

CLINICAL THYROIDOLOGY

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EDITORS' COMMENTS 2

EDITORS' CHOICE — THYROID HORMONE REPLACEMENT IN PREGNANCY

Adding two additional tablets of levothyroxine per week, when instituted immediately upon confirmation of pregnancy to women with known hypothyroidism significantly reduces the risk of maternal hypothyroidism throughout pregnancy
Yassa L, Marqusee E, Fawcett R, Alexander EK. Thyroid hormone early adjustment in pregnancy (The THERAPY) Trial. *J Clin Endocrinol Metab* 2010; May 12 [Epub ahead of print]. 3

EDITORS' CHOICE — MATERNAL THYROID FUNCTION DURING GESTATION

Pregnant women with TSH levels higher than 2.5 IU/L during the end of gestation are at risk for breech presentation, and obstetrical complications.
Kuppens SM, Kooistra HA, Wijnen HA, Crawford S, Vader HL, Hasaart TH, Oei SG, Pop VJ. Maternal thyroid function during gestation is related to breech presentation at term. *Clin Endocrinol (Oxf)* 2009. doi: 10.1111/j.1365-2265.2009.03729.x. 7

PAPILLARY MICROCARCINOMA

Central neck compartment lymph-node-metastases in papillary thyroid carcinoma can be effectively managed with prophylactic CLND, without a high complication rate and with very few recurrences
So YK, Son YI, Hong SD, Seo MY, Baek CH, Jeong HS, Chung MK. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. *Surgery* 2010. doi:10.1016/j.surg.2010.01.003 10

LYMPH-NODE SURGERY FOR PAPILLARY THYROID CANCER

Persistent cervical PTC lymph-node metastases may require several surgical resections to achieve biochemical or clinical evidence of disease-free outcome
Al-Saif O, Farrar WB, Bloomston M, Porter K, Ringel MD, Kloos RT. Long-term efficacy of lymph node reoperation for persistent papillary thyroid cancer. *J Clin Endocrinol Metab* 2010;95:2187-94. 14

THYROID CANCER

Cancer-specific survival is significantly improved by total thyroidectomy and by a trend for ¹³¹I RRA, but not for disease-free recurrence
Doi SA, Engel JM, Onitilo AA. Total thyroidectomy followed by postsurgical remnant ablation may improve cancer specific survival in differentiated thyroid carcinoma. *Clin Nucl Med* 2010;35:396-9. 18

REVIEW ARTICLES, GUIDELINES & HOT NEW ARTICLES

HOT ARTICLES 22
REVIEWS GUIDELINES AND META-ANALYSIS 22
DISCLOSURE 22

CALL FOR APPLICATIONS

Editor-in-Chief of *Clinical Thyroidology* 23

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EDITORS' COMMENTS

This is the sixth 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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Adding two additional tablets of levothyroxine per week, when instituted immediately upon confirmation of pregnancy to women with known hypothyroidism significantly reduces the risk of maternal hypothyroidism throughout pregnancy

Yassa L, Marqusee E, Fawcett R, Alexander EK. Thyroid hormone early adjustment in pregnancy (The THERAPY) Trial. *J Clin Endocrinol Metab* 2010; May [First published ahead of print May 12, 2010 as doi:10.1210/jc.2010-0013].

SUMMARY

BACKGROUND

Maternal hypothyroidism during the first half of pregnancy may result in serious harm to fetal development. As a consequence, it is important for pregnant women with hypothyroidism to maintain biochemical euthyroidism during gestation. Pregnant women thus must increase their levothyroxine dose during pregnancy, as the thyroid hormone requirement increases 20 to 40% during gestation. Yet how this should be accomplished remains uncertain.

METHODS

A total of 60 women with treated hypothyroidism who were newly pregnant or were planning to become pregnant were prospectively enrolled in this study. Once pregnant, the women were randomly assigned to increase their levothyroxine (L-T₄) by either two tablets per week (group A) or three tablets per week (group B). Biweekly thyroid-function tests were performed through midpregnancy and at 30 weeks of gestation, and levothyroxine doses were adjusted to maintain the target thyrotropin (TSH) concentrations. The primary objective of the study was to assess the efficacy of preventing maternal hypothyroidism and the safety of levothyroxine intervention.

Prior to pregnancy, data were collected to document the demographic characteristics of the women and the type of thyroid dysfunction and to confirm a stable dose of L-T₄ for at least 6 weeks. Newly pregnant women were enrolled only if they were less than 11 weeks pregnant and had normal baseline serum TSH concentrations for 6 months preceding enrollment in the study. Women with thyroid cancer were enrolled if thyroid-function tests confirmed a serum TSH of 0.01 to 2.5 mIU/L. Subjects without thyroid cancer were enrolled if prepregnancy thyroid-function tests confirmed a TSH of 0.05 to 5.0 mIU/L. Once pregnancy was suspected, patients had confirmatory serum human chorionic gonadotropin tests and the serum TSH, total thyroxine (T₄), and thyroid hormone binding ratio were measured.

Subjects were then randomly assigned to increase their prepregnancy doses of L-T₄ by either two tablets per week (29%) (a total of nine tablets per week in group A) or three additional tablets per week (43%) (a total of 10 tablets per week in group B). Patients were instructed to take double doses of their current L-T₄ tablets on Saturdays and Wednesday (group A) or on Mondays, Wednesdays, and Fridays (group B). The patients were instructed to take L-T₄ on an empty stomach and to avoid calcium, iron, or prenatal vitamins within 4 hours

of L-T₄ ingestion. This was based on a 20 to 40% increased requirement of levothyroxine among pregnant women, which had been previously documented.

Patients returned for follow-up testing every 2 weeks until 20 weeks of gestation (midpregnancy) and once more at 30 weeks, during which approximately 10 serum samples of serum TSH, total T₄, and thyroid hormone binding ratio had been obtained in each patient; and L-T₄ dosage was adjusted every 4 weeks, at weeks 4, 8, 12, 16, 20 and 30 weeks according to the protocol. During the intervening weeks (6, 10, 14, and 18) the L-T₄ dosage was modified if TSH was 10 mIU/L or <0.01 mIU/L both in patients with hypothyroidism and those with thyroid cancer.

The estimated date of delivery was based on the first day of the woman's most recent menstruation or on a sonographic examination performed at the request of the treating obstetrician. The primary and secondary analysis was performed only on the 48 patients who completed the randomized protocol. A total of 10 women had a miscarriage shortly after enrollment in the study, 6 of whom had initial blood work that confirmed pregnancy but had not yet been assigned to a treatment group, and thus

Baseline Data from 48 Treated Women with Hypothyroidism who Completed the Study Protocol

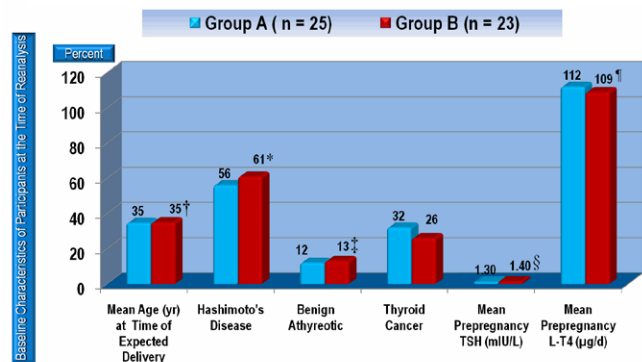


Figure 1. This figure depicts the baseline data from 48 women with treated hypothyroidism who completed the study protocol. *P = 0.85 comparing mean age at the time of expected delivery in groups A and B. †P = 0.91 comparing mean pregnancy TSH in group A and group B. §P = 0.89 comparing prepregnancy L-T₄ in group A with that in group B. ‡P = 0.89 comparing mean prepregnancy requirement of L-T₄ (µg/d) in group A versus group B. The data for this figure are derived from Table 2 of Yassa et al.

did not participate in the study, and 4 who were randomly assigned to the study protocol had no blood tests before the miscarriage occurred.

RESULTS

Patient demographics (Figure 1)

A total of 60 women with treated hypothyroidism were enrolled in the study, 48 of whom (80%) successfully completed the protocol (25 in group A and 23 in group B). The mean age of patients completing the protocol was 34.4 years. Miscarriage occurred in 10 women (16.6%), at a mean age 35.9 years and an average of 7 weeks of gestation, which was not different from the expected miscarriage rate among women of the same age in the study group. The miscarriages were one stillbirth at 20 weeks of gestation due to an incompetent cervix and one from a molar pregnancy (Figure 1).

The mean prepregnancy serum TSH concentration of the 12 women who did not complete the protocol was 1.2 µIU/ml, which was not significantly different from that in women who did complete the protocol (P = 0.81). Eight of these women were treated with L-T₄ for Hashimoto's disease, two had thyroid cancer, and two were athyreotic from benign disease (Figure 1). In this group, the mean prepregnancy L-T₄ requirement was 99 µg/day (P = 0.35), as compared with the 48 women who completed the protocol.

Among the 48 women who completed the protocol, 25 (52%) were randomly assigned to increase their L-T₄ to two extra tablets per week (group A). A total of 8 (32%) had a history of thyroid cancer, and 17 (68%) had hypothyroidism caused by Hashimoto's disease or ¹³¹I ablation. A total of 23 women were randomly assigned to increase their L-T₄ dose by three extra tablets per week (group B); 6 of them had thyroid cancer (26%) and 17 (74%) had hypothyroidism due to Hashimoto's disease, surgery, or ¹³¹I ablation for thyroid cancer. In all, 28 of 48 patients (58%) had hyperthyroidism due to Hashimoto's thyroiditis and 14 (29%) had thyroid cancer. The demographic data for these women as well as their mean prepregnancy TSH concentrations and L-T₄ requirements are shown in Figure 1.

The pregestational TSH was <2.5 mIU/L in 41 of 48 women (85%) and <3.0 mIU/L in 43 of 48 women (90%). For women with Hashimoto's disease, the mean serum TSH concentration was 1.8 mIU/L (range, 0.5 to 4.3), for women with benign athyreotic hypothyroidism, 1.5 mIU/L (range, 0.4 to 4.8), and for women with thyroid cancer it was 0.5 mIU/L (range, 0.1 to 0.9). Pregnancy was confirmed in all women 11 weeks before pregnancy. Enrollment occurred at a median of 5.5 weeks of pregnancy (mean, 6.3 weeks); nonetheless, on their initial postconception test, 13 of 48 women (27%) had serum TSH concentrations >5.0 mIU/L, which confirmed that L-T₄ replacement was inadequate in early gestation. Preconception TSH values in the 13 women revealed that 4 (31%) had values of <1.0 mIU/L, 8 (62%) had values of 1.0 to 2.5 µIU/ml, and 1 of 13 (8%) had values of 2.6 to 5.0 µIU/ml.

Protocol for Thyroid Hormone early Adjustment (Figure 2)

Increasing the L-T₄ dose at the time of entry into the study by either two or three additional tablets per week normalized the serum TSH at <5.0 mIU/L in all women for the remainder of

the first trimester. Two women in group A (8%), both of whom had athyreosis, one after thyroidectomy and the other for benign disease, had an elevated serum TSH of 5.1 and 6.2 µIU/ml during pregnancy at weeks 14 and 16, respectively, requiring a further increase in L-T₄. In group B, 1 of 23 women (4%) had a serum TSH of 7.7 and 7.4 µIU/ml during pregnancy at weeks 14 and 16, respectively, which required a similar increase in L-T₄. This woman had Hashimoto's disease. No other serum TSH concentrations >5.0 mIU/L occurred during the study.

For all women who completed the study protocol, the mean TSH concentration decreased throughout the first trimester, especially during weeks 10 to 14 of gestation, and thereafter a normal serum TSH was maintained. The initial L-T₄ augmentation early in pregnancy caused suppression of TSH to <0.5 µIU/ml (<0.1 µIU/ml with thyroid cancer) in 8 of 25 (32%) women in group A, as compared with 15 of 23 (65%) women in group B (P<0.01). A total of 78% of these events occurred before gestational week 14, although the mean serum TSH concentration was only mildly below the lower reference range as defined in nonpregnant women. In patients without thyroid cancer, a mean TSH of 0.3 mIU/L (range, 0.06 to 0.44 mIU/L) triggered an L-T₄ dose reduction. Whereas in women with thyroid cancer, the TSH trigger averaged 0.06 µIU/ml (range, 0.01 to 0.09). Seventeen of these 23 women (74%) had a free T₄ index (FTI) within the accepted reference range of 10.8 to 13.1 (mean, 11.7).

However, during this study, new data were released providing trimester-specific TSH reference ranges in 13,000 pregnant women without thyroid dysfunction, indicating that the 2.5th percentile, and thus the lower limit, in a healthy pregnant women during the first trimester was 0.1 IU/mL, and the 97.5th percentile (the upper reference limit) was 2.5, 3.0, and 3.0 mIU/L in the first, second, and third trimesters, respectively. Using these new reference data, group A had only 2 patients (8%) with a TSH <0.01 µIU/ml at any point during pregnancy. Thus, a woman with benign athyreotic hypothyroidism experienced a TSH of 0.05 µIU/ml and an FTI of 8.4 at pregnancy week 14, and a patient with thyroid cancer experienced a TSH of 0.05

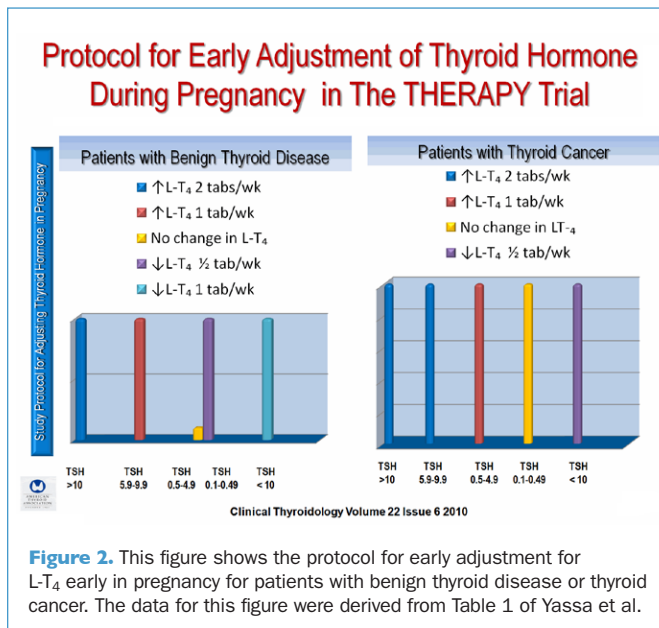


Figure 2. This figure shows the protocol for early adjustment for L-T₄ early in pregnancy for patients with benign thyroid disease or thyroid cancer. The data for this figure were derived from Table 1 of Yassa et al.

μIU/ml and an FTI of 11.93 at pregnancy week 16. In group B, 6 of 23 patients (26%) had a serum TSH <0.01 μIU/ml during pregnancy. Thus, five patients with thyroid cancer experienced TSH and FTI values of 0.09 mIU/L and 10.5 at gestation week 10; 0.09 μIU/ml and 10.1 at week 14; 0.01 μIU/ml and 13.1 at week 8; 0.05 μIU/ml and 9.8 at week 12; and 0.02 μIU/ml and 12.2 at week 10. One patient in group B who had Hashimoto's disease experienced a TSH of 0.06 μIU/ml with an FTI of 10.8 at week 16. Thus, among all 48 patients, FTIs were elevated beyond the reference limits in only 4 of 8 patients at the time TSH was <0.01 μIU/ml.

The data were analyzed separately to determine the proportion of patients with serum TSH concentrations from 2.5 to 5.0 μIU/ml at any point during the investigation. Although two subjects in group A experienced a single TSH concentration >5.0 μIU/ml at least once during the study, eight women experienced TSH concentrations of 2.5 and 5.0 μIU/ml during the study. Among seven of eight women, this was a single isolated occurrence throughout all of gestation, while one woman had two separate values in this range. In group B, four patients experienced a single TSH concentration between 2.5 and 5.0 mIU/L during the study. None of the subjects experienced an FTI of <5.0 at any point throughout the study.

Multivariate Analysis of L-T₄ Dose as It Relates to Subsequent Serum TSH Suppression (Figure 3)

To identify which variable predicted an increased risk for TSH suppression after L-T₄ treatment intervention, data from all 48 patients who completed the protocol were analyzed. In all, 18 of 29 women (37.5%) with prepregnancy serum TSH concentrations <0.1.5 μIU/ml required L-T₄ dose reductions during pregnancy as compared with 5 of 19 women (33%) with prepregnancy serum TSH concentrations of 1.5 μIU/ml or higher; the odds ratio (OR) was 4.6 (95% confidence interval [CI], 1.3 to 16.2). Likewise, 20 of 32 women (62.5%) receiving prepregnancy L-T₄ doses of at least 100 μg/day required L-T₄ reductions during pregnancy, as compared with 3 of 16 women (19%) receiving less than 100 μg/dl (OR, 7.2; 95% CI, 1.7 to 30.6). Lastly, 13 of 20 (65%) women with athyreotic hypothyroidism due to surgery or ¹³¹I ablation, required L-T₄ dose reductions during pregnancy, as compared with 10 of 28 women (36%) with Hashimoto's disease (OR, 3.3; 95% CI, 1.1 to 11.1) (Figure 3).

Multivariate analysis demonstrated that a prepregnancy L-T₄ dose of at least 100 μg/day was independently predictive of the risk for subsequent TSH suppression (OR, 5.6; 95% CI, 1.3 to 29.3; P = 0.02). Prepregnancy TSH concentration <1.5 μIU/ml

(OR, 1.7; 95% CI, 0.6 to 12.6; P =0.19) and having athyreosis (OR, 0.0; 95% CI, 0.2 to 5.0; P = 0.90) were not statistically significant (Figure 3).

Lastly, to investigate the optimal frequency of TSH evaluation after an initial L-T₄ dose increase, the 25 patients in group A who completed the protocol after an increase in L-T₄ dosage of two tablets per week were analyzed. Reviewing all TSH concentrations in these 25 patients documented 26 abnormal TSH values that were outside the range of 0.01 to 2.5 μIU/ml and that triggered a dose adjustment as per the protocol. After analyzing the effectiveness of an every-4-week testing protocol, 24 of 26 (92%) abnormal TSH concentrations would have been detected regardless of an increased interval between TSH tests, and if an every-6-week protocol had been followed, abnormal TSH values would have been detected.

CONCLUSION

An increase of two levothyroxine tablets at the time pregnancy is confirmed significantly reduces the risk for maternal hypothyroidism during the first trimester and mimics normal physiology. The authors recommend monitoring serum TSH levels every 4 weeks through midgestation.

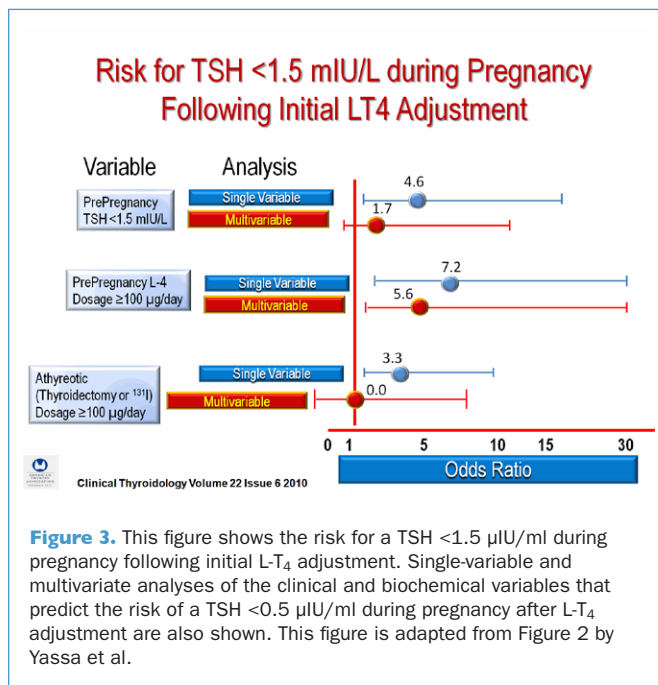


Figure 3. This figure shows the risk for a TSH <1.5 μIU/ml during pregnancy following initial L-T₄ adjustment. Single-variable and multivariate analyses of the clinical and biochemical variables that predict the risk of a TSH <0.5 μIU/ml during pregnancy after L-T₄ adjustment are also shown. This figure is adapted from Figure 2 by Yassa et al.

COMMENTARY

When thyroid deficiency occurs simultaneously in a pregnant woman and her fetus, the child's neuropsychological development is adversely affected (1,2). Moreover, hypothyroidism is common among women of childbearing age, and this poses a major threat to the fetus. This is compounded by an increased demand on T₄ requirements that occurs very early—within 4 to 5 weeks—of pregnancy (3), and the demand increases through midgestation at 16 to 20 weeks and is then sustained until delivery. To protect the fetus, L-T₄ must be administered in a way that replicates this pattern of L-T₄.

Yassa et al. found that merely adding two tablets of L-T₄ per week, when instituted immediately upon confirmation of pregnancy, significantly reduced the risk of maternal hypothyroidism throughout pregnancy. This protocol prevents maternal TSH elevation to >2.5 mIU/L and >5.0 mIU/L in 85% and 100% of women, respectively, thus reducing the risk of maternal hypothyroidism throughout pregnancy.

This protocol was found superior to adding three tablets of L-T₄ per week. Patients who have athyreosis require a prepregnancy

L-T₄ dose of at least 100 µg/dl and those with prepregnancy serum TSH concentrations below 1.5 IUm/L are at highest risk for subsequent L-T₄ modification after the initial L-T₄ intervention.


The authors point out that this important recommendation can be conveyed to patients during prenatal counseling by their endocrinologist, obstetrician, or primary care physician, thus reducing the risk for maternal hypothyroidism and its harmful impact. It should be noted that monitoring thyroid function approximately once monthly is required through midpregnancy because a minority of patients may require L-T₄ modifications to maintain appropriate TSH levels. The authors provide the caveat that this is largely predicted by assessment of a woman's prepregnancy L-T₄ requirement, TSH concentrations, and underlying cause of thyroid dysfunction.

This important study should be read by physicians and other health care providers who provide information to women with hypothyroidism who may become pregnant. The authors' discussion in this article contains considerable insight into this important problem.

— Ernest L. Mazzaferri, MD MACP

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EDITORS' CHOICE —
MATERNAL THYROID FUNCTION DURING GESTATION

Pregnant women with TSH levels higher than 2.5 IU/L during the end of gestation are at risk for breech presentation, and obstetrical complications.

Kuppens SM, Kooistra HA, Wijnen HA, Crawford S, Vader HL, Hasaart TH, Oei SG, Pop VJ. Maternal thyroid function during gestation is related to breech presentation at term. Clin Endocrinol (Oxf) 2009. doi: 10.1111/j.1365-2265.2009.03729.x

SUMMARY

BACKGROUND

Breech presentation at term is the most common abnormal fetal presentation, and it is associated with neonatal and maternal morbidity and mortality. There are many factors associated with breech presentation, including, among other causes, prematurity, low birth rate, primiparity, and smoking during pregnancy. The objective of this study was to evaluate the relationship between suboptimal maternal thyroid function during gestation and breech presentation at term.

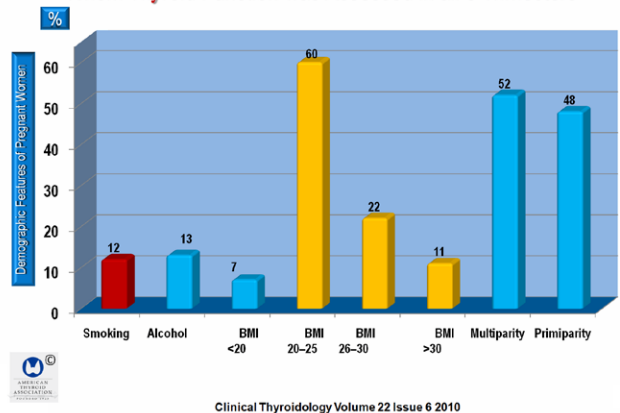
METHODS AND STUDY PATIENTS

Over a 2-year period, 1507 pregnant white Dutch women in five community midwifery practices, living in and around the city of Eindhoven, The Netherlands, were invited to participate in the study at the time of their first antenatal visit at 12 weeks of gestation. A total of 1190 women (79%) agreed to participate in the study. Nonresponders did not differ from the responders in age, parity, and educational level. Excluded from the study were 8 women who were taking thyroid medications for known clinical hyperthyroidism, 2 with hypothyroidism at screening, 8 who became pregnant after hormonal stimulation, and 5 with type 1 diabetes, leaving 1149 women who were eligible for further participation and had follow-up at 24 and 36 weeks of gestation. Because spontaneous change of fetal position at term was an outcome measure, four women with successful

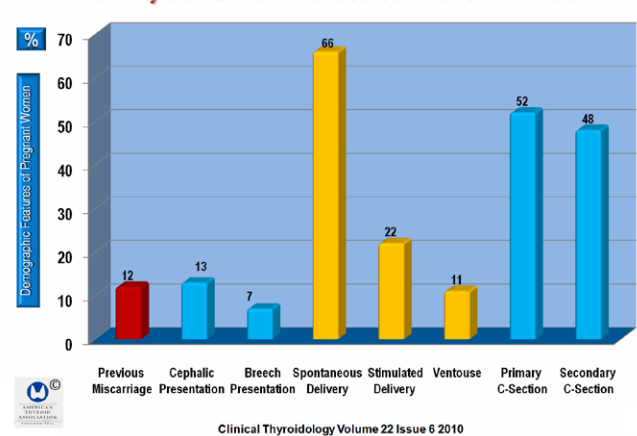
external cephalic version were excluded. Also excluded were 11 women with incomplete data and 4 whose babies were born with severe congenital abnormalities that were a possible determinant of fetal position.

Of the remaining 1130 women, 72 (6%) delivered prior to 37 weeks of gestation, but because breech position before term is

Characteristics of 1058 Pregnant Women ≥37 Weeks of Gestation in Whom Thyroid Function was Assessed in all 3 Trimesters



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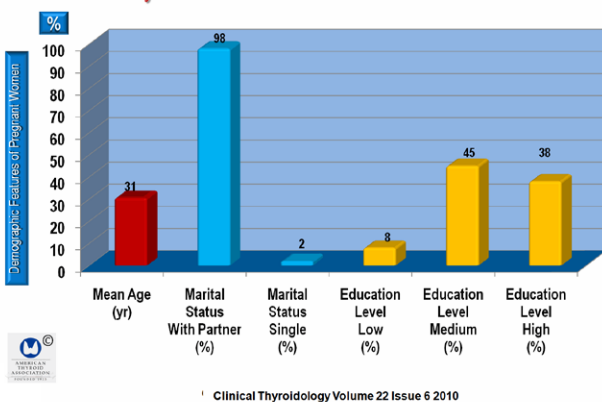


Figure 1. This figure shows the characteristics of 1058 term (≥37 weeks of gestation) pregnant women in whom thyroid parameters were assessed during all three trimesters. The data for figures 1 through 4 are derived from Table 1 of Kuppens et al.

Figures 2 and 3. These figures show the characteristics of 1058 term (≥37 weeks of gestation) pregnant women in whom thyroid parameters were assessed in all three trimesters. BMI = body-mass index, which is the weight in kilograms divided by the square of the height in meters.

not regarded as an abnormal fetal position, these women were also excluded from the study. The final sample comprised 1058 women who delivered at term (≥ 37 weeks of gestation) and in whom thyroid function was assessed in all three trimesters. None of the women in this group were treated for thyroid disease during gestation, but gestational diabetes developed in 8 of the 1058 women (0.8%).

ASSESSMENTS

Obstetric parameters Term was described in two ways: first from the date of the last menstrual period, and second from an ultrasound scan (US) in the first trimester. A second US was performed within 2 weeks to reassess gestational age if there was a discrepancy of more than 7 days in the two initial assessments. Gestational age was expressed as weeks and days. Fetal positions at birth were classified as cephalic or breech (i.e., complete or incomplete, or frank breech). During follow-up, possible confounders such as previous obstetrical history such as parity, previous cesarean section, demographic features, body-mass index, and lifestyle habits such as smoking and alcohol intake were assessed. The findings are shown in Figures 1 to 3.

Thyroid parameters (Figure 4)

Thyrotropin (TSH), free thyroxine (FT₄), and autoantibodies to thyroid peroxidase (TPO-Ab) were assessed at 12, 24, and 36 weeks of gestation. Women with serum TPO-Ab concentrations higher than 35 IU/ml at 12 weeks of gestation were regarded as TPO-Ab-positive.

RESULTS

During gestation, a decrease in mean FT₄ was accompanied by an increase in mean serum TSH. The number of women with elevated TPO-Ab concentrations decreased toward term. Figure 5 shows the differences in thyroid parameters between 58 women (5.5%) who presented with breech position at term versus the 100 remaining women who presented with a fetal cephalic position. At 36 weeks of gestation, women with breech fetuses had significantly higher serum TSH concentrations, as compared with those who had fetuses in a cephalic position

($P = 0.007$), whereas there no differences in TSH at 12 and 24 weeks of gestation. The FT₄ was not significantly related to breech presentation in any trimester. Likewise, the prevalence rates of TPO-Ab did not differ among the groups (Figure 5).

The 5th, 10th and 95th percentile cutoff points for serum TSH at 36 weeks were as follows: <5th percentile, <0.51 mIU/L ($n = 54$); 5th to 10th percentiles, 0.51 to 0.71 mIU/L ($n = 54$); 90th to 95th percentile, 2.50 to 2.89 mIU/L ($n = 49$); and 95th percentile, >2.89 mIU/L ($n = 59$). Figure 5 shows the percentage of women who presented with a breech presentation at delivery for each of the four percentile groups. The 90th and 95th percentile TSH groups at 36 weeks of gestation were 11% and 14% among the women who presented in fetal breech position at delivery, whereas there were no breech presentations in the lowest 5th percentile TSH group ($P = 0.02$).

Gestational Thyroid Function, TSH, and FT₄ in All Three Trimesters

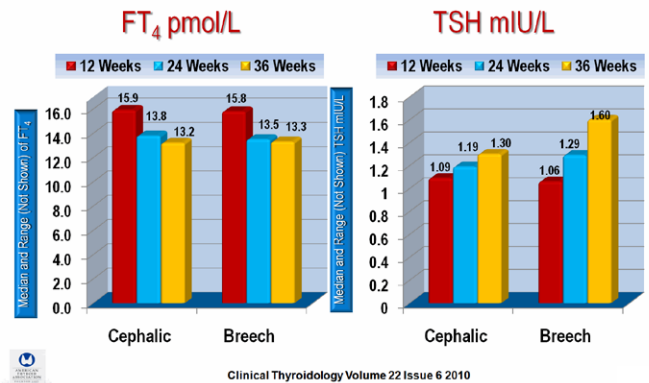


Figure 5. This figure shows the thyroid FT₄ and TSH levels during 12, 24, and 36 weeks of gestation in women who had cephalic presentation or breech presentation. The data for this figure were derived from Table 2 of Kuppens et.al.

Gestational Thyroid Function in All Three Trimesters

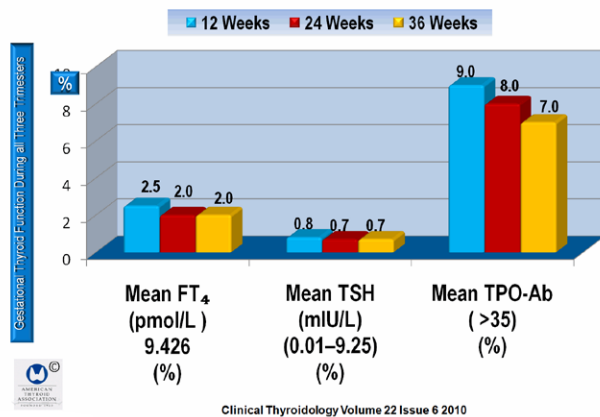


Figure 4. This figure shows the thyroid tests, FT₄ (in pmol/L), and TSH (in mIU/L) results at 12, 25, and 36 weeks of gestation.

Logistic-Regression analysis Depended Variable is Breech Presentation at Term

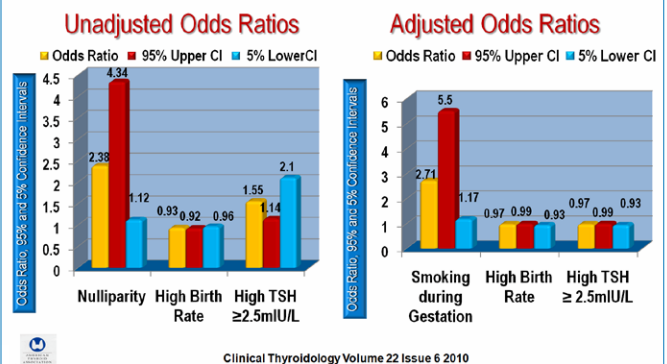


Figure 6. This figure shows the results of logistic-regression analysis in which the dependent variable is breech presentation at term. The figure shows the odds ratio and 95% and 5% confidence intervals (CI). The data for this figure were derived from Table 3 in Kuppens et.al.

The prevalence of breech presentation in the subgroup of women with a TSH ≥ 2.5 mIU/L (≥ 90 th percentile) was 11% (12 of 108), as compared with 4.8% in the women with TSH < 2.5 mIU/L ($P = 0.006$). When similar categories for FT₄ were assessed, there was no relationship between FT₄ and breech presentation.

Odds Ratios (Figure 6)

Figure 6 shows the unadjusted odds ratios (ORs) using logistic-regression analysis (OR 95% confidence interval [95thCI]). Breech position at birth is the dependent, and nulliparity, birth weight, and high TSH (> 2.5 mIU/L) at 36 weeks of gestation, were all significantly related to breech presentation.

Figure 6 also shows the results of adjusted OR using multiple-logistic-regression analysis. Breech presentation at birth, is the dependent variable. High TSH levels at 36 weeks of gestation, nulliparity, birth weight, and smoking status were all significantly related to breech presentation. Elevated TPO-Ab levels were not related to breech presentation.

A total of 17 of the 108 women (16%) with high TSH levels at 36 weeks of gestation had a history of parental thyroid disease, as compared with 66 women (6.6%) in the group with low TSH levels ($P = 0.001$). Likewise, of the 108 women with high TSH levels at 36 weeks of gestation, 20 (18%) had elevated TPO-Ab at 12 weeks, as compared with 66 (7%) in those with TSH < 2.5 IU/ml ($P = 0.001$). Lastly, of the 83 women with a history of parental thyroid disease, 20% had elevated serum TPO-Ab at 12 weeks of gestation, as compared with 8% of the women with no history of thyroid disease ($P = 0.001$). None of the women with gestational diabetes had an elevated TSH level at 36 weeks of gestation.

CONCLUSION

Women with TSH levels > 2.5 IU/ml during the end of gestation are at risk for breech presentation, and thus for obstetrical complications.

COMMENTARY

This is one of the first studies to identify a relationship between maternal thyroid function and fetal position at birth. The authors of this study published a previous prospective cohort study of pregnant women aimed at evaluating the relation between breech position at term (> 37 weeks of gestation) and low maternal FT₄ levels (1). The main outcomes of the study were that breech presentation at term delivery was independently related to FT₄ levels < 10 th centile at 12 weeks of gestation (OR, 4.7; 95% CI, 1.1 to 19), but was not related to an FT₄ level below the 10th centile at 12 weeks of gestation, and was also related to primiparity (OR, 4.7; 95% CI, 1.3 to 15). The study did not find a relationship between serum TSH levels and breech presentation. The conclusion of the study was that women with hypothyroxinemia (FT₄ at the lowest 10th centile) during early gestation without overt thyroid dysfunction are at risk for fetal breech presentation at term (> 37 weeks of gestation).

The present study, which is much larger, found that that breech position at birth is related to maternal thyroid hormone status during pregnancy. Indeed, not only was breech delivery almost 2.5-fold more common in women with TSH levels ≥ 2.5 mIU/L, regression analysis confirmed that elevated maternal TSH at 36 weeks of gestation is a key predictor for breech presentation. In addition, high TSH levels were significantly associated with

increased TPO-Ab levels and a parental history of thyroid disease. In sharp contrast, none of the women with TSH levels below the 5th percentile presented with breech position at term. The study also found no group differences for FT₄ levels at 12, 24, and 36 months of gestation.

This is a remarkably important study, as breech presentation at term is the most common abnormal fetal presentation and is associated with neonatal and maternal morbidity and mortality (2). There is considerable evidence of a relationship between subclinical thyroid dysfunction and impaired obstetrical outcome (3,4).

The authors of this study suggest that research is needed to detect the most appropriate tool for screening of maternal thyroid function during gestation.

This is a timely study that complements that of Yassa et al. (5), which precedes this study in this issue of CT. Together, they underscore the importance of carefully screening women at the time of pregnancy and meticulously performing follow-up and adjusting levothyroxine in pregnant women known to have hypothyroidism.

— Ernest L. Mazzaferri, MD, MACP

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Central neck compartment lymph-node-metastases in papillary thyroid carcinoma can be effectively managed with prophylactic CLND, without a high complication rate and with very few recurrences

So YK, Son YI, Hong SD, Seo MY, Baek CH, Jeong HS, Chung MK. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. *Surgery* 2010. doi:10.1016/j.surg.2010.01.003

SUMMARY

BACKGROUND

Initial preoperative neck ultrasonography performed in preparation for thyroidectomy ordinarily fails to identify central-compartment lymph-node metastases, especially in papillary thyroid microcarcinoma (PTMC). Lymph-node metastases are usually identified only when prophylactic central-compartment lymph-node dissection (CLND) is performed, in which case the rate of lymph-node metastases may be as high as 65%. Nonetheless, this approach has been widely debated for papillary thyroid carcinomas (PTCs) of all sizes. The ATA guidelines suggest that prophylactic CLND, ipsilateral or bilateral, may be performed in patients with PTC with clinically uninvolved central-neck lymph nodes, especially for advanced primary tumors (T3 or T4). PTMC is often treated with hemithyroidectomy alone and is almost never treated with prophylactic CLND, despite the 10-year incidence of PTMC lymph-node recurrence of 5% that has been found in large studies. The debate concerning CLND thus revolves around the balance of efficacy versus the complication rates of this surgery. The aim of this study was to assess the clinical factors associated with subclinical central compartment lymph-node metastases, in order to determine when prophylactic CLND might be performed in these small tumors.

METHODS

The study cohort comprises 551 patients treated at the University School of Medicine in Seoul, Korea, from January 2005 through March 2009. Patients selected for study were those with PTMC who had no preoperative evidence of lymph-node metastases based on clinically negative neck ultrasonography and fine-needle aspiration (FNAB). All patients had total thyroidectomy with bilateral CLND, defined as dissection of bilateral paratracheal and prelaryngeal lymph nodes. The diagnosis of PTMC was reconfirmed by histology from the surgical specimen.

Tumor classification

Adequacy of CLND was based on the surgeon's description of bilateral complete CLND. The removal of selected lymph nodes ("node picking") was not performed by this group of surgeons. Excluded from the study were patients who had unilateral CLND, leaving 73.8% of the 551 patients with bilateral CLND for the study. The extent of tumor was stratified into three categories according to pathology results: confined within the thyroid capsule, capsular invasion, and extrathyroidal extension, including microscopic capsular breach with extension into perithyroidal tissues.

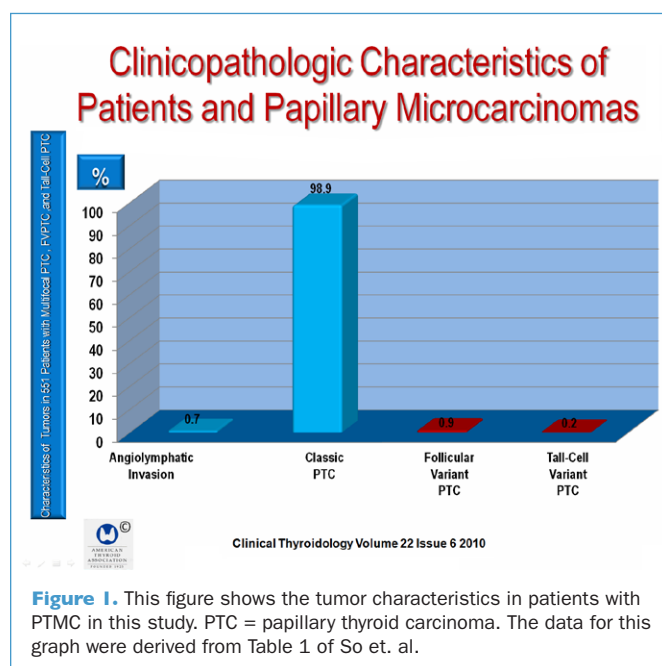
Postoperative radioiodine treatment and follow-up

Postoperative radioiodine (¹³¹I) was administered to patients with unfavorable pathologic characteristics such as multifocal

tumors, extrathyroidal extension, angiolymphatic invasion, and lymph-node metastases. As a consequence, 444 of the 551 patients (80.6%) were treated with ¹³¹I within 2 to 3 months after thyroidectomy. Patients were prepared with a 4-week cessation of levothyroxine to increase TSH to >30 mIU/L. The mean initial ¹³¹I treatment was 42.6 mCi (median, 30.0; range, 30 to 150). A total of 242 patients had two or more ¹³¹I treatments. Subsequent ¹³¹I treatments were assessed by serum thyroglobulin (Tg) levels, anti-Tg antibody (TgAb), and the findings on post-¹³¹I-treatment scans. Follow-up studies with unstimulated serum Tg levels were performed every 6 months, during which recurrences were identified with ¹³¹I whole-body scans, ultrasonography, and FNAB.

Postoperative complications

Hypocalcemia was defined as at least one event in which symptoms of hypocalcemia such as perioral numbness, or paresthesia of hands and feet, or at least one event of hypocalcemia with an ionized blood calcium level <1.0 mmol/L or a total calcium level <8.0 mg/dl that was assessed at every follow-up until the calcium returned to normal. Permanent hypocalcemia was defined as persistent symptoms or hypocalcemia lasting more than 6 months. Patients were evaluated for other complications, including postoperative vocal-cord palsy, chyle leakage, and hematoma. Laryngoscopy was performed at every follow-up, regardless of corrective laryngoplasty.



RESULTS

Clinicopathologic characteristics of 551 patients (Figures 1 and 2)

The study comprised 440 women (79.9%) and 111 men (20.1%) with a mean (±SD) age of 50.2±9.2 years. The mean size of the primary tumors was 0.6±0.2 cm, and for multifocal tumors, the diameter of the largest tumor was used in the analysis. The tumors comprised classic PTC in 98.9% of the patients, follicular-variant PTC in 0.9%, and tall-cell-variant PTC in 0.2% (Figure 1). Capsular invasion was found in 11 patients (2.0%), and extrathyroidal extension was found in 292 patients (53.0%) (Figure 2). Most of the extrathyroidal extension was minimal invasion of perithyroidal soft tissue or strap muscle (pT3). Only 4 patients had invasion of adjacent organs (pT4), all of whom had posterior extension of tumor to the recurrent laryngeal nerve.

Subclinical CLND lymph-node metastases and clinicopathologic risk factors (Figure 2)

Subclinical CLND lymph-node metastases were detected in 202 of 551 patients (36.7%) who had clinically node-negative lymph-node metastases. The mean number of lymph-node metastases was 2.4±1.9 (Figure 2).

The frequency of lymph-node metastases was greater in men (49.5%) than in women (33.4%) (P = 0.02), in patients with multifocal tumors (44.3%) versus solitary tumors (31.9%) (P = 0.003), and in patients with tumors within the thyroid capsule (28.2%) versus extrathyroidal tumor extension (43.5%) (P = 0.01). Also associated with subclinical lymph-node metastases was primary tumor size >0.5 cm (P = 0.01), as compared with larger tumors, and tumors without angiolymphatic invasion (36.2%), as compared with those with angiolymphatic invasion (P = 0.008) (Figure 2).

Multivariate analysis (Figures 3 and 4)

Multivariate analysis found that the following three factors were independently predictive of subclinical CLND lymph-node metastases: men (odds ratio [OR], 2.184; P = 0.001); multifocal tumor (OR, 1.582; P = 0.015), and extrathyroidal extension (OR, 1.893; P = 0.01) (Figure 4).

The probability that a woman with a solitary tumor confined within the thyroid capsule did not have CLND lymph-node metastases was 80.6%. (Figure 4A and 4B). The sensitivity of this probability was 28.6% and the specificity 85.6%.

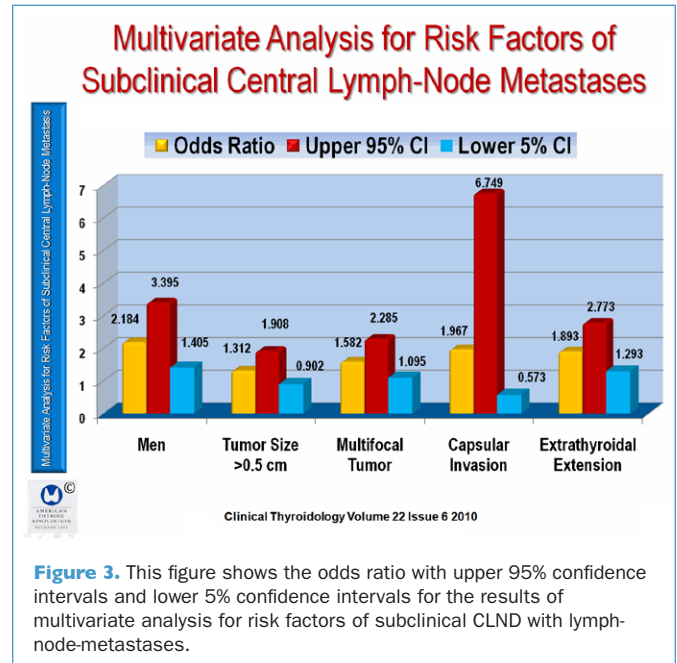


Figure 3. This figure shows the odds ratio with upper 95% confidence intervals and lower 5% confidence intervals for the results of multivariate analysis for risk factors of subclinical CLND with lymph-node-metastases.

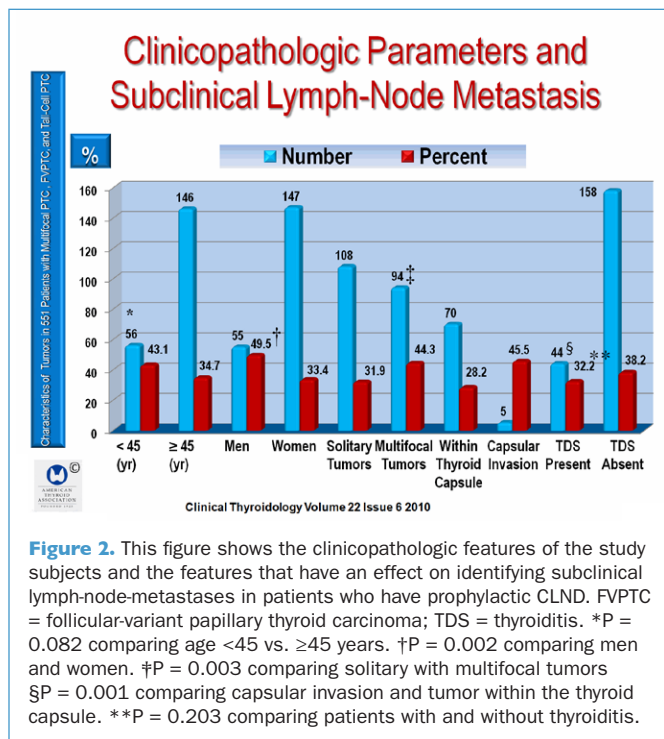


Figure 2. This figure shows the clinicopathologic features of the study subjects and the features that have an effect on identifying subclinical lymph-node-metastases in patients who have prophylactic CLND. FVPTC = follicular-variant papillary thyroid carcinoma; TDS = thyroiditis. *P = 0.082 comparing age <45 vs. ≥45 years. †P = 0.002 comparing men and women. ‡P = 0.003 comparing solitary with multifocal tumors §P = 0.001 comparing capsular invasion and tumor within the thyroid capsule. **P = 0.203 comparing patients with and without thyroiditis.

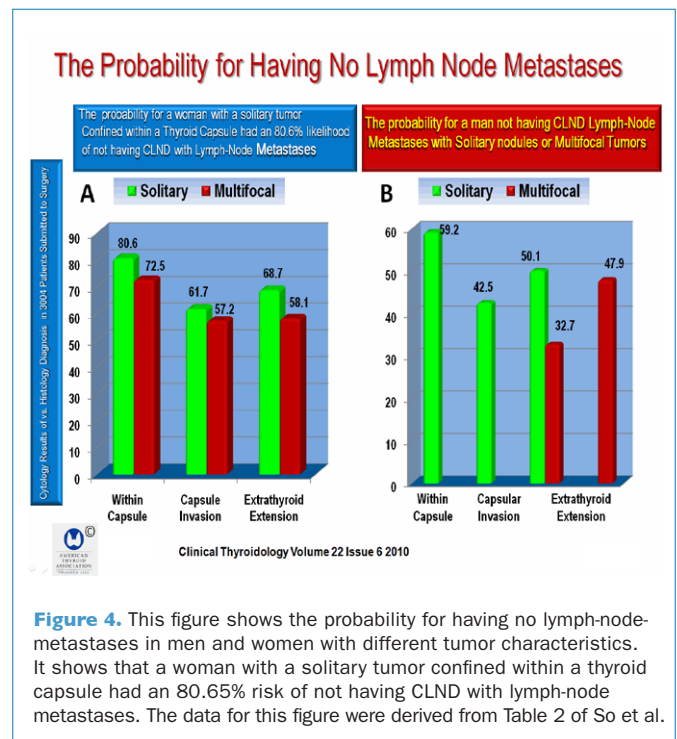


Figure 4. This figure shows the probability for having no lymph-node-metastases in men and women with different tumor characteristics. It shows that a woman with a solitary tumor confined within a thyroid capsule had an 80.65% risk of not having CLND with lymph-node metastases. The data for this figure were derived from Table 2 of So et al.

Postoperative complications (Figure 5)

Transient hypocalcemia developed in 152 of 551 patients (27.6%), which resolved within 6 months, whereas permanent hypocalcemia developed in 6 of 551 patients (1.1%).

Vocal-cord palsy developed in 28 patients (5%); 21 of these cases (3.8%) resolved within 6 months (transient vocal-cord paralysis), while 7 cases (25%) persisted for >1 year (permanent

vocal-cord paralysis) and laryngoplasty was necessary.

Chyle leakage occurred in 3 patients (0.5%), and the rates of leakage were <100 ml/day in all cases, which was controlled nonoperatively with a fat-free diet. Postoperative hematoma developed in 3 patients (0.5%) and was treated with reoperation (Figure 5).

RECURRENCE

Six patients (5.4%) were lost to follow-up and 104 had follow-up for more than 3 years after thyroidectomy. The median duration of follow-up was 40.5 months. During this time, there were no recurrences in the central cervical compartment (VI). At 19 months after thyroidectomy, only 1 patient had a recurrence outside the central cervical compartment ipsilateral to the primary tumor that required resection. No patient had a Tg level >2 ng/ml at 3 years after thyroidectomy; thus, the 3-year locoregional rate of no evidence of disease was 99%.

CONCLUSION

There is a high incidence of occult central-neck-compartment lymph-node-metastases that can be effectively managed with prophylactic CLND, without a high complication rate and with very few recurrences. The authors suggest that prophylactic CLND should be considered for patients with certain clinicopathologic features such as male sex, tumor multifocality, and extrathyroidal extension which may be particularly beneficial in patients with PTMC.

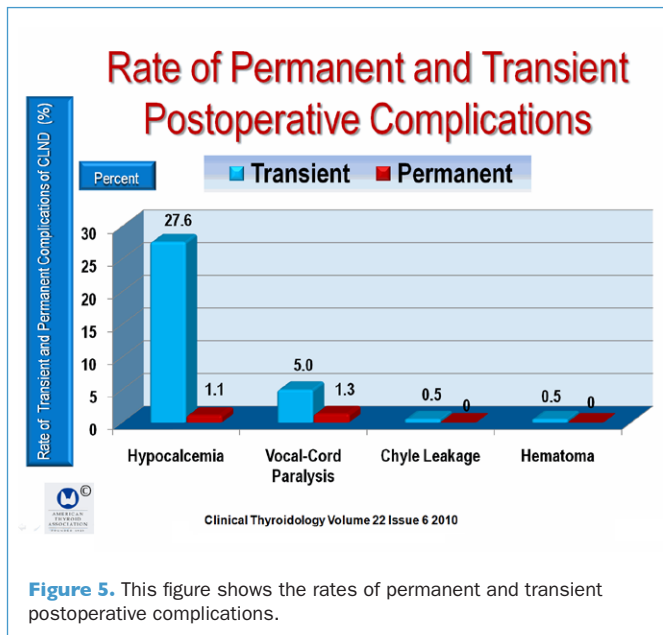


Figure 5. This figure shows the rates of permanent and transient postoperative complications.

COMMENTARY

This is one of the largest studies to address the utility and safety of CLND in patients with PTMC, which explores the patient and tumor characteristics that relate to the selection of patients for prophylactic CLND and the patient and tumor features that are most likely to help identify patients with lymph-node metastases when treated with central-neck CLND. In addition, the authors address the safety of this surgery and the likelihood of complications and tumor recurrence following this surgical approach of total thyroidectomy with prophylactic CLND. This is a sound study of 551 patients, all of whom had histopathological evaluation of the resected tumors. The main results of the study were that male sex, tumor multifocality, and extrathyroidal tumor extension all were independent predictors of occult central-compartment lymph-node metastases. Although age is a significant prognostic factor in the outcome of PTC, age in this study did not predict occult central lymph-node metastases, although patients ≥45 years of age were slightly more likely to have lymph-node-metastases with CLND.

Primary tumor size was not an independent predictor of occult lymph-node-metastases in patients who had undergone CLND. This may be related to the size of the study cohort, despite its relatively large size. For example, a study by Bilimoria et al. of 52,173 patients with PTC found that cumulative 10-year recurrence rates for patients with primary tumors ranging in size

from <1 cm through >8 cm, found recurrence rates increased by 1-cm tumor increments from 4.6% with tumors <1 cm, to 24.8% with tumors >8 cm, a fivefold increase in recurrence rates (1).

During the 3-year follow-up in the So study, there were no recurrences in the central cervical compartment, which may be related to the CLND, but most patients also had ¹³¹I remnant ablation. Nonetheless, the outcome after more than 3 years of follow-up after thyroidectomy and CLND, excluding 6 patients (5.4%) who were lost to follow-up, found that only 1 patient had a recurrence outside the central cervical compartment, and at 9 months after surgery, this recurrence was resected, and no patient had a Tg level >2 ng/ml, leaving 99% of the cohort free of disease. Still, this would have been more convincing had the serum Tg been undetectable after TSH stimulation rather than >2 cm for the cutoff to identify disease-free outcome.

The postoperative complication rates were very low, with transient hypocalcemia in 27.6 %, which resolved in 6 months. Permanent hypocalcemia developed in 6 patients (1.1%). Vocal-cord palsy, which developed in 28 patients, recovered spontaneously within 6 months in 21 cases, and it remained present in 7 patients for more than 1 year (permanent vocal-cord palsy) and required therapy. Three patients had chyle leakage that resolved spontaneously with a fat-free diet, and postoperative hematoma in 3 patients (5%) was treated by reoperation.

This complication rate is approximately that seen in the hands of other well-trained surgeons. An article by Mazzaferri et al. (2) debated the pros and cons of prophylactic CLND and found that the mean rate of transient laryngeal-nerve injury in eight studies in which patients had total thyroidectomy and CLND was $4.5 \pm 2.0\%$ for transient nerve damage and in nine studies it was $0.9 \pm 1.8\%$ for permanent nerve injury. The mean (\pm SD) complication rates for transient hypoparathyroidism were $26.8 \pm 11.8\%$ in five studies and $2.7 \pm 22\%$ in four other studies.

The rate of lymph-node metastases may be as high as 65% in patients with PTMC who have had prophylactic CLND (3). One retrospective study by Scheumann et al. (4) found that systematic compartment-oriented dissection of cervical lymph-node metastases improved survival with PTC ($P < 0.005$) and recurrence ($P < 0.001$) especially in patients with T1 to T3 tumors. The authors concluded that lymph-node-metastases in a cohort with a significant incidence of young age and male sex had a substantial effect on survival and recurrence, especially in those with pT1 to T3 tumor, and that systematic compartment-oriented dissection of lymph-node metastases results in better survival and a lower recurrence rate; however this study had no contemporary controls, which leaves some question about this outcome as compared with patients treated without prophylactic lymph-node dissection.

Noguchi et al. (5) reported their findings in 2070 patients with PTMC ranging from 6 to 10 mm that were not treated with CLND

and in whom 14% had tumor recurrence at 35 years of follow-up, as compared with 3.3% in patients with smaller tumors (< 6 mm). Among patients older than 55 years, the recurrence rate was 40% at 30 years, with a worse prognosis in older than younger patients who had a recurrence rate of less than 10%. Extracapsular invasion by the primary tumor also had a higher rate of recurrence, the majority of which were in the neck, with some invading organs in the neck and others with distant metastases. The authors concluded that PTMC is similar to larger papillary carcinomas with tumor characteristics and age-based recurrence rate that extends for many years, justifying long surveillance after surgery.

So et al. have made important observations, especially that male sex, tumor multifocality, and extrathyroidal tumor extension all were independent predictors of occult central-compartment lymph-node metastases. Their study also raises questions about the long-term recurrence rates in patients treated with thyroidectomy alone.

The debate concerning prophylactic CLND likely will extend over several decades to produce prospective randomized studies, which hopefully will bring a solution to this dilemma. Until then, physicians should carefully inform their patients concerning the pros and cons to provide sufficient information for the patient to make a knowledgeable choice of therapy.

— Ernest L. Mazzaferri, MD, MACP

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CLINICAL THYROIDOLOGY FOR PATIENTS
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Persistent cervical PTC lymph-node metastases may require several surgical resections to achieve biochemical or clinical evidence of disease-free outcome

Al-Saif O, Farrar WB, Bloomston M, Porter K, Ringel MD, Kloos RT. Long-term efficacy of lymph node reoperation for persistent papillary thyroid cancer. *J Clin Endocrinol Metab* 2010;95:2187-94.

SUMMARY

BACKGROUND

Papillary thyroid cancer (PTC) is the most common form of thyroid cancer, comprising about 80% of thyroid cancers. Although thyroid cancer generally has a good prognosis, about 7% of patients die from this tumor within 10 years after the diagnosis of PTC. Local recurrences are found in 5 to 20% of patients with this disease, about 60% of which are localized to cervical lymph-node metastases. The objective of this study was to determine the outcome of surgical resection of metastatic PTC in cervical lymph-node metastases

METHODS

This is a retrospective study of 95 consecutive patients with cervical-lymph-node recurrence or persistent PTC treated at the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute at Ohio State University from 1999 through 2005. Lymph-node metastases of all sizes were chosen for surgical excision. Excluded from the study were patients with distant metastases identified by preoperative chest x-ray in all patients and by chest computed tomography (CT) when basal or TSH-stimulated serum thyroglobulin (Tg) was >2ng/ml. A minority of patients had 18-fluorodeoxyglucose positron-emission tomography (18FDG-PET), bone scans or extracervical magnetic resonance imaging (MRI).

Data were extracted from medical records and reviewed for the following variables: patient age, sex, tumor capsule invasion and

tumor size, lymph-node metastases, and tumor stage at the time of thyroidectomy. Recurrence was identified by preoperative Tg, both unstimulated and TSH-stimulated, postoperative Tg levels, and ultrasound (US)-guided fine-needle aspiration biopsies (FNABs). The total amount of radioiodine (¹³¹I) administered preoperatively, and the number and type of neck lymph-node compartments dissected, the number of lymph nodes with PTC resected, surgical complications, disease-free intervals, and total duration of follow-up were also extracted.

Between May 1999 and May 2005, 95 consecutive patients with recurrent or persistent PTC neck metastases were performed by the same surgeon. Excluded from the analysis were 25 patients with anti-Tg antibodies (TgAb). All serum Tg measurements were performed by the same laboratory using the same method with an analytic sensitivity of 0.07 ng/ml and a functional sensitivity of 0.5 ng/ml.

RESULTS

Patient and tumor demographics and radioiodine therapy (Figures 1 to 4)

Patients were predominantly women with a median of 3 years from thyroidectomy to neck exploration for recurrent or residual disease. Of the 70 study patients, 22 (31%) were men and 48 (69%) were women. Median age at the time of PTC diagnosis was 35 years for men (range, 15 to 71) and 41 years for women (range, 18 to 73). Time from thyroidectomy to the first reexploration was a median of 3 years. Age was grouped as 40 years or younger in 10 of 22 men (46%) and in 38 of

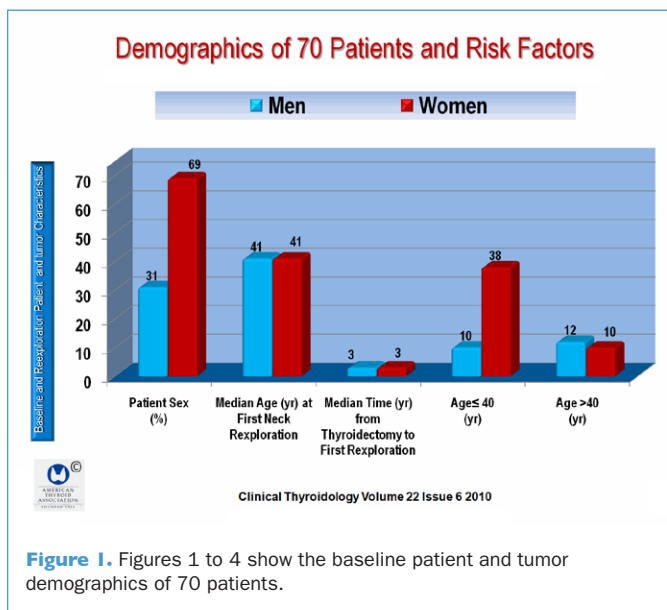


Figure 1. Figures 1 to 4 show the baseline patient and tumor demographics of 70 patients.

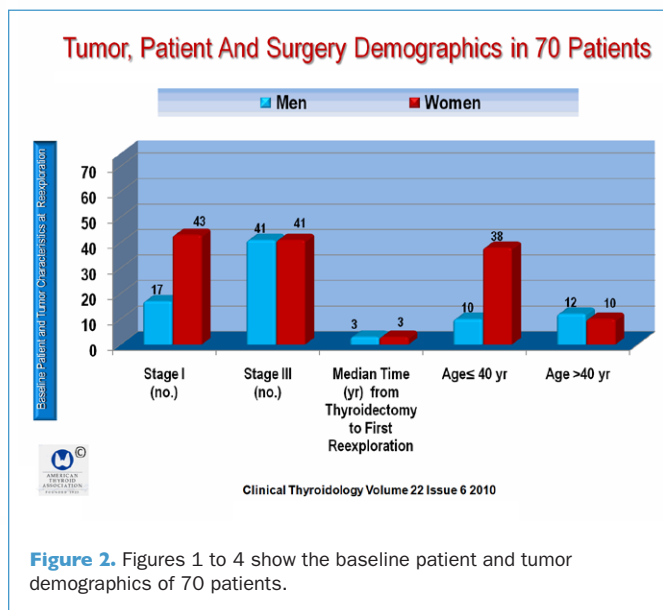


Figure 2. Figures 1 to 4 show the baseline patient and tumor demographics of 70 patients.

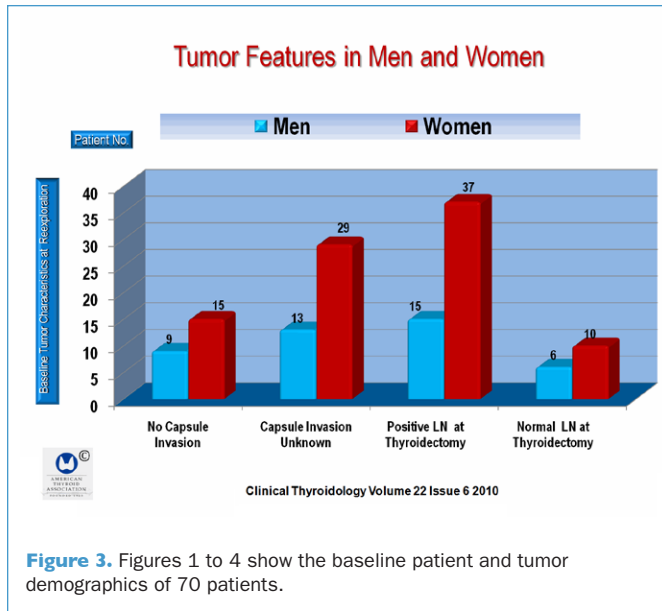


Figure 3. Figures 1 to 4 show the baseline patient and tumor demographics of 70 patients.

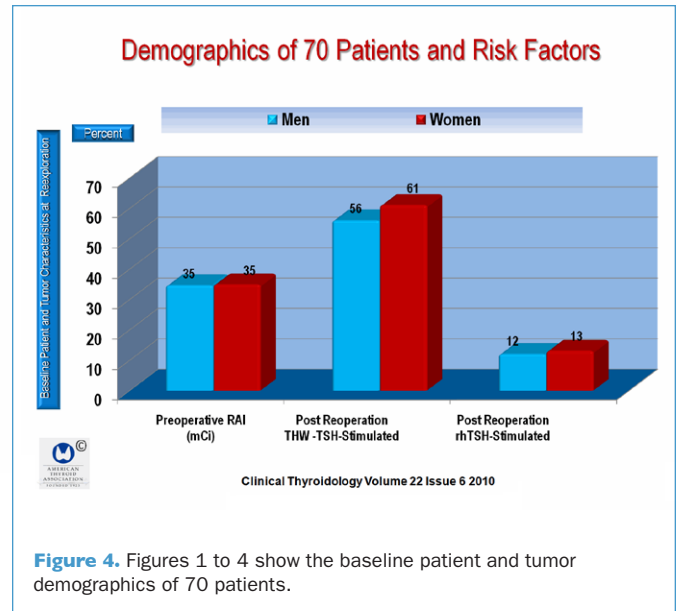


Figure 4. Figures 1 to 4 show the baseline patient and tumor demographics of 70 patients.

48 women (79%) and as 40 years or older in 12 of 22 men (55%) and in 10 of 48 women (20%) (Figure 1). The majority of patients had lymph-node metastases identified during the initial thyroid surgery, and the majority had tumor penetrating the thyroid capsule. All patients had at least one ¹³¹I treatment and posttreatment whole-body scans. The patient and tumor features and radioiodine treatment are shown in Figures 1 to 4.

Surgical outcome (Figure 5)

A total of 107 lymphadenectomies were performed in 70 TgAb-negative patients between May 1999 and January 2010, 10 of which (9%) failed to identify recurrent PTC, which was based on US with FNAB (n = 7), palpation (n = 2), and 18FDG-PET (n = 1). Neck US with selective use of FNAB was performed in 102 of 107 patients (95%) before lymphadenectomy with FNAB performed in 48 of 102 patients (47%) that accurately identified recurrent PTC in 95 of 102 patients (93%).

Four of the seven patients with positive US findings had negative histology and a positive preoperative US-guided FNAB. One of the four had a preoperative Tg of 2.2 ng/ml during TSH suppression that decreased to <0.5 ng/ml postoperatively despite a negative surgical histology finding. Another of the four patients with positive preoperative US-guided FNAB cytology on two occasions had negative surgical findings; however, the lymph node was still present on postoperative neck US; in another patient, it was decided intraoperatively that the lesion could not be resected safely because of dense adhesions. Another patient with a positive US but no FNAB findings had positive surgical histology of the same target lesion at the third reoperation.

For all reoperations combined, neck US with selective use of FNAB accurately identified recurrent PTC in 100 of 102 lymphadenectomies (98%). The median number of lymph nodes removed was 11 (range, 1 to 61), with median positive PTC histology in 2 patients (range, 0 to 11). After the second reoperation, the median number of lymph nodes removed

was 7 (0 to 55), with median positive histology in 2 patients (range, 0 to 12). After the third reoperation, the median number of lymph nodes removed was 3 (range, 1 to 34), with median positive histology in 2 (range, 1 to 5). The total number of lymph nodes removed, and the number of positive lymph nodes, was similar among the patients who achieved biochemical complete remission (BCR) as compared with the median number of lymph nodes dissected with pathology that did not identify recurrent PTC (range, 0 to 22) in four patients.

No patients had long-term hypoparathyroidism or recurrent laryngeal-nerve injury. One patient (1%) had a chyle leak during the second reoperation that was fixed with ligation of the thoracic duct but did not achieve BCR.

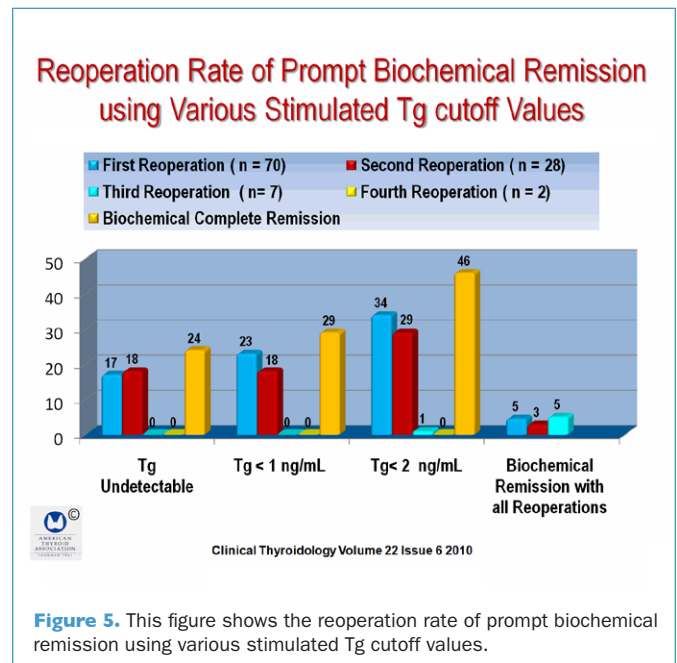


Figure 5. This figure shows the reoperation rate of prompt biochemical remission using various stimulated Tg cutoff values.

Biochemical complete remission

During long-term follow-up, two patients, both with stage I tumors, initially had detectable postoperative stimulated Tg of 0.5 and 1.2 ng/ml, respectively, after their first reoperations. Both achieved BCR, with repetitive TSH-stimulated Tg that persisted for 6.8 and 3.5 years, respectively, with negative neck US examinations being the only intervention, save for levothyroxine therapy, since reoperation. This delayed BCR was not included in the analysis of prompt postoperative BCR and may reflect the results of both surgery and late effects of the last radioiodine treatments 10.8 and 3.8 years before the BCR had occurred. However these two patients are included in the total of 19 of 70 patients (27%) who achieved BCR.

Prompt postoperative biochemical complete remission

Prior to the initial reoperation, mean basal Tg was 8.4 ng/ml (median, 4.0; range, undetectable to 100.5), and after this surgery, BCR occurred promptly in 12 of 70 patients (17%). The 12 who achieved BCR promptly had a mean basal Tg of 12.5 ng/ml (median, 4.2; range, undetectable to 200.5). Of the remaining 58 patients, 28 had a second reoperation, with prompt BCR in 5 (18%). Before the second reoperation, the mean basal Tg was 9.1 ng/ml (median, 1.3; range, undetectable to 99.1); however, the 5 who had prompt BCR had a median basal Tg that was undetectable (range, undetectable to 1.2 ng/ml).

Prior to the third reoperation, the mean basal Tg was 23.8 ng/ml (median, 4.5; range, undetectable to 116.0). Third reoperations were performed on seven patients, and none resulted in BCR. The mean and median basal Tg levels before the first reoperation in patients who experienced a prompt BCR with any reoperation was 9.7 and 2.7 ng/ml, respectively. In contrast, patients who failed to achieve BCR from that operation had significant reductions in unstimulated serum Tg levels after both the first operation (median decrease, 1.7 ng/ml; interquartile range, 0.3 to 7.4; $P = 0.001$) and the second reoperation Tg had a median decrease of 0.8 ng/ml; interquartile range, 0 to 6.2; $P = 0.06$).

In all, BCR was promptly achieved after 17 of 107 surgical procedures (16%), leading to prompt postoperative BCR in 17 of 70 patients (24%). Sixteen patients who achieved prompt BCR (94%) had stage I tumors; the remaining 20 patients all had stage III tumors.

Prompt BCR was achieved after the first reoperation in 5 of 15 patients (33%) when the preoperative Tg was detected only by

stimulation, as compared with 7 of 55 (13%) in whom Tg was detected without stimulation ($P = 0.11$). In patients who had a second reoperation, prompt BCR was achieved in 3 of 8 (38%) when Tg was detected only with TSH stimulation, as compared with 2 of 20 (10%) when preoperative Tg was performed without stimulation ($P = 0.12$) (Figure 5).

For all patients after all surgical procedures, prompt BCR was achieved in 5 of 15 (33%) when preoperative Tg before the first reoperation was detected only by TSH stimulation, as compared with 12 of 55 (22%) in whom Tg before the first reoperation was detected without TSH stimulation ($P = 0.05$).

None of the following variables were significantly associated with BCR on univariate analysis: age at initial PTC diagnosis, sex, primary tumor capsular invasion, primary tumor size, lymph-node involvement, TNM stage at thyroidectomy, age at first reoperation, magnitude of the preoperative unstimulated Tg level, number of lymph nodes resected, one versus more than one resected metastatic lymph nodes at reoperation, number of lymph nodes containing PTC during lymphadenectomy, central versus lateral neck in more than one lymph-node compartment, and the number of lymph-node compartment reoperations.

LONG-TERM FOLLOW-UP

For patients achieving prompt postoperative BCR, overall, the mean follow-up was 60 months (range, 4 to 116), but no patient had evidence of biochemical or clinical recurrence. During long-term follow-up through January 2010, 10 of 53 the patients (19%), who did not achieve prompt BCR, were not tested for distant metastases, while the remaining 43 (81%) did achieve BCR and were evaluated by CT (in 36), chest radiograph (in 20), skeletal imaging with bone scan or MRI (in 5), whole-body 18FDG-PET (in 8), or Tg in the absence of TgAb (in 2).

After a median of 3.9 years, no distant metastases or deaths from thyroid cancer were identified from the first reoperation until the last test for distant metastases (range, 0.2 to 8.9 years). One patient treated with external-beam radiotherapy for FDG-avid cervical and upper mediastinal lymphadenopathy progressed even with four reoperations and sorafenib therapy.

CONCLUSION

Surgical resection of persistent cervical PTC lymph-node metastases may require several surgeries to achieve biochemical or clinical evidence of disease.

COMMENTARY

Lymph-node metastases from PTC are a common problem, routinely occurring in 5 to 10% of patients with PTC (1), reaching an incidence of 60% when routine lymph-node compartment dissection is performed (2). The risk for lymph-node metastases is generally greater in older patients and in those with some histologic subtypes, such as solid-variant PTC, the lymph-node treatment of which has not been fully elucidated. This multifaceted problem is related to the size and number of lymph-node metastases, their propensity to invade soft tissues, and the impact of oncogenes such as BRAF that portend a poor long-term outcome (3), to name a few (4;5). Whether radioiodine, surgical treatment, or both should be used to treat recurrent/persistent locoregional disease, thus, continues to be debated.

A stage-adapted approach to the treatment of regional lymph-node metastases is one method (6). Still, residual lymph-node metastases are relatively common after adjuvant ¹³¹I therapy with serum Tg levels that remain detectable, especially in high-risk patients who have tumors with little or no ¹³¹I uptake (6). Most experts agree that routine (i.e., prophylactic) lymph-node dissection is unnecessary for low-risk well-differentiated thyroid cancer. Because lymph-node metastases are often occult, surgery of cervical lymph-node compartments may be associated with a more than usual risk for surgical complications (7). It is especially important to note the size of lymph nodes, as the outcome of macrometastases is prognostically much more serious as compared with that for micrometastases that have a low rate of recurrence and a generally good prognosis (8).

This study by Osama et al. provides important information concerning the outcome of lymphadenectomy in 58 patients with cervical recurrent/persistent PTC. Biochemically complete remission was achieved in 12 patients (17%), using the most stringent definition for no evidence of disease, which is that of the European Thyroid Association (9) and American Thyroid

Association (10); they recommend the following criteria for no evidence of disease: (1) no clinical evidence of tumor, (2) no imaging evidence of tumor (no uptake outside the thyroid bed on the initial posttreatment whole-body scan, or, if uptake outside the thyroid bed had been present, no imaging evidence of tumor on a recent diagnostic scan and neck US), and (3) undetectable serum Tg levels during TSH suppression and stimulation in the absence of interfering antibodies.

After a mean follow-up of 60 months (range, 4 to 116), no patient had a relapse. Still, patients who did not achieve a remission had a reduction in serum Tg after the first and second operations ($P < 0.001$ and $P = 0.008$, respectively). Moreover, no patient had distant metastases or died of disease. Among the patients who did not experience a remission, Tg levels were significantly reduced, and the authors acknowledge that further follow-up will be necessary for this group of patients.

Lastly, the multiple surgeries were performed without long-term hypoparathyroidism or recurrent laryngeal-nerve injury. One patient had a chyle leak during the second reoperation that was fixed with ligation of the thoracic duct.

This study shows the significance of ongoing surveillance and the careful selection of patients for repeated surgery without repeating ¹³¹I therapy. The validation of retreating patients with persistent lymph-node metastases may rest on a unique study by Links et al. (11), in which survival rates were transformed into standardized survival time to adjust for the baseline mortality rate in the general population. The outcome of the study was that disease-free patients had a normal residual life span, whereas life expectancy was reduced to 60% in patients with persistent disease. This suggests that residual disease should not be treated lightly.

— Ernest L. Mazzaferri, MD, MACP

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Cancer-specific survival is significantly improved by total thyroidectomy and by a trend for ¹³¹I RRA, but not for disease-free recurrence

Doi SA, Engel JM, Onitilo AA. Total thyroidectomy followed by postsurgical remnant ablation may improve cancer specific survival in differentiated thyroid carcinoma. Clin Nucl Med 2010;35:396-9.

SUMMARY

BACKGROUND

Most patients with differentiated thyroid cancer (DTC) have low-risk tumors. As a result, the extent of thyroidectomy that provides optimal outcome is a matter of debate, mainly because there are no prospective randomized studies of the optimal initial surgery and the role of postoperative radioiodine (¹³¹I) for thyroid remnant ablation (RRA) in this group of patients with low-risk tumors. The goal of this study was to determine the effect of thyroidectomy followed by postsurgical RRA on the survival of patients with DTC after adjusting for the risk of tumor stage.

METHODS AND PATIENTS

The data for this study are derived from Marshfield Clinic electronic medical records, which provided a cohort of patients with DTC treated from January 1, 1987, through January 31, 2006. Patients with medullary or anaplastic thyroid cancer and cases with missing data were excluded from the study. The following data were obtained on each patient with DTC: age, sex, tumor histology, tumor size, and presence of distant metastases, lymph-node metastases, pathological diagnosis, recurrence and location of recurrence, cause of death, and length of survival.

Patients were stratified by the extent of surgery into one of two heterogeneous groups to distinguish total or near-total thyroidectomy versus less thyroid resection. One group was designated as “total,” which included total, or near-total thyroidectomy, and the “other” category included subtotal thyroidectomy or lobectomy with or without isthmusectomy.

Patients who had removal of less than a lobe were categorized as having nodulectomy or were classified as thyroidectomy, not otherwise specified, which was included in the category “other.” If a patient initially had lobectomy and then went on to have a complete thyroidectomy, the patient was categorized as having had total thyroidectomy.

Data on the type of radiation therapy were obtained using the cancer registry database and were verified manually from the Marshfield Clinic electronic medical record. The amount of ¹³¹I therapy was determined from the database by manually extracting these data. External beam radiation was used as adjuvant treatment in few cases and was not examined in this analysis.

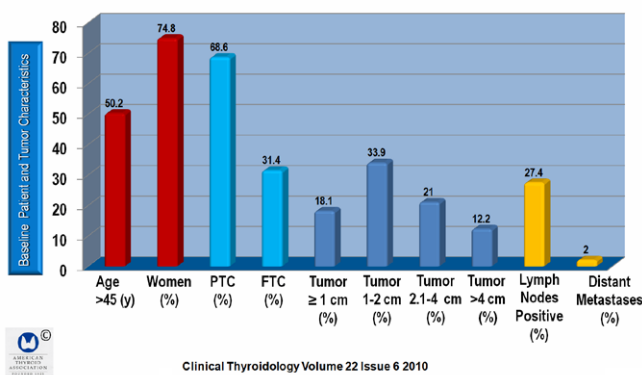
The Marshfield Clinic risk stratification

The Marshfield quantitative tumor–node–metastasis score was used, which is a unique score that is the sum of the following: histopathology, score 1 = not papillary thyroid carcinoma (PTC), otherwise score 0; age, score 4 was age ≥45 years, otherwise 0; lymph-nodes, score 4 was regional lymph-node metastasis, otherwise score 0; tumor, score 6 was tumor >4 cm in greatest dimension limited to the thyroid or any tumor with extrathyroid extension. The resulting continuous distribution of total risk scores across all patients in the model ranges from 0 to 15 and was used to adjust the Cox proportional-hazards model.

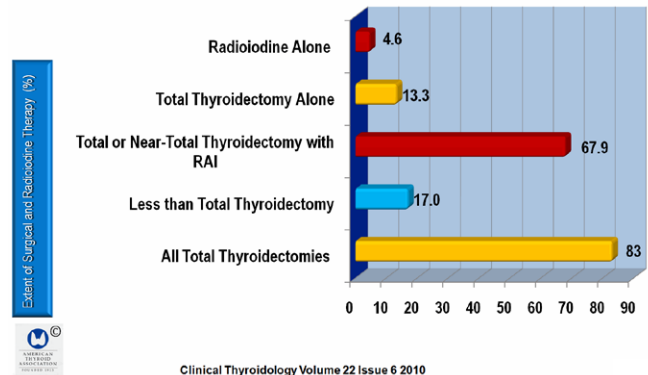
Multivariate analysis

Two treatment variables were dichotomized into the extent of surgery (total thyroidectomy vs. a composite of total thyroidectomy and RRA).

Baseline Characteristics of Patients, Tumors and Metastases



Characteristics of Surgical and Radioiodine Therapy



Figures 1A and 1B. 1A, This figure shows the baseline characteristics of patients, primary tumor size, lymph-node metastases and distant metastases. 1B, This figure summarizes the surgical and radioiodine features in the study group (%). RAI = radioactive iodine. The data for these figures are derived from the text and Table 3 of Doi et al.

RESULTS

Patient and tumor demographics (Figure 1)

The study cohort comprised 614 patients, among whom 459 were women (74.8%) and 155 were men (25.2%). Of this group of 614 patients, 308 (50.2%) were more than 45 years of age. A total of 421 (68.6%) had PTC, and the remaining 193 (31.4%) had follicular thyroid carcinoma. The primary tumor was ≥ 1 cm in 111 patients (18.1%), 1 to 2 cm in 208 (33.9%), 2.1 to 4 cm in 166 (27%), >4 cm in 75 (12.2%), and of unknown size in 54 (8.8%). Lymph-node metastases were positive in 168 patients (27.4%), negative in 416 (67.8%), and not examined in 30 (4.8%), and metastases were present in 12 (2%) (Figure 1).

Surgical and radioiodine therapy (Figure 2)

Of the 614 patients with DTC, 608 had either total thyroidectomy with bilateral resection, including total or near-total thyroidectomy or lobectomy, or subtotal or unilateral resection, including lobectomy with or without isthmusectomy. Of the 608 patients, 504 (83%) had total thyroidectomy, 104 (17%) had less surgery, and 569 (93.6%) had complete information on tumor size. Treatment was total (bilateral total) or near-total thyroidectomy with RRA in 417 patients (67.9%), total thyroidectomy alone in 82 (13.3%), radioiodine alone in 28 (4.6%), and neither treatment in 59 patients (9.6%) or no information in 28 (4.6%)

Multivariate analysis (Figure 3)

For multivariate analysis, two treatment variables were created: surgical extent dichotomized to total versus other surgery, and a composite of total surgery and RRA, comprising 4 groups: (1) both total surgery and RRA, (2) total surgery only, (3) RRA

only, and (4) neither intervention. The outcome was cancer-specific survival, defined as time from diagnosis to a cancer specific-death. The odds for each group was compared with the reference standard of reaching the end point first (i.e., early cancer-specific death after adjusting for the Marshfield quantitative tumor-node-metastasis risk score.

The odds ratio (OR) with 95% confidence interval (95% CI) was an independent variable predicting an adverse outcome of cancer-specific mortality earlier than expected in an individual without effective surgery and RRA. The reference range for expected survival was initial therapy with total thyroidectomy plus RRA (n = 398 patients). Having neither total thyroidectomy nor RRA was associated with a fourfold greater risk of reaching an early end point of cancer-mortality (OR, 8.1; 95% CI, 0.8 to 79.9; P = 0.07). RRA without total thyroidectomy was associated with reaching an early end point of cancer-specific mortality (OR, 3.7; 95% CI, 0.9 to 15.4; P = 0.07). Total thyroidectomy without RRA had an OR of 3.7 (95% CI, 0.9 to 15.4; P = 0.07) of reaching an early end point of cancer-specific mortality. Treatment with both total thyroidectomy and RRA had an OR of 2.0 (95% CI, 0.04 to 9.8; of reaching an early end point.

There was a trend for cancer-specific death occurring earlier in patients who did not have RRA. There was no relationship between disease-free survival and either surgical status or RRA.

CONCLUSION

The data in this study supports the routine use of total or near-total thyroidectomy with a trend for ^{131}I RRA for cancer specific-survival but not for tumor recurrence.

Adjusted Odds Ratio of Cancer-Specific Death, Adjusted Marshfield Risk Score According to Surgical Status Only

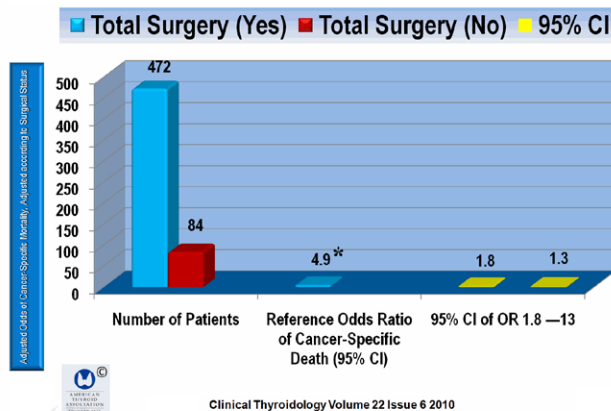


Figure 2. This figure shows the odds ratios of cancer-specific death adjusted for the Marshfield risk score according to surgical status. Total or subtotal thyroidectomy was designated as total surgery, and less surgery comprises subtotal thyroidectomy or lobectomy with or without isthmusectomy. The data for this figure were derived from Table 2 of Doi et al.

Adjusted Odds of Cancer-Specific Death, and Adjusted Marshfield Risk Score According to Surgical Status and Radioiodine Ablation

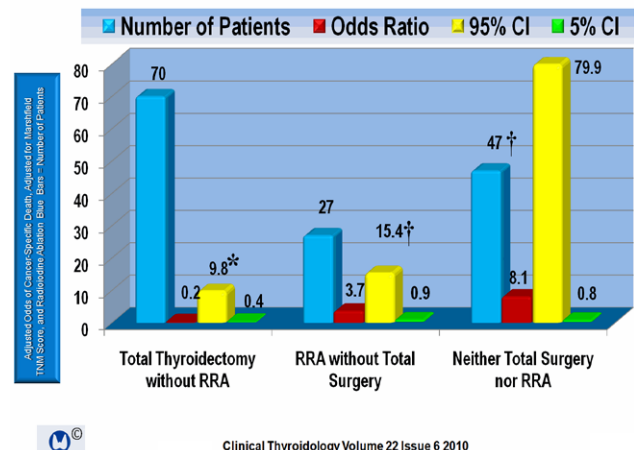


Figure 3. This figure shows the adjusted odds ratios of cancer-specific death, adjusted by Marshfield Risk TNM Score) according to the surgical status, and RRA by multivariable Cox regression analysis.

COMMENTARY

Of 614 patients with DTC, 504 (83%) had total thyroidectomy and 104 (17%) had less surgery. A total of 24 to 297 mCi (mean, 116) was administered to 394 patients who had total thyroidectomy. Ten-year survival rates were higher for patients who had total thyroidectomy as compared with lobectomy (96% vs. 84%, $P < 0.001$). Ten-year survival for complete versus incomplete surgery for tumor stages 1 and 2 was 99% versus 96%, and for stages 3 and 4 it was 88% versus 52%. Cancer-specific deaths tended to occur earlier in patients not treated with RRA. There was no overall relationship between disease-free survival and RRA or surgery, but in the higher-risk categories, surgery remained significant. As a consequence, the authors advise the routine use of both total and near-total thyroidectomy followed by RRA postoperatively for all risk categories in DTC. Still, although the effect of surgery seems clear, there was only a trend toward improvement with RRA for cancer-specific survival. Still, the study found a lack of surgical and RRA effect on disease-free survival, based on the premises that the patients have low-risk tumors.

Much of this study is predicated on the unique Marshfield quantitative tumor–node–metastasis tumor score, published in 2009 (1), which was formulated on the basis of simplifying the TNM staging system, which requires some edification. The 2009 study (1) was based on the notion that the TNM system can be cumbersome to implement clinically, given the large number of stages within the TNM system. The authors thus decided to quantify each variable in the TNM system to arrive at a simplified quantitative alternative to the TNM system, termed QTNM. The Marshfield electronic record system was used to identify 614 cases of DTC managed from 1987 to 2006 (the same patients in the current study). Cancer-specific survival and disease-free survival were calculated by the Kaplan–Meier method, and a simplified QTNM score was devised with a Cox proportional-hazards model that quantified the TNM system as follows: 4 points each for age >45 years and presence of neck lymph-node metastases, 6 points for a primary tumor >4 cm or extrathyroidal extension, and 1 point for nonpapillary DTC.

A sum of 0 to 5 points was designated as low risk, 6 to 10 points as intermediate risk, and 11 to 15 points as high risk. The authors compared this with the conventional TNM system and two other systems, demonstrating a similar or better discrimination with the QTNM that was maintained when this risk stratification was applied to a unique validation set. The authors concluded that the QTNM system as opposed to the conventional TNM system seems to be a simple and effective method for risk stratification for both recurrence and cancer-specific mortality. Still, in the present study, the stratification of various surgical procedures was relatively wide, raising the question whether this grouping might have produced an ascertainment bias.

It is difficult to evaluate the efficacy of surgical therapy and RRA without directly integrating the multiple features of patient age, tumor size, tumor invasion, lymph-node metastases, and distant metastases to mention a few, and it is hence difficult to translate the QTMN score back to the TNM score, for those who use the TNM score.

Several conclusions in the study by Doi et al. are troublesome. The use of RRA in this group of low-risk patients showed a trend in the improvement of cancer-specific mortality. Although total thyroidectomy has a positive effect on cancer-specific mortality, RRA is of only borderline significance for the end point, although hazard ratios for RRA are indicative of improved cancer-specific survival. Moreover, the study could not verify an effect of disease-free survival. The authors suggest that the potential for recurrent disease is more strongly associated with risk score than with the therapeutic interventions, implying that low-risk patients have better disease-free survival, regardless of the use of therapeutic interventions, but suggest that if these interventions are used, cancer-specific survival is probably related to the initial tumor and is improved even in low-risk patients. As a consequence, the authors advocate total thyroidectomy at initial diagnosis along with RRA, which they opine confers the best possible prognosis for the patient. Yet the authors were unable to run analyses on the low-risk group alone, as there were few outcomes in this group and a stratified analysis was not possible. Lastly, tumor size was unknown in 54 patients (8.8%), suggesting that the tumor staging in this study may have not been fully responsive to tumor size, which has a well-described effect on cancer-specific mortality and disease-free survival.

There are a few robust studies that have found total thyroidectomy to significantly decrease cancer-specific mortality in patients with DTC, including some older studies that find a decrease in mortality and recurrence rates with ^{131}I therapy (2-4). All of these studies have been tightly linked to tumor features, patient age, and histology. Two meta-analyses by Sawka et al. (5,6) failed to find an effect of RRA on thyroid cancer–specific mortality; however, a pooled analysis of 10-year outcomes found that locoregional recurrence was 4% in ^{131}I treated patients and 10% in controls (relative risk, 0.31) and the rate of distant metastases was 2% in ^{131}I treated patients and 4% in controls, and was associated with an absolute decrease in distant metastases in ^{131}I -RRA-treated patients. Still, PTMC fails to show a significant response to ^{131}I RRA, whereas patients with PTMC may be responsive to RRA in tumors invading surrounding tissues or organs, but this occurs rarely.

A relatively recent study by Bilimoria et al. (7) found that 10-year cancer-specific mortality and disease-free recurrence rates were especially related to tumor features and thyroid surgery, especially tumor size and total thyroidectomy, which clearly were found to have a major impact on outcome. For example, the rates of PTC recurrence increased incrementally with tumor sizes ranging from <1 cm (4.6%) to >8 cm, with a recurrence rate of 24.8%. Likewise, the 10-year cancer-specific mortality rates of PTC increase from 2% with tumors <1 cm and incrementally increase to 19% with tumors >8 cm. This study concluded that for patients with primary tumors ≥ 1 cm, lobectomy was associated with a 15% higher recurrence rate ($P = 0.04$) and a 31% higher risk of 10-year cancer-specific mortality ($P = 0.04$). Still, the trend for cancer-specific death occurring earlier in patients who did not have RRA is found in few studies.

— Ernest L. Mazzaferri, MD, MACP

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HOT ARTICLES

1. Khan A, Smellie J, Nutting C et al. Familial Nonmedullary Thyroid Cancer: A Review of the Genetics. *Thyroid* 2010.
2. Kim ES, Lim DJ, Baek KH et al. Thyroglobulin Antibody Is Associated with Increased Cancer Risk in Thyroid Nodules. *Thyroid* 2010.
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DISCLOSURE

Dr. Mazzaferri is a consultant to Genzyme.

Dr. Sipos Lectures for Abbott Pharmaceutical and Genzyme.



Call for Applications

Editor-in-Chief of *Clinical Thyroidology*

The Publications Committee of the American Thyroid Association (ATA) is soliciting applications for the position of Editor-in-Chief of *Clinical Thyroidology*. The new Editor-in-Chief (EIC) will officially assume responsibility for the journal on January 1, 2011 but should be willing to assume some responsibilities by November/December 2010. The Committee seeks an individual who will continue the growth, quality, reputation, and scholarship of this important ATA publication. The applicant should be a respected thyroid clinician or investigator who is well organized, innovative, energetic and dedicated to making *Clinical Thyroidology* indispensable to clinicians and scientists interested in thyroid diseases. She/he should have experience as a writer and as an editor, associate editor, or editorial board member of a peer-reviewed journal. The initial appointment will be for a three-year term renewable by mutual agreement between the EIC and the ATA.

Applicants should submit a cover letter, their curriculum vitae, and a general statement outlining their vision and aims for *Clinical Thyroidology* to Dr. James Fagin, Chair of the ATA Publications Committee, by email to Ms. Bobbi Smith, CAE, ATA Executive Director (bsmith@thyroid.org).

The deadline for applications is August 1, 2010. The applications will be reviewed during August/September, and candidates should be available to be interviewed in person at the 14th International Thyroid Congress (ITC) in Paris, France. Questions regarding this position may be directed to Dr. James Fagin, Search Committee Chair [Phone 646-888-2136 Email faginj@mskcc.org].

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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).
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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 >>
ATA Marketplace
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ATA Thyroid Marketplace

Thyroid MP3 Downloads

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



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

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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!