

CLINICAL THYROIDOLOGY

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EDITORS' COMMENTS

This is the fourth 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.

WHAT'S 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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There is a strong relationship between subclinical hyperthyroidism and all-cause and cardiovascular mortality in Japanese–Brazilians, but not with subclinical hypothyroidism

Sgarbi JA, Matsumura LK, Kasamatsu TS, Ferreira SR, Maciel RM. Subclinical thyroid dysfunctions are independent risk factors for mortality in a 7.5-year follow-up: the Japanese-Brazilian thyroid study. *Eur J Endocrinol* 2010;162:569-77.

SUMMARY

BACKGROUND

The influence of subclinical thyroid disease (SCTD) on morbidity and mortality remains uncertain. The object of this prospective study was to investigate the relationships between SCTD and the cardiometabolic profile and cardiovascular disease, and all-cause and cardiovascular mortality.

METHODS

The study was conducted by survey of a uniform population of Japanese–Brazilian individuals living in Bauru, a Brazilian city in the midwestern region of São Paulo, with the aim of estimating the prevalence of diabetes mellitus and associated diseases in this population, a description of which was published previously. The age of the original cohort of 1751 individuals was ≥ 30 years. Among this group, 1330 (76%) agreed to participate in the study. Excluded from the study were those who self-reported thyroid disease; were taking amiodarone, lithium, or corticosteroids; or had missing data on electrocardiograms (ECGs) and ankle-brachial pressure indexes. The cross-sectional phase of the study was conducted from 1999 through 2000, during which the prevalence of thyroid dysfunction and the association of SCTD with cardiovascular disease were assessed. A total of 1110 individuals thus comprise the study cohort. Follow-up of this group was performed from 1999 through 2007 to investigate the influence of SCTD on all-cause and cardiovascular mortality.

Definitions Subclinical hyperthyroidism (SCHyper) was defined as a serum thyrotropin (TSH) < 0.45 mIU/L with elevated free thyroxine (FT_4). Subclinical hypothyroidism (SCHypo) was defined as a TSH > 4.5 mIU/L with a normal FT_4 , and overt hypothyroidism was a TSH > 4.5 mIU/L with low FT_4 , or a TSH > 20 mIU/L. Hypertension was defined as a blood pressure $\geq 140/90$ mm Hg or as the use of antihypertensive drugs. Diabetes mellitus was defined according to the American Diabetes Association criteria, and dyslipidemia was defined as total cholesterol ≥ 200 mg/dl or triglycerides ≥ 150 mg/dl or low-density lipoprotein (LDL) cholesterol > 130 mg/dl. At baseline, cardiovascular disease was defined as a history of myocardial infarction (MI) as recorded by a physician or as shown by major electrocardiographic (ECG) abnormalities of an old MI (Q waves) or a history of angioplasty or revascularization or stroke. Peripheral arterial disease was defined as any ankle-brachial pressure index < 0.9 .

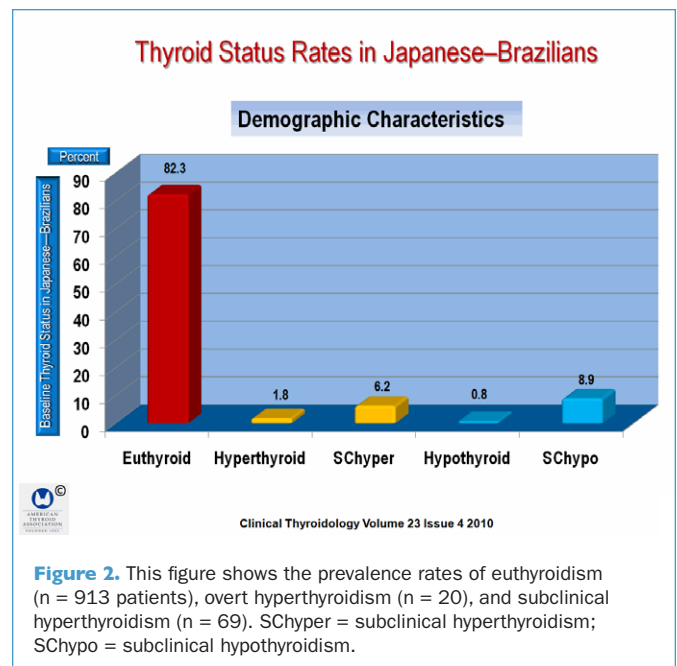
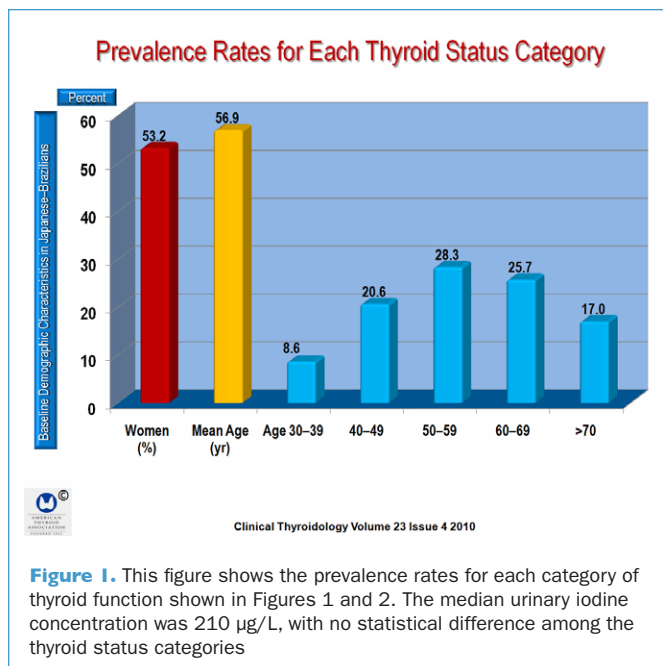
RESULTS

Patient Demographics (Figure 1)

There were no significant differences in the demographics of patients excluded ($n = 220$) as compared with those included (1110) in the study. The study cohort comprised 591 women (53%) with a mean (\pm SD) age of 56.9 ± 12.5 years. The demographics and thyroid status of the study group are shown in Figure 1.

Cross-Sectional Analysis (Figures 1 to 4)

The prevalence rates for each thyroid status category, including



age are shown in Figure 1. Euthyroidism, overt hyperthyroidism, and SChyper were found in 82.3, 1.8, and 6.2%, of the participants, respectively, (Figure 2), with no difference in sex distribution (Figure 3). However, unsuspected overt hypothyroidism and SChypo were identified in 0.8% and 8.9% of the participants, respectively, and both were significantly more common in women (P = 0.04) (Figure 3). The mean age was similar among the groups, except for the SChyper group, which had a significantly higher age as compared with the euthyroid group (Figure 4). Among the groups, there were no statistically significant differences in body-mass index, smoking status,

systolic and diastolic blood pressure, fasting blood glucose, homeostasis model assessment for insulin resistance insulin (HOMA-IR), high-density lipoprotein cholesterol, or triglyceride levels. However, mean total cholesterol (P = 0.03) and LDL cholesterol (P = 0.02) were both significantly increased in subjects with overt hypothyroidism as compared with euthyroid subjects, but not in those with SChypo (Figures 3 and 4). There were significantly more subjects with overt hypothyroidism and with SChypo taking statins as compared with the euthyroid group. For the use of statin, the odds ratio (OR), adjusted for age and sex, was significantly higher in the SChypo subjects

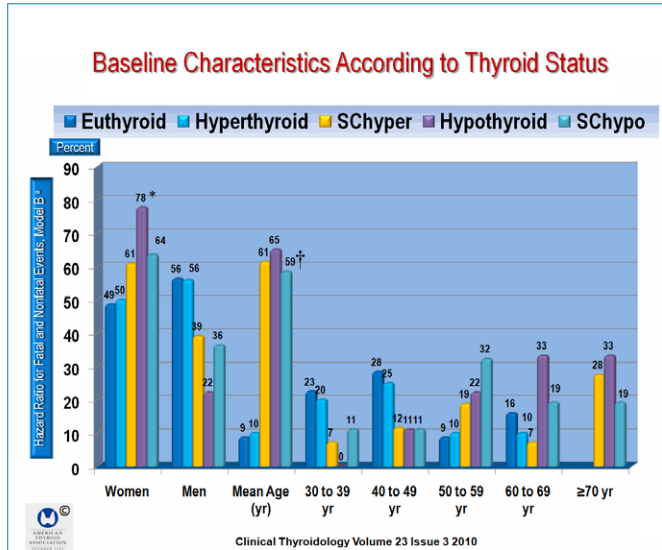


Figure 3. This figure shows the baseline characteristics according to thyroid status. Data are mean percentages (±SD [not shown]) SChyper = subclinical hyperthyroidism; SChypo = subclinical hypothyroidism. *P<0.05. †P<0.01. ‡P<0.001. §P<0.0001. Values were log-transformed for statistical analysis. Data for this figure were obtained from Tables 1 to 4 in Sgarbi et al.

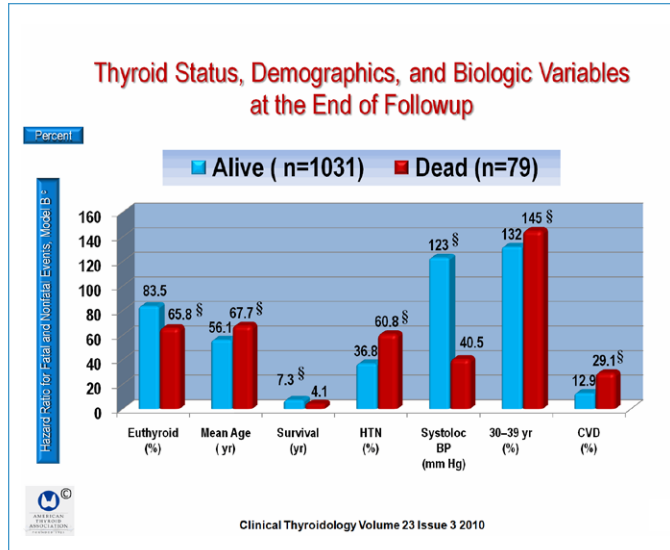


Figure 5. This figure shows the status and demographics and biologic variables at the end of follow-up. BP = blood pressure; CVD = cardiovascular disease; HTN = hypertension These data were derived from Table 3 of Sgarbi et al. *P<0.05. †P<0.01. ‡P<0.001. §P<0.0001.

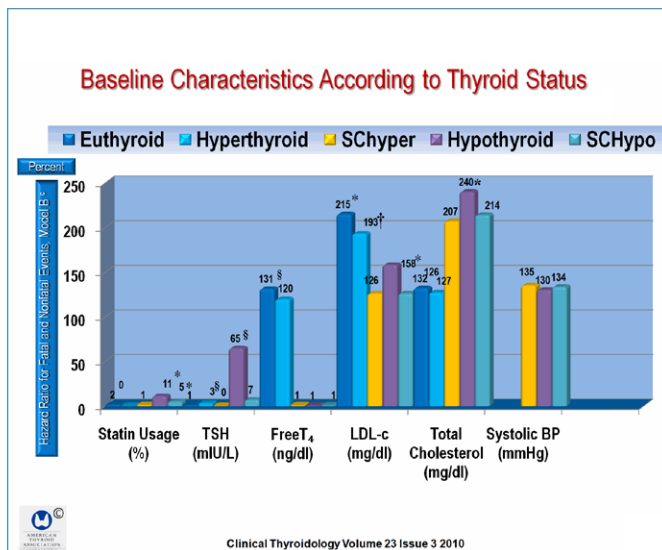


Figure 4. This figure shows the baseline characteristics according to thyroid status. Data are presented as the percent of mean (±SD), unless otherwise noted. BP = blood pressure (in mm Hg); LDL-c = low-density lipoprotein cholesterol; T4 = thyroxine; TSH= thyrotropin

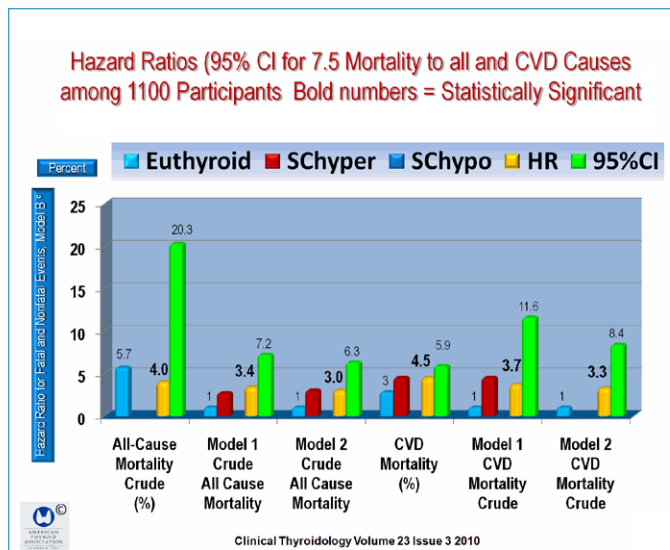


Figure 6. This figure shows the hazard ratios (HR) and the 95% confidence intervals (CIs) for 7.5-year mortality due to all cardiovascular causes among 1110 Japanese –Brazilians. CVD = cardiovascular disease. These data were derived from Table 4 of Sgarbi et al.

(OR, 3.4; 95% confidence interval, 1.2 to 9.8), as compared with euthyroid individuals (Figure 4).

Longitudinal Analysis during 7.5 Years of Follow-up (Figure 5)

During the 7.5 years of follow-up, there were 83 deaths (7.5%), 4 of which were by unnatural causes (suicide or trauma) and 3 by unknown causes. Deaths mainly were the result of cardiovascular events, (51.3%), cancer (22.3%), or infectious disease (14.5%). Among the dead, 50 (65.8%) were characterized as euthyroid, 14 (17.7%) as SChyper, and 13 (16.5%) as SChypo. No patients with overt thyroid disease were reported to have died. However, baseline serum FT₄ levels were significantly higher (P = 0.018) (Figure 4) among individuals who had died as compared with those who were alive at the end of follow-up, but there was no difference in TSH among the two groups. Figure 4 shows the relationship between SCTD and mortality. All-cause mortality was significantly higher in SChyper (20.3%) and SChypo (13%) as compared with euthyroid individuals (5.7%) (P<0.0001).

Kaplan–Meier analysis demonstrated that overall mortality for both SChyper (P<0.0001) and SChypo (P = 0.0035) as compared with the euthyroid group (Figure 5). Cardiovascular mortality was significantly associated with SChyper (P<0.0001). Cox regression analysis demonstrated that the associations of SChyper and SChypo remained as independent features, even after adjusting for age, sex, and multiple potential confounders (Figure 6).

CONCLUSION

This study shows that subclinical hypothyroidism is an independent risk factor for all-cause cardiovascular mortality, whereas subclinical hypothyroidism is associated with all-cause mortality among Japanese–Brazilians.

This study shows a strong relationship between SChyper and all-cause and cardiovascular mortality, whereas SChypo was significantly associated with all-cause mortality, which was apparent after 4 years of follow-up.

COMMENTARY

The main finding in this study was a strong relationship between SChyper all-cause and cardiovascular mortality, but not with SChypo, in Japanese–Brazilians.

The relationship of subclinical thyroid dysfunction with cardiovascular morbidity and mortality is controversial. Especially controversial is the treatment of cardiovascular disease. A comprehensive review of subclinical hypothyroidism by Biondi and Cooper (1) found four double-blind, randomized, controlled trials that concluded that replacement therapy may have had a beneficial effect on the lipid profile but does not appear to affect on lipoprotein (a), homocysteine, or C-reactive protein. The relatively high prevalence rates of subclinical thyroid dysfunction reported by Sgarbi et al. is consistent with that in several studies (2,3). Haentjens et al. (2) found that individuals with subclinical hyperthyroidism demonstrate a 41% increase in relative mortality as compared with control subjects, and for SChypo, the relative risk of all-cause mortality is increased only in patients with comorbid conditions. Likewise, Ochs et al. (3) concluded that SChypo and SChyper may be associated with a modest increased risk for congestive heart disease and mortality. On the other hand, Rodondi et al. (4) concluded that as compared with euthyroid older adults, those with a serum TSH concentration ≥ 10.0 mIU/L have a moderately increased

risk of heart failure and alterations in cardiac function, which was not found in older adults with a serum TSH <10.0 mIU/L. A relatively recent review by Völzke et al. (5) concluded that the currently available evidence for a causal association of both hyperthyroidism and hypothyroidism with mortality is weak and should not be used to decide whether patients with subclinical thyroid conditions should be treated.

The Sgarbi study found that subclinical hypothyroidism was significantly associated with death by all causes, but not with cardiovascular mortality. They point out that the small number of cardiovascular deaths (five events) probably limited their ability to detect an association between subclinical hypothyroidism and cardiovascular mortality and that the hazard ratios might have been statistically significant with a larger number of outcomes. Also, the data in this study are based on a baseline set of thyroid tests, with which the authors acknowledge they cannot exclude the possibility of an undetected influence of progression from subclinical to overt thyroid dysfunction. Another limitation that the authors mention is the lack of analysis stratified according to age, sex, and TSH levels due to the small number of events. In addition, they were unable to exclude the possibility of overt thyrotoxicosis in some of the subjects with SC hyperthyroidism and SChypo.

— Ernest L. Mazzaferri, MD, MACP

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Salivary stimulation with vitamin C at any time after ¹³¹I administration has a minimal effect on salivary ¹³¹I absorption

Liu B, Kuang A, Huang R, Zhao Z, Zeng Y, Wang J, Tian R. Influence of vitamin C on salivary absorbed dose of ¹³¹I in thyroid cancer patients: a prospective, randomized, single-blind, controlled trial. J Nucl Med 2010. doi:10.2967/jnumed.109.071449

SUMMARY

BACKGROUND

Radioiodine (¹³¹I) used in the treatment of thyroid cancer is taken up by a variety of tissues other than the thyroid, including the salivary glands, with sodium iodine symporters. As a result, ¹³¹I exerts a toxic effect on the salivary glands, which are highly sensitive to β-radiation from ¹³¹I. Because of this, the combination of radiation sialadenitis and xerostomia is one of the most common complications of ¹³¹I therapy, which occurs even with relatively small amounts of therapeutic ¹³¹I. There is uncertainty regarding how this complication can be ameliorated. The purpose of this study was to test the use vitamin C as a sour stimulant to decrease the effect of salivary ¹³¹I absorption.

METHODS

This is a prospective randomized, single-blind, controlled study of patients referred to the West China Hospital Department of Nuclear Medicine for thyroid remnant ablation. Patients had stage pT1–T₃,NO–N1,M0 tumors (by tumor–node–metastasis classification) and were at least 18 years of age and had thyroidectomy for papillary or follicular carcinoma prior to being prepared for remnant ablation by thyroid hormone withdrawal. Excluded from the study were patients who had distant metastases, a history of salivary-gland disorders, collagen-tissue disease, diabetes mellitus, previous ¹³¹I therapy or external radiation to the head or neck, or difficulty drinking a large amount of water.

After achieving hypothyroidism, patients were divided into four groups, A, B, C and D, all of which were treated with 3.7 GBq (100 mCi) of ¹³¹I 4 to 6 weeks after thyroidectomy, including

a 2-week low-iodine diet, without preceding diagnostic whole-body scanning. Patients were put on levothyroxine therapy after salivary dosimetry measurements were performed.

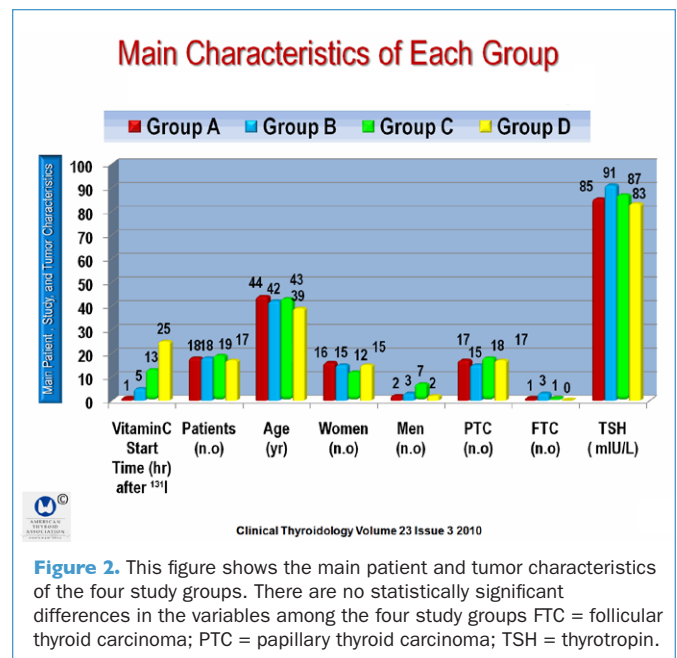
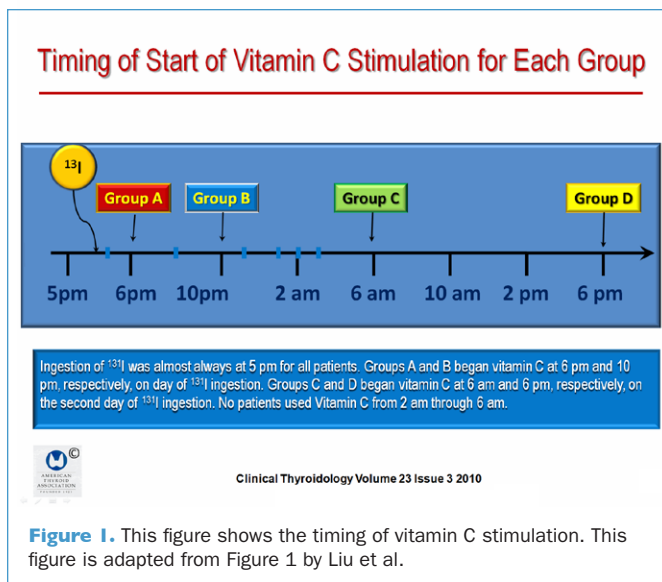
Six days after being treated with ¹³¹I, patients were instructed to stop taking lemon candy, gum, or other sialogogues, and anticholinergic or antidepressant medications were temporarily discontinued before the study patients in all four groups began sucking on lozenges of 100 mg of vitamin C at 1, 5, 13, and 24 hours in the groups A, B, C, and D, respectively (Figure 1). Patients were treated with 10 mg of prednisone every 8 hours after ingesting at least 3000 ml of nondairy liquids.

The amount of absorbed ¹³¹I was estimated using high-energy collimators that provided counts of salivary-gland uptake of ¹³¹I after the detectors were positioned to cover an area from the brain to the thyroid from 1 to 48 hours after ¹³¹I ingestion. The residence time of ¹³¹I in salivary glands was calculated, and the salivary gland size was measured by computed tomography.

RESULTS

Patient Demographics (Figure 2)

A total of 80 patients were recruited from October 2006 through December 2008. Eight were excluded from the study, 5 did not complete salivary dosimetry measurements (2 from group A and 3 from group D), and the others had lung metastases identified on the posttherapy scans. A total of 73 patients were thus eligible for the analysis of salivary dosimetry. The main characteristics of the four study groups, including age, sex, histologic features, and thyrotropin (TSH) levels, were comparable (Figure 2).



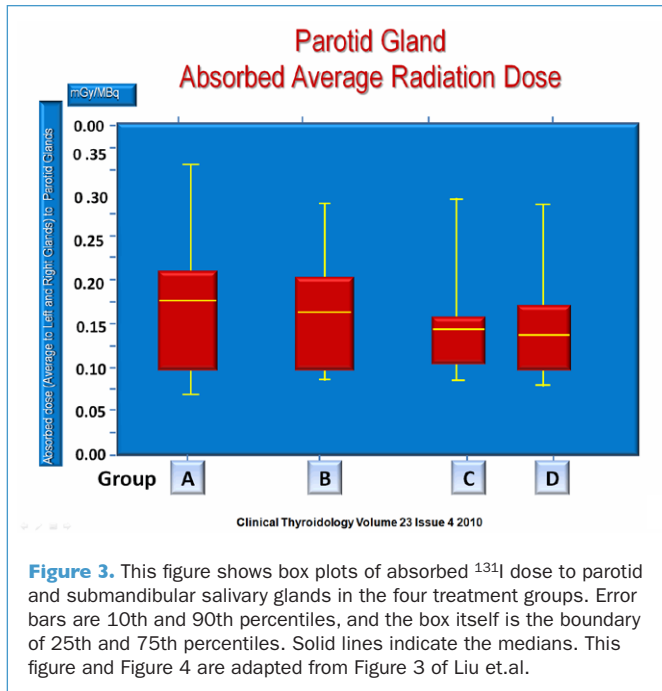


Figure 3. This figure shows box plots of absorbed ¹³¹I dose to parotid and submandibular salivary glands in the four treatment groups. Error bars are 10th and 90th percentiles, and the box itself is the boundary of 25th and 75th percentiles. Solid lines indicate the medians. This figure and Figure 4 are adapted from Figure 3 of Liu et.al.

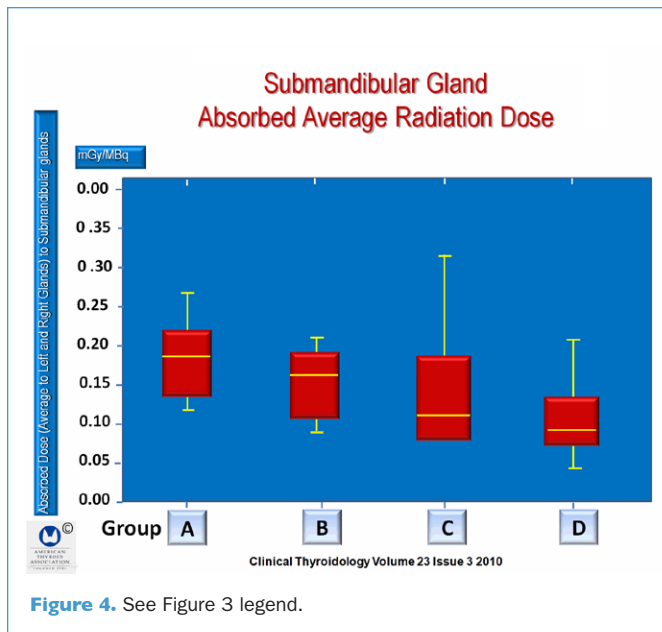


Figure 4. See Figure 3 legend.

Salivary Absorbed Dose of ¹³¹I to Parotid and Submandibular Glands in All Four Groups (Figure 3)

The dose of ¹³¹I absorbed by the patient's single parotid gland in groups A, B, C, and D were 18±0.11, 0.16±0.07, 0.16±0.09, and 16±0.12 mGy/MBq (0.1 rad/37 mCi), respectively (P = 0.37). For the single submandibular gland, the values of the four groups were 0.19±0.05, 0.17±0.05, 0.18±0.07, and 0.17±0.06 mGy/MBq, respectively (P = 0.28) (Figure 3).

Salivary Absorbed ¹³¹I Dose during the First 24 Hours (Figures 4 and 5)

The cumulative salivary ¹³¹I activities arising from the first 24 hours after ¹³¹I ingestion accounted for 86.08±.89% of the total cumulative ¹³¹I activities, which ranged from 75 to 98% (Figure 4). There was no significant difference in the salivary absorbed dose among the four groups during the first 24 hours after ¹³¹I administration (Figure 5).

Conclusion

Salivary stimulation with vitamin C at any time after ¹³¹I administration had only a limited effect on salivary ¹³¹I absorption in patients with thyroid cancer treated with ¹³¹I for remnant ablation.

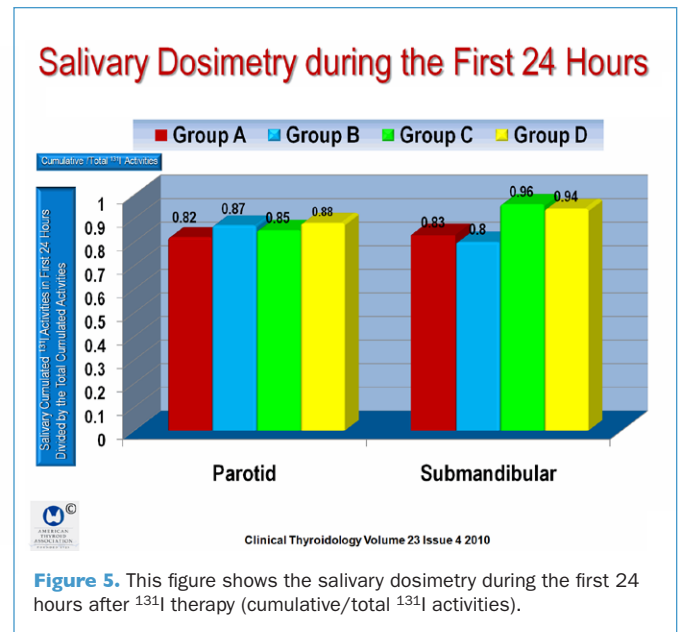


Figure 5. This figure shows the salivary dosimetry during the first 24 hours after ¹³¹I therapy (cumulative/total ¹³¹I activities).

CLINICAL THYROIDOLOGY FOR PATIENTS
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COMMENTARY

This study was based on the assumption that ^{131}I uptake by salivary glands would not plateau until 24 hours after the administration of ^{131}I , similar to the uptake by thyroid tissue, and that an early start of a sour stimulation of the salivary gland in the form of vitamin C would further deliver ^{131}I by increasing blood flow to the salivary glands. There are many recognized risks of ^{131}I therapy, including hematologic malignancy and damage to other nontarget tissues. Kloos summarized this group of problems in an editorial entitled “Protecting Thyroid Cancer Patients from Untoward Effects of Radioactive Iodine Treatment” (1). In that editorial, he pointed out that the American Thyroid Association guidelines recommend the lowest activity possible for remnant ablation, especially in patients with low-risk tumors. Still, even relatively small amounts of ^{131}I , in the range of 50 mCi, may produce salivary damage (2). Several strategies have been suggested to decrease the risk of salivary damage by ^{131}I therapy.

One strategy is to use amifostine to protect normal tissue against the harmful effects of ^{131}I . In a double-blind, placebo-controlled study, Bohuslavizki et al (3) found that amifostine protected salivary glands against ^{131}I damage, thus concluding that the drug could protect patients from salivary-gland damage induced by high-dose ^{131}I treatment. Although others have confirmed this observation (4), a randomized trial by Kim et al. (5) found a minimal effect of amifostine on ^{131}I treatment. In addition, concern has been raised that this drug might also reduce the therapeutic effect of ^{131}I .

For decades, physicians advised patients to suck lemon candy to decrease the amount of radiation to the salivary glands. In the first study to question this advice, Nakada et al. (6) performed a prospective study of 116 patients who were instructed to suck one or two lemon candies every 2 to 3 hours during the day for 5 days starting within 1 hour after ^{131}I therapy (group A), and 139 others were given the same instructions, except that they were told to wait until 24 hours after ^{131}I therapy to begin using

lemon candies (group B). During a 24-month period, patients were studied using interviews and questionnaires, which found that acute sialadenitis, taste dysfunction, dry mouth, and xerostomia were reported by patients who sucked lemon candies within an hour after ^{131}I therapy, as compared with those in group B, who waited 24 hours before starting the therapy. The incidences of sialadenitis, hypogeusia (taste loss), and dry mouth with or without repeated sialadenitis in group A as compared with group B were 64% versus 37% ($P < 0.001$), 39% versus 2% ($P < 0.01$), and 23.8% versus 11% ($P < 0.005$), respectively. Permanent xerostomia occurred in 14% of the patients in group A and in 6% in group B ($P < 0.05$). In both groups, bilateral involvement of the parotid gland was most frequently seen and was followed by bilateral involvement of the submandibular gland in group A, the first cohort. However, patients in group B were treated more aggressively for side effects, including the use of steroids or nonsteroidal antiinflammatory drugs for sialadenitis, and a drug containing zinc acetate or vitamin B12 for taste dysfunction. Moreover, 52% of group A and 81% of group B received such treatment. Whether this more aggressive treatment altered the outcome of group B is unknown. Nonetheless, the study findings raised serious questions about this practice.

The study by Liu et al. is the first prospective, randomized, controlled dosimetry-based trial to explore the effect of sour stimulation on the salivary glands. They also investigated the effect of the timing of salivary-gland stimulation to detect the effect of sour stimulation on the absorption of ^{131}I by salivary glands. Liu et al. also point out that similar studies should be performed on patients prepared with recombinant human TSH for remnant ablation. Their results confirm those reported by Nakada et al. and Liu et al. also suggest that in view of the high incidence of salivary-gland injury and the wide availability of sour stimulation, future controlled studies are needed to determine not only whether sour stimulation is necessary and when it should be started, but also how the dose and frequency of the stimulation should be titrated.

— Ernest L. Mazzaferri, MD, MACP

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Treating thyroid hormone abnormalities during pregnancy decreases adverse outcomes, but neither case finding nor universal thyroid screening decrease adverse outcomes in pregnancy.

Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. *J Clin Endocrinol Metab* 2010. doi:10.1210/jc.2009-2009

SUMMARY

BACKGROUND

Multiple adverse outcomes are associated with thyroid disease during pregnancy. The object of this study was to determine whether treatment of thyroid disease during pregnancy decreases the incidence of adverse outcomes and whether universal screening or case finding is better for detecting thyroid dysfunction in this setting.

METHODS

Women were recruited from the Division of Obstetrics and Gynecology in the Vito Fazzi Hospital and in the Casa Di Cura Salus in Italy. Women were recruited from March 2005 through February 2008, and the study was completed in December 2008. The study subjects were spontaneously pregnant women with a singleton pregnancy in the first 11 weeks of gestation without a history of thyroid disease. A total of 4562 white women in their first trimester of pregnancy were recruited into the study (Figure 1). On the first obstetrical visit, all had blood samples tested and were randomly assigned to either the case-finding group (n = 2282, 50%) or the universal-screening group (n = 2280, 50%). Women were considered to be at high risk if they had any of the following risk factors: family history of

autoimmune thyroid disease, goiter, signs and symptoms of thyroid disease, thyroid dysfunction, history of type 1 diabetes mellitus or other autoimmune disease, prior neck irradiation, or previous miscarriages or preterm deliveries. The obstetricians were not informed about which group the woman had been assigned to. The Endocrine Society guidelines for screening women at high risk were used in the universal screening group and in high-risk women in the case-finding group. Serums were immediately tested for thyrotropin (TSH), free thyroxine (FT₄) and thyroid peroxidase antibody (TPOAb). Frozen serums were stored at -70°C in the low-risk women and assayed post partum.

Women were classified as hypothyroid based on a serum TSH >2.5 mIU/L and TPOAb-positivity, as hyperthyroid on the basis of an undetectable serum TSH and an elevated FT₄, and as euthyroid if they were TPOAb-negative and were not further tested. During the second and third trimester, women who were TPOAb-positive with a TSH >2.5 mIU/L were treated with levothyroxine titrated to keep the TSH <3.0 mIU/L and antithyroid drug treatment of hyperthyroidism, based on the endocrinologist's clinical judgment. Thyroid function was tested in the second and third trimesters in euthyroid, TPOAb-positive women.

After randomization, 46 women did not perform all the tests or had delivery in other hospitals and were lost to follow-up. These women were evenly divided between the two arms of the study and did not differ significantly in the proportion of high- and low-risk individuals as compared with women not lost to follow-up. Ten of them (5 in each group) were at high-risk and the remaining women were at low-risk, 20 in the case-finding group and 16 in the universal screening group.

The statistical analysis tested the hypotheses that universal screening would be associated with a lower rate of adverse outcome events, that abnormal thyroid function would be associated with a higher rate of adverse outcome events, and that the impact of universal screening would depend on risk classification and abnormal thyroid function. Analysis was conducted on an intention-to treat basis.

RESULTS

Thyroid Status (Figure 2)

In the case-finding high-risk group, 454 (19.9%) met the criteria for high risk, whereas 1828 (80.1%) were low risk (Figure 2). In the universal screening group, 482 (21.1%) would have been classified as high risk and 1798 (78.9%) as low risk, which was not a statistically significant difference (P = 0.31). In the case-finding high-risk group, 432 (95.2%) were euthyroid, 20 (4.4%) were hypothyroid and two (0.4%) were hyperthyroid. In the case-finding low-risk group, 1789 (97.9%) were euthyroid, 34 (1.9%) were hypothyroid, and 5 (0.2%) were hyperthyroid. Low-risk women in the case-finding group were more likely to

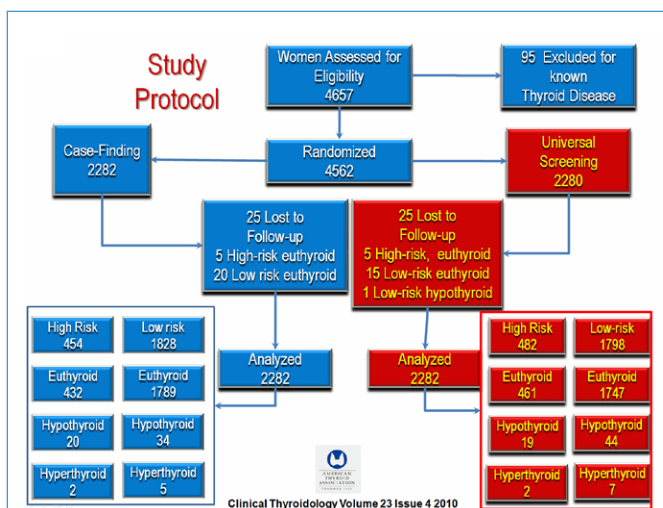


Figure 1. This figure shows the study protocol and number of patients assigned to each group in this study and the thyroid status of women in each group. The thyroid status of women deemed to be at low risk for an adverse outcome of pregnancy is based on frozen serum analyzed post partum. This figure is adapted from Figure 1 of Negro et al. Approximately 5% of euthyroid women in the universal-screening and the case-finding groups were TPOAb-positive, which is lower than in an earlier study by Negro et al. that defined euthyroidism as a TSH <4.2 mIU/L, whereas the current study defined euthyroidism as a serum TSH <2.5 mIU/L.

be euthyroid than high-risk women in this group (P = 0.005). In the case-finding low-risk group, 39 women were hypothyroid or hyperthyroid, and were thus not diagnosed or treated.

In the universal screening group, 2208 (96.8%) were euthyroid, 63 (2.8%) were hypothyroid, and 9 (0.4%) were hyperthyroid. Because all women in this group had been screened, those with hypothyroidism or hyperthyroidism were treated. There was no difference in thyroid function by study-group assignment (P = 0.83). Figure 2 shows that approximately 5% of euthyroid women in the universal screening and case-finding groups were TPOAb-positive, which is lower than in an earlier study by Negro et al. that defined euthyroidism as a TSH <4.2 mIU/L, whereas the current study defined euthyroidism as a serum TSH <2.5 mIU/L. None of the TPOAb-negative women had a TSH level >5.0 mIU/L. The number of TPOAb-positive women who had a TSH >2.5 mIU/L were as follows: in the case-finding high-risk group, 68 of 427 (15.9%); in the case-finding low risk group, 282 of 1769 (15.9%); in the universal-screening high-risk group 50 of 456 (11%); and in the universal-screening low-risk group, 242 of 1732 (14%). Euthyroid women who were TPOAb-positive in the first trimester and subsequently requiring treatment are as follows: case-finding high-risk group, 3 of 25 (12%); universal-screening high-risk group, 3 of 27 (11.1%); and universal-screening low-risk group, 10 of 105 (9.5%).

Among hypothyroid patients treated with levothyroxine, the number who had a TSH <3.0 mIU/L in the second trimester was: in the case-finding high risk group, 18 of 20 (90%); in the universal-screening high-risk group, 18 of 20 (90%); in the universal-screening high-risk group, 14 of 19 (73.4%), and in the universal-screening low-risk group, 43 of 44 (97.7%). The number of women who had a TSH <3.0 mIU/L in the third trimester was: in the case-finding high-risk group, 19 of 20 (95%); in the universal-screening high-risk group, 18 of 19 (94.7%); and in the

universal-screening low-risk group, 44 of 44 (100%). None of the women with hypothyroidism treated with thyroxine had TSH values >5.0 mIU/L during the second or third trimester. Sixteen patients had hyperthyroidism, 11 of whom were investigated (2 in the case-finding high-risk group, 2 in the universal-screening high-risk group, and 7 in the universal-screening low-risk group). Of the 11 patients, one woman had an autonomously functioning nodule, 3 had gestational thyrotoxicosis, and 7 had Graves' disease, 4 of whom were treated with antithyroid drugs.

Relationship between Risk Classification and Thyroid Status (Figures 2 to 4)

Risk status was associated with thyroid status. There were

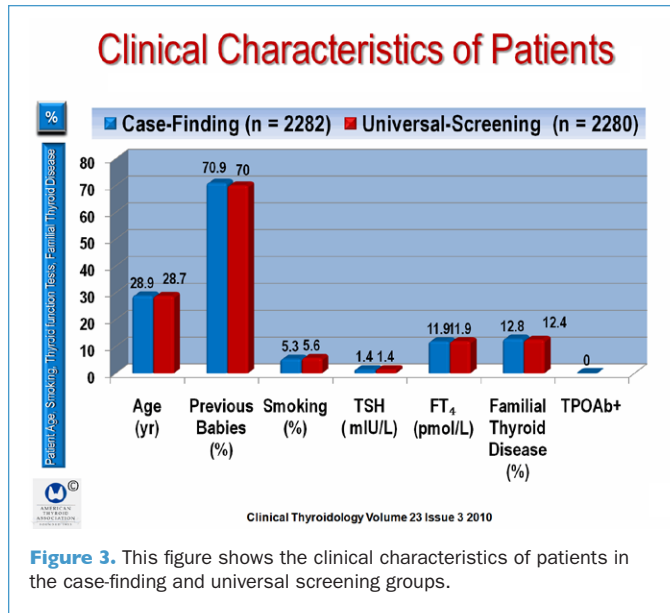


Figure 3. This figure shows the clinical characteristics of patients in the case-finding and universal screening groups.

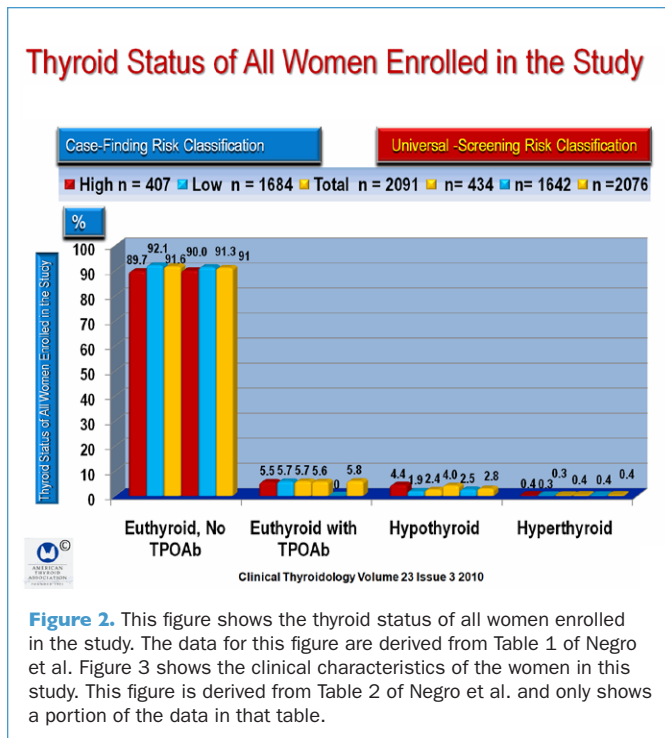


Figure 2. This figure shows the thyroid status of all women enrolled in the study. The data for this figure are derived from Table 1 of Negro et al. Figure 3 shows the clinical characteristics of the women in this study. This figure is derived from Table 2 of Negro et al. and only shows a portion of the data in that table.

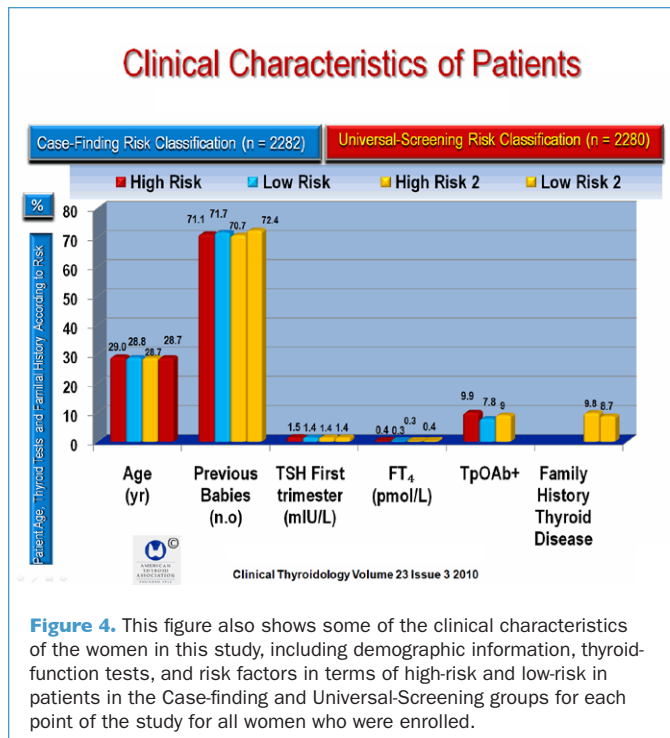


Figure 4. This figure also shows some of the clinical characteristics of the women in this study, including demographic information, thyroid-function tests, and risk factors in terms of high-risk and low-risk in patients in the Case-finding and Universal-Screening groups for each point of the study for all women who were enrolled.

fewer women with hypothyroidism and more euthyroid women without antibodies who would be classified as low risk than among women who would be classified as high risk (P = 0.005) (Figure 2). The relationship between risk classification and hypothyroidism was also significant in the case-finding group, in which 1.9% of low-risk and 4.5% of high-risk women had hypothyroidism (P= 0.01); however, this did not reach significance in the universal screening group, among whom 2.4% of low-risk women and 4.0% of high-risk women had hypothyroidism (P = 0.062). Figures 3 and 4 show the demographic data and thyroid status of the women enrolled in the study, randomly assigned to two groups, and also by the four analyzed cohorts (high-risk and low-risk). In the two randomized groups, there were no significant demographic differences. The probability of abnormal thyroid function, hyperthyroidism, or hypothyroidism in a 29-year-old woman was 2.8%. However advancing age was mildly associated with an increasing probability of abnormal thyroid function (odds ratio [OR] for each additional year of age, 1.05; 95% confidence interval [CI], 1.02 to 1.09).

Adverse Outcomes (Figures 5 and 6)

The adverse outcomes among the women in this study ranged from none to eight, and across the groups, 59.5% had no adverse outcomes, 25.6% had one, 6.6% had two, and 3.5% had four or more. At least 1 of the 930 women in the case-finding group and 900 in the universal-screening group experienced an adverse outcome (Figures 5 and 6). There were no significant differences between the total number of adverse outcomes in the case-finding group of 1545 women and the universal-screening group of 1559 women (P = 0.69).

The mixed logistic-regression model found that women in the screening group did not have fewer overall adverse outcomes, but there was a significant interaction between the trial arm and thyroid status (P = 0.014). The mixed logistic-regression

model also found relationships between adverse outcomes and other characteristics of low-risk women. The OR for age was 1.09 (95% CI, 1.08 to 1.10). The OR for the number of previous births was 1.51 (95% CI, 1.35 to 1.69). The OR for smoking was 1.71 (95% CI, 1.35 to 1.69). All were associated with an increased risk of adverse outcomes. These are general risk factors for adverse outcomes in pregnancy, independent of thyroid function. In women at high risk for adverse outcomes of pregnancy, there was no difference between the case-finding and universal-screening arms of the study. An adverse event was not significantly different for the women in the high-risk as compared with the low-risk universal-screening group, but it was higher for the low-risk case-finding group, as a consequence of the events associated with undetected and untreated hypothyroidism and hyperthyroidism (Figure 6).

Benefit of Treating Women with Low-Risk Hypothyroidism or Hyperthyroidism

To describe the benefit of treating low-risk hypothyroid or hyperthyroid women, the authors compared the likelihood of at least one adverse outcome for hyperthyroid women in the case-finding (untreated) group with that in the low-risk hypothyroid or hyperthyroid women in the universal screening (treated) group. For these women, treatment was of significant benefit; the inferred number needed to treat to prevent one woman from experiencing any adverse outcome was 1.8 (95% CI 1.4), 2.5).

Benefit of screening women for low-risk thyroid dysfunction

To further characterize the benefit of screening low-risk women, the authors compared the likelihood of at least one adverse outcome for all low-risk women in the case-finding group with that for the low-risk women in the universal screening group. Because many low-risk women with normal thyroid function had adverse outcomes in both groups, screening did not show a

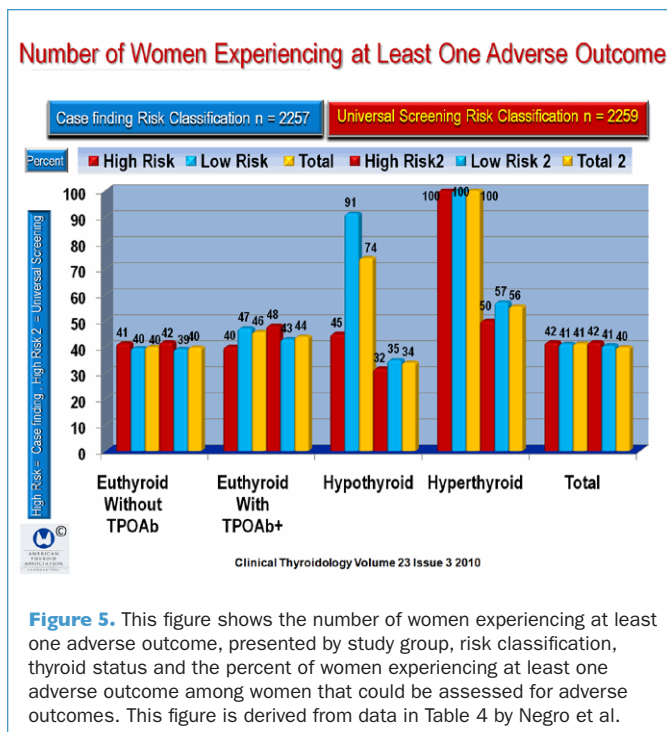


Figure 5. This figure shows the number of women experiencing at least one adverse outcome, presented by study group, risk classification, thyroid status and the percent of women experiencing at least one adverse outcome among women that could be assessed for adverse outcomes. This figure is derived from data in Table 4 by Negro et al.

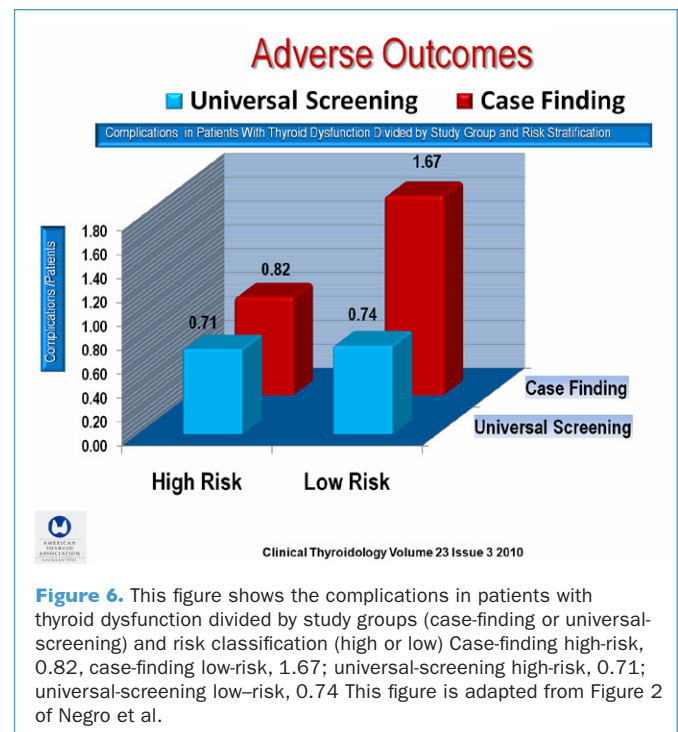


Figure 6. This figure shows the complications in patients with thyroid dysfunction divided by study groups (case-finding or universal-screening) and risk classification (high or low) Case-finding high-risk, 0.82, case-finding low-risk, 1.67; universal-screening high-risk, 0.71; universal-screening low-risk, 0.74 This figure is adapted from Figure 2 of Negro et al.

significant benefit. The number needed to screen to prevent one woman from having any adverse outcome was 60 (95%CI21,); However, the authors performed a mixed-model analysis that suggested this is likely an underestimate of the true benefit of screening because some women may be identified and treated, but still experience fewer adverse outcomes had they not been treated. Based on mixed-model results, screening low-risk women was associated with 2.48% fewer adverse events that would have been otherwise expected ($P < 0.012$), which corresponds to a inferred number needed to screen to prevent a single adverse outcome (but not all adverse outcomes) in a low-risk woman of approximately 40 years of age.

The Benefit of Screening for Low-Risk Women

Screening 1798 low-risk women identified 51 with abnormal thyroid function, who were then treated. The overall screening yield thus was 51 of 1798 (2.8%; 95% CI, 2.1 to 3.7), excluding the value of identifying euthyroid women with thyroid antibodies. The number needed to screen to detect one woman with hypothyroidism or hyperthyroidism was approximately 36 (95% CI, 27 to 48).

To further characterize the benefit of screening low-risk women, the likelihood of at least one adverse outcome for all low-risk

women in the case-finding group was compared with that for low-risk women in the universal-screening group. Because many low-risk women with normal thyroid function had adverse outcomes in both groups, screening did not show a significant benefit; however, the number needed to screen to prevent one woman from having any adverse outcome was 60 (95% CI, 21 to ∞). Still, the mixed-model results suggested that this is likely to be an underestimate of the true benefit of screening, as some women may be identified and treated but still have adverse outcomes, but fewer would have experienced an adverse outcome had they not been treated. On the basis of mixed-model results, screening low-risk women was associated with 2.48% fewer adverse events than would have been expected ($P = 0.012$), which corresponds to an inferred number needed to screen to prevent a single adverse outcome, but not all adverse outcomes, in a low-risk woman of approximately 40 years of age.

CONCLUSION

There were no significant differences in adverse outcomes between the case-finding and the universal-screening groups for thyroid dysfunction during pregnancy. Treatment of hyperthyroidism or hypothyroidism identified by screening a low-risk group was associated with a lower rate of adverse outcomes.

COMMENTARY

Thyroid disease has a number of deleterious effects on pregnancy, the developing fetus, and during the postpartum period. Complications include miscarriage, decreased intelligence quotient, visual-motor deficiencies in the children born to these women, preterm delivery, and postpartum thyroiditis (1-3). Screening for thyroid disease during pregnancy is controversial (4,5). The main issue of the debate concerns the impact of treating thyrotoxicosis in pregnant women (4,5).

This is the first prospective, randomized trial to compare case finding with universal screening for thyroid dysfunction during pregnancy. Universal screening as compared with case finding did not decrease the rate of adverse outcomes. Low-risk women in the universal-screening group had fewer adverse outcomes as compared with low-risk women in the case-finding group. However, low-risk women in the universal-screening group with

abnormal thyroid function who were treated avoided adverse outcomes more often than did low-risk women in the case-finding group with abnormal thyroid function that was not detected and thus not treated.

This study demonstrates that although universal screening did not result in a decrease in adverse outcomes, treatment of identified thyroid-hormone abnormalities during pregnancy resulted in a significant decrease in adverse outcomes. The study confirms that case finding fails to detect the majority of pregnant women with thyroid disease.

The authors of this important study suggest that a comprehensive cost-effectiveness analysis is required to resolve the debate of universal screening for thyroid disease in pregnancy.

— Ernest L. Mazzaferri, MD, MACP

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Proto-oncogene mutation detection in fine needle aspiration is a useful adjunct to cytology for diagnosing malignancy

Cantara S, Capezzone M, Marchisotta S, Capuano S, Busonero G, Toti P, Di Santo A, Caruso G, Carli AF, Brillì L, Montanaro A, Pacini F. Impact of proto-oncogene mutation detection in cytological specimens from thyroid nodules improves the diagnostic accuracy of cytology. *J Clin Endocrinol Metab* 2010;95:1365-9. First published ahead of print on February 3, 2010 as doi:10.1210/jc.2009-2103

SUMMARY

BACKGROUND

Cytology is currently the gold-standard for the preoperative diagnosis of malignancy in thyroid nodules. There are important limitations to its use, however. False negative rates may be as high as 6%. Likewise, the malignant potential of an indeterminate or follicular neoplasm cannot be determined by cytology alone, necessitating surgery to obtain a diagnosis. Recent insights into the molecular pathogenesis of thyroid cancer have sparked interest in using oncogenes to aid in the preoperative diagnosis of malignancy. Analysis of tumor tissues has revealed the high frequency of BRAF and RAS mutations and RET/PTC rearrangements in thyroid cancers and their absence in benign lesions. This study by Cantara et al. seeks to evaluate the efficacy of using these oncogenes to predict malignancy when molecular analysis is performed on cytologic samples.

PATIENTS AND METHODS

In this prospective study, 174 consecutive patients scheduled to undergo thyroid surgery were evaluated. Included in this analysis were patients undergoing surgery for cytology suspicious (n = 22) or positive (n = 48) for malignancy (40.2%), for indeterminate lesions/follicular neoplasms (n = 50, 28.7%), and for compressive symptoms with benign or inadequate cytology (n = 54, 31.1%). Prior to surgery, all patients underwent repeat fine-needle aspiration (FNA) with cytologic evaluation and molecular analysis. At surgery, all nodules were again sampled to undergo molecular analysis.

All samples were screened for mutations in BRAF (V600E and K601E); H-, K-, N-RAS point mutations in codons 12, 13, and 61; and RET/PTC rearrangements. In the absence of any of these mutations, TRK and PAX8-PPAR γ rearrangements were sought.

DNA extraction from FNA samples was performed using the QIAamp DNA microkit. RNA extraction was performed with the SV total RNA isolation system then reverse-transcribed into cDNA using the IScript cDNA synthesis kit. All samples were confirmed to the thyroid tissue through gene amplification for thyroglobulin.

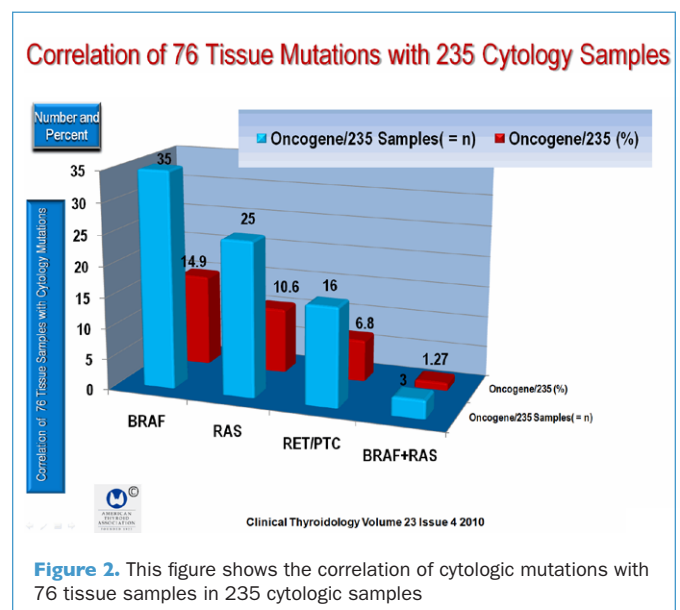
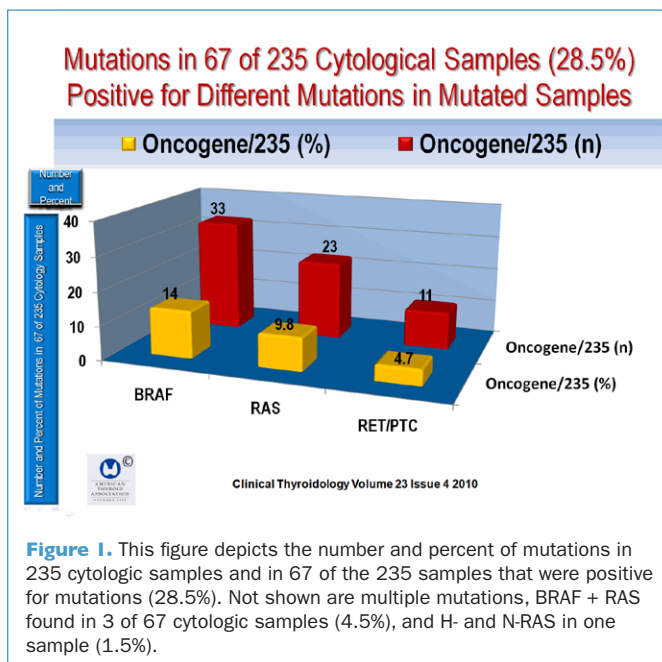
Results All cytologic and tissue samples were able to be analyzed for BRAF and H-, K-, N-RAS mutations. The cytologic yield was too low to detect a RET/PTC rearrangement in 51% of the FNA samples. All tissue samples, however, were able to be analyzed for RET/PTC.

Mutations in Cytologic Samples (Figure 1)

In the 235 FNA specimens, BRAF (V600E and K601E) and N-, K-, and H-RAS mutations were possible in all FNA cytologic and tissue samples. Oncogene mutations were identified in 67 of 235 cytologic samples (28.5%). Of the 67 mutations, the most frequent was BRAF in 33 of 67 samples (49.3%), followed by RAS mutations in 23 (34.3%), and 11 RET/PTC rearrangements (16.4%). Four cases had two mutations present; RAS and BRAF coexisted in three nodules, and H- and N-RAS occurred simultaneously in one (Figure 1).

Mutations in Tissue Samples (Figure 2)

There were 76 mutations (32.3%) in the tissue samples, including BRAF (V600E) in 35 (14.9%), RAS in 25 (10.6%),



and RET/PTC in 16 (6.8%). Four cases were noted to have two mutations, all of which corresponded to those seen on cytologic examination. There was an 88.2% concordance of the mutations between FNA and tissue samples. The 11.8% of discrepant results were attributed to mutations found in tissues but not identified in cytologic material. RET/PTC rearrangements were the most frequent mutations missed on cytology. Several cases of RAS mutations also went undetected on cytology. There were no TRK or PAX8-PPAR γ mutations found in both the cytologic and surgical specimens.

Correlation of Benign Cytologic Mutations with Tissue Mutations (Figure 3)

Analysis of the 87 nodules with benign cytology revealed a mutation in 9 (10.3%) (Figure 2). There were two nodules with BRAF mutations, two with RET/PTC rearrangements, and five with

RAS mutations. Final histology on the nodules with mutations revealed PTC in six and follicular adenomas in three. The 78 nodules with no mutations had two papillary thyroid carcinomas (PTCs) and one follicular thyroid carcinoma (FTC). The remainder were follicular adenomas and hyperplastic nodules.

Correlation between Cytologic Results and Final Histologic Diagnosis (Figure 4)

The mutations in cytologic samples correlated with the cytologic diagnosis and are shown in Figure 4. Of the nodules with a cytologic diagnosis suspicious for thyroid cancer (n = 54), 37 (68.5%) were found to have a mutation (21 BRAF, 6 RET/PTC, 10 RAS) and all were confirmed to be PTC on tissue histology. Of the remaining 17 patients with suspicious cytology but no mutations, 9 were diagnosed with PTC, 4 with follicular adenomas, and 4 with hyperplastic nodules.

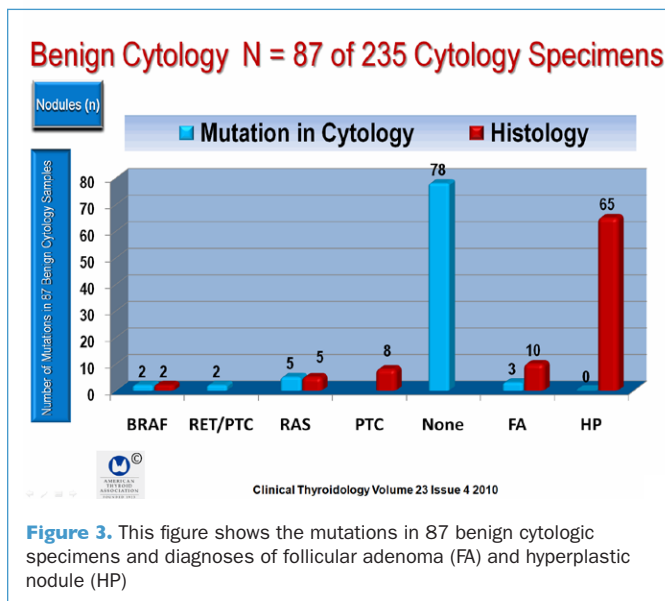


Figure 3. This figure shows the mutations in 87 benign cytologic specimens and diagnoses of follicular adenoma (FA) and hyperplastic nodule (HP)

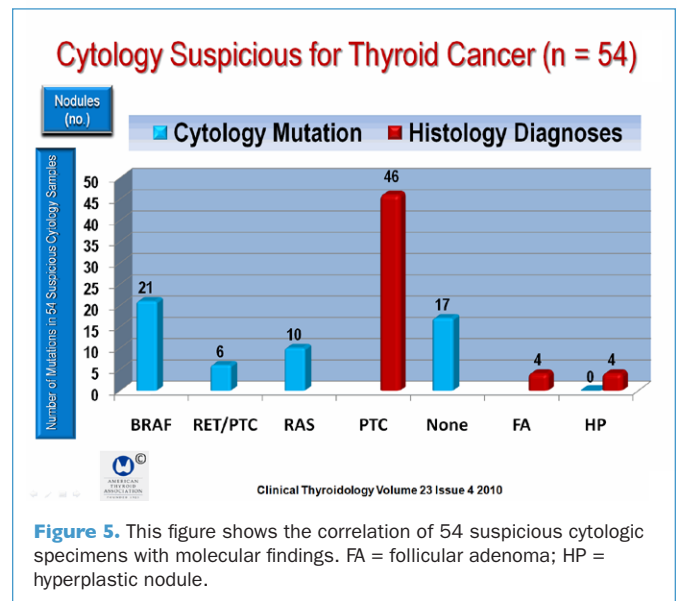


Figure 5. This figure shows the correlation of 54 suspicious cytologic specimens with molecular findings. FA = follicular adenoma; HP = hyperplastic nodule.

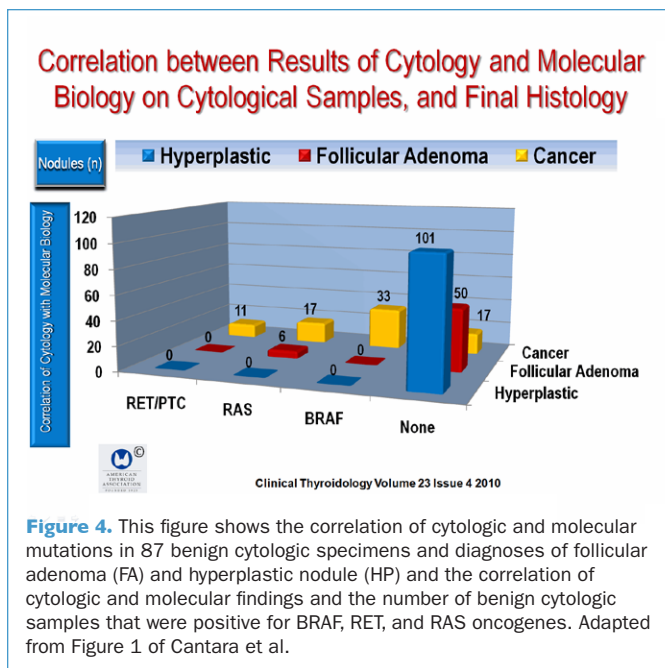


Figure 4. This figure shows the correlation of cytologic and molecular mutations in 87 benign cytologic specimens and diagnoses of follicular adenoma (FA) and hyperplastic nodule (HP) and the correlation of cytologic and molecular findings and the number of benign cytologic samples that were positive for BRAF, RET, and RAS oncogenes. Adapted from Figure 1 of Cantara et al.

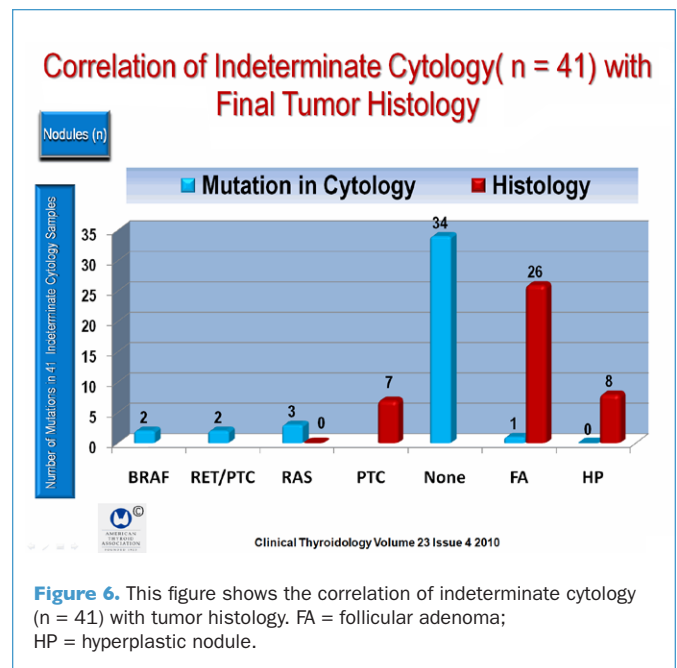


Figure 6. This figure shows the correlation of indeterminate cytology (n = 41) with tumor histology. FA = follicular adenoma; HP = hyperplastic nodule.

Correlation between Suspicious Cytologic Samples and Histologic Diagnosis (Figure 5)

Of the 235 nodules evaluated, there were 78 cancers found on final histology. The molecular analysis of FNA specimens correctly identified 61 (78.2%) malignancies, as compared with cytology, which diagnosed 46 (58.9%). Mutations (all RAS) were detected in 10.7% of follicular adenomas; no hyperplastic nodules were associated with a mutation. The presence of a mutation was associated with a diagnosis of cancer in 91.1% and follicular adenomas in 8.9%.

Correlation of Indeterminate Cytologic Mutations with Tumor Histology (Figure 6)

There were 7 mutations (17%) in the nodules with indeterminate cytology (Figure 3). On final histologic sectioning, the diagnosis was PTC in all but one, which was follicular adenoma. Among the 34 indeterminate nodules without mutations, only 1 was PTC; the remainder were hyperplastic nodules and follicular adenomas.

Correlation of Mutations in Inadequate Cytology with Tumor Histology (Figure 7)

The nodules with inadequate cytology had 14 (26.4%) mutations (8 BRAF, 1 RET/PTC, 5 RAS); histology revealed that all but two were malignant (Figure 7). The two benign lesions were follicular adenomas with RAS mutations. The inadequate samples with

no mutations had 4 cancers (2 PTCs and 2 FTCs), 11 follicular adenomas, and 24 hyperplastic nodules. RAS mutations were associated with malignancy rate 74% and follicular adenomas 26% of the time. In contrast, BRAF and RET/PTC were always associated with malignancy. Approximately 10% of malignancies had no associated malignancy.

Diagnostic Performance of Cytology, Molecular Analysis, or Both (Figure 8)

The specificity of cytology was strong at 94.9%, but was encumbered by a low sensitivity at 59%. The positive predictive value was 85.2% and the negative predictive value (NPV) 82.3%, giving a total accuracy of 83%. In contrast, molecular analysis had a specificity of 96.2% and improved sensitivity at 78.2%. The positive and negative predictive values were 91.1% and 89.9%, respectively, and total accuracy of 90.2%. Combination of these two techniques further improved the sensitivity and NPV, at 89.7% and 94.9%, respectively. Accuracy improved to 93.2% by combining the two techniques.

CONCLUSIONS

Molecular analysis of FNA samples in conjunction with cytology offers increased sensitivity and negative predictive value as compared with either method alone.

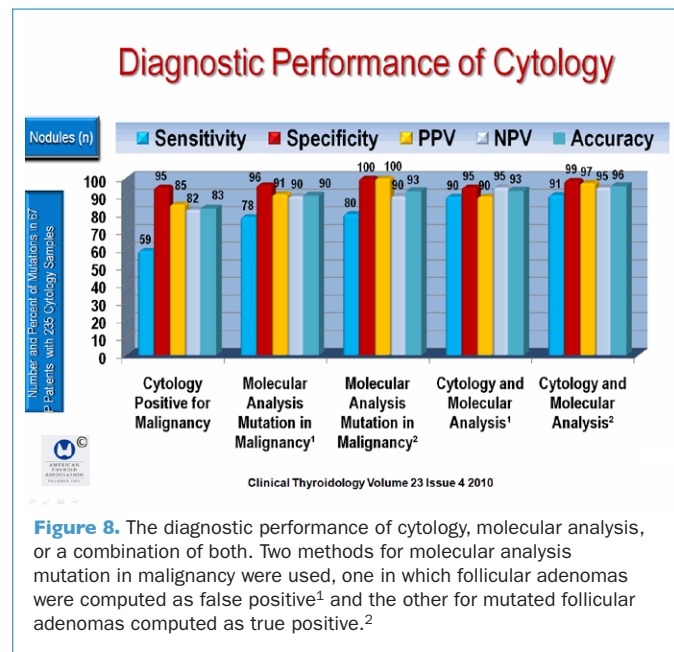
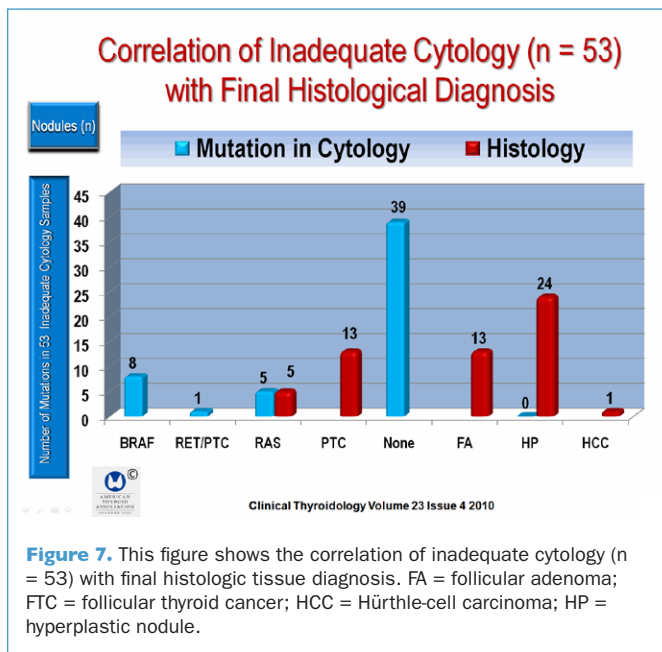


Figure 8. The diagnostic performance of cytology, molecular analysis, or a combination of both. Two methods for molecular analysis mutation in malignancy were used, one in which follicular adenomas were computed as false positive¹ and the other for mutated follicular adenomas computed as true positive.²

COMMENTARY

The problem of indeterminate cytology has plagued clinicians for years, and the search for alternatives to surgery that will determine which nodules are malignant has been extensive. Ultrasound characteristics (1), in combination with patient characteristics (2), have been analyzed, and scoring systems have been created to predict the likelihood of malignancy in a given nodule. To date, studies of various combinations of these features have failed to provide sufficient sensitivity and specificity to routinely advocate their use. Likewise, fluorodeoxyglucose–

positron-emission tomographic scanning has poor sensitivity and specificity for predicting malignancy in indeterminate nodules (3). One promising method, elastography, had a 100% positive predictive value to differentiate benign from malignant nodules in a pilot study (4). Its routine use, however, is limited by the need for expensive equipment and highly trained technicians. Thus, molecular analysis of FNA samples offers a glimmer of hope for a readily available test that can distinguish benign from malignant lesions. It is an attractive technique because molecular analysis can be performed on FNA samples; no additional testing of the patient is needed beyond the existing standard of care.

Numerous studies have paved the way for the current analysis by Cantara et al. (5;6). A great deal of emphasis has been placed on determining the presence of BRAF in FNA samples. Indeed, it is an exquisitely specific test; of the 2766 samples in the literature tested for its presence, there has only been one false positive result (7). Restriction of the molecular examination to BRAF mutations alone results in missing many tumors, however, as multiple mutations have been identified in differentiated thyroid cancers, these oncogenes are mutually exclusive (7). The authors of the present study sought to examine the feasibility of screening FNAs for multiple oncogenes. In addition, this article augments the existing literature in that all patients proceeded to surgery, removing the element of doubt about the true false negative rate of molecular analysis. The utility of molecular analysis on FNA samples was further validated in this study by comparing the results to those performed on the histologic samples; the concordance rate was very high.

Molecular analysis was very specific for BRAF mutations and RET/PTC rearrangements; in all cases, the presence of one of these mutations was associated with malignancy. In contrast, RAS was less specific, as 26% of the time it was associated with a diagnosis of a follicular adenoma. Although technically categorized as a false positive finding, it may provide clinically useful information. Such tumors may represent a precursor lesion to the RAS-positive follicular carcinomas (8). If a malignant transformation is made in an individual nodule, the presence of N-RAS mutations is associated with a more aggressive tumor phenotype (9). As such, some might justify the removal of these tumors to prevent progression to overt carcinoma (7).

It is important to note that molecular analysis of FNA samples cannot replace cytology. A significant number of patients had a false negative mutational analysis. Specifically, there were 9 nodules with suspicious cytology that had no mutations identified. In patients with suspicious cytology, molecular analysis adds little useful clinical information because the false positive rate is so low with cytologic examination. Rather, mutational

analysis appears to be most beneficial in patients with benign, indeterminate, or insufficient diagnoses on cytology. When used in this manner, the sensitivity and specificity for diagnosing malignancy is significantly improved over cytology alone.

There were eight patients with negative cytology and negative molecular analysis who were identified on final histology as having thyroid cancer. This group of nodules with false negative findings represents an important area for further study. It may be beneficial to include other molecular markers to see whether the sensitivity of this technique can be improved. An attractive candidate is microRNAs (miRs), endogenous noncoding RNAs that regulate gene expression posttranscriptionally (7). Many miRs that are dysregulated in thyroid cancer have been identified (10). Preliminary studies have confirmed that the up-regulation of these specific miRs in thyroid cancer may be useful to predict malignancy in thyroid nodules on FNA (10). It is important to note that the use of miR expression profiling is in the early stages of investigation, however. Additional studies are needed to confirm its utility in distinguishing malignant thyroid nodules from FNA samples.

While the current study reduces the false negative rate of cytology alone, it may not be appropriate to routinely test all nodules with benign, indeterminate, or inadequate cytology. Studies of the most cost-effective use of molecular analysis in thyroid nodules are needed. Clinical risk factors and sonographic appearance may also play a role in deciding which nodules merit further investigation with molecular analysis. Nevertheless, this study provides confirmation that molecular analysis of FNAs is an accurate method to distinguish benign from malignant lesions and will provide valuable insight into which patients should proceed to thyroidectomy and which may safely avoid it. Further, its use can reduce the costs and morbidity associated with hemithyroidectomies performed on nodules with indeterminate cytology that ultimately are deemed benign on final histologic examination. This is an exciting new technology with broad-reaching benefits for patients and clinicians alike.

— Jennifer A. Sipos, MD

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Preparation of thyroid remnant ablation using recombinant human TSH and 30 mCi of ¹³¹I is as effective as thyroid hormone withdrawal

Lee J, Yun MJ, Nam KH, Chung WY, Soh EY, Park CS. Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. *Thyroid* 2010;20:173-9.

SUMMARY

BACKGROUND

Few studies have examined the efficacy of 30 mCi of radioiodine (¹³¹I) using recombinant human thyrotropin- α (rhTSH) in preparation for thyroid radioiodine remnant ablation (TRRA) with 30 mCi in low-risk patients with differentiated thyroid cancer. This study investigated whether preparation with rhTSH was comparable to conventional preparation with thyroid hormone withdrawal (THW), providing the same therapeutic effect as preparing patients with rhTSH. The study also compared the quality of life (QOL) of patients with thyroid cancer who were prepared with rhTSH versus those prepared with THW.

METHODS

This is a randomized, controlled, open-label, single center study designed to compare the efficacy of various patient preparation methods prior to postsurgical remnant ablation using 30 mCi of radioactive iodine (¹³¹I) and to explore the QOL of patients being treated with ¹³¹I.

Patients age 18 years of age or older who recently were treated for differentiated thyroid cancer (DTC) with total or near-total thyroidectomy and central-compartment neck dissection were recruited for this study from February 2006 through March 2007. Excluded from the study were patients who had evidence of distant metastases (M1), lateral cervical lymph-node

metastases (N1b) with or without significant extrathyroidal tumor invasion (T₄), clinical laboratory studies showing hematologic or blood chemistry abnormalities, or abnormal serum creatinine levels. After surgery, all patients were started on 2 μ g/kg of levothyroxine (L-T₄).

At least 30 days after surgery, patients were randomly assigned to one of three groups: the L-T₄ withdrawal group (T₄-WD) in which L-T₄ was discontinued for 4 weeks; the T₃ (triiodothyronine) withdrawal group (T₃-WD) in which L-T₄ was discontinued for 4 weeks followed by 2 weeks on and 2 weeks off L-4 before ¹³¹I; and the rhTSH group that was on L-T₄ since surgery with a short cessation for 4 days prior to the day of rhTSH administration.

All patients were on a 2-week low-iodine diet prior to ¹³¹I therapy, and all had a 24-hour urine test and creatinine excretion measurement on the final day of the low-iodine diet. The authors devised a seven-item written QOL questionnaire to measure the impact of social life and mood changes and medical resource utilization. The success of TRRA was assessed at 12 months with a whole-body diagnostic ¹³¹I scan (DXWBS), serum thyroglobulin (Tg) measurement after TSH stimulation, and neck ultrasonography.

RESULTS

Patient Characteristics (Figures 1 and 2)

A total of 291 patients were recruited into the study and randomly assigned into the three study groups after total thyroidectomy.

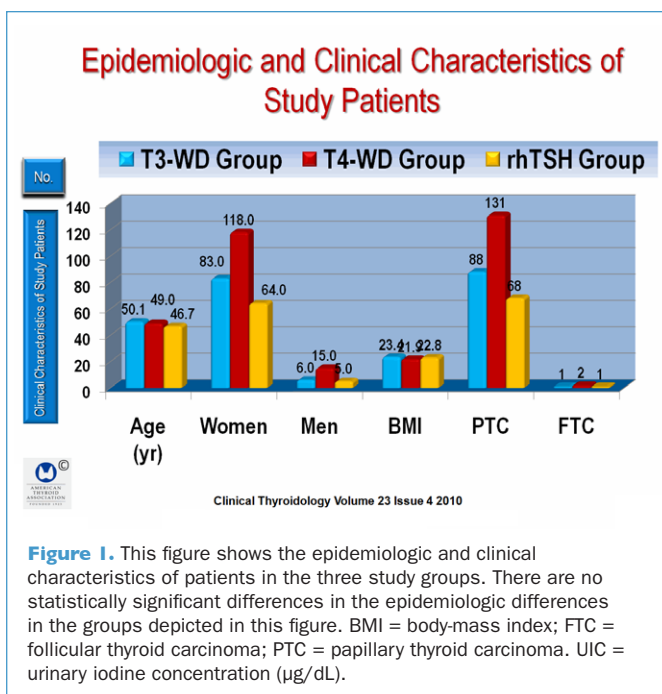


Figure 1. This figure shows the epidemiologic and clinical characteristics of patients in the three study groups. There are no statistically significant differences in the epidemiologic differences in the groups depicted in this figure. BMI = body-mass index; FTC = follicular thyroid carcinoma; PTC = papillary thyroid carcinoma. UIC = urinary iodine concentration (μ g/dL).

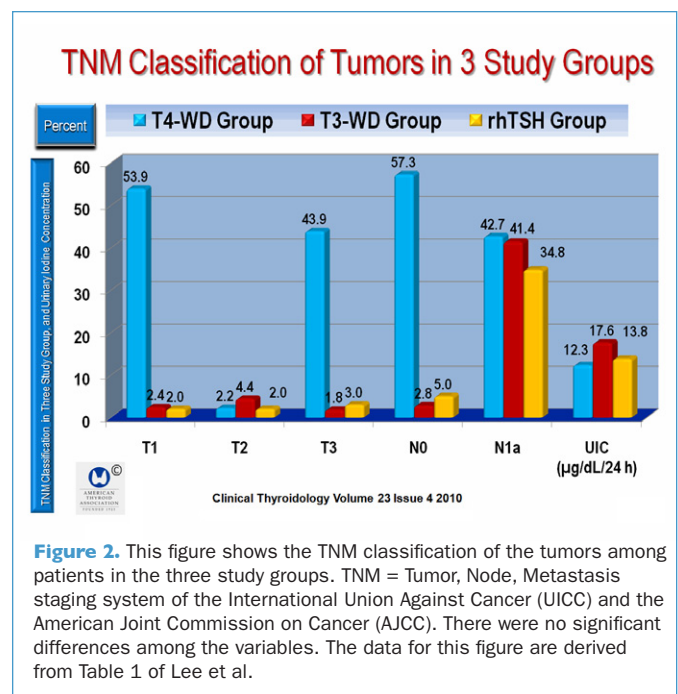


Figure 2. This figure shows the TNM classification of the tumors among patients in the three study groups. TNM = Tumor, Node, Metastasis staging system of the International Union Against Cancer (UICC) and the American Joint Commission on Cancer (AJCC). There were no significant differences among the variables. The data for this figure are derived from Table 1 of Lee et al.

Patient demographics and tumor stage are shown in Figure 1. There was no significant difference in age, ratio of women to men, body-mass index, and ratio of papillary to follicular cancer among the three groups. After 12 months of follow-up, the mean (\pm SD) serum Tg levels after TSH stimulation were 0.18 ± 0.14 ng/ml (range, 0.01 to 2.9) in the T₄-WD group, 0.14 ± 1.9 (range, 0.1 to 2.9) in the T₃-WD group, and 0.14 ± 0.05 ng/ml (range, 0.1 to 0.2) in the rhTSH group. There were no statistically significant differences in the tumor–node–metastasis (TNM) tumor classifications in the three groups (Figure 2).

TRRA Outcomes among the Three Study Groups (Figure 3)

To assess the efficacy of each preparation method, each patient had a DXWBS, neck ultrasonography, and TSH-stimulated serum Tg measurement at 12 months. The comparative ablation rates are shown in Figure 3. The rhTSH ablation rate was equivalent to that achieved by the two THW groups. In the T₄-WD group, serum Tg >1.0 ng/ml (n = 8) was associated with persistent residual thyroid tissue in six patients and with two lymph-node metastases identified by DXWBS and neck ultrasonography.

In the T₃-WD group, 10 patients had elevated serum Tg levels associated with persistent residual disease in seven patients with lymph-node metastases that were detected by neck ultrasonography in three patients but were missed by DXWBS

in one patient. In the rhTSH group, detectable serum Tg was found in five patients, which was associated with a persistent thyroid remnant in three, with lymph-node metastases detected by DXWBS in two patients, but was missed by ultrasonography. Five patients, (two in T₄-WD group, two in the T₃-WD, and one in the rhTSH group, had lymph-node metastases that persisted after surgery and disappeared after the second ¹³¹I ablation and was verified by DXWBS, neck ultrasonography, and undetectable serum Tg, and in 2 patients (one in the T₃-WD group and one in the rhTSH group) missed by DXWBS but identified by TSH-stimulated serum Tg and neck ultrasonography was confirmed by fine-needle aspiration biopsy.

Quality of Life (Figure 4)

There was a highly significant difference in QOL status between the three thyroid hormone withdrawal groups (T₄-WD and T₃-WD groups), and the rhTSH group. Still, there was no difference in the QOL during preparation for DXWBS between patients in the two thyroid hormone withdrawal groups (Figure 4).

CONCLUSION

The use of rhTSH effectively stimulated the uptake of 30 mCi of ¹³¹I for thyroid remnant ablation as effectively as thyroid hormone withdrawal and maintains the QOL of patients who are remaining euthyroid during preparation for thyroid remnant ablation.

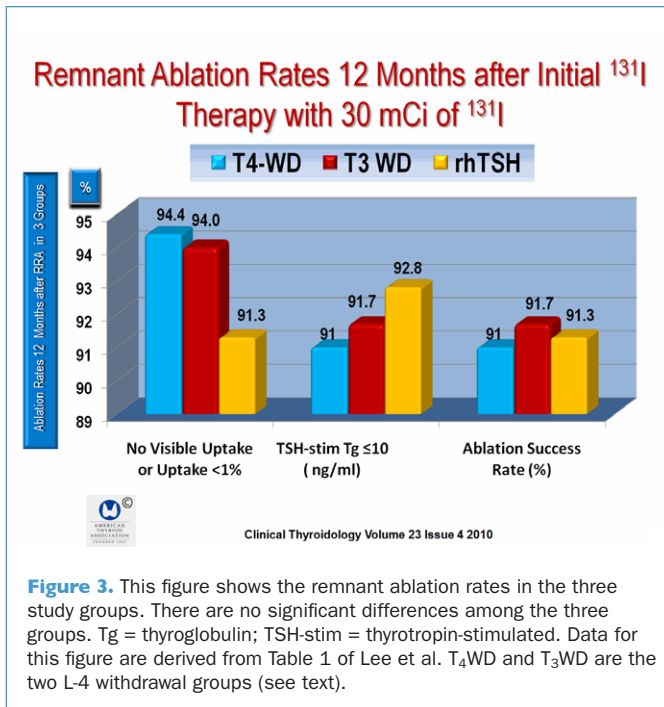


Figure 3. This figure shows the remnant ablation rates in the three study groups. There are no significant differences among the three groups. Tg = thyroglobulin; TSH-stim = thyrotropin-stimulated. Data for this figure are derived from Table 1 of Lee et al. T₄WD and T₃WD are the two L-4 withdrawal groups (see text).

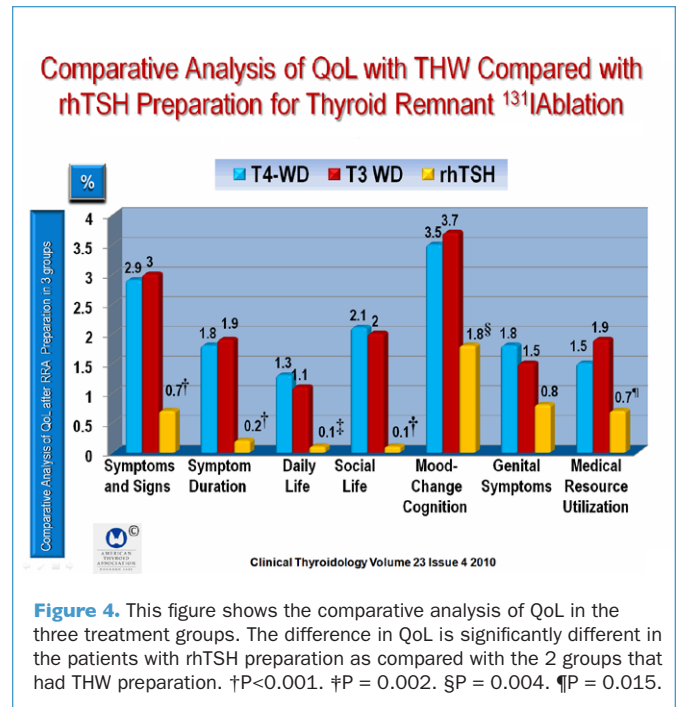


Figure 4. This figure shows the comparative analysis of QoL in the three treatment groups. The difference in QoL is significantly different in the patients with rhTSH preparation as compared with the 2 groups that had THW preparation. †P < 0.001. ‡P = 0.002. §P = 0.004. ¶P = 0.015.

COMMENTARY

This is one of the few prospective, randomized studies that analyze the efficacy of 30 mCi of ^{131}I for TRRA (1), and even fewer compare rhTSH-stimulated TRRA with 30 mCi as compared with THW (2). The main message from the Lee study is that rhTSH is at least as effective as THW in preparation for TRRA with 30 mCi (2). In fact, after 12 months of follow-up, the mean success TRRA rate was over 90% in all three study groups. This is a bit higher than usual, which may be the result of several factors. The results were reported after a 12-month follow-up during which patients were deemed to have successful TRRA based on no visible ^{131}I neck uptake or an uptake $<1\%$ and a negative DXWBS and neck ultrasonography and a TSH-stimulated $\text{Tg} \leq 10$ ng/ml. While this may be a reasonable end point to identify patients who have no evidence of disease, one would be more certain about the completeness of TRRA with a TSH-stimulated Tg that is undetectable (3). Still, the rhTSH-stimulated Tg was

in the same range as those of patients in the two THW groups. Another reason for the high TRRA success rate may be because all patients had good adherence to a low-iodine diet. Although some have suggested that there is enough iodine in L-4 to blunt the therapeutic effect of ^{131}I in patients treated with rhTSH (2), prospective studies have failed to confirm this finding (4). In the Lee study, the rhTSH group had a 4-day L-4 withdrawal just before rhTSH was administered, and it is not likely that this had a robust effect on TRRA.

The most important finding in this carefully crafted study is that rhTSH can be used in lieu of thyroid hormone withdrawal, and patients with low-risk thyroid cancer can be prepared for TRRA using rhTSH with very small amounts of ^{131}I , in the range of 30 mCi, thus diminishing total-body irradiation and decreasing damage to nonthyroidal tissues.

— Ernest L. Mazzaferri, MD, MACP

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HOT ARTICLES

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DISCLOSURE

Dr. Mazzaferri is a consultant to Genzyme,

Dr. Sipos Lectures for Abbott Pharmaceutical and Genzyme.

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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)	<i>Program subject to change</i>
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)		 AMERICAN THYROID ASSOCIATION FOUNDED 1923 www.thyroid.org
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)	

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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
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Annual 80th Meeting
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 80th Meeting
Palm Beach, Florida
September 23-27, 2009
AMERICAN THYROID ASSOCIATION
Online Registration >>

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EVENTS CALENDAR

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We invite you to join the ATA!

Are You Intrigued by the Study of the Thyroid? You Belong in the ATA!

- 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!