The conclusion was that 0.9 mg of rhTSH may result in a profound stimulation, not only of thyroid function but also of thyroid size and that further dose-response studies are needed to clarify the potential hazards of this therapeutic regimen.

In 2006, the authors of the article under discussion (7) found that injection of 0.3 mg of rhTSH produced goiter enlargement in up to 24% of patients with MNG, raising the concern that this might lead to significant cervical compression when using rhTSH to augment ^{131}I uptake in patients with MNG. The authors concluded that the use of lower rhTSH doses needs to be explored and that further dose-response studies are needed to clarify the potential hazards of this therapy before its routine use for MNG.

In 2009, Fast and associates (8) pointed out that conventional ^{131}I therapy has been used for two decades as an effective and safe alternative to surgery in the treatment of symptomatic nontoxic MNG. They further call attention to the fact that since much higher ^{131}I activities are used when treating nontoxic rather than toxic MNG, there has been reluctance to use this treatment method in many countries, and the ^{131}I uptake in a nontoxic MNG is low, making ^{131}I therapy less feasible. The authors opined that another important matter is the negative correlation between the initial goiter size and goiter volume reduction. With its ability to more than double the thyroidal ^{131}I uptake, rhTSH increases the absorbed radiation dose and thus enhances the reduction of goiter volume by 35 to 56% at the expense of up to a fivefold higher rate of permanent hypothyroidism. The authors suggest that another option is to reduce the amount of ^{131}I with rhTSH preparation, which induces a significant increase in ^{131}I uptake. Extrathyroidal irradiation thus can be reduced without compromising the efficacy of rhTSH-stimulated ^{131}I therapy. They concluded that while still under study, rhTSH-augmented ^{131}I therapy for nontoxic MNG may considerably alter the nonsurgical treatment of benign nontoxic MNG.

The current study by Fast and associates is the next phase in the development of this therapy for patients with benign nontoxic MNG. This is the first study in which the same individuals were given rhTSH repeatedly. Also, in no subjects did the thyroid gland have signs of damage affecting thyroid size, morphology, or function. They acknowledge that theoretically, an acute thyroiditis-like alteration due to rhTSH stimulation might elicit the development of thyroid autoantibodies. Yet, except for a single subject in whom a low titer of TgAb developed on day 28 after 0.3 mg of rhTSH, this otherwise did not happen in this study. The authors suggest that large-scale confirmation trials are needed to fully support this study. Lastly, the authors suggest that the optimal dose of rhTSH in the context of ^{131}I therapy for nontoxic MNG remains to be established.

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Residual lymph-node metastases are relatively common in patients with high-risk PTC, who often have non-avid ^{131}I metastases

Kaneko K, Abe K, Baba S, Isoda T, Yabuuchi H, Sasaki M, Hatakenaka M, Honda H. Detection of residual lymph node metastases in high-risk papillary thyroid cancer patients receiving adjuvant I-131 therapy: the usefulness of F-18 FDG PET/CT. Clin Nucl Med 2010;35:6-11.

SUMMARY

BACKGROUND

This is a retrospective study aimed at evaluating the incidence of residual lymph-node metastases in patients with high-risk papillary thyroid cancer (PTC).

METHODS

The study subjects comprise a total of 37 patients who were treated with adjuvant radioiodine (^{131}I) therapy in the Department of Clinical Radiology in Kyushu University in Japan from 2006 through 2008. Excluded from the study were patients with tumor recurrence, distant metastases, or any other uncontrolled malignancy. Of the 37 patients, 13 were men (35%) and 24 were women (65%). The mean age was 52 years (range, 21 to 72); 10 patients were <45 years (27%) and 27 (73%) were ≥45 years. All patients had one- or two-stage total thyroidectomy, and neck-lymph-node dissection was performed in all patients. The lymph-node dissections included the central compartment (level VI) in 10 patients (27%), the lateral neck compartment in 25 patients (68%), the bilateral lateral compartment in 2 patients (5%), and the mediastinal lymph node in 2 patients (5%). A total of 23 patients (62%) were treated with ^{131}I (first treatment) and the remaining 14 (38%) had ^{131}I therapy 1 year after initial ^{131}I therapy (second treatment) to eliminate the thyroid remnant or malignant tissue. Patients were prepared for ^{131}I therapy with thyroid hormone withdrawal, which increased the mean (±SD) thyrotropin (TSH) to 151±79.8 mIU/L. Patients were treated with 100 to 122 mCi of ^{131}I. The initial ^{131}I therapy was given within 6 months of surgery (range, 1 to 6; mean, 3) to all patients.

RESULTS

Study Patient Characteristics (Figure 1)

A total of 33 residual lymph-node metastases (range, 1 to 14 per patient) were found in 9 patients (24%). Metastases were diagnosed by histology in 18 lesions (55%), by computed tomography (CT) in 6 (18%),, and by positive ^{131}I whole-body scan (WBS) in 14 (42%). (Some lymph-node metastases were identified by more than one imaging method). Of the 9 patients with lymph-node metastases, 7 (78%) were in the initial ^{131}I therapy group and 2 (22%) had second ^{131}I therapy. Five lesions were diagnosed by CT and also had positive ^{131}I WBS and one lesion was identified only by CT, showing an increase in size on the CT obtained 11 months after the initial ^{131}I therapy (Figure 1).

Characteristics of Lymph-Node Metastases (Figure 2)

Of the 33 residual lymph-node node metastases, 22 (67%) were located in the lateral neck (13 in the ipsilateral neck (33%)and 9 in the ipsilateral contralateral area(27%, 1 in the contralateral retropharyngeal region, 5 in the supraclavicular region, and 5 in the upper mediastinum.

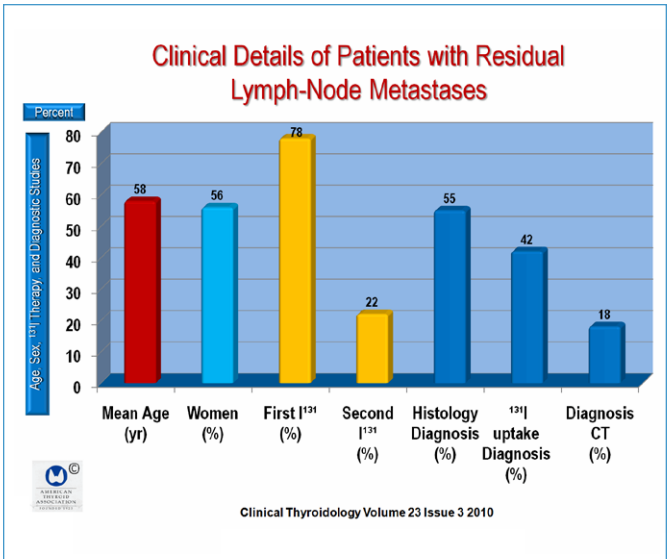

Figure 1. This figure shows the clinical details of patients with residual lymph-node metastases treated with adjuvant ^{131}I therapy. The most sensitive imaging studies in this setting is FDG CT/PET scans.

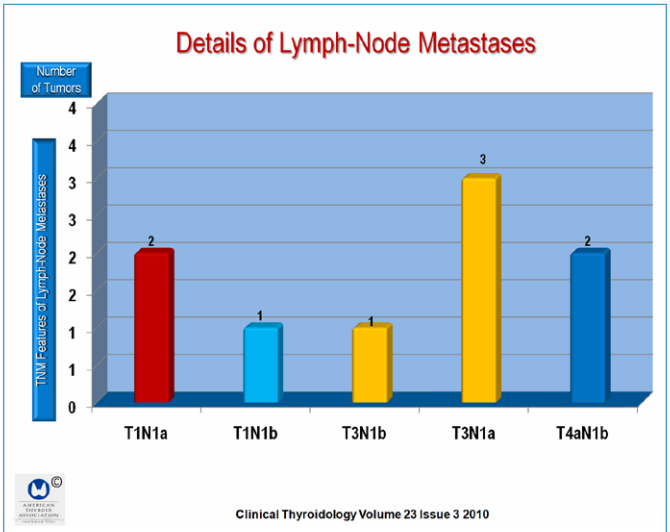

Figure 2. This figure shows the tumor–node–metastases (TNM) staging of residual tumors in this study. A T1N1a is a tumor ≤2 cm with metastases to level IV and prelaryngeal/Delphian lymph nodes. A T1N1b is a similar tumor that has metastases to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph-node metastases. A T3N1b is a tumor >4 cm that is limited to the thyroid or any tumor with minimal extrathyroid extension to sternothyroid muscle or perithyroid soft tissues. A T3N1a tumor is the same size and level of lymph-node metastases as noted above. A T4aN1b tumor is a primary tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.

Abnormal fluorodeoxyglucose (FDG) accumulation was found in 100% of the 33 lymph-node metastases, and the standardized uptake value was significantly higher in lesions without ^{131}I accumulation as compared with lesions that had ^{131}I uptake (6.6±2.8 vs. 4.2±1.8; P = 0.007). Serum thyroglobulin (Tg) levels were significantly higher in patients with residual lymph-node metastases, as compared with patients without lymph-node metastases (709±1470 vs. 25.6±37.1 ng/ml, P = 0.005). Serum Tg concentrations were significantly higher among patients with residual lymph-node metastases as compared with patients without lymph-node metastases (35% vs. 0%, P = 0.03)

CONCLUSION

Residual lymph-node metastases are relatively common in patients with high-risk PTC, despite being treated with adjuvant ^{131}I therapy, which is often caused by metastases that do not accumulate^{131}I. Non–iodide-avid tumors usually accumulate FDG, making CT/positron-emission tomography (PET) scans a highly sensitive means of identifying residual tumors that do not concentrate ^{131}I.

COMMENTARY

Residual lymph-node metastases are relatively common in patients with high-risk PTCs that often do not respond to adjuvant ^{131}I therapy because the tumors have a pattern of non-avid ^{131}I uptake and aggressive tumor recurrences. These tumors often harbor a BRAF mutation, which is most common in tall-cell PTÇs, is second most prevalent in classic PTC, and is least common in follicular variant PTC (1,2).

A comprehensive series of studies by Xing et al. (2,3) found a significant association between BRAF mutation and extrathyroidal tumor invasion (P<0.001), lymph-node metastasis (P<0.001), and advanced tumor stage (P = 0.007) at the time of initial surgery. They found that during a 15-year follow-up, BRAF mutation is significantly associated with tumor recurrence rates, with 25% recurrence with BRAF mutation versus 9% without BRAF mutation (P = 0.004). Xing et al. found on multivariate analysis that conventional predictors of recurrence, including the PTC subtype (odds ratio, 4.0; 95% confidence interval, 1.1 to 14.1; P = 0.03), are significant independent predictors of recurrence. BRAF mutation was even an independent predictor of recurrence in patients with stage I or II tumors (22% with vs. 5% without BRAF mutation; P = 0.002). BRAF mutation was also more commonly associated with non-avid ^{131}I tumors and treatment failure with recurrent disease. Thus, BRAF mutation in PTC is associated with poorer outcomes and independently predicts recurrence. It is likely that what Kaneko et al. are describing are BRAF-positive tumors.

Kaneko et al. report that many of the lymph-node metastases in their series were not recognized on ^{131}I whole-body scans, but were uniformly identified by 18FDG-CT/PET. This is in accord with the ATA thyroid cancer guidelines suggesting that 18FDG-CT/PET studies are particularly useful in the initial staging and follow-up of high-risk patients with poorly differentiated or metastatic tumors, which may be missed with ^{131}I scanning and conventional imaging. This approach is widely accepted and is especially well suited in patients with high-risk PTCs (4-6). Levothyroxine therapy does not influence 18FDG-CT/PET studies, and the positive results often correlate with high Tg levels. The 18FDG-CT/PET results are even more sensitive when recombinant human TSH is given prior to the scan (5).

The observations by Kaneko et al. are in accord with many studies that find that lymph-node metastases are relatively common in patients with high-risk PTC, despite receiving adjuvant ^{131}I therapy, especially when serum Tg levels are high after surgery and ^{131}I therapy has been performed. Also, the finding by Kaneko et al. that high-risk PTCs often have lymph-node metastases that fail to concentrate ^{131}I despite adequate preparation is also in accord with most studies. PTCs that display aggressive growth and resistance to initial therapy are often the sign of a BRAF mutation.

— Ernest L. Mazzaferri, MD, MACP

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The first administration of radioiodine following total thyroidectomy for differentiated thyroid cancer ablates both the thyroid remnant and residual tumor

Tuttle RM, Lopez N, Leboeuf R, Minkowitz SM, Grewal R, Brokhin M, Omry G, Larson S. Radioactive iodine administered for thyroid remnant ablation following recombinant human thyroid stimulating hormone preparation also has an important adjuvant therapy function. Thyroid 2010;20:257-63.

SUMMARY

BACKGROUND

Previously undetected radioiodine-avid metastases are often found in the process of treating patients with radioiodine (^{131}I) for postsurgical thyroid remnant ablation (RRA). It is not entirely clear whether this happens only when using thyroid hormone withdrawal for RRA (THW-RRA) or also occurs with recombinant human thyrotropin (rhTSH-RRA). Moreover, there is uncertainty about whether RRA effectively ablates these previously undetected metastases. The aim of this study was to determine whether rhTSH-RRA has an adjunctive therapeutic effect on metastases found during rhTSH-RRA.

METHODS

The study subjects were 394 patients treated for well-differentiated PTC or follicular cancer at the Memorial Sloan-Kettering Cancer Center from 1997 through 2005. Excluded from the study were patients with known distant metastases or antithyroglobulin antibodies. The decision to prepare patients for RRA with rhTSH or THW was made at the discretion of the attending physicians. The amount of ^{131}I used for RRA in each patient was based on the opinion of a multidisciplinary group of the Thyroid Cancer Board. All had total or near-total thyroidectomy with no known residual tumor or metastatic disease, which was followed by RRA performed without dosimetry. Of this group, 84 (21%) had ^{131}I uptake outside the thyroid bed.

Cross-sectional imaging studies were not routinely performed at the time of RRA in patients known to have ^{131}I-avid cervical uptake. However, all patients who had ^{131}I-avid uptake in the lungs had computed tomography (CT) of the chest. The authors were thus able to identify structural correlates in patients with lung ^{131}I uptake on the RRA scans, but not in patients with ^{131}I uptake outside the bed but confined to the neck.

Follow-up was done at 6- to 12-month intervals in most patients, depending on the patient's risk for persistent disease. Follow-up at 12 to 18 months after RRA included an rhTSH-stimulated whole-body diagnostic ^{131}I scan (DxWBS), which was done in most patients, at the discretion of the attending physician, with or without CT studies. Patients were classified as having no evidence of disease (NED) if they had a negative DxWBS or a serum thyroglobulin (Tg) <2 ng/ml, whereas patients were classified as having persistent disease if the DxWBS showed ^{131}I-avid disease with or without a stimulated serum Tg >2 ng/ml.

RESULTS

Of the 84 patients who had ^{131}I-avid uptake in metastatic lesions outside the thyroid bed, 63 had uptake on the initial diagnostic ^{131}I scan (75%) and 21 (25%) had ^{131}I-avid tumors identified in the posttreatment scan (RxWBS). Of the 84 patients 64 (76%) were prepared for rhTSH-RRA and 20 (24%) were prepared with THW-RRA. In 68 patients (81%) the DxWBS was performed 12 to 18 months after RRA (Figure 1).

Patient and Tumor Characteristics (Figures 1, 2, and 3)

Age, sex, tumor histology, clinical tumor–node–metastasis (TNM) classification, and disease stage were not statistically different in the rhTSH-RRA and THW-RRA groups (Figure 1). Although all patients were considered to be free of distant metastases prior to ablation, 8 of the 84 patients with ^{131}I-avid metastatic tumors had distant metastases (4 each with rhTSH-RRA or THW-RRA), five of whom had lung metastases alone (Figure 2). Their TNM tumor stage was thus changed from M0 to M1. The median ^{131}I activity administered was 144 mCi in the rhTSH-RRA group and 108 mCi in the THW-RRA group (P = 0.307) (Figure 2).

The ^{131}I-avid tumors were initially identified on the ^{131}I DxWBS in most patients either with rhTSH-RRA (75%) or THW-RRA (90%) (P = 0.2). In both groups, ^{131}I-avid tumors were mainly identified as locoregional ^{131}I-avid metastases alone that were found in 60 of 64 patients prepared with rhTSH-RRA (94%) and in 16 of 20 prepared with THW-RRA (80%) (Figure 3). The rest of the patients either had lung metastases alone, 3 in the rhTSH-RRA group (5%) and 2 (10%) in the THW-RRA group, or with locoregional metastases with lung metastases, 6% in the rhTSH-RRA group and 20% in the THW-RRA group) (Figure 3).

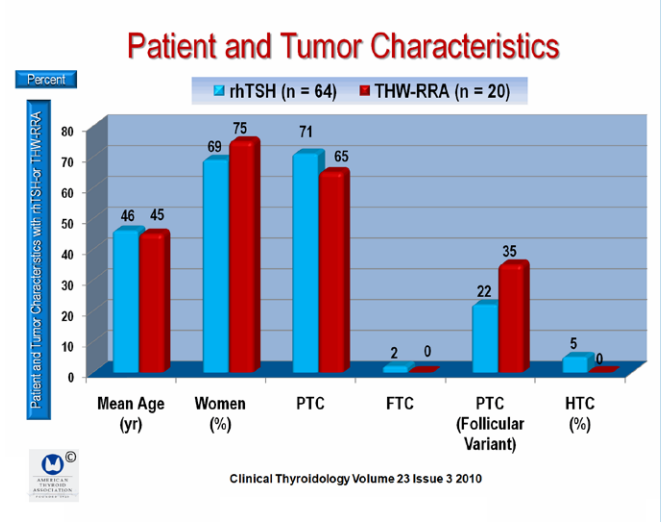

Figure 1. This figure shows the patient and tumor characteristics in the study cohort. FTC = follicular thyroid cancer; HTC = Hürthle-cell cancer; PTC = papillary thyroid cancer; rhTSH = recombinant human thyrotropin; RRA = thyroid remnant ablation; THW = thyroid hormone withdrawal.

Clinical Outcomes (Figure 4 and 5)

A median of 2.7 years after performing RRA, a total of 45 of 64 patients (70%) in the rhTSH-RRA group, and 11 of 20 in the THW-RRA group (55%) were classified as having NED, together comprising 56 of 84 patients with NED (67%). The others were classified as having NED. (Figure 4)

Persistent Disease

Persistent disease was identified in 19 of 64 patients in the rhTSH-RRA group (30%) and in 9 of 20 patients (45%) in the THW-RRA group (Figure 4), comprising 28 of 84 patients (33%) with persistent disease (Figure 4)

Cross-sectional imaging obtained during follow-up identified persistent locoregional tumors in 5 of 19 patients in the rhTSH-RRA group (26%) and in 4 of 9 in the THW-RRA group (44%), with persistently abnormal serum Tg levels during followup. One patient in the rhTSH-RRA group had non–^{131}I-avid lung nodules suspicious for metastases.

Undetectable serum Tg <0.6 ng/ml was achieved in 28 of 64 patients in the rhTSH-RRA group (44%) and 6 of 20 (30%) of the THW-RRA group. However, when NED was defined as an undetectable TSH-stimulated serum Tg value, 25 of the 64 patients (39%) in the rhTSH-RRA group and 5 of the 20 patients

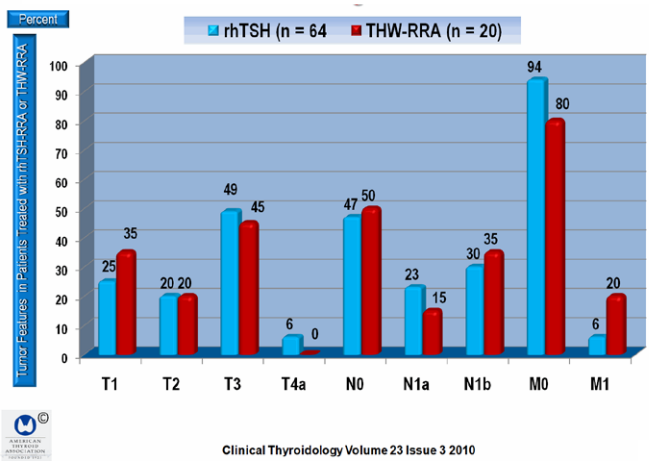

Figure 2. This figure shows the tumor–node–metastasis (TNM) stages of the tumors, lymph nodes, and distant metastases (M0 = no distant metastases, M1 = distant metastases). See Figure 1 for definitions of abbreviations.

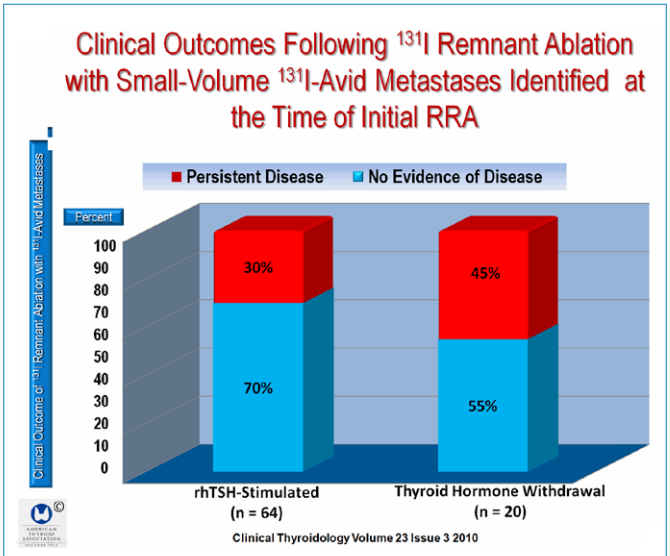

Figure 4. This figure shows the clinical outcomes in patients with small-volume ^{131}I-avid RRA in patients prepared with rhTSH-RRA and THW-RRA. NED = no evidence of disease; rhTSH = recombinant human thyrotropin; RRA = thyroid remnant ablation; THW = thyroid hormone withdrawal.

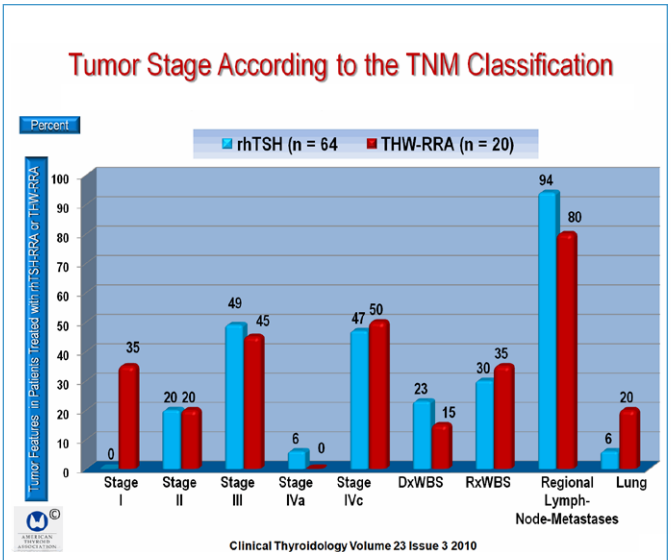

Figure 3.This figure shows tumor stage according to the tumor–node–metastasis (TNM) classification. AJCC = American Joint Committee on Cancer; DxWBS = whole-body diagnostic ^{131}I scan; RxWBS = posttreatment whole-body ^{131}I scan.

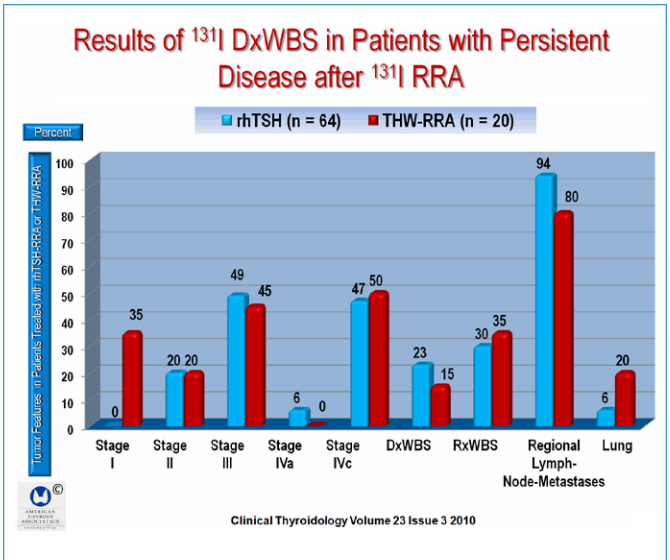

Figure 5. This figure shows tumor stage and locations in patients with persistent disease after remnant ablation performed as rhTSH-RRA and THW-RRA. DxWBS = whole-body diagnostic ^{131}I scan; rhTSH = recombinant human thyrotropin; RRA = thyroid remnant ablation; RxWBS = posttreatment whole-body ^{131}I scan; THW = thyroid hormone withdrawal.

(25%) in the THW-RRA group were classified as NED at 12 to 18 months after RRA (P = 0.19).

Among the patients with ^{131}I-avid tumors identified on the initial DxWBS prior to RRA, 48 of 64 (75%) in the rhTSH-RRA group and 18 of 20 (90%) in the THW-RRA group were found to have persistent disease in the same location on followup DXWBS, which identified persistent tumor in the same location in 9 of 48 (19%) of the rhTSH-RRA group and 0 of 18 in the THW-RRA group (P = 0.01).

New areas of ^{131}I-avid tumor were detected on the follow-up rhTSH-stimulated DxWBS in 1 of 48 patients (2%) in the rhTSH-RRA group and in 2 of 18 (11%) in the THW-RRA group. In this group, there was 1 patient with new uptake in the neck and 1 with new uptake in the lungs (P = 0.17). (Figure 5)

Still, new sites of ^{131}I-avid tumor were detected during the follow-up rhTSH-stimulated DxWBS in 1 of 48 (2%) patients in the rhTSH-RRA cohort (new uptake in the neck) and in 2 of 18 (11%) in the THW-RRA group (1 patient with new uptake in the neck and 1 with new uptake in the lungs) (P = 0.17).

Results of the Followup ^{131}I DXWBS and TSH-stimulated Tg in Patients Classified as having persistent disease after RRA.(Figure 6)

Among the rhTSH-RRA group, structurally identifiable tumor was associated with a TSH-stimulated Tg >2 ng/ml in all five cases and positive DxWBS in one case. Among the THW-RRA group, three of four patients with structurally identifiable tumor had a stimulated Tg >2 ng/ml and two had a positive DxWBS. Based on the follow-up DxWBS in patients with persistent tumor, the site of persistent ^{131}I uptake correlated with the site of ^{131}I uptake on the preablation DxWBS. The site of persistent ^{131}I uptake correlated with the site of uptake on the initial preablation DxWBS in 11 of 12 patients (92%). Only one patient in the rhTSH-RRA group had new uptake in the anterior superior mediastinal lymph node that was not seen on the preablation DxWBS (Figure 6).

At the time of initial ^{131}I-RRA, small-volume ^{131}I-avid metastases were identified in the lungs in eight patients (four each in the rhTSH-RRA and THW-RRA groups). Preoperatively, none had structurally identifiable tumor in chest radiographs or high-resolution chest CT after ^{131}I-avid disease was detected during ablation. For the eight patients with lung metastases, the mean (±SD) ^{131}I activity was 136±40 mCi. Abnormal foci of ^{131}I lung uptake were identified on the RxWBS in one patient in each group (one of four each in the rhTSH-RRA and THW-RRA groups) and were seen in all eight patients on the RxWBS study. After this initial RRA, three of the four patients in the rhTSH group (75%) and one of four (25%) in the rhTSH group were rendered NED (P = 0.49)' by comparison 75% of the rhTSH group with locoregional disease were rendered NED, as compared with 63% of the THW group with locoregional disease (P = 0.41). (Figure 7)

CONCLUSION

The first ^{131}I administration following total thyroidectomy for differentiated thyroid cancer has both an ablative and an adjuvant (tumoricidal) function.

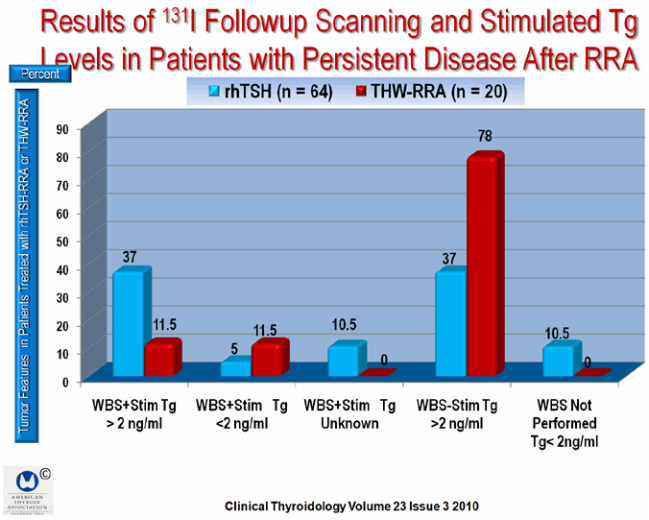

Figure 6. This figure shows the results of ^{131}I DXWBS scanning and stimulated serum Thyroglobulin measurements in patients classified as having persistent disease after ^{131}I RRA. This figure is constructed from Table 2 of Tuttle et al.

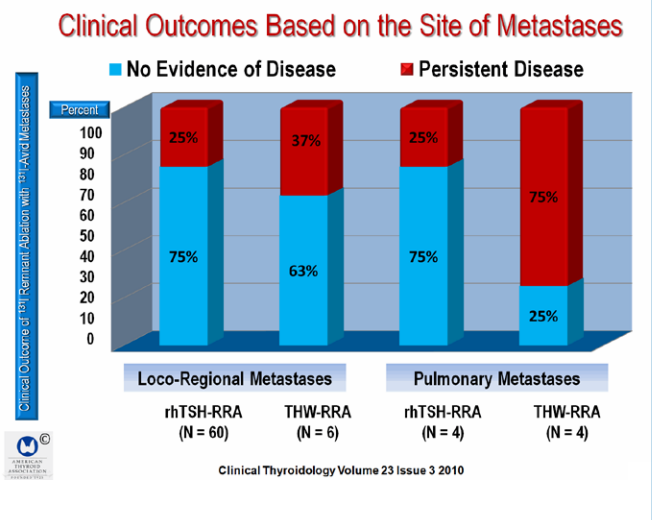

Figure 7. This figure shows the clinical outcomes based on the site of ^{131}I Metastatic disease. Similar adjuvant therapy effects were seen in the locoregional metastases in both rhTSH –RRA and THW-RRA preparation.

COMMENTARY

The aim of this study was to determine whether ^{131}I effectively destroys previously undetected metastases in the process of performing RRA, either by rhTSH stimulation or THW. Although this seems to be a simple, straightforward goal, several variables have an impact on the final conclusion of this study. For instance, the first signal of residual disease in the 84 patients in this study was the finding of ^{131}I-avid uptake outside the thyroid bed during the initial RRA. Metastases were found in 64 of the 84 patients(76%) who had rhTSH-RRA and 20 (24%) who had THW-RRA. This depends on the accuracy of RxWBS and the specific imaging studies used to identify the disease. Also, how the absence of disease is determined rests heavily on the outcome of the study. The results of this study show that rhTSH-RRA was successful as adjuvant therapy in 70% of the patients when NED was designated as a Tg <2 ng/ml; however, when NED was designated as undetectable Tg, 30 of 84 patients (36%) were free of disease. The authors mention that in trying to determine whether the administered activity for RRA destroyed a specific tumor, they chose to use an outcome of either NED or persistent disease.

In a relatively recent prospective randomized study, Pilli et al. (1) performed a multicenter study of 72 patients with differentiated thyroid cancer aimed at identifying whether patients randomly assigned to receive 50 or 100 mCi for RRA by rhTSH preparation had similar outcomes. The outcome of rhTSH-RRA was assessed 6 to 8 months after the initial therapy. Successful RRA was designated as no visible uptake on an rhTSH-stimulated DxWBS, and an undetectable rhTSH-simulated serum Tg <1 ng/ml in 79% of the patients treated with 50 mCi and 67% in the group treated with 100 mCi (P = 0.46), showing that therapeutic activities of 50 and 100 mCi of ^{131}I were comparable, even in the presence of lymph-node metastases. In this group, lymph nodes were present at surgery in 13 patients, and 5 had lymph node metastases discovered on the rhTSH-RRA posttreatment scans. Thus, 18 patients had N1 at initial treatment and rhTSH-RRA, 4 of whom had no evidence of disease after surgery, and in 11 patients lymph-node metastases disappeared after rhTSH-RRA and 2 patients had persistent disease. Of the patients with lymph-node metastases, most had uptake on the RxWBS. In most of these cases, rhTSH-RRA ablated not only the thyroid remnant but also the lymph-node metastases. The authors of this study mention that their study lacks long-term follow-up, and as a result, it cannot be interpreted as a definitive cure, but only as an indication of apparent remission. It remains uncertain whether smaller amounts of ^{131}I, in the range of 50 mCi, can achieve a therapeutic effect on lymph-node metastases, although RRA can be successful achieved with 30 to 50 mCi of ^{131}I (2-4).

The study by Tuttle et.al also provides evidence that remnant ablation may destroy preoperatively unrecognized lymph-node metastases. The strength of this study is the large number of patients and the followup of nearly 3 years. One of the weaknesses of the study is the criteria used to identifying patients with no evidence of disease. Patients were classified as having no evidence of disease if they had a negative DxWBS or a serum thyroglobulin (Tg) <2 ng/ml, whereas patients were classified as having persistent disease if the DxWBS showed ^{131}I-avid disease with or without a stimulated serum Tg >2 ng/ml. The best criteria to identify tumor is a rising serum Tg level, or an undetectable serum Tg that fails to increase in response to TSH stimulation, either by THW or rhTSH, with no imaging evidence of tumor. In this regard, the Tuttle study falls somewhat short. The authors also mention that, their patients were treated and evaluated before they incorporated the routine use of single photon emission computed tomography (SPECT) imaging, and therefore, correlating ^{131}I uptake with a specific structural abnormality could not be rigorously pursued. As a result, if the RAI-avid site was seen on the DXWBS prior to ablation, it is not possible to conclude with a ^{131}I DXWBS study that the RAI-avid tumors were destroyed.

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REVIEW ARTICLES, GUIDELINES & HOT NEW ARTICLES

REVIEW ARTICLES

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DISCLOSURE

Dr. Mazzaferri is a consultant to Genzyme.

Dr. Sipos receives honoraria from Abbott and Genzyme for providing lectures.

The ATA invites you to

Join Us!

American Thyroid Association Spring 2010 Meeting

Thyroid Disorders in the Era of Personalized Medicine

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

Invited Audience...

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

Program Design...

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

American Thyroid Association

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

Registration is now open.
Meeting information: www.thyroid.org

SPRING 2010 MEETING-AT-A-GLANCE

TIME	THURSDAY May 13, 2010	FRIDAY May 14, 2010	SATURDAY May 15, 2010	SUNDAY May 16, 2010
6:45 AM - 8:00 AM	FELLOWS CONFERENCE (7:00 AM-3:30 PM)		EARLY RISER SYMPOSIUM	
8:00 AM - 8:15 AM		WELCOME	BREAK	
8:15 AM - 9:15 AM		PLENARY LECTURE (8:15-9:15)	PLENARY LECTURE (8:15-9:15)	SYMPOSIUM (8:00-9:30)
9:15 AM - 9:45 AM	ADVANCED ULTRASOUND WORKSHOP (9:30 AM-1:30 PM)	COFFEE BREAK (9:15-9:45)	COFFEE BREAK (9:15-9:45)	SYMPOSIUM (9:30-11:00)
9:45 AM - 11:15 AM		SYMPOSIUM (9:45-11:15)	SYMPOSIUM (9:45-11:15)	*Program subject to change*
11:15 AM - 12:45 PM		SYMPOSIUM (11:15-12:45)	SYMPOSIUM (11:15-12:45)	
12:45 PM - 1:30 PM	ATA BOARD MEETING (12:00 NOON-4:30 PM)	LUNCH BREAK	LUNCH BREAK	
1:30 PM - 2:30 PM	INTRODUCTORY ULTRASOUND WORKSHOP (12:45-6:00)	ATA COMMITTEE MEETINGS (12:45-1:30)		
2:30 PM - 4:00 PM		MEET THE PROFESSOR WORKSHOPS (3) (1:30-2:30)	MEET THE PROFESSOR WORKSHOPS (3) (1:30-2:30)	
4:00 PM - 4:30 PM		SYMPOSIUM (2:30-4:00)	SYMPOSIUM (2:30-4:00)	
4:30 PM - 6:00 PM	WOMEN IN THYROIDOLOGY MEETING (4:30-6:00)	COFFEE BREAK (4:00-4:30)	COFFEE BREAK (4:00-4:30)	
6:00 PM - 7:30 PM	WELCOME RECEPTION (6:00-7:30)	SYMPOSIUM (4:30-6:00)	PLENARY LECTURE (4:30-5:30)	
		ATA BUSINESS MEETING (6:00-7:00)	ATA RECEPTION AND BANQUET (7:30-11:00)	

AMERICAN THYROID ASSOCIATION
FOUNDED 1923
www.thyroid.org

CME Jointly Sponsored by the American Thyroid Association and the University of Colorado Denver School of Medicine

AMERICAN THYROID ASSOCIATION
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SCHOOL OF MEDICINE
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American Thyroid Association Spring 2010 Meeting

Thyroid Disorders in the Era of Personalized Medicine

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

REGISTRATION FORM

Meeting details available at www.thyroid.org

ALL REQUESTED INFORMATION MUST BE PROVIDED TO PROCESS REGISTRATION FORM. ALL FEES ARE IN US DOLLARS.

NAME: FIRST _____ MIDDLE _____ LAST _____ NICKNAME FOR BADGE _____

PROFESSIONAL TITLE _____

PROFESSIONAL DEGREE(S) (PLEASE CHECK ONE):

a. ☐ MD b. ☐ PhD c. ☐ MD, PhD d. ☐ RN/PA e. ☐ DO f. ☐ OTHER _____

ORGANIZATION _____

ADDRESS 1 _____ PLEASE SPECIFY: ☐ Home ☐ Office ☐ Other

ADDRESS 2 _____

CITY _____ STATE/PROVINCE _____ ZIP CODE + 4 COUNTRY _____ IF OUTSIDE THE U.S., COUNTRY/CITY CODE _____

PHONE _____ FAX _____ E-MAIL ADDRESS _____

SPECIAL NEEDS/DIETARY RESTRICTIONS _____

EMERGENCY CONTACT: _____ DAYTIME PHONE: _____ EVENING PHONE: _____

REGISTRATION CATEGORIES & FEES (PLEASE CHECK APPLICABLE FEES):

	DISCOUNTED (received between March 15 – April 25)	FULL FEE (received **after** April 25)
(M) **ATA MEMBER**	☐ $560	☐ $595
(N) **NON-MEMBER**	☐ $725	☐ $795
ATA FELLOWS (ASSOCIATE MEMBERS)	☐ $200	☐ $200
Focus: ☐ (AC)Clinical or ☐ (AB)Basic		
NON-MEMBER FELLOWS/STUDENTS/RA*	☐ $225	☐ $225
Focus: ☐ (NC)Clinical or ☐ (NB)Basic		
*(*Verification req.; Send letter from Prog. Dir. to 703-998-8893 / thyroid@thyroid.org)*		
(P) **PRESS (VERIFICATION REQUIRED)**	☐ $0	☐ $0
DAILY REGISTRATION RATE		
(M) **MEMBER**	☐ $325	☐ $350
(N) **NON-MEMBER**	☐ $450	☐ $500
Indicate day(s): ☐ (F) *FRI 5/14 (includes Thursday Welcome Reception)* ☐ (S) *Sat./Sun. 5/14 & 5/16*		
(G) **SPOUSE/GUEST**	☐ $95	☐ $95

(Spouse/Guest registration admits attendee (with badge only) to the welcome reception, coffee breaks, exhibit hall and Spring banquet at reduced rate)

(1) Spouse/Guest Name: _____

(2) Spouse/Guest Name: _____

(DS1) Do you want to participate in the **"Bring A Colleague"** Registration Discount of $105 per registrant? ☐ Yes ☐ No

(NOTE: Offer applies to one member/one non-member registration combination only–both registrants must register independently and provide the email address of the attendee they wish to share the discount with below.)

Bring a Colleague Partner Name: _____

Bring a Colleague Partner Email Address: _____

1. I require a CME certificate for my attendance at this meeting. ☐

2. I consider myself primarily (please list one): _____

a. Clinician b. Educator c. Scientist d. Other: _____

3. My work is best described as (please list one): _____

a. Endocrinology b. Nuclear Medicine c. Surgery
d. Internal Medicine e. Family Medicine f. Oncology
g. Other _____

4. My place of work is (please list one): _____

a. Academic b. Private Practice c. Administration
d. Hospital e. Government/Military f. Corporate/Industry
g. Managed Care h. Other: _____

5. What is your membership affiliation (other than ATA)?

a. ☐ ENDO b. ☐ AAES c. ☐ AAO-HNS d. ☐ LWPES e. ☐ AACE
z. ☐ Other: _____

6. How did you hear about the ATA Annual Meeting?

a. ☐ ATA Website b. ☐ ATA E-mail c. ☐ ATA Mailed Promotional Piece
d. ☐ ATA Publication z. ☐ Other: _____

7. ATA Photo Release: ATA uses photographs of conference participants in our promotional materials and journals. By virtue of your attendance at this meeting, ATA reserves the right to use your likeness in such materials.

MEET THE PROFESSOR WORKSHOPS

Meet the Professor (MTP) workshops will be open to attendees at no charge on a first-come, first served basis. There is open seating during each time slot. There will be three workshops offered on Friday and Saturday. Please review the meeting agenda at *www.thyroid.org* for MTP speaker names and topics.

SPECIAL ACTIVITY REGISTRATION (CHECK ALL THAT APPLY)

☐ **$325** **(U1) ADVANCED ULTRASOUND LECTURE AND PRACTICUM**
Thursday, 5/13, 9:00 AM – 1:30 PM *(Limited seating, 1st-come–1st-served basis)*

☐ **$295** **(U2) INTRODUCTORY HANDS-ON ULTRASOUND LECTURE AND PRACTICUM**
Thursday, 5/13, 12:45 – 6:00 PM *(Limited seating, 1st-come–1st-served basis)*

☐ **$0** **(ACO) ATA Committee Meetings**
Friday, 5/14, 12:45 – 1:30 PM *(For current ATA committee members only)*

☐ **$0** **(WIT) Women in Thyroidology** Thursday, 5/13, 4:30 – 6:00 PM

☐ **$0** **(REC) ATA Welcome Reception** Thursday, 5/13, 6:00 – 7:30 PM

☐ **$55** **(BAN) Registered Attendees or Spouse/Guest–Spring Banquet Fee**
Saturday, 5/15, 7:30 – 11:00 PM *(NOTE:* **(BNF)** *Registered Fellows' Rate is $25)*

☐ **$95** **(BNQ) Non-Registered Attendees, Spouse/Guest or Press–Spring Banquet Fee** Saturday, 5/15, 7:30 – 11:00 PM

TOTAL FEES (PLEASE TOTAL EACH LINE ITEM IF MORE THAN ONE):

$ _____	Attendee Registration Fee (sum all appropriate fees here)	
$ _____	Spouse/Guest Registration Fee ($95 per guest)	
$ _____	Introductory Ultrasound Lecture and Practicum ($295)	# _____
$ _____	Advanced Ultrasound Lecture and Practicum ($325)	# _____
$ _____	ATA Meeting Registrant–Spring Banquet Fee ($55)	# _____
$ _____	Registered Spouse/Guest–Spring Banquet Fee ($55)	# _____
$ _____	Non-Registered Attendee/Guest/Press–Banquet Fee ($95)	# _____
$ _____	Registered Fellows–Banquet Fee ($25)	# _____
$ _____	Donation to Fellows' Travel Fund	
$ _____	**TOTAL DUE** *(provide a check or credit card for this amount)*	

SUBMISSION AND PAYMENT

☐ Checks and money orders for registration payable to the **American Thyroid Association** in U.S. dollars drawn on a U.S. bank.

☐ MasterCard ☐ VISA ☐ American Express

CARD NUMBER _____

EXPIRATION DATE (MONTH/YEAR) _____ 3 OR 4 DIGIT SECURITY CODE _____

PRINT CARDHOLDER'S NAME _____ SIGNATURE _____

REGISTER ON-LINE at the secure ATA web site *www.thyroid.org*.
FAX completed form with credit card payment to 678-341-3081. If you **FAX**, DO NOT MAIL.
MAIL your completed registration form with payment to: ATA Registration, c/o QMS, 6840 Meadowridge Court, Alpharetta, GA 30005. Phone: 678-341-3056.
ATA REFUND POLICY: Refund requests must be submitted in writing *(e-mail to thyroid@thyroid.org)*. Requests submitted by fax or e-mail before March 28, 2010, will receive a registration refund less a 50% processing fee. No refunds will be made if submitted after March 28, 2010. Refunds will be processed 30 days after the meeting.
Please keep a copy of this form for your records.

CME Jointly sponsored by the University of Colorado Denver School of Medicine

ATA Thyroid Ultrasound Courses Available: Register Now at www.thyroid.org

Ultrasound Course Date: Thursday, May 13, 2010

(prior to the start of the ATA Spring 2010 Meeting)

Don't miss your opportunity to participate in these great satellite programs. ATA Member Dr. Susan Mandel has organized two excellent sessions geared toward the introductory and advanced ultrasound learner. Sign up for the ultrasound courses when registering for the ATA Spring Meeting.

Advanced Thyroid Ultrasound Workshop and Practicum 9:00 AM – 1:30 PM

(Limited seating – advance registration required)

Lectures: 9:00 AM – 11:30 AM
Metastatic Lymph Nodes: Why They Matter *Jennifer Sipos*
Ultrasound Evaluation of Lymph Nodes *Susan J. Mandel*
Parathyroid Ultrasound *Stephanie A. Fish*
Cytology: Preparation and Interpretation *Nicole A. Massoll*

Hands-On Practicum (11:30 AM – 1:30 PM): Diagnostic Thyroid Ultrasound *Preceptors TBD*

Program Objectives: Upon completion of this educational activity, participants will be able to:

- Review indications for ultrasound examination of cervical lymph nodes in thyroid cancer patients
- Demonstrate the imaging procedure and characteristics of benign and malignant lymph nodes
- Discuss and illustrate the imaging characteristics of parathyroid adenomas
- Practice slide preparation and cytology specimen interpretation

Course Fee: $325 for Registered ATA Spring 2010 Meeting attendees
Credits: 4.5 CME Credits Available

Introductory Hands-On Thyroid Ultrasound Workshop and Practicum 12:45 PM – 6:00 PM

(Limited seating – advance registration required)

Lectures: 12:45 PM – 3:00 PM
Physics of Ultrasound *Stephanie A. Fish*
Ultrasound of Thyroid Nodules *Susan J. Mandel*
Ultrasound of Diffuse Thyroid Disorders *Erik K. Alexander*
Ultrasound-Guided Fine-Needle Aspiration *Bryan R. Haugen*

Hands-On Practicum (3:05 PM– 6:00 PM): Ultrasound-Guided Fine Needle Aspiration *Preceptors TBD*

Program Objectives: Upon completion of this educational activity, participants will be able to:

- Review the technology of ultrasound imaging
- Demonstrate the imaging characteristics of thyroid nodules and diffuse thyroid disorders
- Perform diagnostic thyroid ultrasound imaging and identify normal neck anatomy
- Perform ultrasound-guided fine-needle aspiration biopsies using a simulated model
- Practice slide preparation and cytology specimen interpretation

Course Fee: $295 for Registered ATA Spring 2010 Meeting attendees
Credits: 4.75 CME Credits Available

Full program, registration and meeting details available online at www.thyroid.org. We hope to see you in May!

Clinical Fellows' Track for Trainees

Spring 2010 Meeting
of the American Thyroid Association (ATA)

May 13–16, 2010
The Hyatt Regency, Minneapolis, Minnesota
www.thyroid.org

Description
The Spring 2010 Meeting of the ATA in Minneapolis will include the 6th Annual Clinical Fellows' Track program, a parallel and integrated basic program designed for clinical fellows and trainees that will provide lectures and skill enhancement opportunities. In addition to participating in the regular meeting program, the fellows will attend special presentations by ATA meeting faculty focusing on case studies, hands-on ultrasound experience and career development.

Objective
The ATA's 6th Annual Clinical Fellows' Track will offer multiple presentations throughout the ATA Spring 2010 Meeting May 13–16 to heighten the MD fellow educational experience. The ATA will shepherd fellows through the highly regarded Spring Meeting and interweave faculty presentations, panels, case presentations, workshops and more during this 2 ½ day fellows' track.

Registration policies and procedures

- First step:
  Join the ATA now! It's free! All fellows' track applicants must have joined the ATA – go online to www.thyroid.org to submit a membership application (Fax or email statement from Program Director with start and end date of your fellowship).
- Second step:
  Detailed registration information for the ATA Clinical Fellows' Track will be posted online in March 2010 at www.thyroid.org.
- Third step:
  Questions regarding the ATA fellows' track should be emailed to Jared Hoke at jhoke@thyroid.org. Please be sure to include your full name, university, and phone number.

We look forward to seeing you in Minneapolis!

ATA • 6066 Leesburg Pike, Suite 550 • Falls Church, VA 22041
(703) 998-8890 • www.thyroid.org

ATA Thyroid Marketplace

Thyroid MP3 Downloads

http://www.thyroid.org/marketplace/index.html

AUDIO PRESENTATIONS available as MP3 Files on CD ROM
80th Annual Meeting of the ATA — Palm Beach, Florida

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Ceramic Tumbler

Wall Clock

Stonewashed Cap

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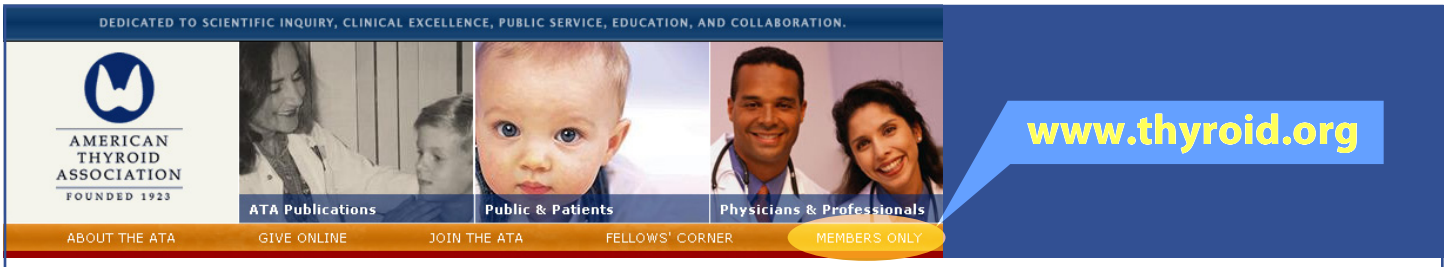

2010 ATA Annual Dues Renewal Online

To access, please go to the ATA Member Sign-In page to login to your account.
Once logged in, please select Pay Dues.

ATA dues provide and support:

- subscription to *THYROID*,
- website inclusion under FIND A SPECIALIST,
- ATA meeting registration discounts,
- important ATA Guidelines,
- *Clinical Thyroidology*, *Clinical Thyroidology for Patients*,
- ATA Research Grants, and
- Patient sources online.

Thank you for supporting the ATA's vital mission and goals in 2010!