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CLINICAL THYROIDOLOGY

EDITORS' COMMENTS

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CLINICAL THYROIDOLOGY STATISTICS We are happy report that there are more than 4,300 subscribers to *Clinical Thyroidology* online. The articles in Volume 21, Issue 1 to 7 have been viewed by more than 27,000 unique times. Our subscribers include 2,502 MDs and 202 phDs, as well as members from 196 different specialties or areas of Interest from 118 countries. We are grateful that so many are using *Clinical Thyroidology*.

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WHATS NEW The last page now has a set of references to **REVIEWS & HOT ARTICLES** which contains references to important reviews and very recent articles that look especially important to the Editors.

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

We welcome your feedback and suggestions on these changes.

CONCISE REVIEW CITATIONS CONCISE REVIEWS can be cited by using the electronic citation at the end of each review.

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Jennifer A. Sipos, MD

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Elevated cardiovascular and renal risk factors in women with subclinical hypothyroidism are normalized by levothyroxine-replacement therapy

SUMMARY

BACKGROUND Overt hypothyroidism is associated with clinically apparent hemodynamic effects, including bradycardia and reduced cardiac output, and other serious effects on the heart such as reduced blood volume, increased systemic vascular resistance, diastolic hypertension, and reductions in renal blood flow. Hypothyroidism is also associated with dyslipidemia and carotid artery intima–media thickness, which may improve with short-term levothyroxine (L-T$_4$)-replacement therapy. Cardiovascular and renal abnormalities that are seen in overt hypothyroidism also have been found in subclinical hypothyroidism (SCH). The aim of this study was to compare cardiovascular and renal variables in healthy women with those in women with SCH, and to assess the effects of L-T$_4$ replacement in women with SCH treated over 18 months.

METHODS This is a cross-sectional study of 64 patients from a cohort of 1895 patients with biochemical evidence of SCH. The inclusion criteria for the study were female sex and age 30 through 60 years with SCH, defined as persistent serum thyrotropin (TSH) elevation with normal serum free thyroxine (FT$_4$) for 6 months prior to commencement of the study. During the 6-month follow-up, a euthyroid status spontaneously developed in 4 individuals, who were thus excluded from the study, and 4 dropped out of the study because they could not follow the protocol. Four others were excluded from the

analysis because of celiac disease (n = 1), pernicious anemia (n = 1), and the need for antihypertensive therapy (n = 1). A total of 56 patients were assessed for cardiovascular risk factors before L-T$_4$ treatment and 52 were evaluated after 18 months of L-T$_4$ therapy. At the same time, 56 healthy women were also evaluated. All patients were assessed for carotid artery intima–media thickness, a surrogate marker for atherosclerosis, before and after L-T$_4$-replacement therapy for 18 months. Healthy women of similar age were also studied. Blood pressure (BP), plasma lipids, homocysteine, and estimated renal glomerular filtration rate (eGFR) were also evaluated during the study periods.

RESULTS
Patient Demographics (Figure 1)
The mean (±SD) age of women with SCH was 50±9 and 52±10 years during the pretreatment and posttreatment periods, respectively, and was 47±8 years in healthy women. Other demographic variables were as follows. The mean body-mass index (the height in meters divided by the square of the weight in kilograms) was 25.5±4.0, 24.9±4.2, and 25.7±4.0, in the pretreatment and posttreatment intervals in women with SCH and in healthy women, respectively. Mean FT$_4$ was 10.4±5.4, 18.0±2.3, and 15.8±2.2 pmol/L (P<0.001, as compared with FT$_4$ values in healthy women, and as compared with the pretreatment and posttreatment FT$_4$ values) (Figure 1).
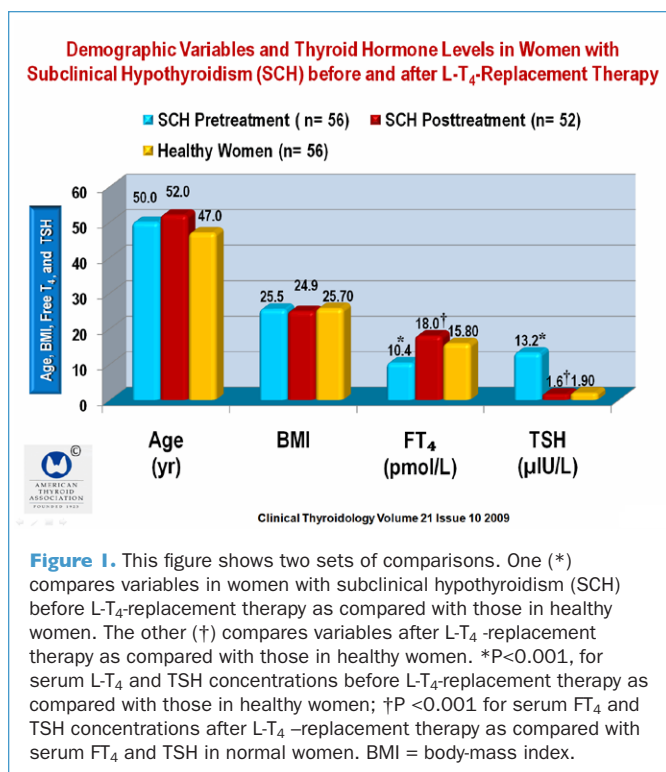
Mean serum TSH was 13.2±4.5, 1.6±1.8, and 1.9±1.0 µIU/ml during pretreatment and posttreatment periods and in healthy women, respectively (P<0.001, comparing paired pretreatment and posttreatment values in women with SCH; and P = 0.001, comparing the pretreatment TSH values in patients with SCH as compared with those in healthy women) (Figure 1).

Thyroperoxidase antibodies were positive in 42 women with SCH (75%), negative in 48 healthy women, and equivocal in the others. All women with SCH tolerated L-T$_4$-replacement therapy. The mean dose of L-T$_4$ normalizing the serum TSH was 100±30 µg/day.

The Cardiovascular Risk Factors before and after L-T$_4$ Therapy (Figures 2A and 2B)
The systolic BP was 134±120 and 120±15 mm Hg in the women with SCH (P = 0.0001, comparing pretreatment and posttreatment (paired) values and 120±13 mm Hg in healthy women (P = 0.0001, comparing pretreatment BP values in women with SCH with those in healthy women).

The diastolic BP was 81±10 and 73±8 mm Hg in the women with SCH (P = 0.005, comparing paired pretreatment and posttreatment values) and 74±3 mm Hg in the healthy women (P = 0.0001, comparing the pretreatment values in women with SCH with those in healthy women).

Figure 1. This figure shows two sets of comparisons. One (*) compares variables in women with subclinical hypothyroidism (SCH) before L-T$_4$-replacement therapy as compared with those in healthy women. The other (†) compares variables after L-T$_4$-replacement therapy as compared with those in healthy women. *P<0.001, for serum L-T$_4$ and TSH concentrations before L-T$_4$-replacement therapy as compared with those in healthy women; †P <0.001 for serum FT$_4$ and TSH concentrations after L-T$_4$–replacement therapy as compared with serum FT$_4$ and TSH in normal women. BMI = body-mass index.

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Figures 2A and 2B. These figures show the cardiovascular risk factors in women with subclinical hypothyroidism before and after L-T$_4$-replacement therapy as compared with risk factors in healthy women. *P = 0.001, comparing pretreatment and posttreatment systolic blood pressure levels combined, as compared with blood pressure in healthy women. †P = 0.006, comparing pretreatment serum total cholesterol as compared with cholesterol concentrations in healthy women. ‡P = 0.016 comparing. LDL cholesterol and Lp(a) that are significantly lower after L-T$_4$ –replacement therapy than that in patients with subclinical hypothyroidism. BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein a.

The mean total cholesterol was 5.68±1.07 and 5.35±1 mmol/L in women with SCH (P = 0.023, comparing paired pretreatment and posttreatment values) and 5.04±0.8 mmol/L in healthy women (P = 0.001, comparing pretreatment values in women with SCH with those in healthy women) (Figure 2A).

The mean serum triglycerides were 1.39±0.7 and 1.41±0.7 mmol/L in women with SCH (P = 0.14, comparing paired pretreatment and posttreatment values) and 1.01±0.43 mmol/L in the healthy women (P= 0.0001, comparing pretreatment values in women with SCH with those in healthy women).

The mean high-density lipoprotein (HDL) cholesterol levels were 1.61±0.7 and 1.57±0.4 mmol/L in women with SCH (P = 0.28, comparing paired pretreatment and posttreatment values) and 1.66±0.44 mmol/L in healthy women (P = 0.33, comparing the pretreatment values in women with SCH with those in healthy women).

The mean low-density lipoprotein (LDL) cholesterol levels were 3.36±0.9 and 3.11±0.85 mmol/L in women with SCH (P = 0.18, comparing paired pretreatment and posttreatment values) and 2.91±0.74 mmol/L in the healthy women (P = 0.016, comparing the pretreatment values in women with SCH with those in healthy women).

The lipoprotein a (Lp(a)) cholesterol levels were 372±53 and 272±38.7 mmol/L in women with SCH (P = 0.18, comparing paired pretreatment and posttreatment Lp(a)), and 1.71±25.5 mmol/L in the healthy women (P= 0.016, comparing the pretreatment values with those in healthy women).

The Renal Function Indexes before and after L-T$_4$-Replacement Therapy in Women with SCH (Figure 3)
Urea concentrations were 4.6±1.07 and 4.4±0.9 mmol/L in the women with SCH (P = 0.008, comparing paired pretreatment

and posttreatment values) and 4.6±1.5 mmol/L in healthy women (P = 0.25, comparing the pretreatment values with the urea values in healthy women).

Creatinine was 84±11 and 77±10 µmol/L in women with SCH (P = 0.008, comparing paired pretreatment and posttreatment values) and 0.78±7 µmol/L in healthy women (P = 0.001, comparing the pretreatment values with the creatinine values in healthy women).

The estimated glomerular filtration rate (eGFR) was 69±4 and 73±5 ml/min in women with SCH (P = 0.001, comparing paired pretreatment and posttreatment values) and 75±3 ml/min in healthy women (P= 0.001, comparing the pretreatment values in women with SCH with the eGFR values in healthy women).

Creatinine was 84±11 and 77±10 µmol/L in women with SCH, (P = 0.008, comparing paired pretreatment and posttreatment values) and 0.78±7 µmol/l in healthy women (P = 0.001, comparing the pretreatment values with the creatinine values in healthy women).

Cystatin C (cystatin C or cystatin 3 (formerly gamma trace, post-gamma-globulin or neuroendocrine basic polypeptide, which is a protein encoded by the CST3 gene, is mainly used as a biomarker of kidney function). Cystatin C was 0.91±0.2 and 0.78±0.1 mg/L in women with SCH (P = 0.001, comparing paired pretreatment and posttreatment levels) and 0.76±0.1 mg/L in healthy women (P = 0.001, comparing the pretreatment values in women with SCH with the cystatin C values in healthy women).

Mean pretreatment common carotid artery (CCA) diameter was 6.13±0.05 mm in women with SCH, and mean posttreatment CCA was 6.57 (P = 0.003, comparing pretreatment and posttreatment CCA diameter) (Figure 4).
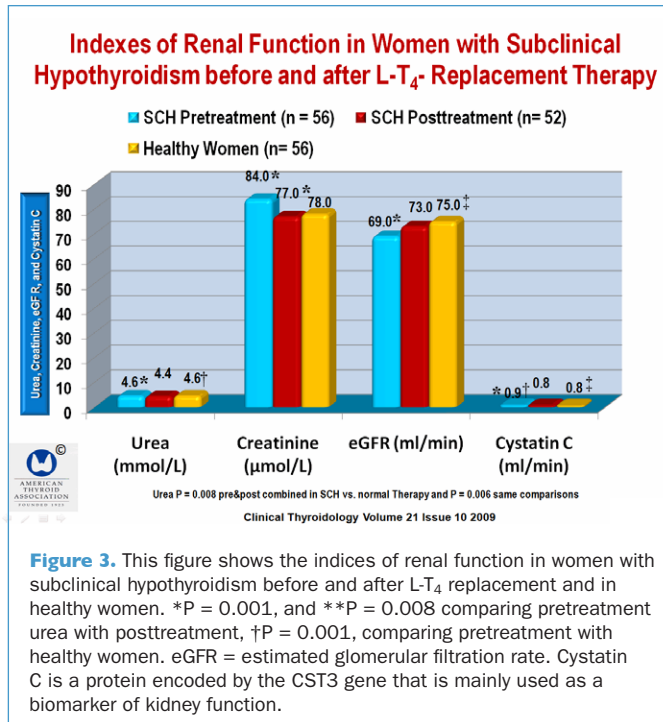
Figure 3. This figure shows the indices of renal function in women with subclinical hypothyroidism before and after L-T$_4$ replacement and in healthy women. *P = 0.001, and **P = 0.008 comparing pretreatment urea with posttreatment, †P = 0.001, comparing pretreatment with healthy women. eGFR = estimated glomerular filtration rate. Cystatin C is a protein encoded by the CST3 gene that is mainly used as a biomarker of kidney function.

Figure 4. This figure shows the cardiovascular variables in women with subclinical hypothyroidism before and after L-T$_4$-replacement therapy. CCA = common carotid artery; CIMT = carotid intima–media thickness; GTN = sublingual glyceryl trinitrate 400-μg spray. *P = 0.003 **P = 0.05 and †P = 0.001; both comparing pretreatment with posttreatment values.

Before and after L-T$_4$-replacement therapy, mean common carotid artery intima–media thickness was 0.82±0.2 and 0.71±0.2 mm (P = 0.046). Likewise, mean brachial artery diameter was 32±0.5 and 4.0±0.1 mm, before and after L-T$_4$-replacement therapy (P = 0.001). The percent change in brachial artery diameter before and after L-T$_4$-replacement therapy was 15.6±2.8 and 4.0±0.1%, respectively (P = 0.001). Sublingual glyceryl nitrate (GTN) increased the brachial artery diameter from 3.8±0.1 mm in the pretreatment assessment
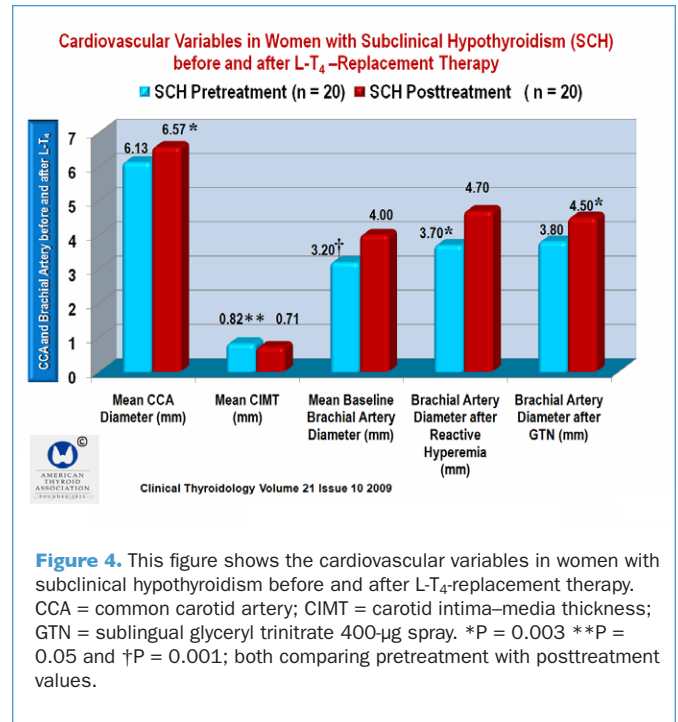
and 4.5±0.5 mm in the posttreatment assessment (P = 0.046); the percent increases were 15.6±2.8% and 17.5±1.2% before and after GTN, respectively.

CONCLUSION Cardiovascular risk factors increase and renal function declines in women with subclinical hypothyroidism. However, treatment with levothyroxine-replacement therapy also improves cardiac risk factors and renal function.

COMMENTARY

The study by Adrees et al. is a cross-sectional retrospective study of 64 patients with biochemical evidence of SCH. The study group, which comprised women ages 30 through 60 years with SCH, had persistent elevation of serum TSH with FT$_4$ for 6 months prior to commencement of the study. After L-T$_4$-replacement therapy for 18 months, there was significant improvement in blood pressure, plasma lipids and homocysteine, and significantly reduced carotid intima–media thickness, a surrogate for reduced progression of atherosclerosis.

Although there is evidence that cholesterol and lipoprotein metabolism is altered with SCH, controversy remains concerning the risk of cardiovascular disease (CVD) that is associated with SCH. A meta-analysis by Danese et al. (1), found that all of the 1786 published studies reported changes in serum total cholesterol concentrations during L-T$_4$-replacement therapy in patients with SCH. Twelve studies reported triglyceride changes, 10 HDL cholesterol changes, and 9 LDL cholesterol changes, and the decline in serum total cholesterol was directly proportional to baseline concentrations. In contrast, patients with hypothyroidism who received suboptimal doses of L-T$_4$ had significantly larger declines in serum total cholesterol after TSH was normalized than did untreated individuals with SCH.

However, serum HDL cholesterol and triglyceride concentrations showed no change. The authors concluded that the results suggested that L-T$_4$-replacement therapy for individuals with SCH lowers mean serum total cholesterol and LDL cholesterol concentrations and that the reduction in serum total cholesterol may be larger in individuals with higher pretreatment cholesterol levels and in hypothyroid individuals taking suboptimal doses of L-T$_4$. The authors found no significant effects of L-T$_4$ on serum HDL or triglyceride concentrations.

A 2006 study by Cappola et al. (2) of 3233 U.S. community-dwelling individuals aged 65 years or older found no differences between SCH or overt hypothyroidism and euthyroidism for cardiovascular outcomes or mortality. Subclinical hypothyroidism had an adjusted hazard ratio of 1.07 (95% confidence interval, 0.90 to 1.28) for coronary heart disease. In short, the data did not support the hypothesis that unrecognized SCH is associated with other cardiovascular disorders or mortality.

Others find an effect of L-T$_4$ on cardiac function and structure in patients with SCH. A double-blind, placebo-controlled study by Monzani et al. (3) found that L-T$_4$-treated patients had a significant reduction of the cardiac preejection/ejection time (PEP/ET) ratio (P<0.05) and an increase in isovolumic relaxation time (P<0.05)

A case–control study by Nagasaki et al. (4) evaluated whether L-T$_4$ replacement might cause regression of the intima–media thickness (IMT) in the common carotid artery (CCA). Thirty-five hypothyroid patients were examined for their CCA IMT before and 1 year after normalization of thyroid function by L-T$_4$ replacement. As compared with 35 healthy controls, mean (±SE) basal CCA IMT was significantly higher in patients with hypothyroidism (0.635±0.018 mm) as compared with control subjects (0.559± 0.021 mm, P<0.005). After 1 year of L-T$_4$ therapy that achieved euthyroidism in 34 of 35 patients, there was a significant decrease of CCA IMT (0.552±0.015 mm, P <0.0001) that was comparable to that among the healthy controls. The CCA IMT change was closely associated with basal levels of total cholesterol (r = –0.472, P = 0.0031), LDL cholesterol (r = –0.441, P = 0.0076) and the HDL/ total cholesterol ratio (r = –0.435, P = 0.0057). The authors concluded that L-T$_4$ therapy might have the potential to reverse the progression of atherosclerosis in hypothyroid patients. They further suggested that increased levels of LDL cholesterol and the total/HDL cholesterol ratio may have an important role in the increased in CCA IMT of patients with hypothyroidism.

The study by Adrees et al. confirmed the above findings, including increased levels of Lp(a) and homocysteine levels in SCH that also improved after L-T$_4$-replacement therapy. The authors suggest that these effects are clinically significant, as supported by the observed reduction in CIMT—which is currently the most widely accepted surrogate marker of atherosclerosis and is independently predictive of stroke and myocardial infarction—after L-T$_4$ replacement. Moreover, Monzani et al. also found reduced CIMT after L-T$_4$-replacement therapy in a 12-week study (3). Others also have observed a beneficial effect of L-T$_4$ on cardiovascular risk factors and endothelial function (5;6)

Adrees et al. suggest that increased arterial vasodilatation might explain the increase in eGFR that was found after L-T$_4$-replacement therapy. They argue that GFR is reduced in overt hypothyroidism. For example, den Hollander et al. (7) found a strong correlation between the change in thyroid status after L-T$_4$-replacement therapy and the change in renal function as a result of therapy expressed as serum creatinine (r2 = 0.81, P<0.0001) and estimated GFR (0.69, P<0.0001). Thus, the kidney seems to be an important target of thyroid hormone action in patients with SCH. There is one small cross-sectional study that found no difference in eGFR in subjects with SCH. Adrees et al. found that eGFR was normalized with L-T$_4$-replacement therapy in their patients with SCH. This was supported by the observation that cystatin C, a biomarker of renal function (8;9). Adrees suggest that the clinical implications of change in renal function are as yet unknown.

The final conclusion by Adrees et al. that normalization of cardiovascular risk factors following L-T$_4$-replacement therapy in SCH potentially explains reduced CIMT seems to be a reasonable conclusion from the data reported in this study.

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Graves' disease is the most common cause of severe hyperthyroidism that is accompanied by greater than usual clinical signs and symptoms and laboratory abnormalities

SUMMARY

BACKGROUND Graves' disease occurs in approximately 0.5% of the population and is the cause of 50 to 80% of the cases of hyperthyroidism. Although the disease generally responds to therapy, severe hyperthyroidism is a serious problem that may pose a threat of survival and thus requires a high level of therapeutic expertise and experience. The aims of this study were to analyze the clinical and laboratory features and outcomes of patients with severe hyperthyroidism and to compare these findings with the features of less-threatening forms of hyperthyroidism.

METHODS This is a retrospective observational cross-sectional study of patients with severe hyperthyroidism who attended the authors' clinic in the Department of Endocrinology, Hospital Ramón y Cajal, in Madrid, Spain, which is in the central area of Spain, a geographic area of low to sufficient iodine intake. The study subjects were patients who attended the clinic for a period of 6 months from January 1, 2006, through June 31, 2006. Excluded from the study were patients with clinical evidence of thyroid storm, subclinical hyperthyroidism defined as a suppressed serum thyrotropin (TSH) with normal free thyroxine (FT_4) and free triiodothyronine (FT_3) levels. Patients were randomly assigned to one of three groups according to the severity of hyperthyroidism as mild (mH), moderate (MH), and severe (SH) based on serum FT_4 levels: SH = FT_4 >7.8 ng/dl (normal range, 0.85 to 1.8) [>100 pmol/L {normal range, 11 to 23}]; mH = FT_4 1.8 to 3.9 ng/dl [23 to 50 pmol/L], and MH = FT_4 3.9 to 7.7 ng/ml [50 to 99 pmol/L].

RESULTS A total of 107 patients with overt hyperthyroidism were evaluated during the study period, 81 of whom were women (76%) with a mean age (±SD) of 46.9±16.1 years.

Clinical Features (Figure 1)

Of the 107 patients, 49 were classified as having mH (46%), 41 of whom were women (84%) 49±15 years of age; 37 were classified as MH (36%), 26 of whom were women (84%) 47±17 years of age; and 21 were classified as SH (20%), 41 of whom were women (84%) 41±17 years of age. Hyperthyroidism was regarded as de novo disease in 33 of 49 patients with mH (67%), 33 of 37 with MH (89%), and 19 of 21 with SH (90%). Hyperthyroidism was considered to be a relapse in 16 of 49 patients with mH (33%), 41 of 32 with MH (13%), and 2 of 21 with SH (10%). The SH group was significantly younger than the other groups, and a greater proportion of SH patients had their first (de novo) episode of hyperthyroidism (P<0.05 for both age and de novo episode as compared with patients who had mH and MH). The clinical features of the patients according to the severity of hyperthyroidism are shown in Figure 1. Here and elsewhere, percentages are rounded to an integer.

Causes of Hyperthyroidism (Figure 2)

Graves' disease was the cause of hyperthyroidism in 79 of the 107 patients (74%), and was significantly more frequent in patients with SH (n = 18, 86%) as compared with Graves' disease in the mH group (n = 31, 63%) and MH group (n = 30,
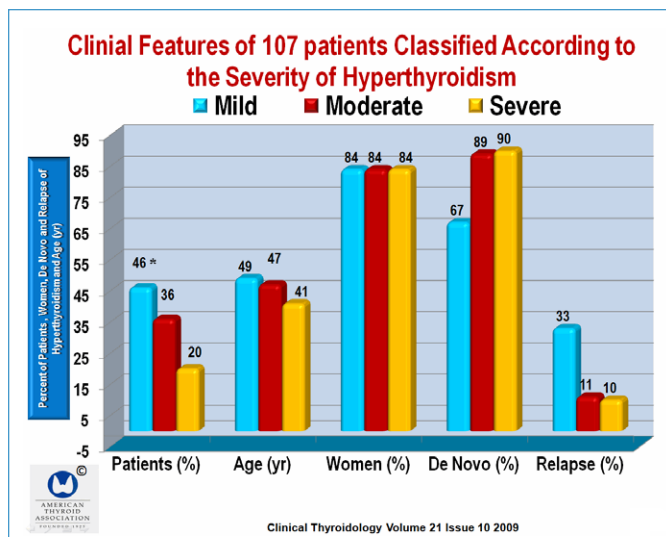

Figure 1. This figure shows the clinical features of 107 patients classified according to the severity of hyperthyroidism. *P<0.05 comparing mild hyperthyroidism versus moderate or severe hyperthyroidism. The data are derived from Table 1 in Iglesias et al.
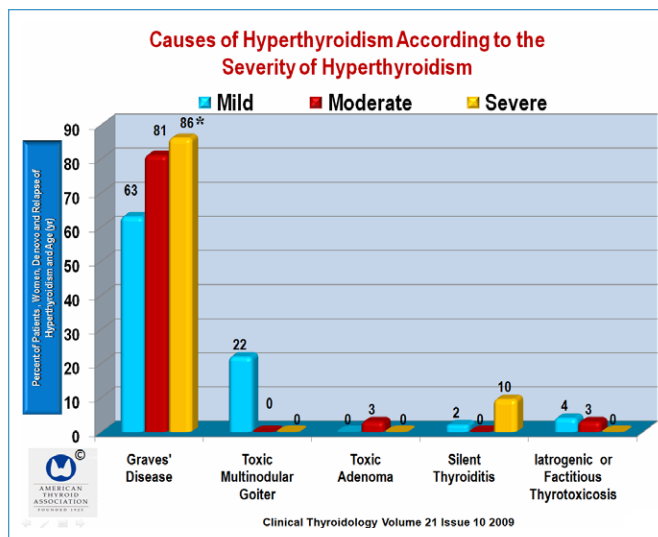

Figure 2. This figure shows the spectrum of causes for hyperthyroidism in this study. The data indicate the number of patients and percentage of each group of patients. *P<0.05 comparing mild and moderate hyperthyroidism groups with the severe hyperthyroidism group. The data are derived from Table 2 in Iglesias et al.

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81%). None of the patients with SH had toxic multinodular goiter or thyroid adenoma. The other causes of hyperthyroidism are shown in Figure 2.

Signs and Symptoms (Figure 3)

The most common symptoms in the SH group were weakness, nervousness, dyspnea, and weight loss. Weight loss was 15.6±17, 5.8±11.7, and 8.6±9.7 lb (7.1±7.7,

Figure 3. This figure shows the significant symptoms and signs of severe hyperthyroidism. †P<0.01 comparing heart rate in patients with mH and MH versus SH. *P<0.05 comparing four or more symptoms in severe hyperthyroidism versus mild and moderate hyperthyroidism. Patients with SH otherwise had similar laboratory findings as compared with the mH group, except for high AST (serum aspartate aminotransferase) (*P<0.01) and serum calcium levels (P<0.05). The data are derived from Table 3 in Iglesias et al.

5.8±5.3, and 3.9±4.4 kg) in the SH, MH, and mH groups, respectively. The heart rate and goiter grade were greater in the SH group as compared with the mH and MH groups (P<0.01). Atrial fibrillation was significantly more frequent in the SH group (16%) as compared with the mH (5%) and MH (0%) groups. However, there were no significant differences in the frequency of exophthalmos, goiter, or tremor in the SH group as compared with the mH and MH groups. Logistic-regression analysis found that the following three features were independently associated with SH: younger age (odds ratio [OR], 0.0958 [95% confidence interval 95%CI, 0.923 to 0.995) P = 0.026), higher heart rate (OR, 1.03 [95% CI, 1.01 to 1.06, P = 0.013), and overall weakness (OR, 4.35 [95% CI, 1.48 to 12.78, P = 0.008])

Laboratory Data (Figure 4)

The only laboratory findings that were significantly different were TSH levels in the SH versus the mild hyperthyroidism group. The SH group had higher serum aminotransferase (AST) (P<0.01) and calcium (P<0.05) levels, and lower serum cholesterol and albumin concentrations (both P<0.05) as compared with the mH and MH groups. There was a positive association between serum FT_4 concentrations and heart rate (r = 0.309, P<0.05), alanine aminotransferase (r = 0.275, P<0.01), and TSH-receptor antibodies (r = 0.238, P<0.01), and a negative correlation with cholesterol (r = 0.313, P<0.01).

Treatment and Outcome (Figure 5)

Follow-up of more than 6 months was performed in 80 patients, 18 with SH (95%), 35 with mH (71%), and 27 with MH (73%). The duration of follow-up was 28.7±18.7 months for SH, 42.7±31.1 months for mH, and 49.8±43.3 months for MH (P = not significant). There were no significant differences in the therapy administered to the three study groups, including
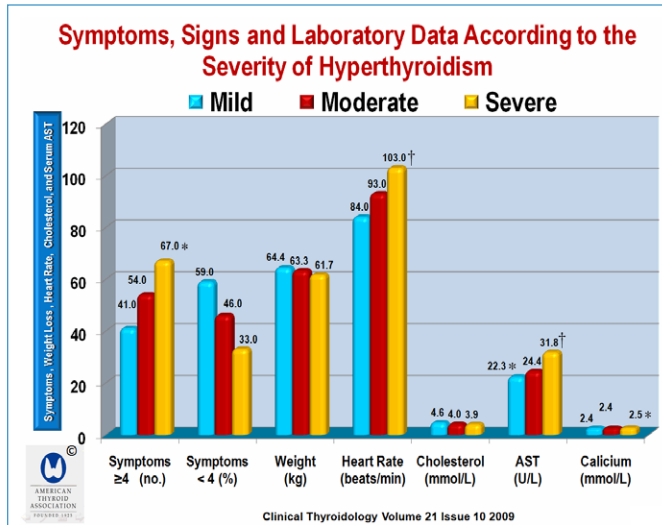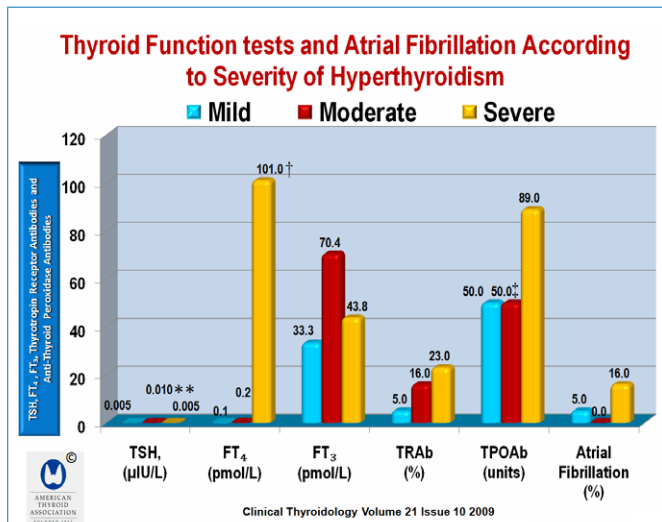

Figure 4. This figure shows thyroid-function test results according to severity of the hyperthyroidism. The mean serum FT_4 level was higher in the SH group than in the mH and MH groups. †P = 0.0001,* P<0.05, and **P = 0.002, comparing mH and MH groups with those with SH. There was a positive association between serum FT_4 levels and heart rate. Atrial fibrillation was significantly more frequent in the SH group as compared with the mH and MH (0%) groups. ALT = alanine aminotransferase; TPOAb = thyroperoxidase antibody; TRAb = TSH-receptor antibodies. The data are derived from Table 3 and the Results section in Iglesias et al.
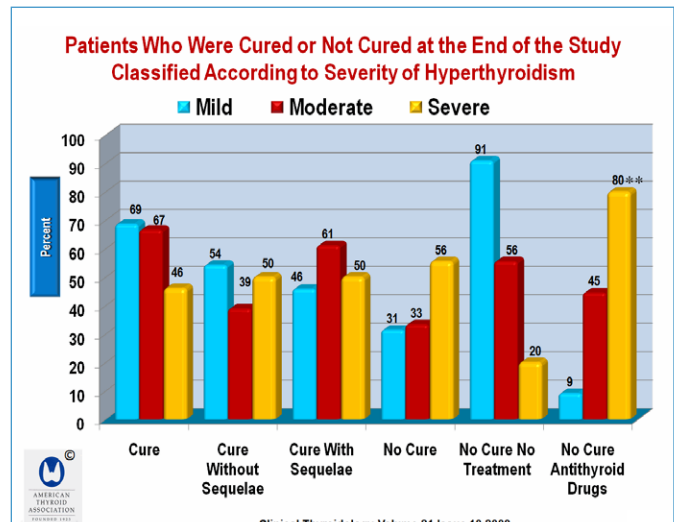

Figure 5. This figure shows the functional thyroid status and need for therapy in patients, who were cured versus those who were not cured at the end of the study. *P<0.01 comparing mH and MH groups versus the SH group. Cure without sequelae indicate post-radioiodine or postsurgical hypothyroidism and the need for L-T_4 therapy verus mH and MH groups, The data are derived from table 4 in Iglesias et al. There were no significant differences in the therapy administered to the study groups, including antithyroid drugs, radioiodine and surgery, nor were there differences in the subsequent rates of hypothyroidism following therapy.

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the administration of antithyroid drugs, radioiodine, and surgery, nor were there differences in the subsequent rates of hypothyroidism following therapy in the three groups. However, patients with SH had a slightly lower cure rate as compared with the other two study groups. The only variable that was an independent predictor of cure was the serum FT_4 concentration (OR, 0.98[95% CI, 0.97 to 0.99 P<0.05); however, at the conclusion of the analysis, the thyroid functional status was similar among the three groups.

CONCLUSION Graves' disease is the most common cause of severe hyperthyroidism and is accompanied by more clinical signs and symptoms and laboratory abnormalities as compared with milder forms of hyperthyroidism

COMMENTARY

In this study, several features characterized the SH group: the majority had de novo hyperthyroidism (90%) as compared with 33% of patients with mH and 13% with MH who had de novo disease. The remaining patients had a relapse of hyperthyroidism. In addition, heart rates were higher and atrial fibrillation was more common in patients with SH as compared with patients who had less severe hyperthyroidism. Still, there were no differences in the type of therapy, cure rate, and time to achieve a cure. Logistic regression found that FT_4 was the only independent predictor of cure. The study was unable to find a difference in treatment, time to achieve a cure, and remission rate among patients in the three groups of hyperthyroidism. Although the symptoms of hyperthyroidism were more severe in patients with SH and MH, symptomatology was not used as a criterion for the diagnosis of severe disease.

The study by Iglesias based the severity of disease on the serum FT_4 levels, which are likely to provide one of the best criteria for severe hyperthyroidism, although the patient's presenting symptoms and cardiovascular manifestations generally provide a reliable set of features to identify patients with severe disease. Moreover severe myopathy and severe asthenia are also harbingers of severe disease. Still, as compared with younger patients, older patients with severe hyperthyroidism, are generally less likely to have tachycardia and tremor, and present with more weight loss (1). Moreover, cardiovascular manifestations of Graves' disease, especially atrial fibrillation, are common presenting symptoms in patients over 50 years of age (1-4).

In a comprehensive review Brent (1) advised antithyroid drugs, β-blockers, and propylthiouracil to block the conversion of T_4 to T_3. Most experienced endocrinologists rely on the symptoms of hyperthyroidism to provide an assessment of the severity of disease. Omitting the clinical presentations of signs and symptoms seems to be an important omission in stratifying the severity of disease.

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The incidence of pediatric thyroid cancer is increasing and is higher in girls than in boys and may have an adverse outcome

SUMMARY

BACKGROUND Thyroid cancer is the most common endocrine malignancy in children. The principal thyroid malignancies in children are of the same histology as those afflicting adults, including papillary, follicular, and medullary thyroid cancer. However, children tend to present with more advanced disease, with a greater frequency of lymph-node metastases and distant metastases at the time of diagnosis and high rates of recurrence during the first decade of life. Most studies are relatively small or are from single institutions, which may not fully reflect the features of this disease, including the extent of tumor at the time of diagnosis and the long-term response to therapy. The latter is particularly important, since healthy children have a long life expectancy that may not be achieved in children with thyroid cancer, even with aggressive therapy. The aim of this study was to examine outcomes and predictors of survival for pediatric patients with thyroid cancer.

METHODS This study was performed on the latest records from the Surveillance, Epidemiology, and End Results (SEER) registry from 1973 through 2004 for all patients with thyroid cancer who were younger than 20 years of age. Tumor histology was identified using morphology codes from the International Classification of Disease for Oncology, 3rd edition. There were no duplicate cases, and patients with missing data were excluded from univariate and multivariate analyses. The SEER staging criteria, which were used in this analysis, are different from the TNM (tumor–node–metastases) staging system. In the SEER staging system, "local" denotes disease confined to the thyroid and "regional" tumor extension into adjacent organs, regional lymph nodes, or both.

RESULTS

Study Subjects and Tumor Features (Figures 1 to 3)

A total of 1753 pediatric patients with thyroid cancer were identified during the study period. The annual incidence of thyroid cancer in 2004 was 0.54 cases per 100,000, and was categorized by sex, race, age group, and histology (Figure 1). The mean age at the time of diagnosis in this cohort was 15.9 years (range, <1 to 19). Girls outnumbered boys more than
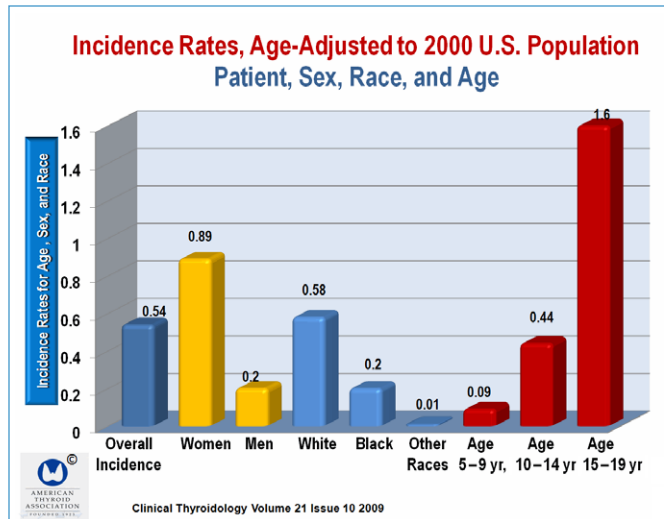

Figure 1. This figure shows the annual incidence rate per 100,000 pediatric population for thyroid cancer in 2004 and the age and race of patients at the time of diagnosis. The age-adjusted incidence was 0.89 cases per 100,000 girls and 0.2 cases per 100,000 boys.
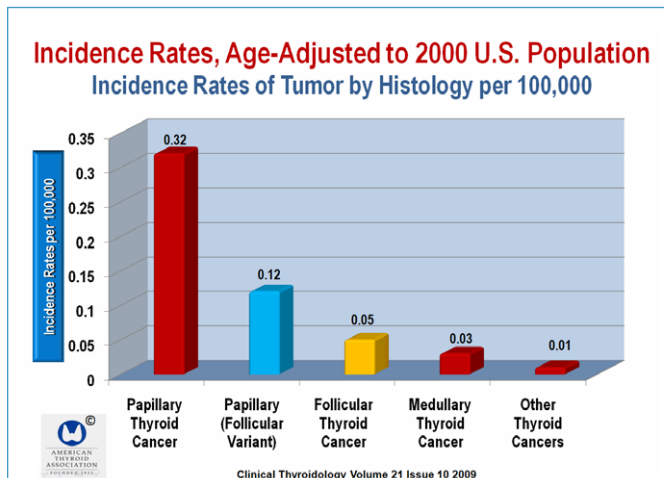

Figure 2. This figure shows the incidence rates per 100,000 age-adjusted to the 2000 U.S. standard population.
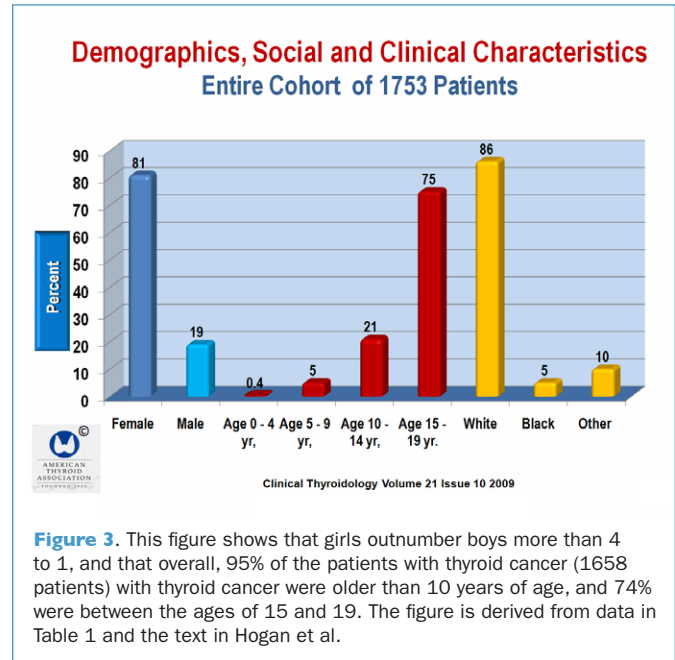

Figure 3. This figure shows that girls outnumber boys more than 4 to 1, and that overall, 95% of the patients with thyroid cancer (1658 patients) with thyroid cancer were older than 10 years of age, and 74% were between the ages of 15 and 19. The figure is derived from data in Table 1 and the text in Hogan et al.

4 to 1 (1424 vs. 329). A total of 1658 patients (95%) were more than 10 years of age, and 1298 (74%) ranged in age from 15 through 19 years (Figure 1). Tumor histology was papillary thyroid cancer (PTC) in 1044 patients (60%), follicular variant papillary cancer (FVPC) in 398 (23%), and medullary thyroid cancer in 87 (7.6%) (Figure 2). Distant metastases were found in 133 (7.6%) of the patients at the time of diagnosis and were most commonly found in the lung and rarely in the bone or liver. Regional lymph-node metastases were found in 814 patients (46%), and disease confined to the thyroid gland was found in 741 (42%). Here and elsewhere, percentages are rounded to the nearest integer.

Initial Surgical and Medical Therapy (Figure 4)
Surgery was performed on 1695 patients (97%), but the extent

of surgery was known in only 901 patients. In this group, total thyroidectomy was performed on 744 patients (86%) and lobectomy was performed on the remaining 157 (18%). Half of the patients received some form of radiation therapy.

Outcome (Figures 5 and 6)
For the entire cohort, the overall mean survival time was 30.5 years, and the mean disease-specific survival was 31.5 years. Overall mean survival was longer in female patients as compared with male patients (40 vs. 20 years, P = 0.0001). However, there were significant differences in survival in patients with tumors of different histology.

Five-, 15- and 30-year survival rates for patients with papillary thyroid cancer were, 98%, 87%, and 91%, respectively, and
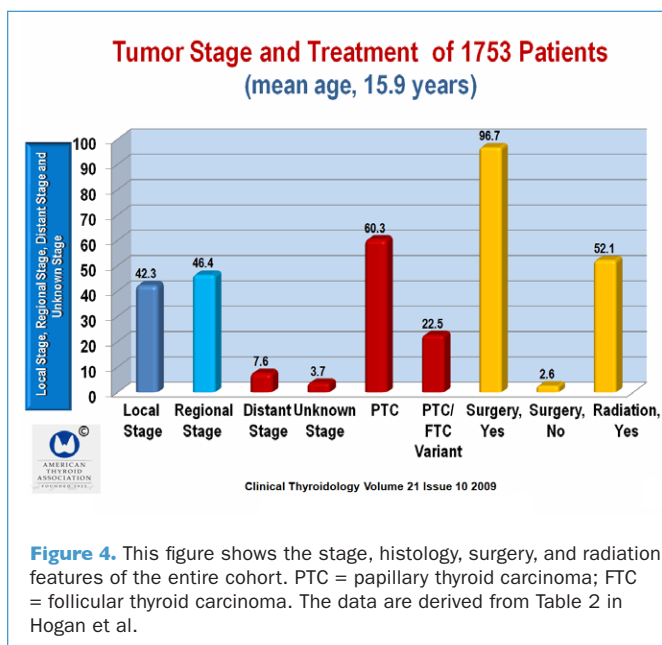

Figure 4. This figure shows the stage, histology, surgery, and radiation features of the entire cohort. PTC = papillary thyroid carcinoma; FTC = follicular thyroid carcinoma. The data are derived from Table 2 in Hogan et al.
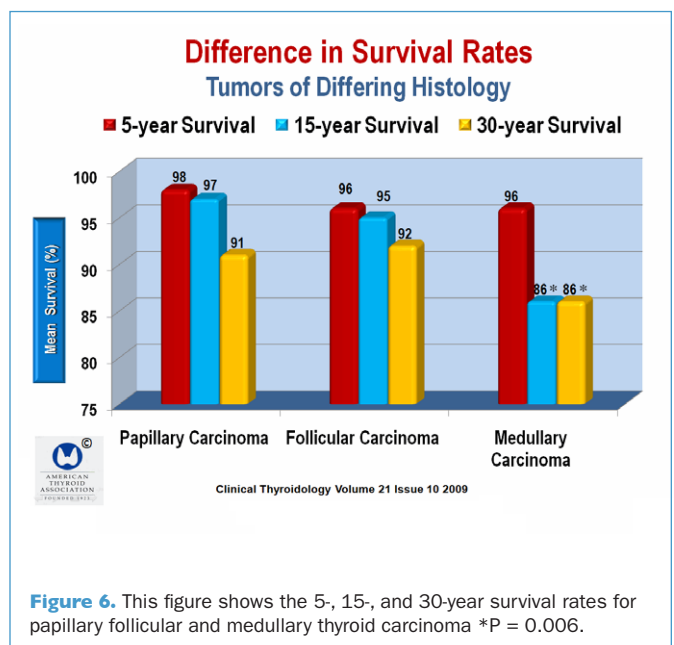

Figure 6. This figure shows the 5-, 15-, and 30-year survival rates for papillary follicular and medullary thyroid carcinoma *P = 0.006.
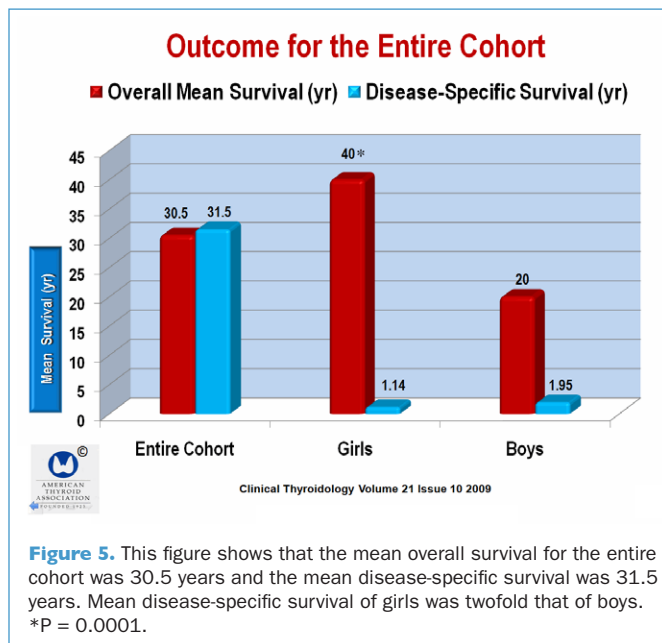

Figure 5. This figure shows that the mean overall survival for the entire cohort was 30.5 years and the mean disease-specific survival was 31.5 years. Mean disease-specific survival of girls was twofold that of boys. *P = 0.0001.
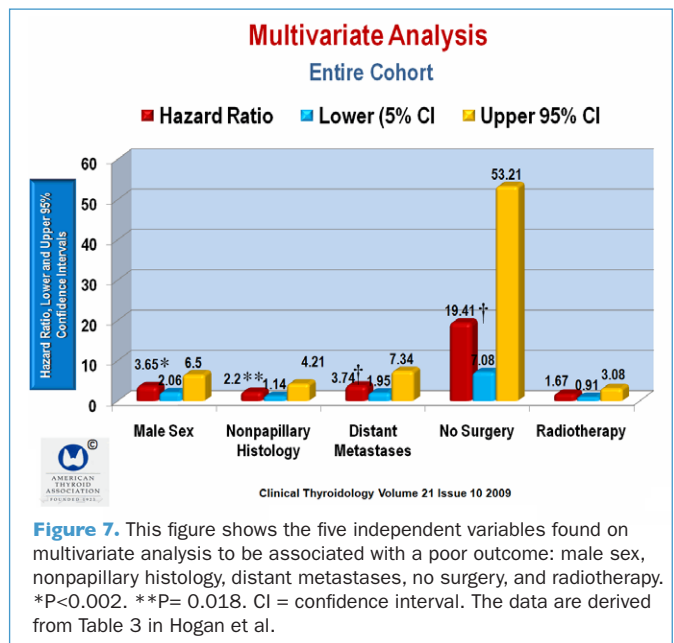

Figure 7. This figure shows the five independent variables found on multivariate analysis to be associated with a poor outcome: male sex, nonpapillary histology, distant metastases, no surgery, and radiotherapy. *P<0.002. **P= 0.018. CI = confidence interval. The data are derived from Table 3 in Hogan et al.

were similar with follicular thyroid cancer, being 96%, 95%, and 92%, but were lower in patients with medullary thyroid cancer, being 96%, 86%, and 15%, respectively. The mean survival of patients with medullary thyroid cancer was 28.3 years as compared with 30.7 years for patients with papillary thyroid cancer (P = 0.006).

Patients who had metastases at the time of initial diagnosis had significantly worse outcome as compared with patients who presented with regional disease (tumor in adjacent organs, regional lymph nodes, or both, P<0.0001).

Survival in patients who had surgery, regardless of the extent, had significantly longer survival as compared with patients who did not have surgery (P = 0.007).

Multivariate Analyses (Figure 7)

Multivariate analysis of the entire cohort revealed that the following were independent variables predicting a poor outcome—male sex: hazard ratio (HR), 3.65 (95% confidence interval [CI], 2.06 to 6.50], P<0.001; nonpapillary histology: HR, 2.20 (95% CI. 1.14 to 4.21), P = 0.018; distant metastases: HR, 3.78 (95% CI, 1.95 to 7.34), P<0.001; no surgery: HR, 19.41 (95% CI, 7.08 to 53.21), P<0.001; and radiotherapy: HR, 1.67 (95% CI, 0.91 to3.08), P not specific.

Multivariate analysis for medullary thyroid cancer found that the following were independent variables predicting a poor outcome: medullary thyroid cancer: HR, 14.82 (95% CI, 3.71 to 59.13), P<0.001; distant metastases: HR, 13.33 (95% CI, 4.24 to 41.84), P<0.001; no surgery: HR, 29.03 (95% CI, 3.09 to 242.81), P = 0.003; radiotherapy: HR, 5.79 (95% CI,) 1.44 to 23.26, P = 0.013.

CONCLUSION The incidence of thyroid cancer in children and adolescents is increasing. The incidence is higher in girls than in boys. Although papillary thyroid cancer has an excellent survival rate in the majority of patients, male sex, nonpapillary tumor, distant metastases, and nonsurgical treatment are predictors for an adverse outcome.

COMMENTARY

This is a study of 1753 patients that was performed on the latest records from the Surveillance, Epidemiology, and End Results (SEER) registry from 1973 through 2004 for all patients with thyroid cancer who were younger than 20 years of age. This is clearly one of the most important studies on pediatric thyroid cancer that has been published to date.

Although thyroid cancer is an uncommon disease in the pediatric population, the incidence of this disease in children and adolescents has been increasing since 2004, when the overall incidence of thyroid cancer was slightly more than 1 per 200,000 children and adolescents. Hogan et al. found that the annual incidence of thyroid cancer in this cohort has been increasing 1.1% per year over a 31-year period. The authors suggest that a possible explanation for this increase may be the use of radiotherapy for childhood malignancies (1). Winship and Rosvoll (2) reported that the latency period between radiation therapy and the development of thyroid cancer averaged 8.5 years. This was further substantiated by analysis of the Chernobyl accident (3). In the Hogan cohort of 1753 patients, 2.4% were treated for an earlier malignancy.

The increased incidence of differentiated thyroid cancer in women is a well-recognized phenomenon (4) that has been attributed to estrogen (5). The first to demonstrate this effect was Imai et al. (5), who found that endogenous estradiol was located in thyroid cancers more frequently in women than in men and that there was estrogen-binding activity in the cells of not only thyroid cancers, but also in normal and benign thyroid tissues. Still, the survival rates in women with differentiated thyroid cancer are considerably higher than the survival rates in men (4). In the study by Hogan et al., female patients outnumbered male patients by more than 4 to 1, and the overall mean survival times were 30.5years, 40 years for girls and 20.4 years for boys. In this study, thyroid cancers were classified as papillary in 60%, follicular variant papillary in 23%, follicular in 10%, and medullary in 5%, a distribution of tumors that closely follows the pattern in adults (6). Patients with medullary thyroid cancer had significantly shorter mean survival than those with papillary cancer (P = 0.006). Of great importance, surgical treatment significantly improved outcome. Multivariate analysis found that the following four variables were independent factors that portended a worse outcome: male sex, nonpapillary histology, distant metastases, and no surgery.

The authors conclude that the incidence of pediatric thyroid cancer is increasing and that girls have a higher incidence of thyroid cancer than boys, but had a more favorable outcome than did boys. The scope of this analysis is wide and the depth of the conclusions is deep and will help physicians manage this disease in children and adolescents.

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Recurrence of papillary or follicular thyroid cancer during the first year after initial surgery has a worse prognosis than occurs with later recurrence

SUMMARY

BACKGROUND Recurrence of papillary and follicular thyroid cancer is a common problem that has been extensively studied. However, data concerning the timing of recurrence are relatively sparse and may be related to the long-term outcome of patients with recurrent tumors. This study was based on the hypothesis that an early recurrence of papillary or follicular thyroid cancer is associated with the response to therapy and, ultimately, to long-term outcome.

METHODS This is a retrospective study of 2148 patients, 1910 with papillary thyroid cancer and 238 with follicular thyroid cancer treated from 1977 through 2006 at the Chang Gung Memorial Hospital in Linkou, Taiwan. Tumors were staged according to the TNM (tumor–node–metastases) criteria (6th edition) and were categorized according to the Clinical Class criteria. All patients were treated postoperatively with thyroid hormone replacement or suppressive therapy. During follow-up, patients were evaluated with whole-body ^{131}I scans (DxWBS), and chest x-ray examinations, and every 6 to 12 months had measurements of serum thyroglobulin (Tg) concentrations. Patients in whom tumor recurrence was suspected had neck ultrasonography with fine-needle aspiration biopsy (FNAB), computed tomography (CT) scans, and ^{18}F-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG–PET) scans. Recurrences were stratified according to a cytologically or histologically diagnosed tumor (group A), a ^{131}I-diagnosed tumor (group B), or other imaging study (group C). The patients were further classified into an early or late recurrence group. The early group was defined as patients with tumor tissue that persisted after surgery or other adjuvant therapy, including distant metastases detected by a DxWBS within 1 year after thyroid surgery. The late recurrence group comprised patients with cancer recurring more than 1 year after initial thyroid surgery and ^{131}I ablation therapy. At the end of the study period, lack of tumor relapse was defined as a negative ^{131}I DxWBS and no local or distant metastases identifiable by a noninvasive examination.

RESULTS

Clinical Features of 2148 Patients with Papillary and Follicular Thyroid Carcinoma (Figures 1 and 2)

Of the 2148 patients, those with follicular cancer were older than patients with papillary cancer, but there was no sex difference between the two groups. Tumor was confined to the thyroid in 1390 of the 2148 patients (65%) with papillary or follicular thyroid cancer. The mean (±SD) tumor size was 2.6±0.04 cm for papillary and follicular tumors combined, 2.40±0.04 cm for papillary cancer, and 4.10±0.20 cm for follicular cancer (P<0.001). Cancer-specific mortality was higher with follicular cancer as compared with papillary thyroid cancer (19% vs. 4%). The clinical features of 2148 patients are shown in Figures 1 and 2. Over half the diagnoses (173 of 325; 53%) were confirmed by cytology or surgical histology, most of which were confirmed by locoregional neck surgery. Here and elsewhere, percentages are rounded to an integer.
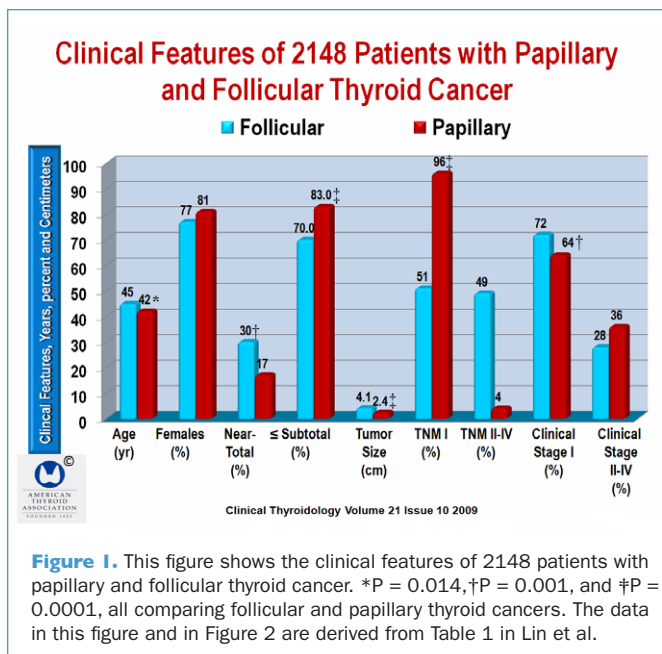

Figure 1. This figure shows the clinical features of 2148 patients with papillary and follicular thyroid cancer. *P = 0.014, †P = 0.001, and ‡P = 0.0001, all comparing follicular and papillary thyroid cancers. The data in this figure and in Figure 2 are derived from Table 1 in Lin et al.
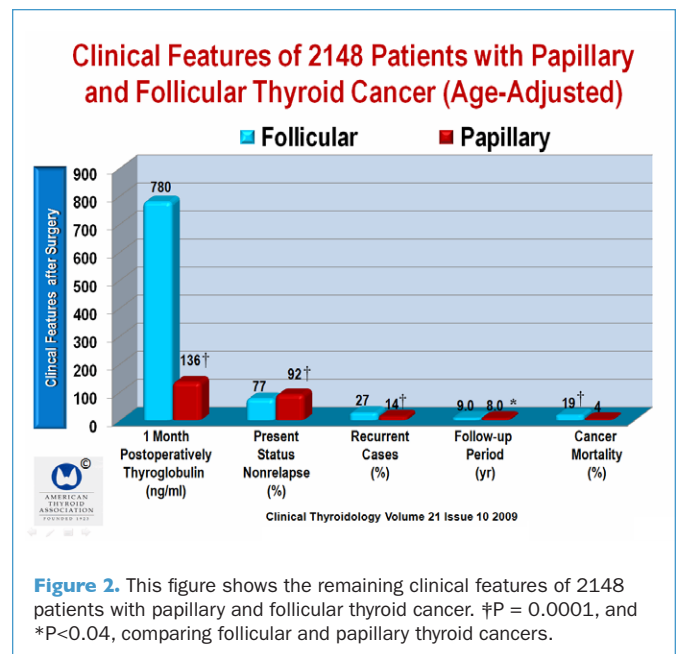

Figure 2. This figure shows the remaining clinical features of 2148 patients with papillary and follicular thyroid cancer. ‡P = 0.0001, and *P<0.04, comparing follicular and papillary thyroid cancers.

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Outcome with Early and Late Recurrence (Figures 3 to 5)
The mean time between the first thyroid surgery and detection of early recurrent cases was 55.0±0.4 years, as compared with 11.5 years in the group with late metastases. The early recurrence group as compared with the late recurrence was characterized by older age (51 vs. 44 yr), more males (40 vs. 28%), higher postoperative Tg value (2115 vs. 153 ng/ml), higher TNM stage (77 vs. 53%), more lymph-node and soft-tissue invasion (28 vs. 35%) , and higher cancer mortality rates (40 vs. 22%) for early versus late recurrences.

Postoperative tumor recurrence was found in 352 of the 2148 cases (15%) of follicular and papillary thyroid carcinoma after a mean follow-up of 9.0±0.4 and 8.1±0.1 years, respectively.

Among the 352 patients with recurrence, 185 were in the early recurrence group (57%) and 140 were in the late recurrence group (43%). In the early recurrence group, 145 of 185 patients (78%) had distant metastases and 72 of 185 had local metastases (39%), whereas in the late recurrence group, 74 of 140 had distant metastases (53%) and 92 of 140 had local metastases (66%). In the early recurrence group, cancer death occurred in 6 of 40 patients with local metastases (15%) and 54 of 113 with distant metastases (48%). However, in the late recurrence group, 8 of 66 patients with local metastases died of disease (12%) and 23 of 74 died of distant metastases (31%).

Of the 325 patients with recurrence, 125 (38%)have survived without relapse. However, after a mean follow-up of 8.7±0.01
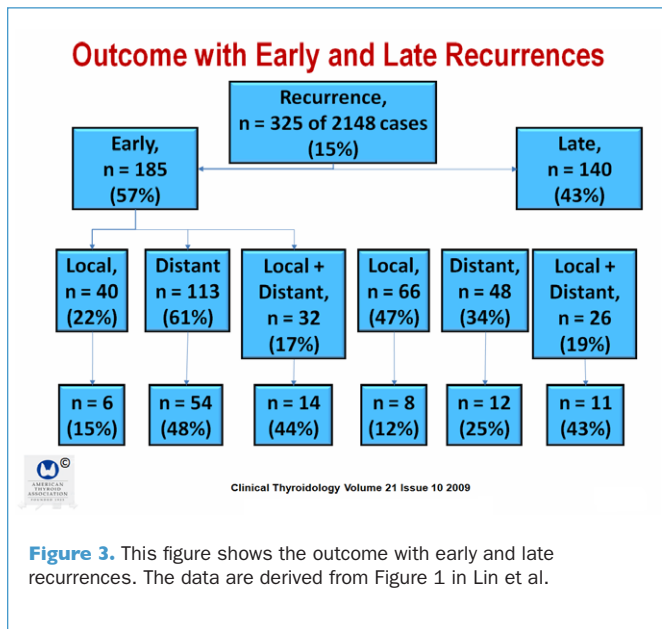
Figure 3. This figure shows the outcome with early and late recurrences. The data are derived from Figure 1 in Lin et al.
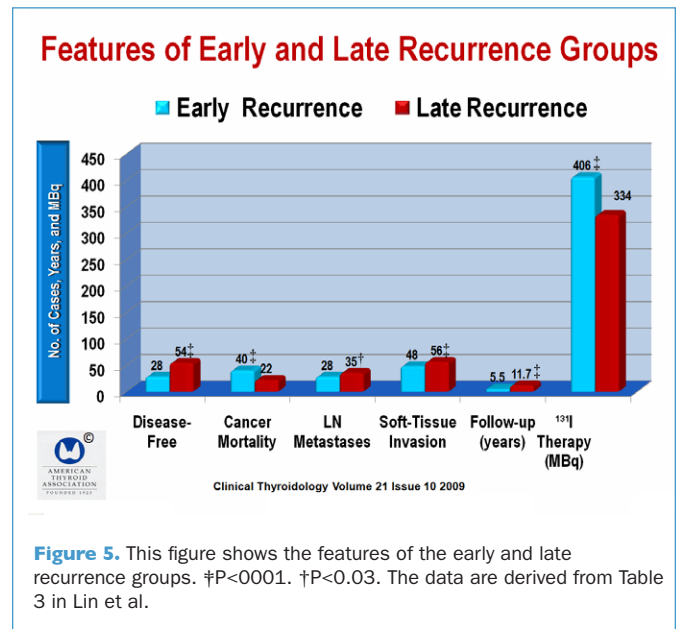
Figure 5. This figure shows the features of the early and late recurrence groups. ‡P<0001. †P<0.03. The data are derived from Table 3 in Lin et al.
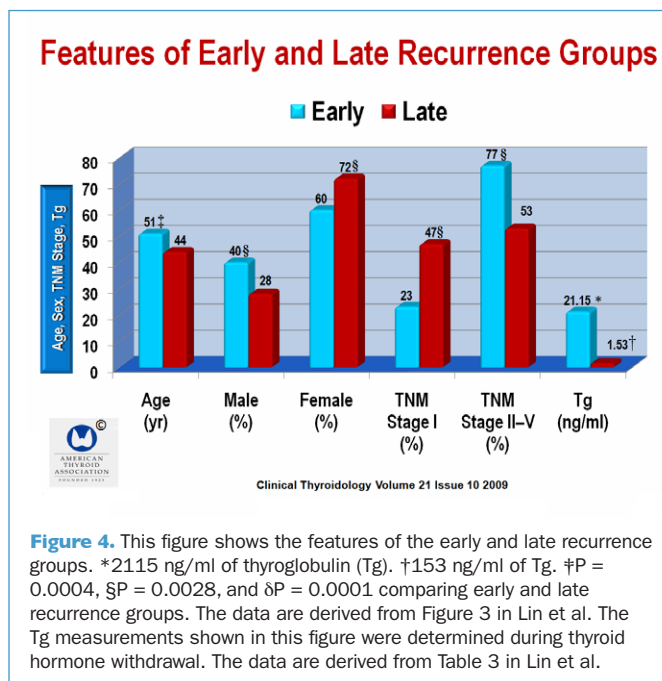

Figure 4. This figure shows the features of the early and late recurrence groups. *2115 ng/ml of thyroglobulin (Tg). †153 ng/ml of Tg. ‡P = 0.0004, §P = 0.0028, and δP = 0.0001 comparing early and late recurrence groups. The data are derived from Figure 3 in Lin et al. The Tg measurements shown in this figure were determined during thyroid hormone withdrawal. The data are derived from Table 3 in Lin et al.
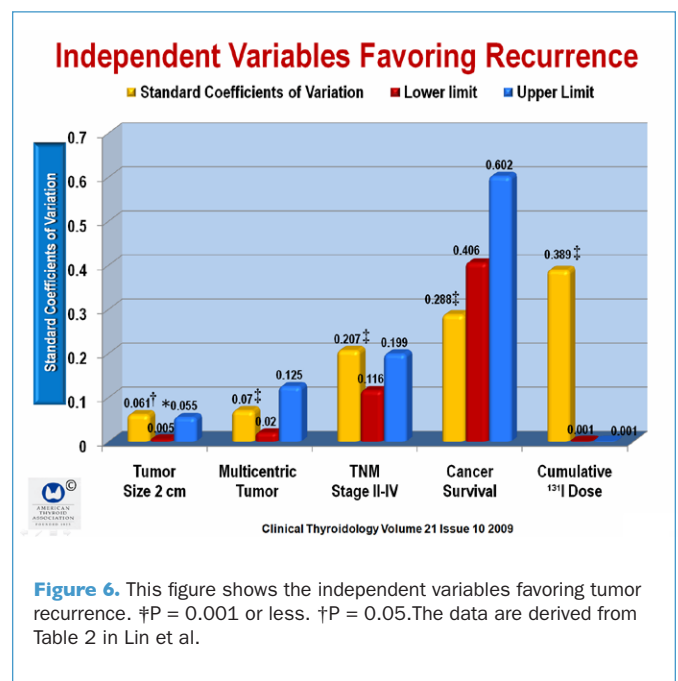

Figure 6. This figure shows the independent variables favoring tumor recurrence. ‡P = 0.001 or less. †P = 0.05.The data are derived from Table 2 in Lin et al.

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years, 105 of the patients with recurrence died of disease (32%). Survival rates were significantly better with papillary cancer than with follicular cancer, with 5-, 10- and 20-year survival rates of 66%, 53%, and 35%, respectively, for the early recurrence group and 94.1%, 85.1%, and 60.2% for the late recurrence group. The survival rates with papillary and follicular cancer were greater in the late recurrence group than in the early recurrence group. Cancer-specific mortality was characterized by older age, male sex, larger tumor size, less aggressive surgery, and more treatment with external-beam radiotherapy. Cumulative ^{131}I was not significantly different in the two groups.

Independent Variables Favoring Recurrence (Figure 6)
Multiple-regression analysis identified the following five independent factors that portended recurrence: tumor size (2 cm), tumor multifocality, TNM stage, survival, and the amount of cumulative postoperative ^{131}I.

CONCLUSION Recurrent papillary and follicular thyroid cancers are associated with high mortality rates and are difficult to eradicate. Recurrent cancer detected during the first year after initial surgery has a worse prognosis than that with late recurrences.

COMMENTARY

Unlike the initial management of papillary and follicular thyroid cancer, the treatment of tumor recurrence is less consistent. This is especially important, since recurrence rates for these tumors may be as high as 50%, and the response rates to therapy depend on multiple variables, such as the location of persistent tumor, the patient's age, and multiple factors including the response to initial therapy and the biologic characteristics of the tumor. Thus, reliable prognostic factors are seriously needed to manage differentiated thyroid cancer tumor recurrences and to devise robust treatment and follow-up schemes for patients with persistent or recurrent disease. Several studies provide insight into this problem. The 10-year survival rates of differentiated thyroid cancer range from 80 to 95% (1). Because age at the time of diagnosis varies widely, survival rates depend heavily on age at the time of diagnosis. In addition, tumor size is a well-recognized factor influencing the rate of tumor recurrence. However, Lin et al. found that patients with small primary tumors (≤2 cm) who do not have extrathyroidal invasion or a history of radiation or a family history of thyroid cancer are at very low risk for recurrence. Nevertheless, there is a small risk for recurrence.

For example, a study of 52,173 patients with papillary thyroid cancer, by Bilimoria et al. (2) found that the effect of tumor size on recurrent papillary thyroid cancer was dramatic. The mean 10-year recurrence rate was almost 5% for primary tumors <1 cm, 7% for tumors 1 to 1.9 cm, and almost 9% for tumors 2 to 3 cm, ranging up to nearly 25% in patients with primary tumors >8 cm.

Leboulleux et al. (3) performed a study aimed at evaluating the prognostic impact of lymph-node metastases and tumor extension beyond the thyroid capsule. The study subjects were 148 consecutive patients with papillary thyroid cancer who had lymph-node metastases with or without extrathyroidal tumor extension. All were initially treated with total thyroidectomy and central and ipsilateral lymph-node dissection followed by ^{131}I ablation. Uptake of ^{131}I outside the thyroid bed was found on the postablation whole-body scan (RxWBS) in 22% of the patients. After a mean follow-up of 8 years, 8 patients (7%) with a normal RxWBS experienced tumor recurrence. The 10-year disease-specific survival rate was 99% (95% confidence interval [CI], 97 to 100). The significant risk factors for persistent disease included the number of lymph-node metastases (>10) and lymph node metastases with extracapsular extension, tumor size >4 cm, and lymph-node metastases in the central neck. The significant risk factors for recurrent disease were the number of lymph-node metastases (>10) and lymph-node metastases with extracapsular tumor extension, and a high Tg level on levothyroxine withdrawal 6 to 12 months after initial treatment.

Lin et al. found that survival rates were significantly better with papillary cancer than follicular cancer, and that survival rates were higher in the late recurrence group than in the early recurrence group. Cancer-specific mortality was characterized by older age, male sex, larger tumor size, less aggressive initial surgery, and more treatment with external-beam radiotherapy. However, cumulative ^{131}I was not significantly different in the two groups. Still, multiple-regression analysis identified survival, 2-cm tumor size, TNM stage, tumor multifocality, and the amount of cumulative postoperative ^{131}I to be independent risk factors influencing recurrence rates.

in a study of 203 patients with papillary microcarcinoma, Chow et al. (4) found that the lymph-node recurrence rate increased 6.2-fold when there were lymph-node metastases at presentation (95% CI, 1.3 to 23.4), which increased 5.6-fold when there were lymph-node metastases and multifocal tumor in the thyroidectomy specimen (95% CI, 1.3 to 23.5; P = 0.02). In addition, ^{131}I ablation reduced the relative risk for lymph-node recurrence to 0.27 (95% CI, 1.30 to 100.00; P = 0.03). Radioiodine ablation reduced the relative risk for lymph-node recurrence to 0.27 (95% CI, 0.08 to 093; P = 0.04). The incidence of lymph-node metastases increased with the presence of multifocal disease in the primary thyroid tumors (34% vs. 20%; P = 0.034).

Another study, by Baudin et al. (4), found that multivariate analysis showed that two parameters significantly influenced papillary microcarcinoma recurrence—namely, the number of histologic foci (P<0.002) and the extent of initial thyroid surgery (P<0.01). Only 3.3% of patients with unifocal multifocal papillary microcarcinoma treated with loboisthmusectomy had tumor recurrence.

A unique study by Links et al. (6) analyzed the risk factors for survival, including the effects of therapy, after adjusting for the baseline mortality rate in the general population to elucidate the adverse effects of treatment on life expectancy. In this study, the initial treatment of 504 patients consisted of thyroidectomy and ^{131}I ablation, and high-dose ^{131}I treatments for patients with residual tumor. Patients who were in complete remission underwent

an annual physical examination and Tg measurements during thyrotropin suppression. Survival time was adjusted to standardized survival rates to account for the baseline mortality rate in the general population. After a median follow-up of 9 years, the 10-year overall survival rate was 83% and the disease-specific survival rate was 91%, and persistent disease was found in 75 patients (15%). Links et al. found that treatment including radioiodine is safe but unsuccessful in 20% of the patients. Moreover, age was not found to be a disease-specific risk factor. The authors thus suggested that age should not be used as an independent factor in treatment algorithms. Univariate analysis found that T4N1M1 status and Hürthle-cell tumors were harbingers of persistent and recurrent disease, and multivariate analysis found that age alone was not predictive of recurrent disease. Clearly, the two most important findings in the Links study were that patients who were disease-free with thyroid cancer had a normal life span, whereas patients with persistent disease had a life expectancy that ranged widely, with a median survival that was reduced to 60%, and the second important finding was that, patient age was not an independent factor predictive of disease recurrence.

The study by Lin et al. adds an important prognostic facet to the management of tumor recurrence for patients with papillary or follicular thyroid cancer—prognosis is considerably worse when recurrence is found during the first year after initial surgery, whereas late tumor recurrence generally has a more favorable prognosis.

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Patients with papillary thyroid microcarcinoma may have a reduced risk for recurrence when treated with total or near-total thyroidectomy

Ross DS, Litofsky D, Ain KB, Bigos T, Brierley JD, Cooper DS, Haugen BR, Jonklaas J, Ladenson PW, Magner J, Robbins J, Skarulis MC, Steward DL, Maxon HR, Sherman SI. Recurrence after treatment of micropapillary thyroid cancer. Thyroid 2009;19:1043-8.

SUMMARY

BACKGROUND The initial treatment of papillary thyroid microcarcinoma (PTMC) is controversial, mainly because of the low mortality and recurrence rates of tumors ≤1 cm. There is even controversy concerning the definition of PTMC. The World Health Organization describes PTMC as a tumor ≤1 cm in diameter that is found incidentally, whereas the TNM (tumor–node–metastases) system simply classifies PTMC as a tumor ≤1 cm. The main clinical problem with these tumors is recurrence, which may be found years after the initial tumor has been treated. This is a study by the National Thyroid Cancer Treatment Cooperative Study Group. The aim of the study was to analyze recurrence in a set of patients with PTMC with or without multifocal tumor or lymph-node metastases.

METHODS This is a retrospective study of a group of nonrandomized patients who were enrolled in the National Thyroid Cancer Treatment Cooperative Study Group, which established a tumor registry in 1987 and has subsequently obtained follow-up data on this group of patients. Approximately 4830 patients were registered from January 1987 through July 2006. Treatment was solely at the discretion of the attending physicians. Initial therapy was surgery, with or without ^{131}I administration, within 6 months after the time of surgery. There were no uniform protocols for initial therapy and follow-up among the 11 North American centers contributing to the registry. At entry, disease stage was classified by the individual clinicians at each center using a previously described staging system. Patient status was based on imaging studies and serum thyroglobulin (Tg) measurement as: (1) no residual disease, (2) biochemical evidence of disease only, or (3) residual disease with documentation of the disease sites. In the present study, death was not considered to be an event for analysis of recurrence-free survival.

RESULTS

Demographics of the Study Group (Figures 1 to 3)

A total of 3923 of the 4830 study patients had papillary thyroid cancer (81%), including all variants of the tumor. Of the 3923 patients, 710 (18%) had PTMC. Excluded from the study were 12 patients with missing data, 27 with gross extrathyroidal invasion of tumor, 9 with distant metastases and another with both gross extrathyroidal invasion and distant metastases. Here and elsewhere percentages are rounded to an integer. The final study group thus comprised 611 patients with intrathyroidal PTMC, all of whom were considered to be free of disease at the time of the
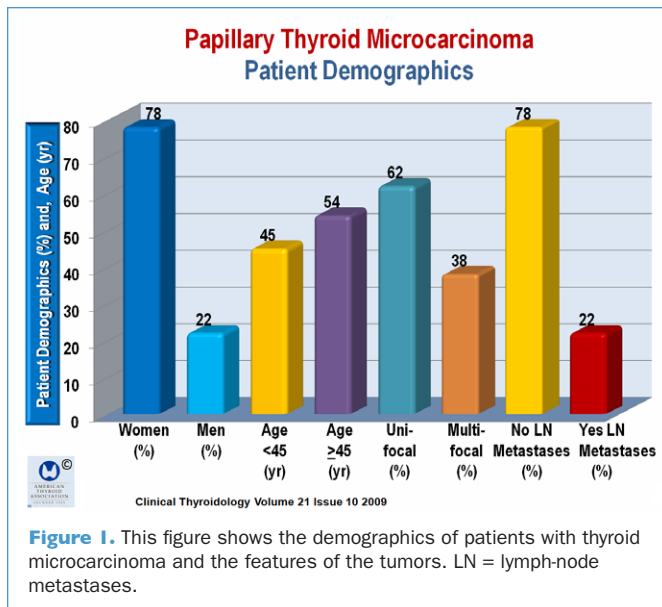

Figure 1. This figure shows the demographics of patients with thyroid microcarcinoma and the features of the tumors. LN = lymph-node metastases.
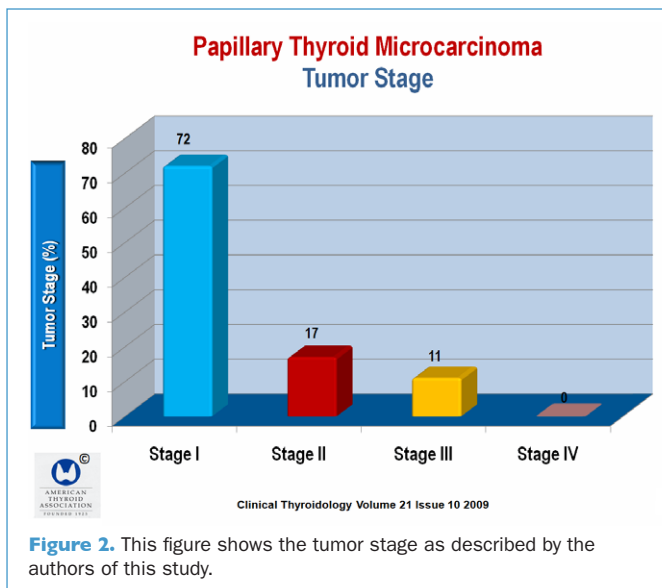

Figure 2. This figure shows the tumor stage as described by the authors of this study.
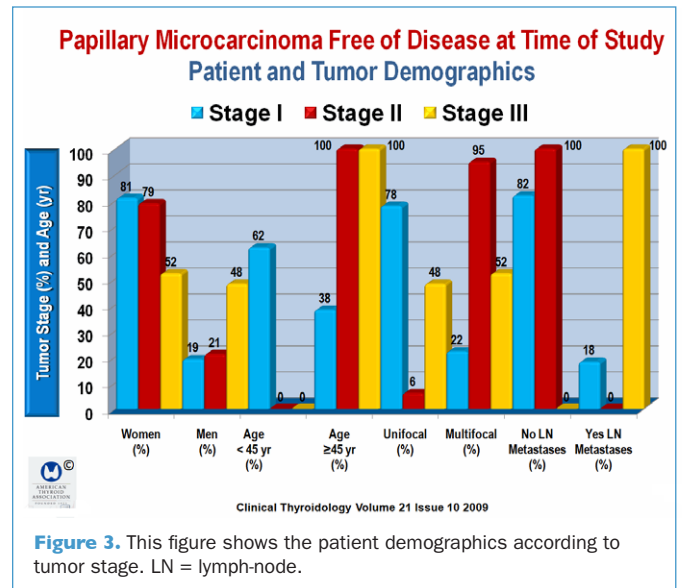

Figure 3. This figure shows the patient demographics according to tumor stage. LN = lymph-node.

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study. Of the 611 patients, 477 were women (78%) and 133 were men (22%); the mean age was <45 years in 276 patients (45%) and ≥45 years in 332 (54%). PTMC was unifocal in 381 patients (62%) and multifocal in 230 (38%). Lymph-node metastases were present in 135 patients (22%) and absent in 476 (78%) (Figure 1). Tumor was stage I in 72% of patients, stage II in 17%, and stage III in 11% (Figure 2). The age, sex, extent of unifocal and multifocal tumors, and lymph-node metastases are shown in Figure 3.

Tumor Recurrence (Figure 4)

After a mean follow-up of 4 years (median, 3), 38 patients (6%) had tumor recurrence. The overall mean (±SD) time to recurrence was 2.8±2.4 years (range, 0.5 to 10.9). Patients who were treated with ^{131}I had a shorter time to recurrence (2.3±2.2 years). The sites of recurrence were known in 34 of 38 patients (89%). Recurrences were found in the thyroid bed in 17 (2.8%) patients ,in regional lymph nodes with or without thyroid

bed recurrences in 14 (2.3%), in mediastinal lymph nodes in 2 (0.3%), and in distant sites in 1 (0.2%) and were not recorded in 4 (0.6%.) There was no significant difference in recurrence rates among patients with unifocal and multifocal tumors.

The Effects of [131]I Therapy and the Extent of Surgery on Outcome (Figures 5 and 6)

A series of univariate analyses are shown in Figures 5 and 6. Patients with lymph-node metastases had higher recurrence rates as compared with patients without lymph-node metastases whether they were treated with total or near-total thyroidectomy (15% vs. 3%; P<0.001) or [131]I (22% vs. 5%; P = 0.003). Among patients who did not have nodal metastases, ^{131}I therapy was associated with an increased rate of recurrence, although the difference was not statistically significant.

Patients with multifocal tumors treated with less than near-total thyroidectomy had higher recurrence rates than those with unifocal tumors (18% vs. 4%; P<0.01). Although recurrence rates were lower in patients with unifocal or multifocal tumors treated with total or near-total thyroidectomy as compared with less than near-total thyroidectomy (6% vs. 18%), the difference was not statistically significant (P= 0.06). There was no statistical difference in recurrence rates in patients with multifocal tumors who were treated with ^{131}I as compared with patients who were not treated with [131]I.

Among patients not treated with ^{131}I, the recurrence rates were higher in patients with multifocal tumors (7%) as compared with patients with unifocal tumors (2%; P<0.02). Still, there were no statistically significant differences whether or not patients were treated with [131]I.

CONCLUSION Patients with multifocal tumors treated with less than near-total thyroidectomy may have higher recurrence rates than those with unifocal tumors. Although recurrence rates are lower in patients with unifocal or multifocal tumors treated with total or near-total thyroidectomy, the difference is not statistically significant.
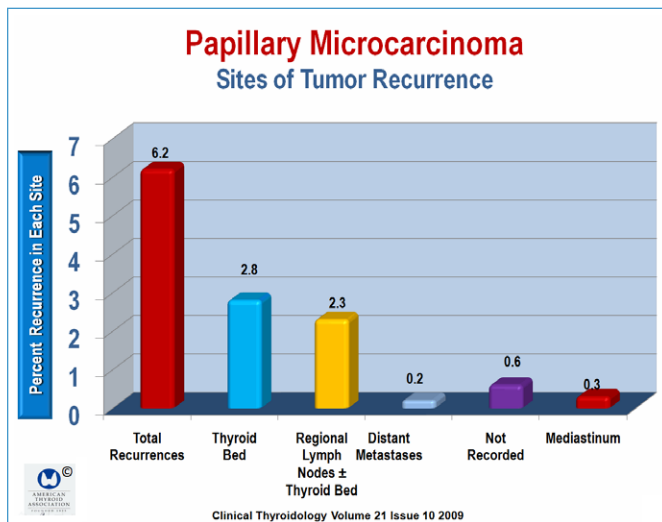

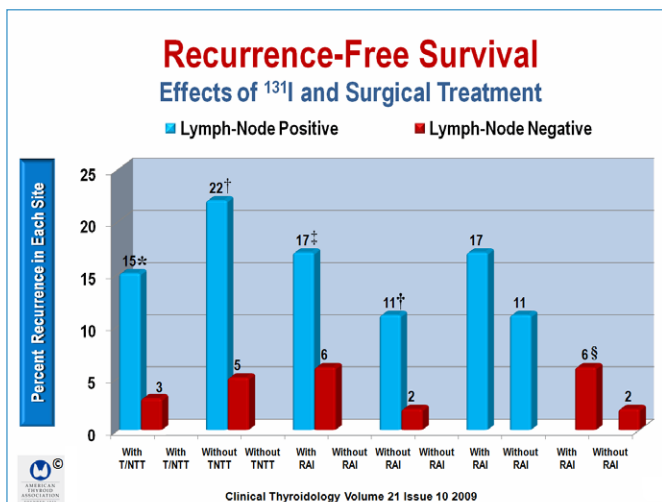**Figure 4.** This figure shows the sites of tumor recurrence for microcarcinomas.

Figure 5. This figure shows some of the effects of ^{131}I therapy and surgical treatment of microcarcinomas in patients with and those without lymph-node metastases. *P<0.0001, †P, 0.003, ‡P<0.006, §P = 0.05, all comparing node-positive patients with node-negative patients.
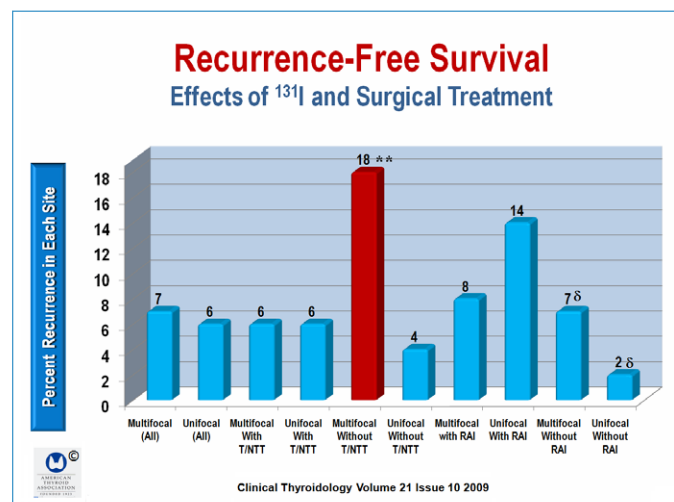

Figure 6. This figure shows some of the univariate analyses among various combinations of therapy. **P = 0.01, comparing unifocal and multifocal tumors with and without [131]I. δP = 0.02, comparing multifocal tumors without ^{131}I and unifocal tumors without ^{131}I therapy. T/NTT = total/near-total thyroidectomy; RAI = [131]I therapy.

COMMENTARY

This interesting study was designed to analyze recurrence rates in patients with multifocal PTMCs and to assess the efficacy of therapy. The study comprised 611 patients with a mean follow-up of 4 years (median 3). Perhaps the most important finding was that patients with PTMC associated with lymph-node metastases had more recurrences than did patients without them, regardless of the extent of surgery or the use of radioiodine. Moreover, the study found that overall recurrence rates did not differ between unifocal and multifocal tumors. Still, patients with multifocal tumors treated with less than near-total thyroidectomy had significantly higher recurrence rates than did patients with unifocal tumors. Although patients with multifocal tumors treated with total or near-total thyroidectomy had fewer recurrences than did patients with unifocal tumors, the differences were marginal and not statistically significant. These findings are at odds with several large studies.

At odds with the findings by Ross et al. is a study by Bilimoria et al. (1) that is arguably the most authoritative analysis on outcome following surgical therapy for papillary thyroid cancer, which analyzed 52,163 patients with papillary thyroid cancer. Of this group, 12,469 patients had PTMC (24%). Total thyroidectomy was performed in 8775 patients (20%), and lobectomy was performed in 3686 (42%) with PTMC. For PTMC <1 cm, the extent of surgery did not impact recurrence or survival, whereas for tumors ≥1 cm, lobectomy resulted in a higher risk of recurrence and death. The study found a 10-year recurrence rate of 5% and a 10-year mortality rate of 2% for patients with PTMC. Largely on the basis of this study, the ATA guidelines suggest lobectomy for PTMCs.

A study by Chow et al. (2) of 203 patients with PTMC found after a follow-up of 8.4 years that multifocal tumor was correlated with lymph-node metastases at the time of presentation. When lymph-node metastases and multifocal disease were present at the time of diagnosis, ^{131}I ablation reduced the lymph-node recurrence rate to 0.27 (P = 0.04). Moreover, in the presence of lymph-node metastases, the rate of distant metastases increased 11.2-fold (P = 0.03). Despite the overall excellent prognosis for patients with PTMC, the authors reported a 1% disease-related rate of mortality and a 5% rate of lymph-node recurrence. Multivariate analysis found no statistically significant difference in outcome between total or near-total thyroidectomy as compared with outcome in patients treated with thyroid lobectomy.

A study by Baudin et al. (3) of 281 patients with PTMC found after a median follow-up of 7.3 years that multifocal tumors had a 20% recurrence rate, as compared with only 2 recurrences(3%) among 60 patients with unifocal PTMC. Multivariate analysis showed two parameters significantly influenced the outcome of PTMC recurrence: the number of histologic foci (P<0.002) and the extent of initial thyroid surgery (P<0.01). The authors concluded that the recurrence rate for PTMC appears to be low (4%) and that lobectomy is the treatment of choice for patients with TMC when only one tumor focus is found, and total thyroidectomy is the optimal treatment for patients with multiple tumor foci.

Ross et al. indicate that their study has are several significant limitations, including the small number of patients. Because of the small number of study subjects, they were unable to analyze groups based on age, and differences among groups were not significant in multivariate analysis. The latter is particularly important, given the several univariate analyses that showed significant differences. The fact that a multivariate analysis found no variables of significance leaves uncertainty about which of the findings represent independent variables that influence outcome.

For now —and based upon the studies of Bilimoria, Chow and Baudin—the most reliable recommendation for therapy for papillary thyroid microcarcinomas seems to be that lobectomy is a the best option for unifocal tumors and total thyroidectomy is best for multifocal tumors, and small amounts of ^{131}I in the range of 30 mCi should be considered when lymph-node metastases are present.

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DISCLOSURE

Dr. Mazzaferri receives honorari from Genzyme for providing lectures.

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

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