

# CLINICAL THYROIDOLOGY

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## EDITORS' COMMENTS

This is the fifth 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  
Jennifer A. Sipos, MD

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# Cytology suspicious for or indicative of PTC is associated with younger age, male sex, and solitary versus multiple nodularity

Rago T, Fiore E, Scutari M, Santini F, Di Coscio G, Romani R, Piaggi P, Ugolini C, Basolo F, Miccoli P, Pinchera A, Vitti P. Male sex, single nodularity, and young age are associated with the risk of finding a papillary thyroid cancer on fine-needle aspiration cytology in a large series of patients with nodular thyroid disease. *Eur J Endocrinol* 2010;162:763-70.

## SUMMARY

### BACKGROUND

Thyroid nodular disease is common, especially in iodine-deficient areas, whereas the incidence of thyroid cancer, while steadily increasing in the past three decades, is relatively low, comprising approximately 1% of all new malignancies. The risk is quite low that a solitary thyroid nodule or multiple nodules within a goiter harbor clinically evident malignancies. Still, the risk of malignancy is higher in patients who have thyroid surgery for compressive symptoms, hyperthyroidism, or Graves' disease, during which occult thyroid cancers are often discovered by serendipity. Fine-needle aspiration biopsy (FNAB) of thyroid nodules has become the main source of distinguishing malignant from benign nodules. While FNAB has reduced surgical intervention by 25% and has increased the yield of cancer in surgical specimens to more than 30%, approximately 20 to 25% of FNAB cytology specimens are nondiagnostic or indeterminate, and a few (5%) have false positive or false negative cytology results. Thus, some patients still may undergo unnecessary surgery on the basis of FNAB. The objective of this study was to evaluate the risk of papillary thyroid carcinoma (PTC) in FNAB cytology in a cohort of 34,120 patients.

### SUBJECTS AND METHODS

#### Thyroid-Function Tests

Serum free thyroxine (FT<sub>4</sub>), free triiodothyronine (FT<sub>3</sub>), antithyroglobulin antibodies (anti-TgAb; normal TgAb, <30 U/ml), antithyroid peroxidase antibodies (anti-TPOAb) (normal, <10 U/ml) were measured by immunoenzyme assays. In addition, serum thyrotropin (TSH), and TSH-receptor antibodies (TRABs), normal ≤2 UI/L) were measured. Serum calcitonin was measured by Immunoradiometric IRMA (normal values, <10 ng/ml).

#### Patients

From 1997 through 2004, a total of 34,266 patients had FNAB performed in the Department of Endocrinology at the University of Pisa. Of this group, 27,826 (81%) were women, with a mean (±SD) age of 48±23 years (range, 13 to 76); 6440 were men (19%), with a mean age of 50±17 years (range, 13 to 80). The diagnosis of thyroid disease was established on the basis of clinical, ultrasound (US), and laboratory criteria as follows: multinodular goiter (MNG; n = 19,923); enlarged thyroid with multiple nodules on US and thyroid scintiscan; solitary nodules (SN; n = 13,549); single nodule in an enlarged thyroid or isolated nodule in a thyroid of normal volume; nodular Graves' disease (GD; n = 286); and nodular Hashimoto's thyroiditis (HT; n = 508). The diagnosis of nodular GD was made by standard criteria, including active or treated hyperthyroidism, goiter with a diffuse hypoechoic thyroiditis pattern on US, ophthalmopathy and positive serum anti-TRABs or TPOAbs. Nodular HT was

diagnosed with a diffuse hypoechoic thyroiditis pattern on US and high TgAb levels, with or without TPOAbs.

FNAB was performed on all scintigraphically cold nodules, either solitary or in MNGs when the tumor was >1 cm, and in those <1 cm in the presence of clinical signs with or without ultrasound suspicious for malignancy. Thyroid surgery was advised for all patients with cytology suspicious or positive for carcinoma and in most patients with indeterminate cytology. Surgery was also advised for patients with thyroid nodules showing benign or nondiagnostic cytology with symptoms of compression or with nodules that were ultrasonographically suspicious for malignancy.

A comparison between cytologic and histologic findings was possible in 3406 nodules from 3004 patients who comprise the study cohort.

### FNAB Cytology

FNAB was performed under ultrasound guidance, using a 23-gauge needle, usually with multiple passes. Cystic or mixed lesions had multiple needle passes in different parts of the nodule, and the sediment was completely aspirated and examined. The aspiration was repeated if the cytology was macroscopically insufficient or on immediate microscopic examination without staining. The sample was considered adequate if the aspirate had at least five or six well-defined and well-preserved groups of follicular epithelial cells, with each group containing at least 10 cells.

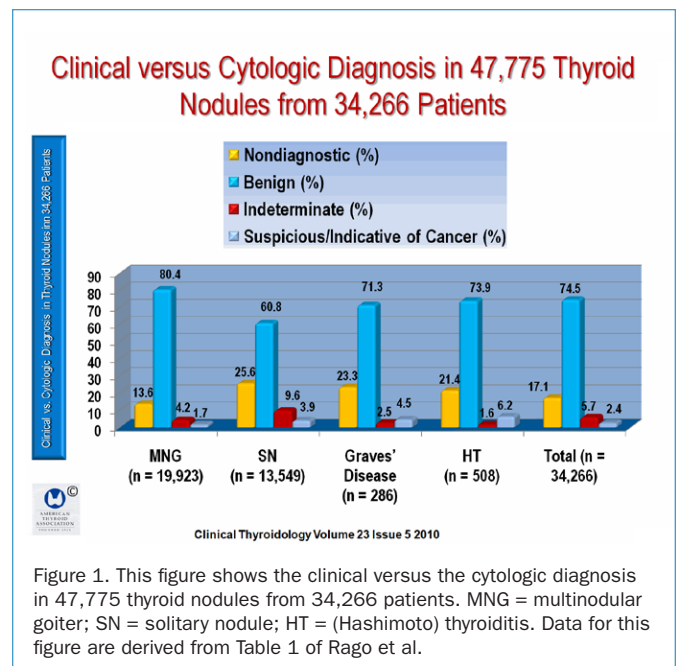


Figure 1. This figure shows the clinical versus the cytologic diagnosis in 47,775 thyroid nodules from 34,266 patients. MNG = multinodular goiter; SN = solitary nodule; HT = (Hashimoto) thyroiditis. Data for this figure are derived from Table 1 of Rago et al.

The cytology was considered adequate according to the British Thyroid Association as follows: (i) nondiagnostic; (ii) nonneoplastic (benign or negative for malignancy); (iii) follicular; (iv) suspicious for malignancy; and (v) indicative of malignancy.

**Histopathologic Diagnosis**

The histopathologic diagnosis was made blindly by two independent pathologists who were unaware of the cytologic result and according to the World Health Organization guidelines. Discordant diagnoses were reconciled by joint reexamination of each case. The histologic diagnosis of a microcarcinoma <1 cm was classified as a benign tumor.

**RESULTS**

**FNAB Cytology in 47,775 Nodules from 34,266 Patients. (Figure 1)**

The overall results of FNAB cytology in 47,775 nodules from 34,266 patients is shown in Figure 1. In all, 74.5% of the nodules were cytologically benign, 5.7% were indeterminate, 2.4% were suspicious for carcinoma, and 17.1% were nondiagnostic. The accuracy of cytology was evaluated by comparing the FNAB results with the histology results from surgery.

**Comparison of FNAB Cytology and Surgical Histology Results (Figure 2)**

Figure 2 shows the comparative results of cytology and histology in 3406 nodules from 3004 patients who had thyroidectomy. All nodules with cytology indicative of carcinoma (n = 504) were confirmed as malignant on the basis of the tumor histology; however, 11 of 391 nodules with an FNAB suspicious for malignancy were benign based on histology. Eight had a nodular goiter, three of which had extensive necrotic features; two had Hashimoto's thyroiditis, one with a 2-mm PTC and one with pseudopapillary organization based on cytology that was suspicious for or indicative of thyroid cancer on the basis of histology.

Of 1295 nodules with benign cytology, 1271 (98.2%) were confirmed as benign hyperplastic nodules or adenomas, whereas 24 of 1295 (1.8%) were found to be malignant on the basis of histology; 23 were PTC, and of these, 19 were follicular variants, 4 were classic variants, and 1 was a minimally invasive follicular carcinoma. Among these 24 patients, 13 had thyroidectomy on the basis of a single isolated nodule, and 11 with MNG had surgery based the size of the nodules in 18, and was performed on the basis of clinical echographic patterns suspicious for malignancy in 5 patients and for toxic MNG in 1.

Of 969 nodules with indeterminate cytology, 283 (29.3%) were malignant based on the histology; 240 were PTCs (164 follicular variants, 66 classic, 2 oxyphilic, and 8 tall-cell variants), 28 were minimally invasive follicular carcinomas, and 10 were poorly differentiated Hürthle-cell carcinomas. In all, 70.7% (686 of 969) of the nodules with indeterminate cytology were benign, of which 159 were hyperplastic nodules, 520 were adenomas, and 7 were benign nodules in HT.

Of 247 nodules with nondiagnostic cytology obtained from patients who had thyroidectomy on the basis of nodule size, or for clinical ultrasound findings suggesting malignancy, 82 (33%) were malignant—63 PTCs, 12 medullary carcinomas, 3

follicular carcinomas, 2 Hürthle-cell carcinoma sand 2 poorly differentiated carcinomas—and 165 (67%) were benign based on the histology (Figure 2).

When indeterminate cytology results were considered as negative for neoplasm, the FNAB cytology had a sensitivity of 69%, a specificity of 99%, and an accuracy of 88%. If indeterminate results were included among the positive results for neoplasm, the sensitivity increased to 92%, while specificity was 67% and accuracy was 76%. Foci of PTC were occasionally found on a histologic examination in 222 of 3004 patients and were not included among malignant lesions under study.

**Clinical Features Associated with PTC on FNAB (Figure 3)**

Patients were classified according to the following cytologic results: (i) nondiagnostic (7126 patients), (ii) benign nodular thyroid disease (BNTD; 23,587 patients), (iii) indeterminate (2506 patients), (iv) suspicious for or indicative of carcinoma (1047 patients) (Figure 3). Patients with MNG were assigned to one of the diagnostic classifications according to the following criteria: BNTD, if all nodules were diagnostic for benign lesion; cancer, if they had at least one nodule with this cytology; indeterminate, if they had at least one nodule with this cytology and none with carcinoma; and nondiagnostic, if they had one or more nodules with this cytology and none with carcinoma or indeterminate cytology. In the cancer group, 901 patients had cytology suspicious for or indicative of PTC and 146 had other types of neoplasia, including 53 medullary carcinomas, 26 poorly differentiated carcinomas, 1 Hürthle-cell carcinoma, and 66 lymphomas or metastases of nonthyroidal neoplasia. To establish risk factors for PTC based on cytology, various clinical parameters of the patients with PTC (n = 901) were reviewed in comparison with all the other diagnostic classes taken together (n = 33,219).

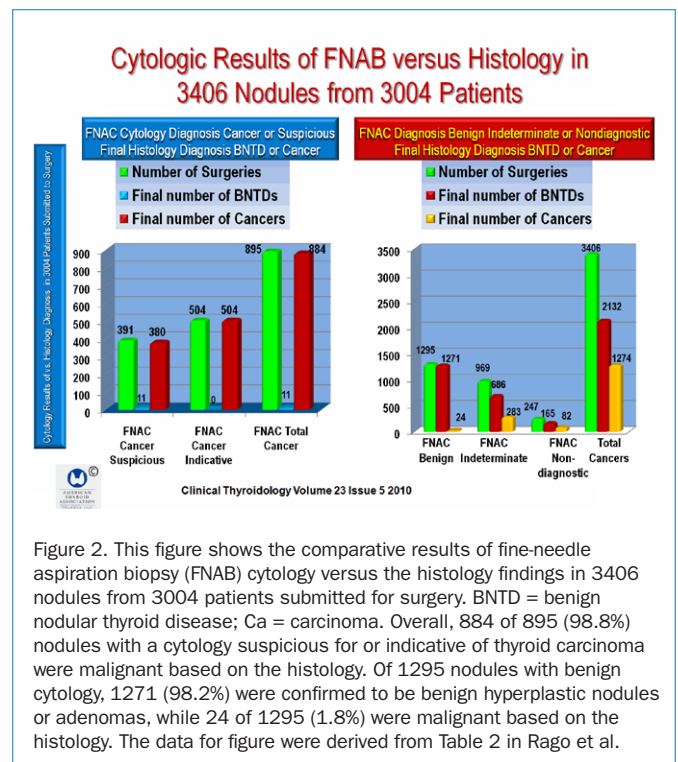


Figure 2. This figure shows the comparative results of fine-needle aspiration biopsy (FNAB) cytology versus the histology findings in 3406 nodules from 3004 patients submitted for surgery. BNTD = benign nodular thyroid disease; Ca = carcinoma. Overall, 884 of 895 (98.8%) nodules with a cytology suspicious for or indicative of thyroid carcinoma were malignant based on the histology. Of 1295 nodules with benign cytology, 1271 (98.2%) were confirmed to be benign hyperplastic nodules or adenomas, while 24 of 1295 (1.8%) were malignant based on the histology. The data for figure were derived from Table 2 in Rago et al.

PTC was significantly more frequent in SN (446 of 13,549 [3.3%]) than in MNG (411 of 19,923 [2%],  $P < 0.0001$ ), and was significantly higher in men (209 of 6382 [3.27%]) as compared with women (648 of 26,945 [2.4%],  $P < 0.0001$ ) in both men with SN (111 of 2820 [3.9%]) and women with SN (335 of 10,644 [3.1%],  $P = 0.03$ ) and in MNG (men: 98 of 3562 [2.7%]; women: 313 of 16,301 [1.9%];  $P = 0.001$ ) (Figure 4).

The prevalence of PTC in patients with nodular GD (31 of 508 [6.1%]) was higher than that found in SN ( $P = 0.003$ ), but not in GD ( $P = 0.2$ ). The frequency of PTC was higher in men than in women, both in Graves' disease (44 of 55 [7.3%] vs. 9 of 231 [3.9%],  $P = 0.27$ ) and in Hashimoto's thyroiditis (4 of 48 [8.3%] vs. 27 of 460 [5.8%],  $P = 0.49$ ) (Figure 1). The age distribution of PTC was higher in younger patients ( $P < 0.0001$ ) (Figure 2). The mean age of patients with PTC ( $43 \pm 14$  years) was significantly lower than that of patients with BNTD ( $48.8 \pm 15.7$ ,  $P = 0.0001$ ) (Figure 4).

**Multiple Logistic-Regression Analysis**

The probability of malignancy in FNAB cytology in six index patients, which was assessed by a formula devised by the authors, showed that of the 4 index men, 3 had solitary nodules and 1 had MNG, and of the 2 women, 1 had solitary nodule and 1 had multinodular goiter. The TSH levels in the 4 men were individually 4,2,6 and 1.9 IUm/L as compared with 8.0, and 0.5 IUm/L in the 2 index patients who were women, and the percent risk of malignancy on FNAB was 35, 15.2, 2,11.5, and 7.5% in men, and 21 and 3.4% in women. Men thus had higher

TSH levels and were at greater risk of having malignant tumors in solitary nodules as compared with women.

Using sex, age and the type of nodularity (solitary and multinodularity) in a multiple regression analysis, PTC cytology was found to be inversely related to age (odds ratio [OR], 0.97; 95% confidence interval [CI], 0.964 to 0.974;  $P < 0.0001$ ), and was positively associated with male gender (OR, 1.440; 95% CI, 1.231 to 1.683,  $P < 0.000$ , and with single nodules, as compared with MNG, (OR = 0.626, 95%CI, 0.547 to 0.717,  $P < 0.0001$ ).

**Risk for PTC on FNAB According to Clinical Parameters and TSH Levels**

There was an association with risk for PTC in 10,182 patients with nonautoimmune nodular thyroid disease who were not taking methimazole or levothyroxine. These 10,182 patients are also included in the present series of patients, together with an additional 1734 who satisfied the same conditions with a mean TSH of  $76 \pm 0.93$  IUm/L; median, 0.5 IUm/L (range, 0.005 to 9.9 IUm/L).

**CONCLUSION**

Cytology suspicious for or indicative of PTC is associated with younger age, male sex, and solitary versus multiple nodularity. These clinical parameters, together with serum TSH, may allow a formulation of an algorithm that could be usefully applied to predict the risk of PTC in individual patients when cytology does not provide a diagnostic result.

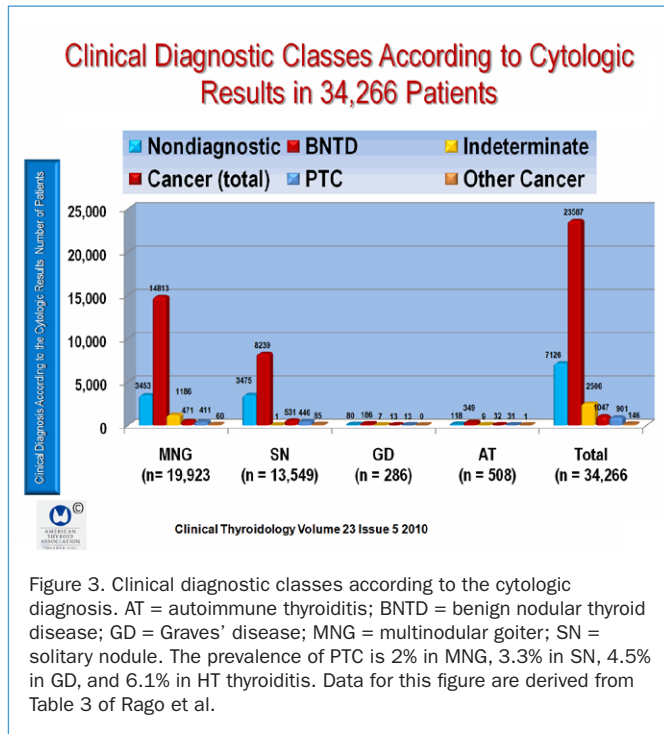


Figure 3. Clinical diagnostic classes according to the cytologic diagnosis. AT = autoimmune thyroiditis; BNTD = benign nodular thyroid disease; GD = Graves' disease; MNG = multinodular goiter; SN = solitary nodule. The prevalence of PTC is 2% in MNG, 3.3% in SN, 4.5% in GD, and 6.1% in HT thyroiditis. Data for this figure are derived from Table 3 of Rago et al.

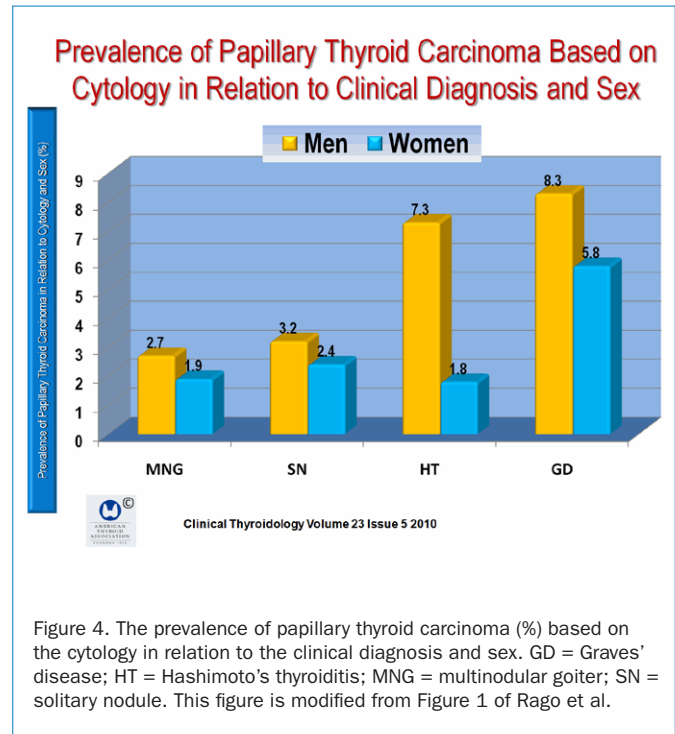


Figure 4. The prevalence of papillary thyroid carcinoma (%) based on the cytology in relation to the clinical diagnosis and sex. GD = Graves' disease; HT = Hashimoto's thyroiditis; MNG = multinodular goiter; SN = solitary nodule. This figure is modified from Figure 1 of Rago et al.

**COMMENTARY**

This is an important study from the group in the Pisa Departments of Endocrinology, Surgery, and Pathology. The study is one of the best to be published. The methodology is meticulously articulated, showing the considerable detail that underpins the findings in this study. The accuracy of FNAB in this article is quite high: 74.5% of the nodules were cytologically benign, 5.7% were indeterminate, 2.4% were suspicious for carcinoma, and 17.1% were nondiagnostic. This accuracy of FNAB cytology is among the most studies published, with a sensitivity of 92%, specificity of 67% and an overall accuracy of 76%, when indeterminate results were considered as positive for neoplasm. Cytology suspicious for or indicative of PTC was associated with younger age, male sex, and solitary versus multiple nodularity.

When indeterminate results were considered negative for neoplasm, the FNAB cytology demonstrated a sensitivity of 69%, a specificity of 99%, and an accuracy of 88%. A false negative cytologic result was found in 24 of 1295 patients (1.8%) in whom surgery was advised because of the size of the nodule in 18 cases, the presence of suspicious clinical ultrasound findings in 5 cases, and toxic MNG in 1 case. Twenty-three were PTCs, 19 of which were follicular variants of PTC, 4 were classic PTC variants, and one was a minimally invasive follicular carcinoma.

Nonetheless, indeterminate cytology continues to be a difficult problem (1). Although most aspirates provide diagnostic cytology, approximately 15 to 25% will be classified as indeterminate (often referred to as follicular neoplasm, suspicious for carcinoma, or atypical), in which case, abnormal cellular findings preclude interpretation of benignity. Although only a minority prove cancerous on final histopathology, in today's practice, patients with indeterminate aspirates are commonly referred for hemithyroidectomy or near-total thyroidectomy for indeterminate cytology. To avoid this dilemma, the use of molecular analysis of cytologic specimens is on the horizon, which is not only feasible, but has been shown to improve the diagnostic performance of traditional indeterminate cytology (2).

The other important problem with FNAB is cytology that is inadequate for diagnosis, which occurs in up to 20% of patients, a major problem that has been recognized for decades (3). FNAB samples, especially those from cystic nodules, continue to be inadequate for diagnosis even with the use of US-guided FNAB. This is extremely important, because when repeated FNAB attempts fail to provide adequate cytology, surgery has been recommended for this problem over the past decade (4, 5) because 5% or more of such nodules are malignant. The severity of this problem is underscored by a study by Yeh et al. (6) of 100 consecutive patients, which found that a single false negative FNAB result delayed surgical treatment by 28 months, sometimes despite clinical evidence suggesting malignancy. Subjects whose tumors were not detected by FNAB experienced delayed treatment, had higher rates of vascular and capsular

invasion, and were more likely to have persistent disease at follow-up (hazard ratio, 2.28).

In 2002, Alexander et al. (7) reported the results of an important study of inadequate FNAB cytology. The study comprised 1128 patients with 1458 nodules that were biopsied over a 6-year period. A total of 1269 aspirations in 950 patients were diagnostic, and 189 nodules in 178 patients were nondiagnostic. The study found that the cystic content of each nodule was the only significant independent predictor of nondiagnostic cytology ( $P < 0.001$ ). The fraction of cytology specimens that were nondiagnostic increased as the cystic content became greater ( $P < 0.001$  for trend). A diagnostic US-guided FNAB was obtained on the first repeat biopsy in 63% of nodules, which was inversely related to the increasing cystic content of each nodule ( $P = 0.03$ ). One hundred nineteen patients with a total of 127 nodules returned for follow-up as advised, and malignancy was documented in 5% of the patients. The authors concluded that despite US-guided FNAB, a significant risk of initial nondiagnostic cytology remains, which was largely predicted by the cystic content of each nodule. The authors recommended repeat aspiration, which is often successful and should be the standard approach to such nodules, given their risk of malignancy.

Thus, despite US-guided cytology, nondiagnostic cytology remains a significant problem, which ranges widely from 5 to 10%, depending on the operator (7) and is largely due to the cystic content of a nodule. This may be improved by US-guided FNAB with on-site evaluation of cytologic specimens, which can substantially increase the adequacy of cytologic specimens and may decrease the number of needle passes required (8).

Rago et al. performed US-guided FNAB on all nodules, and in cystic or mixed lesions, the fluid was aspirated completely and the sediment was examined. The aspiration was repeated if the material was judged as insufficient macroscopically or at an immediate microscopic examination without staining.

It has recently been shown by a series of studies by Haymart et al. that higher serum TSH levels in patients with thyroid cancer not only occurs independent of age and correlates with extrathyroidal tumor extension (9), but is also associated with greater risks of differentiated thyroid cancer in nodular disease and with advanced tumor stage (10). The studies by Rago et al. have not only confirmed these observations, but found that cytology suspicious of or indicative of PTC was associated with younger age, male gender, and solitary nodules versus multiple nodularity, which together with serum TSH may provide information for an algorithm that might be used to predict the risk of PTC in individual patients when cytology does not provide a diagnostic result.

This study by Rago et al. is an important study that should be read in its entirety to appreciate the nuances of this article.

— Ernest L. Mazzaferri, MD, MACP

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# Older patients with hyperthyroidism have fewer symptoms as compared with younger patients

Boelaert K, Torlinska B, Holder RL, Franklyn JA. Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. *J Clin Endocrinol Metab* 2010. jc.2009- 2495 [pii];10.1210/jc.2009-2495 [doi]

## BACKGROUND

The diverse effects of hyperthyroidism are responsible for a wide variety of symptoms. These are related to the multiple effects of thyroid hormone that regulate energy and heat production, and facilitate the development of the central nervous system, somatic growth, puberty, and important hepatic, cardiac, neurologic, and muscular functions. Age plays a major role in the manifestations of hyperthyroidism, regardless of the underlying cause of the syndrome. Perhaps the most extreme example is the absence of symptoms in elderly patients who have apathetic thyrotoxicosis, a syndrome that can barely be recognized as hyperthyroidism. The objective of this study was to determine the prevalence of symptoms and signs of hyperthyroidism according to patient age and sex and the severity and type of hyperthyroidism.

## METHODS

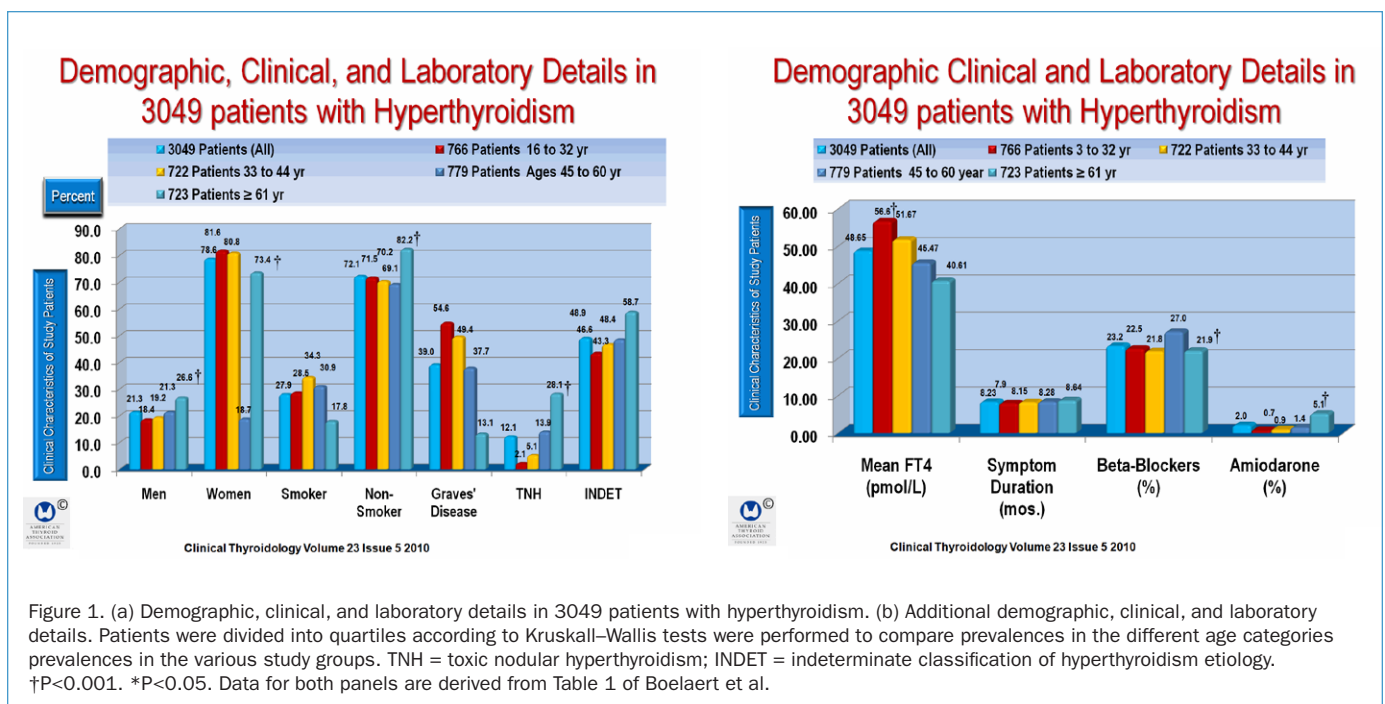
This is a cross-sectional study of 3049 consecutive patients with overt hyperthyroidism, the data from whom were collected from 1984 through September 2006 after presenting to the Multidisciplinary Thyroid Clinic, a secondary/tertiary referral center at the University Hospitals Birmingham. All patients were evaluated by a senior clinician at the time of presentation. A structured questionnaire was used for all patients throughout the study. Symptoms of thyroid ophthalmopathy were determined in patients with Graves' disease. All patients had a physical examination that recorded pulse rate and rhythm, the presence of tremor, and palpable goiter, with or without eye disease.

The diagnosis of hyperthyroidism was confirmed with measurements of serum free thyroxine (FT<sub>4</sub>), with or without a free triiodothyronine (FT<sub>3</sub>), and serum thyroxine (TSH). Thyroid-function tests were performed and thyroid antibody status was determined during the evaluation of symptoms and signs as described in a prior publication.

Ophthalmopathy was classified as no signs or symptoms; only signs without symptoms; signs only; proptosis; eye-muscle involvement; corneal involvement; sight visual acuity reduction (NOSPECS) score as previously described. Absent = (NOSPECS 0); 2 to 3 = periorbital edema/proptosis), 4 = severe NOSPECS, 4 to 6 = eye muscle involvement/corneal involvement/slight loss. The presence of atrial fibrillation was confirmed by electro-cardiography.

Patients were divided into quartiles according to age at the time of diagnosis: 766 were 16 to 32 years of age, 772 were 33 to 44, 779 were 45 to 60, and 732 were ≥61.

Patients were categorized into three diagnostic groups: Graves' disease, toxic nodular hyperthyroidism, and hyperthyroidism of indeterminate cause. Graves' disease was defined as biochemical hyperthyroidism and two of the following: a palpable diffuse goiter, a significant titer of thyroid peroxidase (>1:100), with or without thyroglobulin antibodies and with or without the presence of thyroid eye disease. Toxic nodular hyperthyroidism was defined as hyperthyroidism with a palpable nodular goiter. Patients who did not fulfill these criteria were categorized as indeterminate, thus representing a mixed group with Graves'





disease, toxic nodular hyperthyroidism, or both. Routine radionuclide imaging or thyroid-receptor antibody measurements were not performed. During follow-up, 28 patients were found to have transient hyperthyroidism due to subacute thyroiditis, and the analysis was thus repeated after exclusion of these patients. At the time of diagnosis, the patients' sex, age at diagnosis, and symptom duration were defined. Patients were classified as current smoker or nonsmoker, and a list of current medications, including  $\beta$ -blockers and amiodarone, were also identified.

**RESULTS**

**Clinical, Laboratory and Demographic Characteristics of the Patients (Figure 1)**

The study group comprised 2398 women (79%) and 650 men (21%), 16 through 88 years of age at the time of diagnosis (mean  $\pm$ SD, 46.65 $\pm$ 0.32). The ratio of women to men was lower in those 61 years or older as compared with younger patients. The rate of active smokers was lower in older patients. The highest rate of toxic nodular hyperthyroidism was in the oldest age group ( $\geq$ 61 years) as compared with younger patients, whereas younger patients had more severe hyperthyroidism at the time of diagnosis. The mean duration of symptoms at the time of diagnosis was similar across the age groups. The use of  $\beta$ -blockers was greatest in patients 45 to 60 years of age, but was similar when the youngest and oldest patients were compared (Figures 1A and 1B).

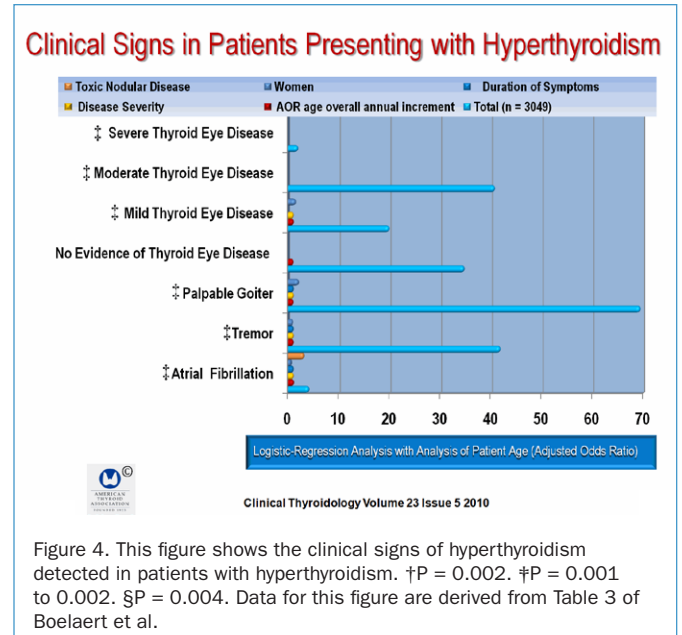
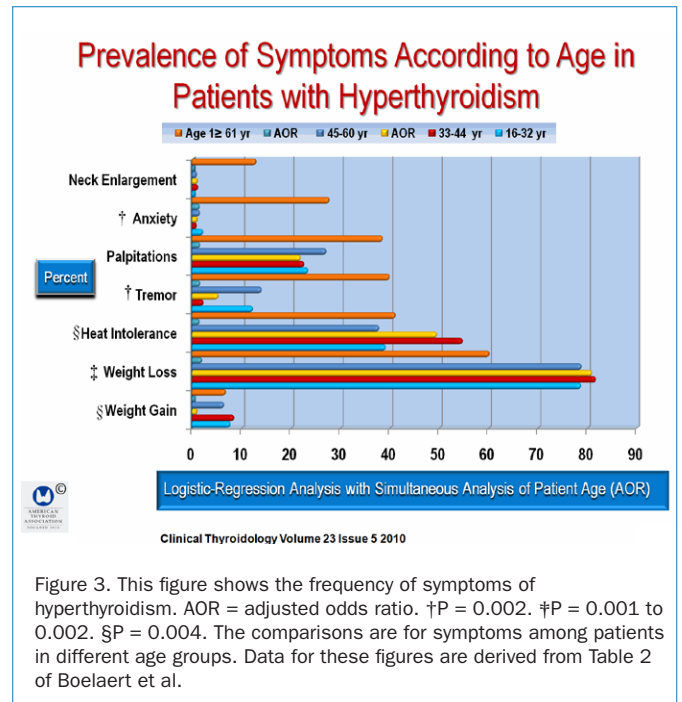
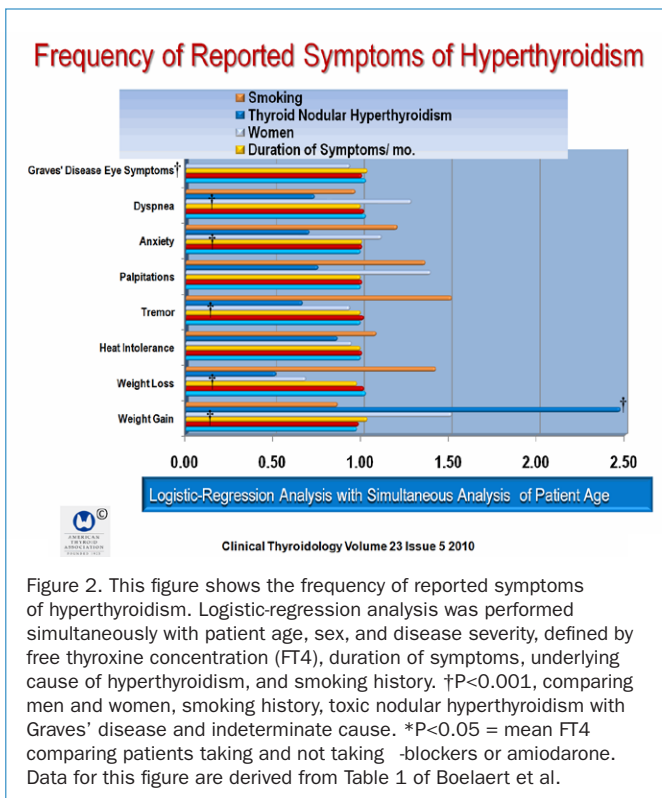
**Frequency of Reported Symptoms of Hyperthyroidism (Figures 2 and 3)**

The most common symptom was weight loss (60.7%), although 7.2% of the patients reported weight gain. About half the patients reported heat intolerance, tremor, and palpitations, and 41% reported anxiety (Figure 2). Eye symptoms were reported by 11.4% of the patients with Graves' disease.

Age 61 years or older was independently associated with reduced adjusted odds ratios (AORs) for the majority of symptoms, except for weight loss and dyspnea, which were more common in older patients as compared with younger patients (Figure 3). Symptoms of thyroid ophthalmopathy were more common in older than in younger patients with Graves' disease.

**Prevalence of Reported Signs of Hyperthyroidism According to Patient Age (Figures 3 and 4)**

Patients with more severe hyperthyroidism had significantly increased AORs for most of the classical symptoms of hyperthyroidism (Figures 3 and 4). However, patients with longer durations of symptoms were less likely to report weight loss, with the prevalence of other symptoms unaffected. Women were more



likely to report weight gain, palpitations, and neck enlargement; however, other symptom patterns were the same in men and women. There were few associations with the prevalence of classical symptoms. However, smoking was associated with increased AOR for weight loss, tremor, and anxiety as compared with nonsmokers. Women were more likely to report weight gain, palpitations, and neck enlargement (Figures 3 and 4).

After excluding 711 patients receiving  $\beta$ -blockers and 60 receiving amiodarone, the same regression analyses were performed. Still, the influence of age, disease severity, and smoking remained similar. However, patients receiving  $\beta$ -blockers were more likely to report weight loss [AOR, 1.50; 95% confidence interval, 1.23 to 1.83;  $P < 0.001$ ]. Evaluation of the number of reported symptoms in different age groups found that the highest proportion of patients with few symptoms—0, 1 or 2—were those 61 years or older (54.4%;  $P < 0.0001$ ), as compared with those 16 to 32 years of age (35.6%), 33 to 44 years (32.4%), and 45 to 60 years (29.8%) (Figures 5 and 6). The majority of patients older than 61 years of age reported a maximum of two symptoms, whereas the lowest fraction of patients reporting five or more symptoms was found among patients older than 61 years (Figure 5) Even after excluding those taking  $\beta$ -blockers or amiodarone, the number of symptoms of hyperthyroidism reported by patients was not substantially different.

**Influence of Demographic, Clinical and Laboratory Parameters (Figures 4 to 6)**

The mean pulse rate in the whole group was 84.4 beats/min, which was unchanged even after excluding those taking  $\beta$ -blockers or amiodarone. Although atrial fibrillation was found in 4.1% of the patients, it was independently associated with increasing age, more severe biochemical disease, and an underlying diagnosis of toxic nodular hyperthyroidism. Women were less likely to have atrial fibrillation, and neither smoking nor a longer duration of symptoms affected the presence of this arrhythmia (Figures 5 and 6). The findings were similar after exclusion of patients with subacute thyroiditis, and neither smoking nor a longer duration of symptoms, or  $\beta$ -blockers or amiodarone significantly affected

the presence of this arrhythmia (Figure 4). Tremor was found in 41.8% of patients, which was associated with more severe hyperthyroidism, a shorter duration of symptoms, and smoking. This association with tremor was no longer present when patients were treated with  $\beta$ -blockers or amiodarone.

**Prevalence of Reported Signs of Hyperthyroidism According to Patient Age (Figure 3)**

Palpable goiters were found in the majority of patients (69.8%), were more common in women, and were associated with younger age, more severe hyperthyroidism, were more common in women and with longer duration of symptoms and smoking, and were present in those not on  $\beta$ -blockers or amiodarone.

Thyroid eye disease was absent or mild in the majority of patients with Graves' disease, but only 1.9% had severe ophthalmopathy. Moderate to severe ophthalmopathy was more common in older patients, current smokers, women, and patients with a longer duration of disease (Figure 4). After excluding patients who were treated with  $\beta$ -blockers or amiodarone, more severe eye disease was found in women.

**Effects of Age on Clinical Signs of Hyperthyroidism (Figures 5 and 6)**

Patients 45 to 60 years of age or older had increased AORs for atrial fibrillation as compared with patients 16 to 32 years of age. Tremor was least common in patients 16 to 32 years of age. Tremors were least common in patients 33 to 44 years of age, but were not different when comparing older with younger age groups. Moderate or severe ophthalmopathy was more common in patients 45 to 60 years of age and those 61 years or older as compared with younger patients.

**CONCLUSION**

Older patients with hyperthyroidism have fewer symptoms as compared with younger patients. Physicians should have a low threshold for performing thyroid-function tests in patients 60 years of age or older, especially those with atrial fibrillation, weight loss, and dyspnea.

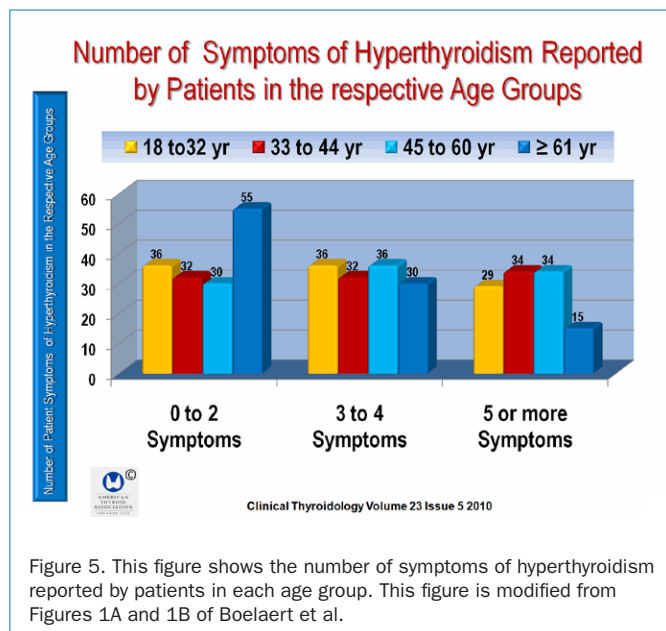


Figure 5. This figure shows the number of symptoms of hyperthyroidism reported by patients in each age group. This figure is modified from Figures 1A and 1B of Boelaert et al.

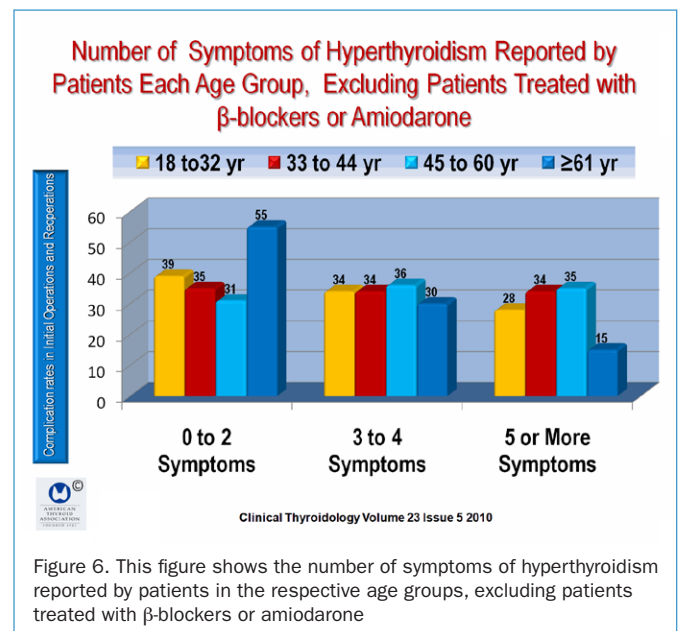


Figure 6. This figure shows the number of symptoms of hyperthyroidism reported by patients in the respective age groups, excluding patients treated with  $\beta$ -blockers or amiodarone

**COMMENTARY**

This is a large study of patients with hyperthyroidism that concurrently investigates the influence of age and a number of other clinical and biochemical features that affect the presenting symptoms and signs of hyperthyroidism. One of the main findings of this unique study is that more than 50% of the patients 61 years of age or older have very few symptoms of hyperthyroidism at the time of diagnosis. However, this occurs in only about 30% of younger patients with hyperthyroidism. Except for weight loss and shortness of breath, most of the usual symptoms of hyperthyroidism in older patients were independent of disease severity. Still, severe hyperthyroidism and current smoking were associated with AOR for most symptoms, while the patient's sex and the cause of hyperthyroidism affected the prevalence of symptoms in the majority of patients.

The risk of atrial fibrillation was increased in older patients, those with higher serum FT<sub>4</sub> concentrations, and men with toxic nodular hyperthyroidism. The signs of Graves' ophthalmopathy were more probable in older women, those with longer disease duration, and current smokers.

The authors opine that the strengths of this study are the large number of patients, the detailed evaluation of symptoms in a standardized manner, and the completeness of patient follow-up. On the other hand, they also acknowledge that the study has a few limitations, including the iodine-replete U.K. population under study, which may not be applicable to patients with different iodine uptake. Also, goiter was identified by physical examination and not routine neck ultrasonography. In addition, routine radionuclide scanning was not performed, because

treatment methods are similar for both Graves' disease and nodular hyperthyroidism. They also acknowledge that dyspnea in older patients might be partially due to underlying cardiovascular disease. And lastly, the authors recognize that patients may have been referred to a tertiary hospital after they were found to have abnormal thyroid function, thus producing some selection bias.

Previous studies by Boelaert et al and others (1,2) have found that advanced age is associated with less severe symptoms of Graves' hyperthyroidism and that there are age-related therapeutic responses to antithyroid drugs in patients with hyperthyroid Graves' disease (3). Boelaert et al. confirmed that older patients with Graves' disease have significantly lower serum FT<sub>4</sub> concentrations as compared with younger patients. Still, the cause for less severe Graves' hyperthyroidism in elderly patients remains uncertain. This study does demonstrate that patients with hyperthyroidism who are smokers are more likely to have weight loss, tremor, palpitations, and anxiety. The study also demonstrates that the severity of Graves' ophthalmopathy is associated with age and male sex (1) and underscores the clinical impact of smoking on the Graves' ophthalmopathy (4).

The study by Boelaert et al. confirms the effects of advancing age on the symptoms and signs of hyperthyroidism that may be readily missed on the initial evaluation, if the primary diagnosis is thought to be atrial fibrillation, dyspnea, or other cardiovascular problems (5, 6) and if this clinical concept is not kept in mind (4).

— Ernest L. Mazzaferri, MD, MACP

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# Sorafenib and sunitinib are effective in patients with widely progressive metastatic DTC

Cabanillas ME, Waguespack SG, Bronstein Y, Williams MD, Feng L, Hernandez M, Lopez A, Sherman SI, Busaidy NL. Treatment with tyrosine kinase inhibitors for patients with differentiated thyroid cancer: the M. D. Anderson experience. J Clin Endocrinol Metab 2010. jc.2009-1923 [pii];10.1210/jc.2009-1923 [doi]

## SUMMARY

### BACKGROUND

Patients with progressive differentiated thyroid cancer (DTC) that is refractory to standard therapy, including surgery, radioiodine, and external-beam radiotherapy (EBRT), now have the option of being treated with novel therapies such as tyrosine kinase inhibitors (TKIs) that may be especially useful for patients with radioactive iodine-resistant tumors. In this study, patients with progressive DTC were treated with sorafenib and sunitinib because they were either unable or unwilling to participate in clinical trials or the trials were not feasible for the patient for various reasons.

### METHODS

All patients with refractory metastatic DTC who were treated with TKI outside a clinical trial were entered into a retrospective database from 2006 through 2008. Adult patients were treated with a single agent, sorafenib, with or without sunitinib. Patients who had a baseline and at least one follow-up imaging study to assess the response to therapy after 3 months were included in the study. Excluded from the study were patients with medullary thyroid cancer or anaplastic thyroid cancer.

Abbreviations of Outcomes OS = overall survival; PD = progressive disease; PFS = progression-free survival; PFT = progression-free time; PR = partial response; SD = stable disease; TL = target lesion.

### Study Objectives

The objective of this study was to determine the response and PFS in patients with DTC treated with sorafenib or sunitinib. Secondary objectives were to determine whether a tissue-specific response occurred and to assess the correlation between response and serum thyroglobulin (Tg) levels over time.

### Laboratory Assessments

Thyrotropin-suppressed serum Tg levels at each scan date were collected on all patients without serum Tg antibodies. BRAF mutation analysis was performed on DNA extracted from formalin-fixed paraffin-embedded tumor tissue in patients with papillary thyroid carcinoma (PTC) that was evaluated for V600E BRAF mutation.

### Radiographic Assessments

Computed tomographic (CT) scans and neck ultrasonography were used to determine the rate of tumor change before and after treatment with sorafenib or sunitinib. Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 is a set of published rules that define patients with cancer who improve with at least a 20% response in the total size of TLs, or stay the same (stabilize) or worsen (progression) during treatment.

### Therapy

All patients but one were treated twice daily with 400 mg of sorafenib. Dose reductions were common as a result of drug toxicity, with the exception of one patient who was started at 200 mg twice daily because of age and comorbidities. The

**Patient Demographics and Tumor Histology**

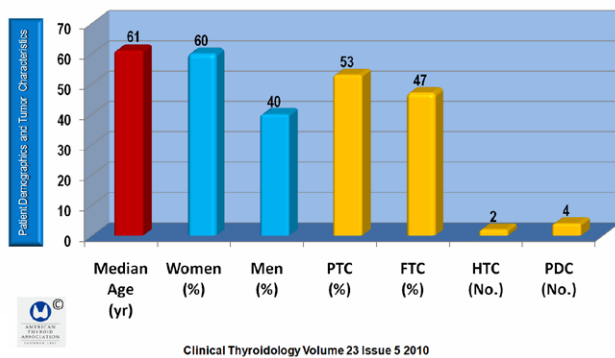


Figure 1A. This figure shows the patient demographics and tumor histology in the study cohort. HTC = Hürthle cell cancer; PDC = poorly differentiated cancer.

**Sites of Metastases and Number of Patients Treated with Sorafenib and Sunitinib**

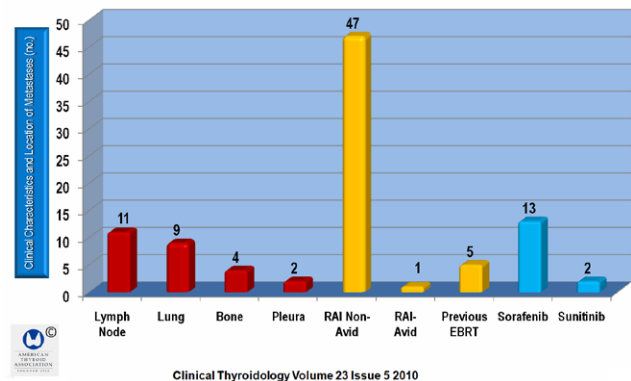


Figure 1B. This figure shows the sites of metastases and the number of patients treated with sorafenib and sunitinib. EBRT = external-beam radiotherapy; RAI = radioactive iodine.

patients treated with sunitinib with either 50 mg by mouth once daily for 4 weeks, followed by 2 weeks off drug, or 50 mg daily for 2 weeks followed by 1 week off drug.

**Clinical Characteristics of the Patients (Figure 1A and 1B)**

A total of 15 patients, 9 women (60%) and 6 men (40%), met the inclusion criteria for the study. The median age was 61 years, 8 (53%) had PTC, 7 (47%) had follicular thyroid cancer, 2 of whom had Hürthle-cell subtypes, and 5 had poorly differentiated tumors. The most common location of metastases (73%) were in the lung, followed by bone (27%) and pleura (13%), and most had more than one tumor location (Figure 1).

**Tumor Assessments**

Two patients with bone metastases and two with lung metastases had received EBRT; they were not included in the response assessments. Fourteen patients had nonavid <sup>131</sup>I tumors; however, one had tumor that retained <sup>131</sup>I avidity but had been treated with over 1000 mCi of <sup>131</sup>I and was accordingly considered to have nonavid tumor. Fourteen of these 15 patients had an increase in tumor size of at least 20% before starting on sorafenib or sunitinib and were considered to have PD per RECIST. Another patient had a malignant pleural effusion before therapy and was considered to have PD. All 15 patients initially were treated with sorafenib, 2 of whom discontinued the drug and resumed sunitinib therapy. One patient had been treated previously but discontinued sorafenib due to PD, and another had a grade 3 hand-foot skin reaction from sorafenib and elected to discontinue the drug.

**Radiographic Responses**

CT scans and neck ultrasounds were used to determine the pace of change before and after treatment with sorafenib or sunitinib. RECIST was used to determine the responses. TLs were defined as soft-tissue lesions that could be accurately measured in at least one dimension with the longest diameter of at least 1 cm. Non-TLs were soft-tissue lesions that could not be accurately measured in at least one dimension. Patients with new lesions were considered to have PD and were assigned a value of a 20% increase in tumor measurement.

**RESULTS**

From November 2006 through June 2008, a total of 33 patients were treated with targeted therapy for their advanced DTC; 18 were excluded from the study for a variety of reasons: 4 had no follow-up or had outside follow-up radiographs in the electronic medical record, and 11 were on combination therapy or on a TKI other than sorafenib or sunitinib. Two were pediatric patients, and one had medullary thyroid carcinoma. Within the first 3 months of therapy, no patients were excluded from the study because of death or PD.

**Radiographic Responses (Figures 2, 3, and 4)**

Waterfall plots were constructed for the best response in TLs (Figure 2). PR was seen in 3 of 15 patients (20%), SD in 9 of 15 patients (60%), and PD in 3 of 15 patients (20%). There were no complete responses. Durable responses were seen in 10 of 15 patients (60%), and PD in 3 of 15 patients (20%). In all, clinical benefit was seen in 80% of the patients. The response

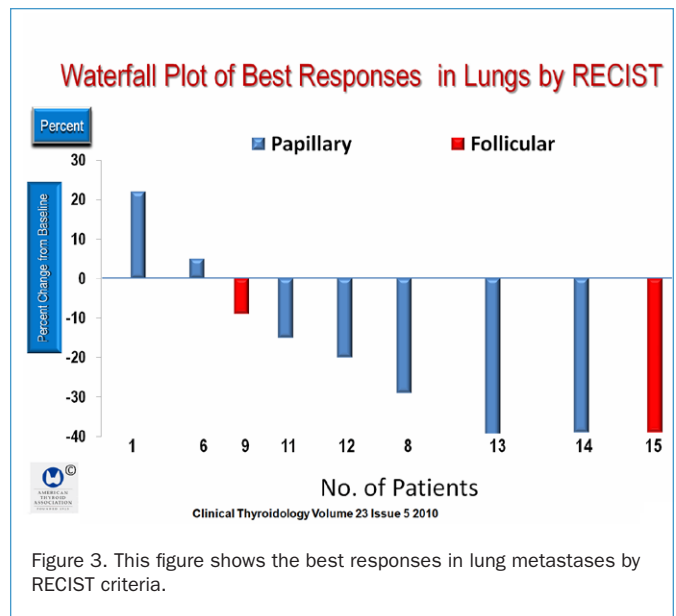


Figure 3. This figure shows the best responses in lung metastases by RECIST criteria.

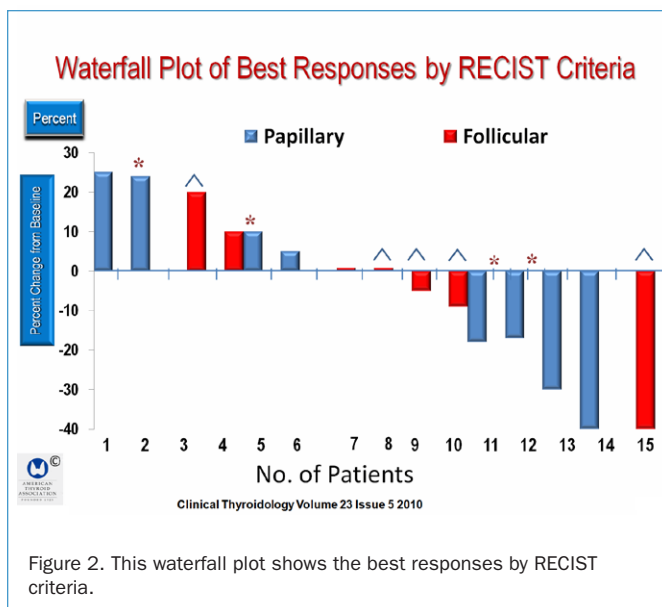


Figure 2. This waterfall plot shows the best responses by RECIST criteria.

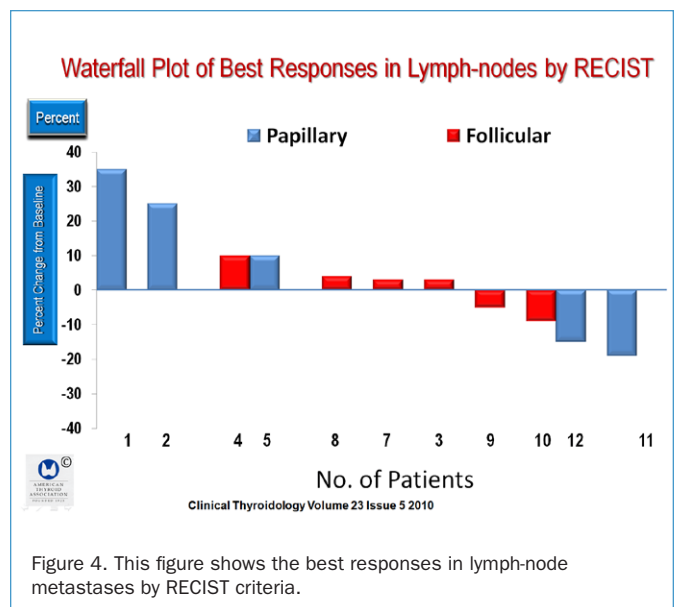


Figure 4. This figure shows the best responses in lymph-node metastases by RECIST criteria.

was similar in all histologic types, including Hürthle-cell and poorly differentiated tumors. The patient who had PD on a phase 2 sorafenib trial had a PR with a decrease of 39% in TLs. Waterfall plots were constructed for response in TLs by organ site.

Lung responses (−22%; range, −38 to 21%) were more robust than those in lymph-node metastases (median change, 0%; range, -18 to 33%) (Figure 3). Two patients with nonirradiated bone metastases had rapidly progressive disease and died from thyroid cancer. A dramatic response to lymph-node metastases occurred in one of these patients, with an average of 72 to 13 Hounsfield units on CT, with minimal change in lymph-node size. Two patients who were treated with EBRT had SD in those lesions, and two had new, progressive bony metastases while on treatment. Another had new liver metastases while on sorafenib, and both patients with pleural metastases had PD in the pleura. Eight patients with a radiographic response of stable disease after treatment with a TKI were plotted (Figure 4). The change of tumor size was 0.44 cm/mo before treatment and approximately 0.48 cm/mo after treatment (P = 0.035), which suggests that stabilization of tumor in these patients is a clinically valid end point.

**BRAF Mutation Analysis**

Seven of the 8 patients with PTC had BRAF testing; 4 (57%) had a V600E mutation, 3 had SD, and 1 had PD as the best response. Among the 5 patients who did not have BRAF mutations, 2 had a PR, 2 had SD, and 1 had PD as their best response.

**Survival Rates**

PFS after starting sorafenib or sunitinib was plotted on a Kaplan–Meier curve. The median PFT was 19 months. The mean (±SD) ratio of PFT (before treatment was started) was approximately 3.0±2.2, demonstrating that, on average, patients experienced a PFT that was three times longer (95% confidence interval, 1.7 to 4.2 after treatment). Although the median OS was not reached, 2-year follow-up OS was 67%.

**Correlation of Tg with Tumor Measurements**

The log Tg correlated significantly with the radiographic response (P = 0.005)

**Adverse Events (Figures 5 and 6)**

The most common adverse events were diarrhea (53%), hypertension (33%), and weight loss/anorexia (20%). The most common dermatologic complication was hand–foot–skin syndrome (60%), followed by maculopapular skin rash (33%) and 4 of 15 patients had squamous-cell carcinoma of the skin, all after sorafenib therapy. The nondermatologic and dermatologic adverse events are shown in Figures 5 and 6.

**CONCLUSIONS**

Sorafenib and sunitinib are effective in patients with widely progressive metastatic DTC. Most patients achieved stable disease or a partial response, despite having progressive disease at baseline before TKI therapy.

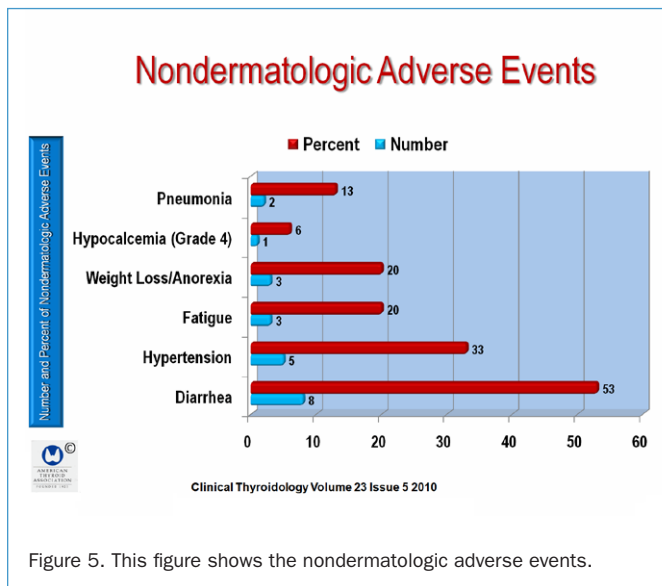


Figure 5. This figure shows the nondermatologic adverse events.

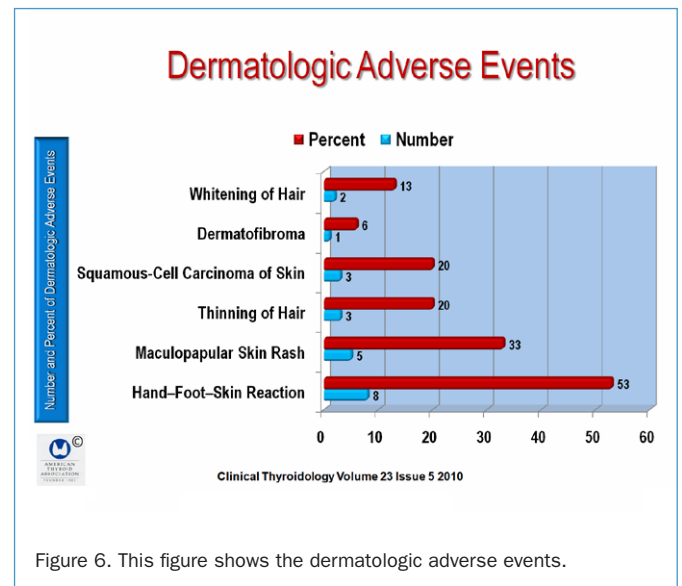


Figure 6. This figure shows the dermatologic adverse events.

**COMMENTARY**

This is an important study that describes the off-label use of sorafenib and sunitinib for patients with progressive metastatic DTC not amenable to radioiodine or other therapy. Sorafenib and sunitinib are approved by the Food and Drug Administration for use in advanced renal-cell carcinoma, hepatocellular carcinoma (sorafenib), and gastrointestinal stromal tumor (sunitinib). Both are TKIs, that inhibit vascular endothelial growth factor (VEGF) receptors 2 and 3, platelet-derived growth factor, Flt-3 c-kit, and RET. Sorafenib also inhibits wild-type and mutant BRAF V600E, which are the most frequent genetic alterations found in PTC, affecting approximately 45 to 70% of these tumors in adults (1). In addition, overexpression of VEGF and other growth factors is often found in thyroid tumors, particularly BRAF mutations. The authors mention that these findings provide the rationale for using sorafenib and sunitinib in patients with metastatic non-radioiodine <sup>131</sup>I-avid thyroid cancer.

Two phase II studies, one by Gupta-Abramson (2) and the other by Kloos et al. (3) have shown efficacy in treating metastatic thyroid cancer. The Ohio State study by Kloos et al. had 46 evaluable patients with PTC, in whom 78% had a diagnosis of PTC. The response rates were 13% PR and 74% SD, and the median PFS was approximately 15 months. The study by Gupta-Abramson found a PR rate of 32%, SD rate of 68%, and no PD, with a median PFS of 21 months in patients with DTC.

The study by Cabanillas et al. found a PR rate of 20%, a durable response rate of 66%, and a clinical benefit rate of 80%, which is similar to the Gupta-Abramson and Kloos studies.

Although there were only 15 patients in the Cabanillas study, the authors point out what seems to be a differential response of metastases to the same drug in the same patients in different tumor tissues. One of the other important observations by

Cabanillas was that patients had a clinical response to sunitinib despite progression on sorafenib, suggesting that treatment failure with one TKI should not exclude the use of another TKI.

The adverse events encountered in this study are consistent with previous reports for sorafenib and sunitinib (2,4,5). Skin cancers, weight loss, hypertension, and diarrhea were some of the important adverse events with sorafenib and sunitinib in this study. One woman with primary hypoparathyroidism had a novel complication from sorafenib; grade 4 hypocalcemia developed despite treatment with calcitriol and calcium supplements, which seems to be a new observation. Also, 3 patients had squamous-cell skin cancer after sorafenib, which has been described in a small number of patients (6). Still, among the small Cabanillas cohort, 20% had squamous-cell skin cancer, suggesting that this might be more common than described. The authors of this study concluded that despite the number of adverse events, their patients seemed to accept these problems.

The authors suggest that there are several limitations to this study, including its retrospective nature, and the small sample size, and since some of the patients were treated by their local physicians, less information was available to the authors.

Nonetheless, this study demonstrates that sorafenib and sunitinib are useful agents in patients with advanced progressive disease, and the toxicity profiles of the drugs were reasonably well tolerated by the patients. Sorafenib prolonged the PFS in this cohort, even the patients in whom SD developed as their best response. Still, the authors point out that the development of skin cancers with the long-term use of sorafenib and sunitinib are potential limitations to the use of TKIs. Moreover, the authors provide the caveat that physicians need to be well versed in the management of the toxicities of these drugs to provide optimal care.

— Ernest L. Mazzaferri, MD, MACP

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# Reoperative central-compartment lymph-node dissection (CLND) has a lower rate of temporary hypocalcemia and the same rates of other complications and recurrence as initial CLND

Shen WT, Ogawa L, Ruan D, Suh I, Kebebew E, Duh QY, Clark OH. Central neck lymph node dissection for papillary thyroid cancer: comparison of complication and recurrence rates in 295 initial dissections and reoperations. Arch Surg 2010;145:272-5.

## SUMMARY

### BACKGROUND

The American Thyroid Association management guidelines for patients with differentiated thyroid cancer recommend ipsilateral or bilateral prophylactic (routine) central-compartment lymph-node dissection (CLND) for patients with papillary thyroid carcinoma (PTC), especially for those with advanced primary tumors (T3 or T4). Some find that the complication rates of CLND may be lower with prophylactic dissection than with therapeutic dissection for patients with clinically apparent recurrent lymph-node metastases. This retrospective study was aimed at testing the hypothesis that the complication and tumor recurrence rates are lower with therapeutic CLND than with prophylactic CLND.

### METHODS

This is a retrospective study of patients treated for PTC from 1998 through December 31, 2007, at the UCSF Mount Zion Medical Center by four endocrine surgeons (W.T.S, E.K., Q.Y.D., and O.H.C.) who performed 295 CLNDs for PTC. Patients selected for study were treated with total thyroidectomy and unilateral or bilateral CLND performed either at the time of initial surgery (prophylactic dissection) or at the time of reoperation for recurrence (therapeutic dissection).

Of 295 CLND operations, 189 were initial operations (64%) and the remaining 106 (36%) were reoperations performed for enlarged CLND tumors. Reoperative CLND was defined as a central (level IV) lymph-node dissection for patients who had prior surgery. This group of patients had growth of previously non-enlarged (i.e., inapparent)

central neck lymph nodes or growth of central neck lymph nodes that were incompletely resected during a prior operation.

The main characteristics identified in the cancer registry database were records of patients who had lymphadenectomy in addition to CLND and postoperative complications comprising neck hematoma, transient or permanent hypoparathyroidism, and transient hoarseness or permanent recurrent laryngeal-nerve injury. Transient hypoparathyroidism was defined as a serum calcium level less than 8.0 mg/dl within 24 hours after surgery. Permanent hypoparathyroidism was defined as a serum calcium level less than 8.0 mg/dl with low parathyroid hormone levels requiring oral calcium carbonate and calcitriol for more than 6 months.

Transient hoarseness was based on the surgeon's assessment of the patient's subjective symptoms during the immediate postoperative period. Permanent recurrent laryngeal-nerve injury was defined by persistent hoarseness for 6 months after surgery, which was confirmed by direct laryngoscopy documenting ipsilateral vocal-cord dysfunction.

## RESULTS

### Patient Demographics (Figure 1)

Although the demographic profiles of the two surgery groups were similar, patients who had reoperation were slightly older. A total of 54 men (28.6%) and 135 women (71.4%), with a mean ( $\pm$ SD) age of 39.8 $\pm$ 16.0 years, had CLND during their initial surgery. On the other hand, 33 men (31.1%) and 73 women (68.9%), with a mean age of 46.5 $\pm$ 16.8 years, had reoperative CLND.

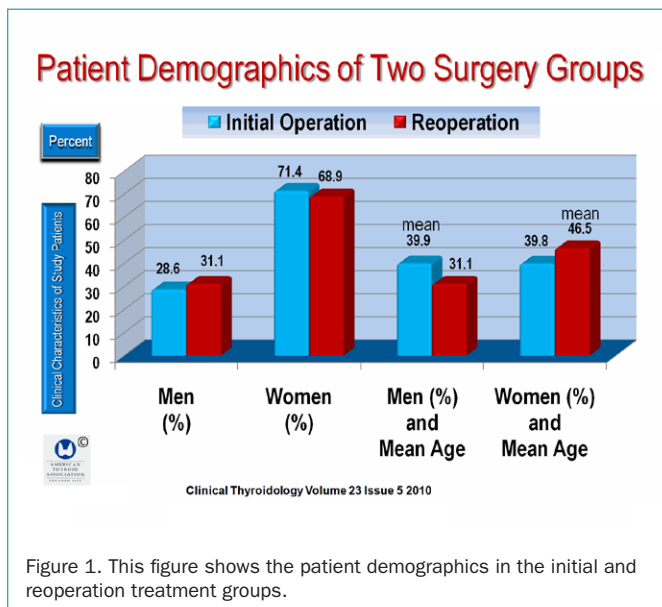


Figure 1. This figure shows the patient demographics in the initial and reoperation treatment groups.

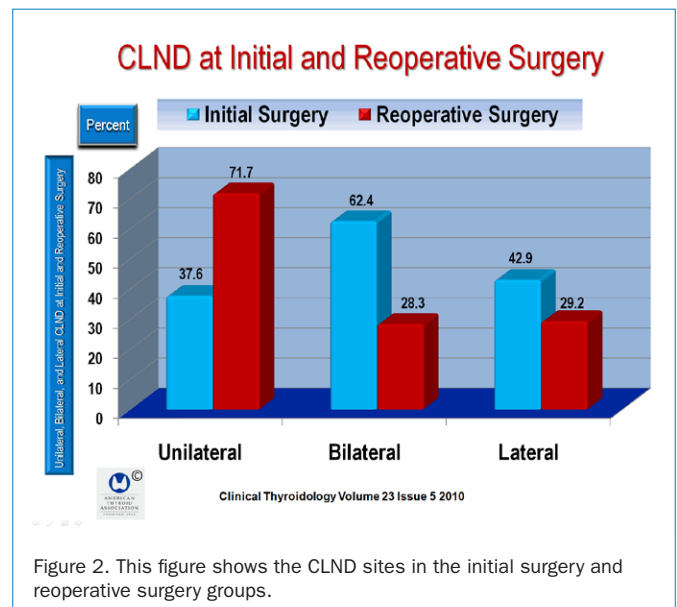


Figure 2. This figure shows the CLND sites in the initial surgery and reoperative surgery groups.



**Differences in CLND at Initial and at Reoperative Surgery (Figure 2)**

Among the 189 initial CLND procedures, 71 (37.6%) were unilateral and 118 (62.4%) were bilateral. However; among the reoperative CLND procedures, 76 of 106 were unilateral dissections (71.7%) as compared with 30 of 106 bilateral (28.3%). Lateral neck lymph-node dissections were performed at cervical levels II, III, and IV, when involved, in 81 of 189 initial CLND procedures (42.9%) as compared with 31 of 106 reoperative CLND procedures (29.2%).

**Complication Rates (Figure 3)**

Nerve monitoring using a nerve-integrity monitor system was used in 20 (10.6%) of the 189 initial operations and in 16 (15.1%) of 106 reoperations. The complication rates for initial surgery were similar with those in the reoperative surgery. Two patients (1.1%) required postoperative reexploration for a hematoma. Of the initial operations, 2 patients required reexploration.

Temporary postoperative hoarseness occurred in 9 patients (4.8%) as a result of the initial operation and in 5 (4.7%) as a result of reoperation. Permanent recurrent laryngeal-nerve injury confirmed by laryngoscopy was found in 5 (2.6%) of the patients who had initial operations and in 2 who had reoperations (1.9%).

The rates of transient postoperative hypocalcemia were significantly different between the two groups: 79 of 189 initial operations (41.8%) as compared with 25 of 106 reoperations (23.6%) (P = 0.0025). Only one patient in each group (0.5% and 0.9%, respectively) had permanent hypoparathyroidism. Of the 189 patients who had initial operations, 31 (16.4%) required autotransplantation, as compared with only 1 (0.9%) in 106 reoperative operations (P<0.001). Of the final operative specimens, 62 (32.8%) of the initial CLND specimens contained normal parathyroid glands, as compared with 10 (9.4%) of the reoperative CLND specimens.

**Average Number of Lymph Nodes in the Two Surgical Groups (Figure 4)**

The average number of lymph nodes was 8 for the initial surgery and 5 for reoperations. The average number of positive central lymph-nodes was 4 of 8 (50%) for the initial operations and 3

of 5 (60%) of the reoperations. The average number of lymph nodes retrieved in the CLND was about the same in the two groups: 7 of 18 (39%) for initial operations and 6 of 17 (35%) for reoperations.

**Recurrence Rates for the Two Surgical Groups (Figure 5)**

PTC recurrence rates were similar in the two groups. Of the 189 patients who had initial CLND, 49 (25.9%) had locoregional or distant recurrences of their disease that required reoperation or other therapy. Of the 106 reoperative CLNDs, 31 (29.2%) had a recurrence. The recurrence was in the central neck for 22 (11.6%) of the initial CLND and 15 (14.1%) of the reoperations. Recurrence was found in the lateral neck in 41 (21.7%) of the initial operations and 18 (17.0%) of the reoperations.

**CONCLUSION**

This study finds that reoperative CLND has a lower rate of transient hypocalcemia and the same rate of other complications and of tumor recurrence as initial CLND surgery for PTC.

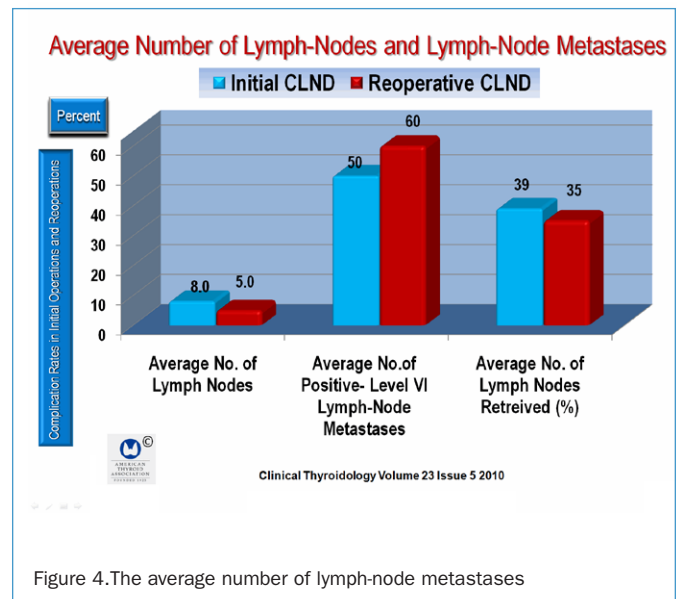


Figure 4. The average number of lymph-node metastases

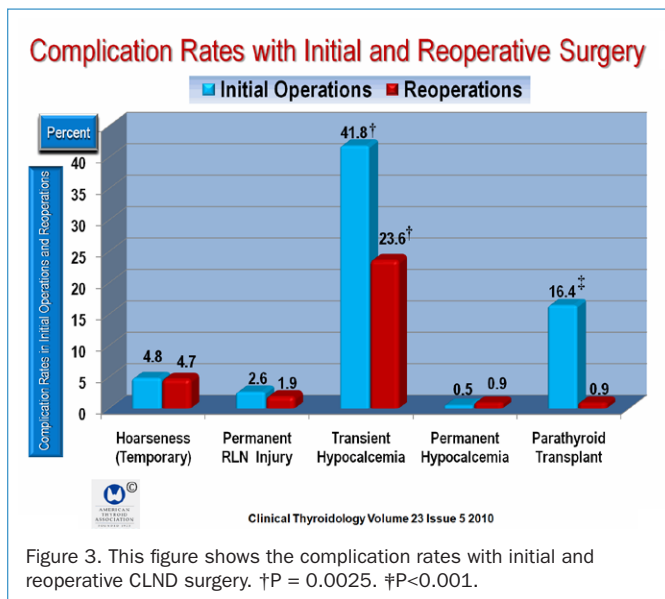


Figure 3. This figure shows the complication rates with initial and reoperative CLND surgery. †P = 0.0025, ‡P<0.001.

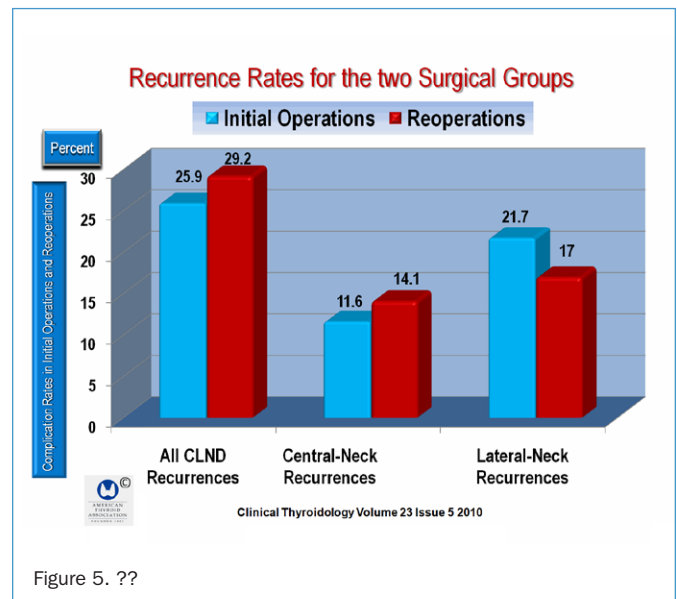


Figure 5. ??

**COMMENTARY**

This is a large retrospective study performed by four highly experienced endocrine surgeons who perform CLND at the time of initial surgery only if enlarged central lymph nodes are detected by palpitation or ultrasonography. The authors had hypothesized that the complication and recurrence rates would be higher in patients who underwent reoperation for CLND because of scarring in the reoperative field and distorted anatomy in the central-neck compartment after thyroidectomy has been performed. However, just the opposite was found: the complication and recurrence rates that occurred with initial surgery were similar to that found with reoperative CLND, with the highest risk of transient hypocalcemia in patients having initial CLND along with total thyroidectomy. The authors mention that their rates of transient hypocalcemia for total thyroidectomy alone in patients with PTC are significantly lower (approximately 10%, unpublished data) than the rates of transient hypocalcemia for patients who were treated with CLND (41.8%), underscoring the underlying risk for injury to the parathyroid glands. Still, the rates of permanent hypoparathyroidism in this study are considerably lower than usual, in the range of 0.5 to 0.9% for both initial and reoperative CLND. Despite favorable outcomes, the authors argue that their findings that CLND, whether initial or reoperative, contributes additional risk of postoperative complications. It is difficult to compare the recurrence rates in this study without further information concerning the tumor and patient features.

An evidence-based systematic review of this issue by White et al. (1) reached three major conclusions:

**First:** Systematic compartment-oriented central lymph-node dissection (CLND) may decrease recurrence of PTC (levels IV and V data (No recommendation)

**Second:** There may be a higher rate of permanent hypoparathyroidism and unintentional permanent nerve injury when CLND is performed with total thyroidectomy as compared with total thyroidectomy alone (Grade C recommendation).

**Third:** Reoperation in the central neck compartment for recurrent PTC may increase the risk of hypoparathyroidism and unintentional nerve injury as compared with total thyroidectomy with or without CLND (Grade C recommendation), supporting a more aggressive initial operation.

White et al. concluded that evidence-based recommendations support CLND for PTC in patients under the care of experienced endocrine surgeons (1).

A recent debate between Drs. G.M Doherty and D.L. Steward summarized the pro and con views of complication rates in patients who have had CLND (2). Given the high odds of leaving residual CLND lymph-node metastases by forgoing prophylactic CLND leaves two options for the patient: watchful waiting, which in some cases can span decades, or empiric radioiodine therapy, which may eradicate the thyroid remnant and smaller lymph-node metastases. A recent study by Bonnet et al. (3,) provides important information concerning prophylactic neck compartment dissections as it relates to the extent of initial lymph-node compartment surgery and the use of postoperative radioiodine ablation therapy. I believe the Bonnet study is a landmark means of identifying the residual lymph-node metastases that require radioactive iodine therapy 4.

There seems to be a consensus that prospective, randomized studies must be done before we can settle the uncertainties of this surgical approach to the management of differentiated thyroid cancer.

— Ernest L. Mazzaferri, MD, MACP

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# Preparation with rhTSH for <sup>131</sup>I remnant ablation is associated with a longer half-life of <sup>131</sup>I in the thyroid remnant while reducing exposure to the rest of the body and the general public.

Taïeb D, Sebag F, Farman-Ara B, Portal T, Baumstarck-Barrau K, Fortanier C, Bourrelly M, Mancini J, De MC, Auquier P, Conte-Devolx B, Henry JF, Mundler O. Iodine Biokinetics and Radioiodine Exposure after recombinant thyrotropin-associated remnant ablation in comparison with thyroid hormone withdrawal. J Clin Endocrinol Metab 2010. Jc.2009-2528-2528 [pii];101210/jc.2009-2528 [doi]

## SUMMARY

### BACKGROUND

Since recombinant human thyrotropin (rhTSH) has been approved for radioactive remnant ablation RRA, several studies have found that patients prepared in this manner receive less whole-body radiation from <sup>131</sup>I, as compared with patients prepared by thyroid hormone withdrawal (THW). The aim of this prospective study was to compare the biokinetics of <sup>131</sup>I in the thyroid remnant, dosimetry, and radiation protection after preparation with rhTSH as compared with THW.

### METHODS

This is a prospective, randomized controlled, open label singled-center study. The rhTSH group was treated with <sup>131</sup>I after two injections of rhTSH, and the hypothyroid control group was prepared by THW, thus treating this group in a hypothyroid state. Patients included in the study were at least 18 years of age. All had newly diagnosed well-differentiated papillary (PTC) or follicular thyroid cancer (FTC) treated with total thyroidectomy in one or two stages. Tumor pTNM staging was done according to the 6th edition AJCC/UICC classification. All patient tumors were staged as pT1 to T3, N0 to Nx, and N1, and M0 tumors, and all patients had fewer than 5 lymph nodes and none had extracapsular tumor invasion. A 15-day iodine restriction was prescribed for all patients before they were treated with 100 mCi (3.7 MBq) which was administered 6 weeks after surgery to the hypothyroid group and 2 to 3 weeks after surgery to the rhTSH group, after which all were hospitalized for 2 days.

Evaluations were performed before the first rhTSH injection (day 2) in the rhTSH group, and before <sup>131</sup>I therapy (day 0) and at 24 hours (day 1), and 48 hours (day 2), and on day 6 after RRA in both groups. Levothyroxine (L-4) at 2µg/Kg was restarted on day 1, and a whole body scan was performed on days 2 and 6.

Dose rate (DR) measurements were performed at day 1 (DR<sub>d1</sub>) day 2, (DR<sub>d2</sub>) and day 6 (DR<sub>d6</sub>). Urine samples were obtained from day 0 after <sup>131</sup>I to day 2 to evaluate radiation exposure to the bladder. Thyroglobulin (Tg) was assessed at day 0 and day 6 by a Tg assay with a lower detection limit of 0.2 µg/L, and was assessed at days 0, 2 and 6. The initial work-up also included evaluation of renal function and urinary iodine excretion. A Tg performed on day 5 above 0.8 µg/L was considered positive. Anti-Tg antibodies (TgAb) less than 20 IU/ml comprised a negative result. In patients with residual TgAb, Tg was determined by recovery tests (reference range 70 to 13% of recovery).

### Evaluation of iodine biokinetics in thyroid remnants

Three parameters were determined: thyroid remnant uptake, effective half-time in the remnant, and the remnant residence time. Remnant uptake was determined from images obtained at days 2 and 6. A mono-exponential decay function was used to fit the uptake values. Individual dose estimate calculations were performed using residence times obtained from the whole body, thyroid remnant, stomach, large intestine, and bladder.

### RESULTS

The study group comprised 43 patients in the rhTSH group and 45 in the hypothyroid group. Of the two groups, 79 patients were eligible for the evaluation of iodine biokinetics, residence time in target organs, and total-body effective half-life. Data from 9 patients were incomplete for a full evaluation.

### Dosimetric analysis

Dosimetric analysis was performed in 61 patients in whom urinary samples were obtained. In the rhTSH group, mean TSH during L-4 therapy was 1 mIU/L. In the hypothyroid group, mean TSH at the time of RRA was 110 mIU/L. Renal function was higher in the rhTSH group (90.3±20.2 ml/min·1.73 m<sup>2</sup>, than that in the hypothyroid group (67.6±15.4 ml/min·1.73m<sup>2</sup>); P = 10<sup>-3</sup> (1.73 is an adjustment for a standard body surface).

## Mean Values of Iodine Biokinetics in Remnants, Residence Time, and Total Body Effective Half-Life

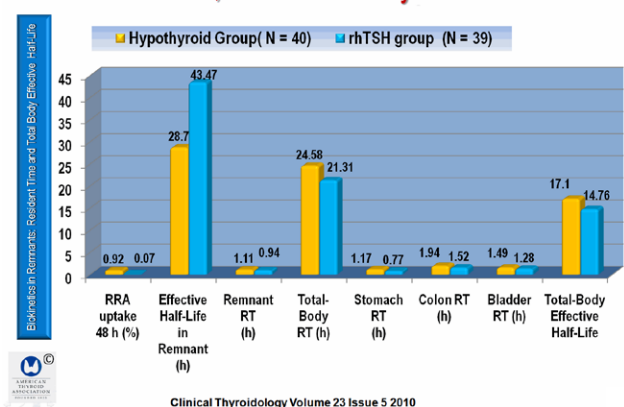


Figure 1. This figure summarizes the median values ± SD (SD not shown) of iodine biokinetics in remnants, residence time (RT), and total-body effective half-life comparing hypothyroidism (THW) and rhTSH groups. P = 0.065 for remnant uptake at 48 hours (%); P = 0.012 for effective half-life in remnant (hours); P < 0.001 for total body RT (hours); P = 0.05 for stomach RT; P = 0.037 for colon RT (hours); P = 0.29 for bladder RT hours; P < 0.001 for total-body effective half-life (hours)

This difference was related to an increase of patients with moderate transient renal function impairment: The hypothyroid group had an estimated GFR from 30 to 59 ml/min · 1.73m<sup>2</sup> (35.1% vs. 2.8% in the rhTSH group). At the 9-month follow-up GFR value returned to normal in the hypothyroid group. There were no significant differences in age, sex, weight, height, body mass index, and urinary iodine excretion 25.8±14.6 µg/dl in the hypothyroid group versus 23.2 ± 12.6 in the rhTSH group. The ablation rate in the two groups was statistically equivalent.

**Iodine biokinetics in remnants and assessment of Tg release (Figure 1)**

The values of iodine kinetics in thyroid remnants after rhTSH stimulation and endogenous TSH stimulation were calculated from 79 patients. (Figure1) For iodine biokinetics, three parameters were determined: remnant uptake, effective half-time in the remnant, and the remnant residence time (Figure 1). The effective half-life in thyroid remnant tissue was significantly longer after rhTSH than during hypothyroidism (P = 0.01). The 48-hour <sup>131</sup>I uptake and residence time of <sup>131</sup>I were not statistically significant between the two study groups, although the values were numerically lower in the rhTSH group. (Figure 1)

**Dosimetry (Figure 2)**

The mean total-body effective half-life was 14.76±2.1 vs. 17.1±2.83 hours in the rhTSH and hypothyroid groups, respectively (P<0.001). Total-body (P< 0.001) and colon (P = 0.037)

residence times were shorter in the rhTSH group as compared with the hypothyroid group. Residence time was also shorter in the stomach, but not significantly different in the two study groups. (P = 0.05). Also, for the bladder, residence time was similar between the two study groups (P = 0.29). For patients in the rhTSH group, absorbed doses were lower for total-body (P = 0.005), and other target organs with a statistical significance for the lower intestine (P = 0.011), ovaries (P = 0.015), and bone marrow (P = 0.006) (Figure 2).

**Radiation Exposure in <sup>131</sup>I-treated patients**

The effective half-life is the time required for deposited radioiodine in tissue divided by 2, from the combined action of physical decay (approximately 8.1 days) and biological disappearance, which is determined by several factors, including renal clearance. To estimate exposure, the effective period after hospital departure was calculated from DR<sub>d2</sub> and DR<sub>d6</sub>.

In this study, exposure was based on a simple model in which only individual effective periods and occupancy factors (OFs) were used as defined by the American Code of Federal Regulations to be the fraction of time that an individual is near the patient. As patients were hospitalized during the initial period, OF was assigned to zero in the first 48 hours after <sup>131</sup>I treatment. Two periods of constraint were defined after hospital: a constraint period including day 3 after hospital departure and an unconstraint period from day to an infinite time. The assumption was that according to the physician's recommendation, the patient slept in a separate bed.

**Assessment of Tg Release**

There is a significant relationship between effective half-life and Tg (max peak), Δ Tg, or ΔTg to 48-hour uptake ratio. Prior to RRA, the stimulated Tg was not significantly different in the two study groups; however the amplitude of Tg release was significantly higher during hypothyroidism than with rhTSH stimulation. (P = 0.005). Tg release was correlated with radioiodine uptake in the thyroid remnant and the THW group in univariate analysis. Multivariate analysis included gender, study group, age, normalized GFR, 48-hour <sup>131</sup>I uptake, thyroid bed effective half-life and Δ Tg (Tg day2 to Tg day 6), and remnant half-life was correlated THW group (P = 0.005) and <sup>131</sup>I uptake (P = 0.019).

**CONCLUSION**

Preparation with rhTSH for <sup>131</sup>I RRA is associated with a longer remnant half-life of <sup>131</sup>I while also reducing exposure to the rest of the body and to the general public who came in contact with patients treated with <sup>131</sup>I.

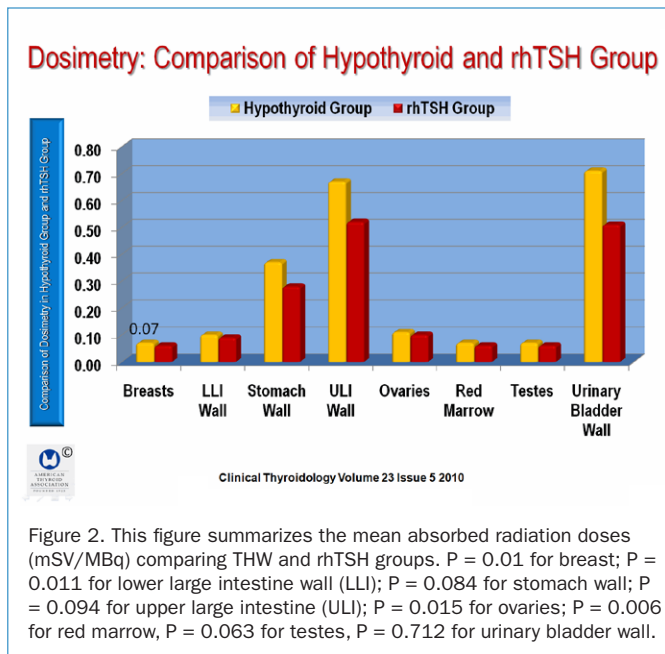


Figure 2. This figure summarizes the mean absorbed radiation doses (mSV/MBq) comparing THW and rhTSH groups. P = 0.01 for breast; P = 0.011 for lower large intestine wall (LLI); P = 0.084 for stomach wall; P = 0.094 for upper large intestine (ULI); P = 0.015 for ovaries; P = 0.006 for red marrow, P = 0.063 for testes, P = 0.712 for urinary bladder wall.

**COMMENTARY**

Taïeb et.al performed an important study that investigated the biokinetics of  $^{131}\text{I}$  in the thyroid remnant, dosimetry, and radiation protection, in patients prepared for  $^{131}\text{I}$  RRA with rhTSH as compared with THW. This is one of several important studies that focus on the effects of whole-body radiation in patients prepared with rhTSH for RRA, which leaves the patient euthyroid, as compared with THW that renders the patient hypothyroid in the process of performing RRA. In these studies, in which patients were treated with 100 mCi, the rates of successful RRA were similar whether patients were prepared with rhTSH or THW. However, the main thrust of these studies concern the effects of whole-body irradiation that occurs with RRA, particularly when patients are prepared with THW. Similar to the studies of Pacini et.al (1), Taïeb et.al found a trend to shorter remnant  $^{131}\text{I}$  uptake in patients treated with rhTSH as compared with those prepared with THW.

Pacini et.al(1) first demonstrated that patients treated with rhTSH in preparation for RRA had a statistically significant, one third lower radiation dose to the blood, as compared with that among patients who were rendered hypothyroid with THW. This was an especially important finding, considering the adverse whole-body effects of  $^{131}\text{I}$  that may occur with  $^{131}\text{I}$  therapy (2).

In 2006, Hãnscheid et.al (3) performed a study of the effectiveness of remnant ablation with 100 mCi of  $^{131}\text{I}$  in patients with differentiated thyroid cancer after stimulation with rhTSH or THW. In this study, 63 patients were randomized after thyroidectomy to either the THW or rhTSH. Starting 48 hours after  $^{131}\text{I}$  administration, scintigraphic neck images were acquired to assess the biokinetics of  $^{131}\text{I}$  in thyroid RRA. The main finding was that the effective  $^{131}\text{I}$  half-time in the remnant thyroid tissue was significantly longer after rhTSH than THW (67.6±48.8 vs. 48.0±52.6 hours, respectively);  $P = 0.01$ , whereas the observed differences of the mean 48-hour  $^{131}\text{I}$  uptakes, (0.5%±0.7% vs. 0.9% ±1.0% after THW;  $P = 0.1$ ), and residence times of 0.9 ±1.3 vs. 1.4±1.5 hours after THW;  $P = 0.1$ ) between the rhTSH and THW groups were not statistically significant. However the study found that the absorbed radiation dose to the blood was significantly lower ( $P < 0.0001$ ) after the administration of rhTSH (mean, 0.109±0.028 mGy/MBq; maximum, 0.18 mGy/MBq) than after THW (mean, 0.167± 0.061 mGy/MBq; maximum, 0.35 mGy/MBq), indicating that higher activities of  $^{131}\text{I}$  might be safely administered after exogenous stimulation with rhTSH. The study thus found an influence of the residence time of  $^{131}\text{I}$  in the blood on the fractional uptake of  $^{131}\text{I}$  into thyroid remnant. The authors proposed a novel regimen in which therapeutic  $^{131}\text{I}$  activities to be administered may be determined from the individual specific blood dose.

As  $^{131}\text{I}$  treatment of patients with thyroid cancer may induce adverse side effects, particularly cancer and leukemia (2), Remy et.al performed an important study in 2008 on the basis that there were still some uncertainties concerning the parameters that might influence the effective half-life of  $^{131}\text{I}$  and the absorbed doses by organs other than the thyroid. In this study, whole-body  $^{131}\text{I}$  retention was measured in 254 patients, and repeated

quantitative whole-body scans and measurements of urinary excretion of  $^{131}\text{I}$  were performed on 30 of these patients. The main finding was that the mean effective half-life (10.5 hours) was shorter by 31%—with little difference between patients—in the 36 patients who received rhTSH as compared with the 218 patients who underwent thyroid hormone withdrawal (15.7 hours). The residence times in the stomach and in the rest of the body were significantly shorter in patients who received rhTSH as compared with patients who underwent THW; however, the residence times were similar in the colon and bladder. The authors concluded that patients who undergo THW, the longer mean effective half-life is mainly due to delayed renal excretion of  $^{131}\text{I}$  and results in dose estimates higher than the data in report 53 of the International Commission on Radiological Protection, which were obtained from healthy, euthyroid subjects.

The study by Taïeb et.al, which is focused on  $^{131}\text{I}$  biokinetics and dosimetric and radioprotection issues in thyroid cancer patients, is the largest prospective study to compare rhTSH and THW for remnant ablation. As reported in previous studies, Taïeb et.al found a statistically prolonged remnant effective half-time in patients treated with rhTSH as compared with those who had RRA after preparation with THW. The study found that the residence time, which is dependent on both fractional thyroid uptake and half-time, was not statistically different between the rhTSH and THW groups, but was lower after Taïeb et.al suggests that the study by Borget et.al (4) illustrates that this finding might be used to shorten hospital stay and reduce costs. In the Taïeb study, all the patients were discharged 48 hours after  $^{131}\text{I}$  therapy. Using a validated model, the authors found that without any recommendations, radiation exposure in patients prepared with THW could exceed the limits recommended for public safety (1 mSv-year) by the International Commission on Radiological Protection. Taïeb et.al also found that 2 days of hospitalization and 3 days of confinement to the home is consistent with current legislation and is applicable to most patients treated with 100 mCi of  $^{131}\text{I}$ . The authors point out that the main limitation of dose exposure in this study is that it was not directly measured by dosimeters on contact persons, which is more reliable, although highly dependent upon patient and contact compliance. The main conclusion of this study is that when 100 mCi of  $^{131}\text{I}$  is given, the iodine biokinetics, dosimetry, and radiation protection favor rhTSH rather than THW. Although the  $^{131}\text{I}$  residence times were not significantly different in rhTSH and THW preparation, the remnant effective half-life was significantly longer with rhTSH. Lastly, total-body and organ dosimetry also favored rhTSH rather than THW.

This is an important study that clinicians should consider when performing RRA.

There is, However one major point important point: A number of prospective randomized studies now show that lower  $^{131}\text{I}$  activities, in the range of 30 to 50 mCi (1110 to 1850 MBq), are as effective as 100 mCi for RRA, which can be performed after rhTSH preparation.(5-9)

— Ernest L. Mazzaferri, MD, MACP

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## DISCLOSURE

Dr. Mazzaferri is a consultant to Genzyme,

Dr. Sipos Lectures for Abbott Pharmaceutical and Genzyme.

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September 23-27, 2009  
PALM BEACH, FLORIDA

**THYROID NEWS**

NIH Seeks High Risk, High Impact Proposals through NIH Director's Pioneer, New Innovator, and Transformative R01 Initiatives

Transformative R01 Program

ICCIDD Newsletter August 2009 (PDF File, 738 KB)

Clinical Thyroidology August 2009 is now available online

The ATA recognizes the serious threat posed by lack of access to treatment due to worldwide medical isotope shortage for patients with cancers, heart disease and many other disorders. We urge you to voice your concern through this link provided by the Society for Nuclear Medicine (SNM).

Another Generic T3 Released

**ATA alert to Florida members:** Florida District Court of Appeals retains levothyroxine on state's negative formulary

FDA MedWatch alert about PTU (www.fda.gov)

ATA and FDA jointly sponsor PTU meeting

ATA publishes first comprehensive guidelines for managing medullary thyroid carcinoma

ATA News Update - Possible Isotope Shortage

**ATA NEWS**

ATA 2009 election guide - Active members: Check your email for your ballot. Vote Now!

"Member bring a non-member colleague" Discount for 80th Annual Meeting (PDF File, 133 KB)

ATA announces Clinical and Basic Fellows' Tracks for the 80th Annual Meeting

Short Call for Abstracts - 80th Annual Meeting of the ATA - open August 7-22, 2009

**A Timeline of Thyroid History** - submit your historical articles, images and archival materials

**UPCOMING ATA MEETINGS**

Annual 80<sup>th</sup> Meeting  
Palm Beach, Florida  
September 23-27, 2009  
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- ATA members are leaders in thyroidology who promote excellence and innovation in clinical care, research, education, and public policy.
- Join us as we advance our understanding of the causes and improve the clinical management of thyroid diseases in this era of rapid pace biomedical discovery.
- A close-knit, collegial group of physicians and scientists, the ATA is dedicated to the research and treatment of thyroid diseases. ATA's rich history dates back to 1923 and its members are respected worldwide as leaders in thyroidology.
- The ATA encourages you to apply for membership. We want you to experience the wealth of knowledge and enjoy the benefits of being active in this highly specialized and regarded society. The ATA looks forward to having you as a member!