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VOLUME 21 • ISSUE 11 NOVEMBER 2009

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EDITORS' COMMENTS

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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.

Ernest L. Mazzaferri, MD, MACP
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Objective responses to motesanib are low in patients with medullary thyroid carcinoma, but the disease becomes stable in most patients while receiving the drug

Schlumberger MJ, Elisei R, Bastholt L, Wirth LJ, Martins RG, Locati LD, Jarzab B, Pacini F, Daumerie C, Droz JP, Eschenberg MJ, Sun YN, Juan T, Stepan DE, and Sherman SI. Phasell Study of Safety and Efficacy of Motesanib in Patients with Progressive or Symptomatic, Advanced or Metastatic Medullary Thyroid Cancer. J Clin Oncol 2009; 27:3794-3801.

SUMMARY

BACKGROUND

The current treatment for medullary thyroid carcinoma (MTC) includes total thyroidectomy with removal of involved metastatic lymph nodes. External beam radiotherapy may also be employed in conjunction with surgery for locoregional disease control. Patients with distant metastases, however, present a challenge to physicians because standard chemotherapeutic regimens are largely ineffective for controlling disease progression. The introduction of targeted molecular therapies aimed at various steps in the oncogenic pathway has renewed hope for the discovery of an agent with the potential to control advanced or progressive MTC. Motesanib, an inhibitor of vascular endothelial growth factor receptors (VEGFR 1-3), platelet derived growth factor (PDGF), and Kit, has been shown to inhibit wild type RET in vitro and induced a partial response in one MTC patient during a phase I trial. The current study seeks to examine the efficacy and tolerability of motesanib in patients with progressive or symptomatic, locally advanced or metastatic MTC.

METHODS

This was an international phase II open-label, single-arm trial, the primary endpoint of which was an objective response by Response Evaluation Criteria in Solid Tumors (RECIST). Additional parameters evaluated were the duration of response, progression-free survival, tumor-related symptoms, and time to response, overall survival time, changes in tumor markers, pharmacokinetics, and safety. Patients were given motesanib 125mg orally once daily until disease progression or unacceptable toxicity occurred. Subjects eligible for the study were adults with locally advanced or metastatic MTC with either disease progression in the 6 months prior to study entry or with symptomatic disease such as MTC-related diarrhea with or without flushing. Also, patients were required to have at least one measurable lesion per RECIST and tumor not amenable to surgery, external beam radiation, or other local therapies. Disease progression was based on radiographic images utilizing RECIST. Excluded from the study were patients with Eastern Cooperative Oncology Group (ECOG) performance scores ≥2, inadequate renal, hepatic, or cardiac function, or previous treatment with motesanib, or with RET or VEGF inhibitors. Patients were given motesanib 125mg orally once daily for up to 48 weeks, or until disease progression or unacceptable toxicity occurs.

Imaging with CT or MR was performed every 8 weeks and when disease progression was suspected. Blood samples were collected from 10 patients after 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours after the first dose of motesanib. Trough levels were also checked in all patients before their scheduled dose every 4 weeks. Serum calcitonin and CEA levels were followed at baseline and every 4 weeks. Tumor-related symptoms were monitored by administration of a questionnaire at baseline and every 8 weeks.

RESULTS

Ninety-one patients received at least one dose of motesanib, most of whom had sporadic MTC (84%). The median baseline calcitonin was 22,489ng/L and the CEA was 114µg/L. Motesanib was discontinued early in 54 patients before study completion because of disease progression in 30, adverse events in 13, death in 3, and for various other reasons in 8 patients. The median treatment duration was 38 weeks.

Responses to motesanib (Figure 1)

A confirmed partial response (PR) was seen in 2 patients according to RECIST; there were no complete responses seen. The majority of patients (n=74, 81%) had stable disease (SD), 44 of whom had durable SD ≥ 24 weeks (48%). A decrease in target lesion measurement from baseline was seen in 69 (76%) patients. Median progression-free survival was 48 weeks; overall survival at 12 months was 75%. Twenty-four patients died during the study period. An extension study was created for 34 patients who completed the 48-week therapy protocol.

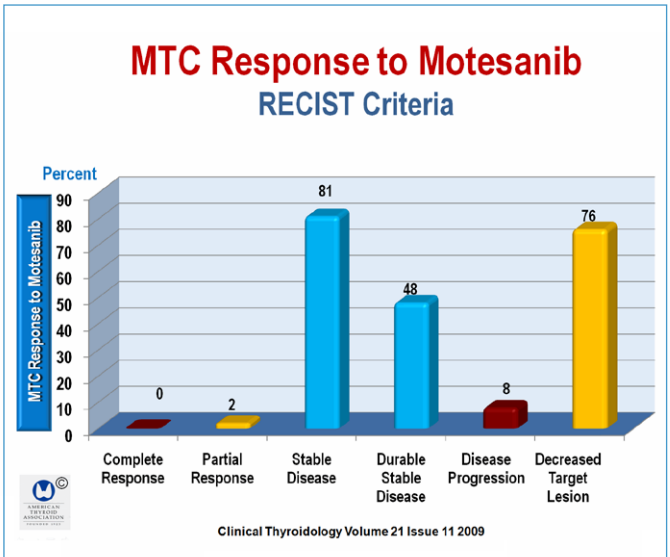

Figure 1. This figure shows the response to motesanib in patients with medullary thyroid carcinoma. RECIST = Response Evaluation Criteria in Solid Tumors. Disease Progression in 8% is the best response in this group. A decrease in target lesion measurement from baseline was seen in 69 (76%) patients. Figure derived from data in Table 2 of Schlumberger et al.

A total of 78 patients had a baseline and at least one post-baseline assessment of tumor related-symptoms. Of this group, 55 reported diarrhea at baseline. By week 16, the mean rate (±SE) of diarrhea frequency decreased significantly to (4.1±0.5 episodes/d) as compared with the number of baseline of (5.2±0.4 episodes/d; P = 004). Still, by week 48, this group reported (5.1±0.7) episodes/d; P = 0.5) or any other times between weeks 16 through 48. Among the 18 patients without self-reported diarrhea at baseline, the frequency of diarrhea increased from 0 at baseline to 1 to 3 episodes/d at week 24, and increased significantly by week 32 to (5.4±7 episodes/d; P = 0.02), and stayed elevated at 1 to 3 episodes/d for the remainder of the study.

Adverse events to motesanib (Figures 2 to 4)

The majority of patients (88%) had at least one motesanib-related adverse event. The most commonly encountered were diarrhea (41%), fatigue (41%), hypertension (27%), anorexia (27%), and nausea (26%). There were 35 grade 3 events and 3 patients experienced a grade 4 adverse event. Of particular note, acute gallbladder toxicity was seen in 8 patients, which included 3 with cholecystitis, 3 with cholelithiasis, and 1 with gallbladder enlargement. In addition, elevated TSH levels were found in 37 patients (41%).

Pharmacokinetics

The pharmacokinetics revealed motesanib was rapidly absorbed.

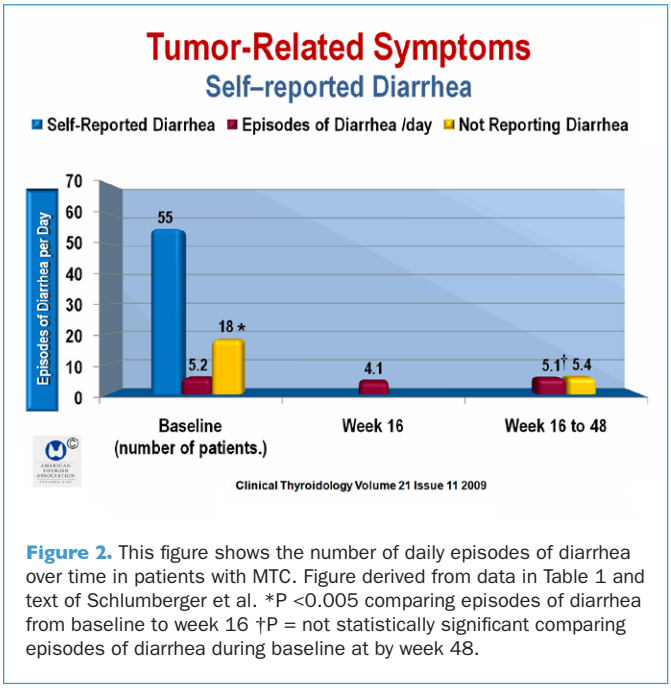

Figure 2. This figure shows the number of daily episodes of diarrhea over time in patients with MTC. Figure derived from data in Table 1 and text of Schlumberger et al. *P <0.005 comparing episodes of diarrhea from baseline to week 16 †P = not statistically significant comparing episodes of diarrhea during baseline at by week 48.

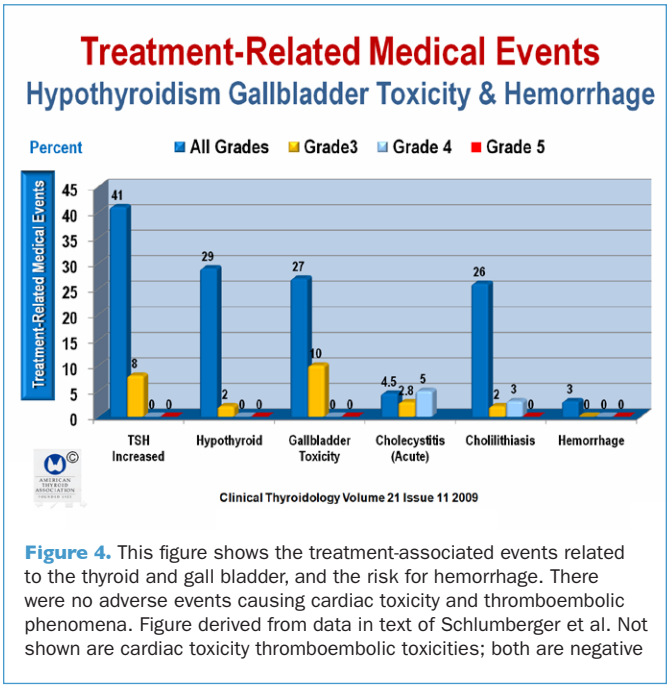

Figure 4. This figure shows the treatment-associated events related to the thyroid and gall bladder, and the risk for hemorrhage. There were no adverse events causing cardiac toxicity and thromboembolic phenomena. Figure derived from data in text of Schlumberger et al. Not shown are cardiac toxicity thromboembolic toxicities; both are negative

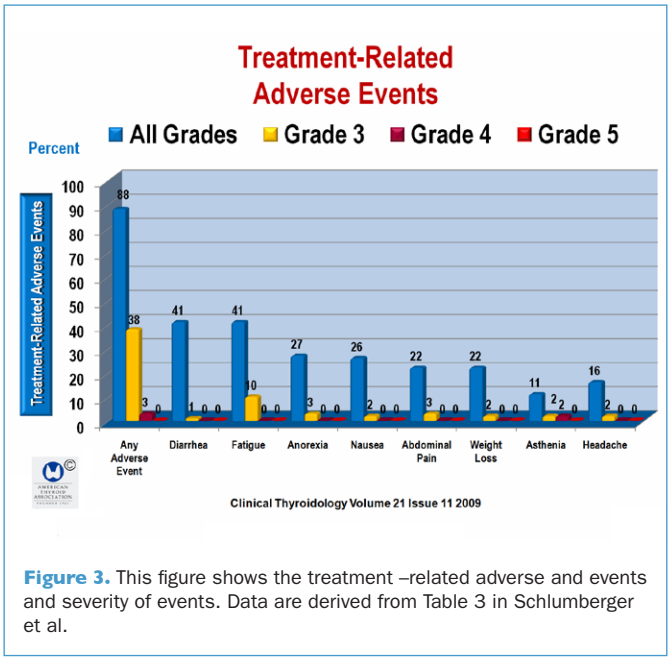

Figure 3. This figure shows the treatment –related adverse and events and severity of events. Data are derived from Table 3 in Schlumberger et al.

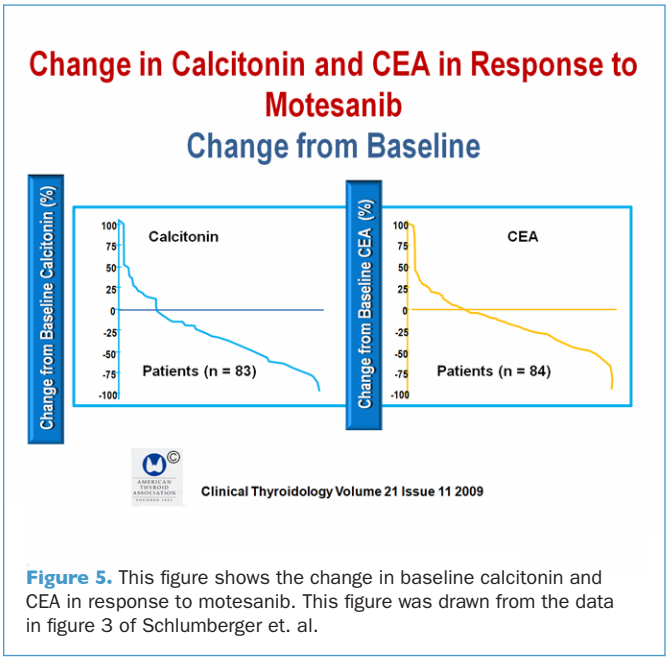

Figure 5. This figure shows the change in baseline calcitonin and CEA in response to motesanib. This figure was drawn from the data in figure 3 of Schlumberger et. al.

The mean (±SD) maximum motesanib plasma concentration of 589±314 ng/ml, was reached in a median of 0.73 hours (range 0.25 to 2 hours), and the mean plasma concentration of the drug 24 hours after the first dose was 7.86 ± 6.58 ng/ml. The mean maximum plasma concentration and area under the curve values were significantly lower than those observed in patients with differentiated thyroid cancer (DTC). Likewise, median trough concentrations were also lower as compared with patients with DTC on the same dosing schedule.

Serum tumor markers (Figure5)
Among the patients with tumor marker analyses, the baseline plasma calcitonin concentrations decreased from baseline in 69 of 83 patients (83%). There also was a decrease in the serum CEA concentration during the study in 63 0f 84 patients (75%). (Fig 3) At some point during the study, calcitonin and CEA levels were ≥50% lower than baseline in 37% and 17% of patients, respectively. A sustained decrease (≥24 weeks) in calcitonin and CEA ≥ 50% as compared with baseline was observed in 2% and 1% of patients, respectively.

CONCLUSION Motesanib achieved low partial response rates; however, the majority of patients (81%) had stable disease. In addition, the medication was well-tolerated.

COMMENTARY

The treatment paradigm for MTC is shifting. Previously, patients with advanced progressive disease were relegated to receiving traditional parenteral chemotherapies which are notorious for their toxic side-effect profile and low response rates (1). With evolving insight into the pathways that promote tumorigenesis and metastatic spread, and apoptosis inhibition, multiple new agents have been created to target refractory thyroid cancers (2). These targeted molecular therapies were initially received with much enthusiasm with the hope that one may offer a cure for MTC. While there have been no complete responses seen with the various agents tested, not all optimism is lost. Vandetanib, an inhibitor of VEGFR 1-3, RET, and EGFR, showed promise for patients with MTC with a partial response rate of 20% and a 30% rate of stable disease (3). Likewise, 87% of patients treated with sorafenib, a multikinase inhibitor with activity against VEGFR 1-3, PDGFR, RET, and BRAF, achieved stable disease as reported in a recent phase II trial (4). These findings, coupled with the high rate of stable disease in this trial by Schlumberger, et al, are encouraging in that VEGFR inhibitors appear to be effective cytostatic agents for patients with progressive MTC.

Because disease stabilization is considered an acceptable endpoint in patients with thyroid cancer, the current methodology of determining objective responses in clinical trials may not be ideal. Further, the existing RECIST criteria do not consider some clinically meaningful endpoints that translate into reductions in tumor burden. For example, patients with bone metastases or bilateral subcentimeter pulmonary metastases are deemed to have non-measurable lesions by RECIST, and a significant proportion of thyroid cancer patients may fall into this category. Reductions in the size of such tumors will not be represented with the existing RECIST criteria. In the study by Schlumberger et al, 76% of patients had significant reductions in tumor burden but were categorized as stable disease by RECIST. Other indications of improving clinical course include tumor markers and symptom control; RECIST does not capture these clinical parameters.

Another important consideration when analyzing the results of the motesanib trial is the pharmacokinetics data. Plasma concentrations of motesanib were consistently lower in the MTC patients than their DTC counterparts on a parallel study (5). It is not known whether the higher objective response rate (14%) in patients with differentiated tumors is attributable to this discrepancy in serum concentrations. The authors have speculated that the higher incidence of diarrhea in MTC patients at study entry may be responsible for a reduction in the absorbed dose of motesanib. It would certainly be valuable to know whether higher doses of motesanib would result in improved response rates; additional studies may be warranted.

Jennifer A. Sipos, MD

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Thyroid dysfunction is not linked with a significantly increased risk for coronary heart disease

Boekholdt MS, Titan SM, Wiersinga WM, Chatterjee K, Basart DC, Luben R, Wareham NJ, Khaw KT. Initial thyroid status and cardiovascular risk factors: The EPIC-Norfolk prospective population study. Clin Endocrinol (Oxf) 2009 doi: 10.1111/j.1365-2265.2009.03640.x

SUMMARY

BACKGROUND

Overt hypothyroidism is associated with cardiovascular risk factors; however, whether subclinical hypothyroidism alters cardiac risk factors, especially, dyslipidemia and coronary heart disease (CHD) remains uncertain. The aim of this study was to explore the relationship between subclinical thyroid status, cardiovascular risk factors, and the risk for CHD and mortality.

METHODS

The Study Population

The European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study is a population-based study of 25,633 men and women, 45 through 79 years of age residing in Norfolk, United Kingdom. Participants were recruited by mail from age-sex registries of primary care practices in Norfolk as part of a 10-country collaborative study designed to investigate dietary and other causes of cancer. Data were also obtained to facilitate assessment of the causes of other diseases. Eligible participants completed a baseline study conducted from 1993 through 1997 during which a detailed health and lifestyle questionnaire was completed and nonfasting fresh blood specimens were obtained to measure high-density lipoprotein cholesterol (HDL-C) and triglyceride levels and to calculate low-density lipoprotein cholesterol (LDL-C) levels with the Friedewald formula. Thyroid-function tests were measured on stored (–80°C) baseline samples for thyrotropin (TSH) and free thyroxine (FT4). For TSH, the sensitivity was 0.03 µIU/ml (normal range, 0.4 to 4.0); for FT_4, the sensitivity was 2.0 pmol/L (normal range, 8.0 to 20). Thyroid-function tests were randomly measured in approximately half the participants, a choice made as the result of limited funding. Vital statistics were ascertained for the entire cohort, and death certificates from the Office of National Statistics were evaluated and coded by trained nosologists. Participants with CHD were identified during follow-up if they had a hospital admission and died of CHD or had this diagnosis as an underlying cause of death.

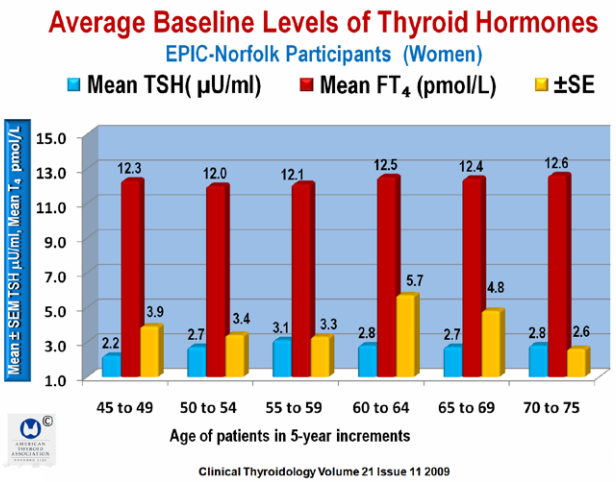
Definitions of Thyroid Dysfunction

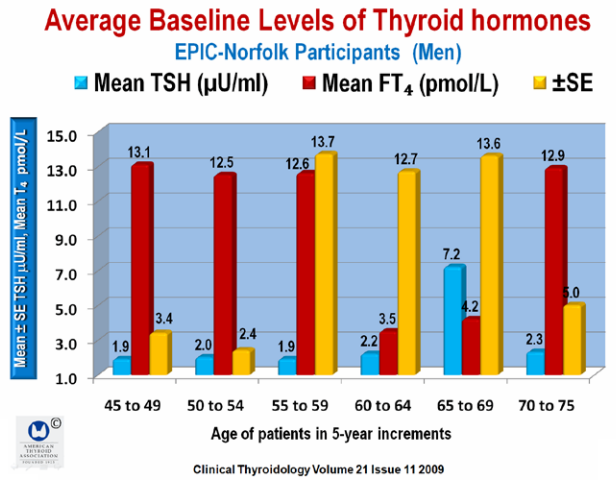
Hyperthyroidism was defined as a serum TSH <0.1 µIU/ml with a free thyroxine (FT_4) >20 pmol/L. Subclinical hyperthyroidism was defined as a serum TSH ranging from 0.1 through 0.4 µIU/ml or a TSH <0.1 µIU/ml with FT_4 in the normal range. Euthyroidism was defined as a TSH in the normal range. Subclinical hypothyroidism was defined as a TSH >4.0 µIU/ml with an FT_4 ranging from 9.0 through 20.0 pmol/L. Hypothyroidism was defined as a TSH >4.0 µIU/ml with an FT_4 <9 pmol/L.

RESULTS

Baseline Characteristics of Study Subjects (Figures 1 and 2)

Serum TSH and FT_4 was measured in 13,076 participants. After excluding participants with self-reported thyroid disease and those taking thyroid hormone, complete data were available for 11,554 participants, 5206 men (45%) and 6348 women (55%). The association between age and FT_4 was not very strong, and





Figures 1 and 2. These figures show means, standard errors, and percentages of abnormal values of TSH and FT_4 in 5-year age groups in women (Figure 1) and men (Figure 2) 45 to 75 years of age in the EPIC-Norfolk cohort. Although mean TSH levels increase with age, median levels (not shown in this figure) show only a slight increase, which is a consequence of the skewed distribution of TSH in both sexes. Data for these figures are derived from Table 1 in Boekholdt et al.

although TSH increased with age, the median TSH was only slightly increased. (Figure 1 for women; Figure 2 for men). All percentages in the text are reduced to the nearest integer; however, the figures show the exact percentages.

The Prevalence of Thyroid Dysfunction in the Study Group (Figure 3)

Of the entire study group, 10,301 were euthyroid (89%). Subclinical hypothyroidism was present in 800 persons, of whom 238 were men (5%) and 562 were women (9%). Undiagnosed hypothyroidism was found in only 47 men (1%) and 158 women (2.5%). The rate of subclinical hyperthyroidism was relatively low, at 2% in both women and men, and overt hyperthyroidism was present in less than 1% of the entire group. The prevalence of subclinical and clinical thyroid disease in the population without self-reported thyroid disease or the use of thyroid medication is shown in Figure 3.

Baseline Characteristics of Cardiovascular Status in Men and Women According to Thyroid Function (Figures 4 to 6)

Men with subclinical hypothyroidism were older and had higher waist circumference and body-mass index (BMI) than did the euthyroid group; those with overt hypothyroidism were also older and had higher LDL-C levels and glycated hemoglobin

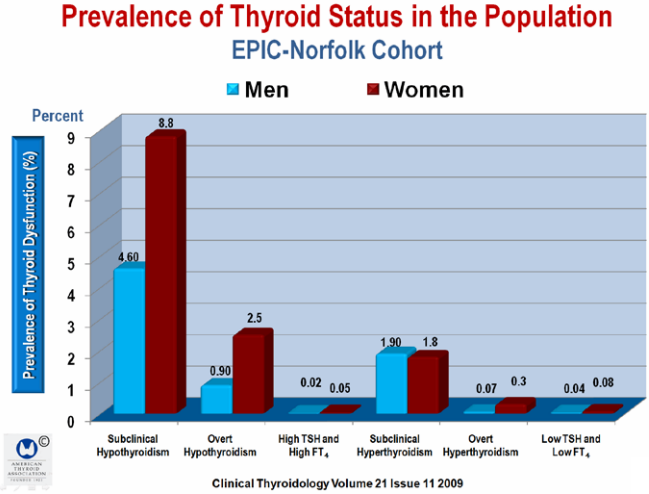


Figure 3. This figure shows the prevalence of thyroid dysfunction in men and women in the EPIC-Norfolk Cohort. Data for this figure are derived from Table 2 in Boekholdt et al.

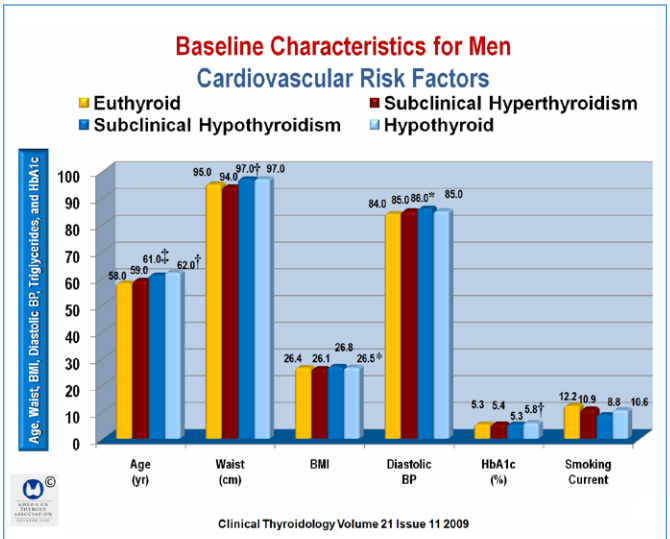


Figure 4. This figure shows the baseline cardiovascular characteristics of thyroid dysfunction in men as compared with euthyroid participants. Data for this figure are derived from Table 3 in Boekholdt et al. *P<0.05.†P<0.01. ‡P = 0.001. BMI = body-mass index (the weight in kilograms divided by the square of the height in meters); BP = blood pressure; HbA1c = glycated hemoglobin.

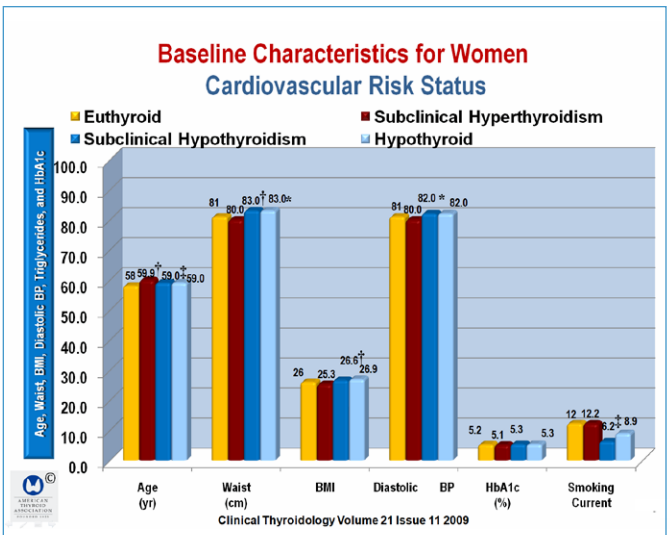


Figure 5. This figure shows the baseline characteristics cardiovascular of thyroid dysfunction in women as compared with euthyroid participants. Data for this figure are derived from Table 3 in Boekholdt et al. *P<0.05. †P<0.01. ‡P = 0.001. BMI = body-mass index (the weight in kilograms divided by the square of the height in meters); BP = blood pressure; HbA1c = glycated hemoglobin.

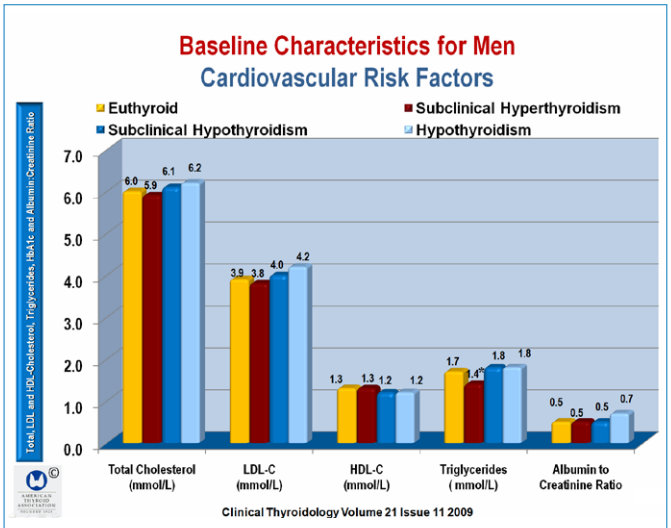


Figure 6. This figure shows the lipid characteristics in men as they relate to thyroid status and as compared with healthy euthyroid participants*P<0.05. †P<0.01. ‡P = 0.001. Data are derived from Table 3 in Boekholdt et al. HbA1c = glycated hemoglobin.

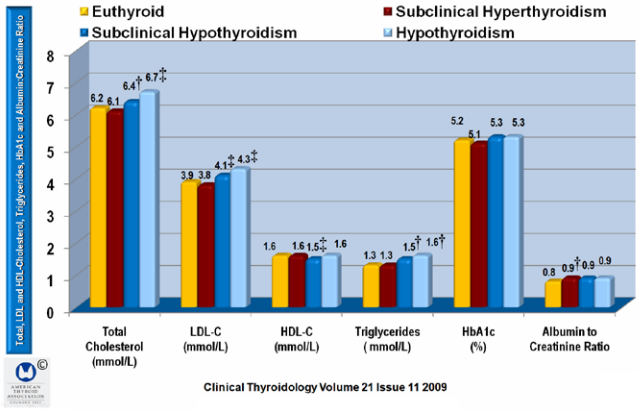


Figure 7. This figure shows the lipid characteristics in women as they relate to thyroid status and as compared with healthy euthyroid participants. *P<0.05. †P<0.01. ‡P = 0.001. Data are derived from Table 3 in Boekholdt et al. HbA1c = glycated hemoglobin.

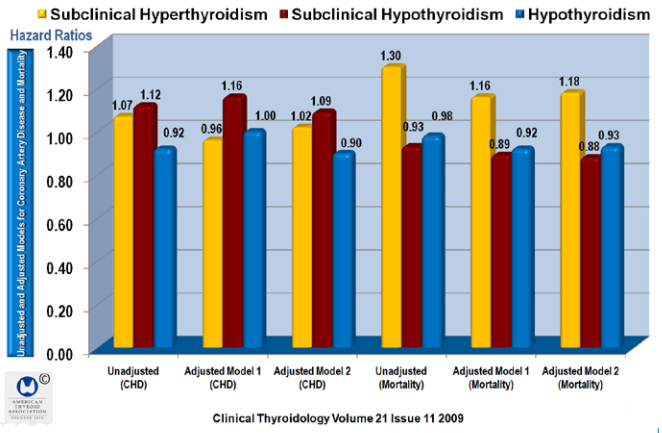


Figure 8. This figure shows the hazard ratios (the corresponding 95% confidence intervals are not shown). Model 1 is adjusted for sex, age and smoking; model 2 is adjusted for sex, age, smoking, diabetes mellitus, waist: hip ratio, systolic blood pressure, LDL-C and HDL-C. Euthyroid participants were the reference group. This figure shows that despite the association between thyroid hormone levels and cardiovascular risk factors, thyroid status was not significantly associated with the risk for future CHD or all-cause mortality. Euthyroid people comprised the reference group.

(HbA1c) levels than the euthyroid group (Figure 4). Among men with normal TSH and FT_4 levels, the TSH levels were significantly associated with total cholesterol, LDL-C, and HDL-C levels and diastolic blood pressure, whereas FT_4 levels were inversely associated only with BMI.

Baseline Characteristics of thyroid hormone levels and cardiovascular status in Women

Among women, TSH levels were associated with HDL-C levels, BMI, and systolic blood pressure, whereas FT_4 levels were associated only with HDL-C levels. There was no evidence for an important interaction between thyroid hormone levels and lipid levels, blood pressure, or smoking, nor was there a significant interaction between TSH and age with lipids, BMI, and diastolic blood pressure (Figure 5). The interaction between TSH and sex was statistically significant with total cholesterol and LDL-C, suggesting that the association between TSH and lipids differs between the sexes (Figure 6. The interaction between FT_4 and sex was statistically significant for total cholesterol, LDL-C, HDL-C, BMI, and systolic blood pressure (Figure 7).

Moreover, the interaction between FT_4 and age was statistically significant for LDL-C, HDL-C, BMI, and diastolic blood pressure. However, neither subclinical hyperthyroidism nor subclinical hypothyroidism nor overt hypothyroidism was associated with a statistically significantly increased risk for coronary heart disease, as compared with euthyroid people (Figures 4, 7 and 8). Women with subclinical hypothyroidism and overt hypothyroidism had substantially worse cardiovascular risk profiles and lipid levels than did euthyroid women (Figure 5).

CONCLUSION

Although there is an association between thyroid hormone levels and cardiovascular risk factors, the thyroid dysfunction is not linked with a significantly increased risk for coronary heart disease.

COMMENTARY

Considerable controversy surrounds the notion that subclinical hypothyroidism (SCH) has a significant effect on the risk profile of cardiovascular disease. The study by Boekholdt and associates provides important information that addresses this issue in a large cohort of participants. The study found that participants with thyroid dysfunction had an altered cardiovascular risk profile. Specifically, women with SCH and overt hypothyroidism had elevated LDL-C levels and higher systolic blood pressure. TSH levels, even in the normal range, were independently associated with LDL-C and HDL-C, BMI, and systolic blood pressure in both men and women. Finally, the participants in the EPIC-Norfolk cohort with thyroid abnormalities did not have a statistically significantly increased risk for future cardiovascular heart disease (CHD), which was comparable to that in other studies of people younger than 65 years of age (1).

Most studies have confirmed that an association exists between dyslipidemia and hypertension. A meta-analysis by Danese et al. (2) aimed at estimating the expected change in serum lipoprotein concentrations after levothyroxine ($L\text{-}T_4$) treatment found that all 13 studies in the analysis reported changes in serum total cholesterol concentration during $L\text{-}T_4$ treatment, 12 reported triglyceride changes, 10 reported HDL-C changes, and 9 reported LDL-C changes. Furthermore, they found that a decline in serum total cholesterol was directly proportional to its baseline concentration, and that studies enrolling

hypothyroid participants on suboptimal doses of L-T_4 reported significantly larger decreases in serum total cholesterol after TSH normalization than studies enrolling previously untreated individuals with mild thyroid failure. The results, although based on fewer than 250 patients, suggested that L-T_4 therapy in individuals with mild thyroid failure lowers mean serum total and LDL-C concentrations.

Boekholdt and associates found that even in a completely euthyroid population, there is an association between serum TSH and lipid levels, suggesting to the authors that a physiological mechanism may underlie this relationship. On the other hand, this study did not confirm the previously reported interaction between thyroid dysfunction and the metabolic effects of smoking. The study also found significant interactions between serum TSH and sex for lipid outcomes, suggesting to the authors that these lipid levels differ between men and women. Perhaps of most importance, the results of this study did not support an association between SCH and a substantial increase in CHD.

Still, a recent meta-analysis (3) found that SCH may be associated with a modest increase in cardiovascular risk. Ten of the 12 studies in the analysis, which included 14,449 participants, examined risks associated with SCH (2134 CHD events and 2822 deaths). The relative risk (RR) for CHD in patients with SCH was 1.20 (95% confidence interval [CI], 0.97 to 1.49; P for heterogeneity = 0.14). The estimates of risk were lower when higher-quality studies were pooled (RR, 1.02 to 1.08) and were higher among participants with a mean age of <65 years (RR, 1.51; 95% CI, 1.09 to 2.09), as compared with participants ≥65 years (RR, 1.05; 95% CI, 0.90 to 1.22). The RR was 1.18 (95% CI, 0.98 to 1.42) for CVD mortality and 1.12 (95% CI, 0.99 to 1.26) for total mortality. For subclinical hyperthyroidism, the RR was 1.21 (95% CI, 0.88 to 1.68) for CHD, 1.19 (CI, 0.81 to 1.76) for cardiovascular mortality, and 1.12 (95% CI, 0.89 to 1.42) for total mortality (P for heterogeneity >0.50.

Another relatively recent meta-analysis by Razvi et al. (4) was aimed at investigating whether age and sex influence the prevalence, incidence, and mortality of CHD in people with SCH. Fifteen studies were included in the analysis of 2531 participants with SCH and 26491 euthyroid individuals. The incidence and prevalence of CHD were higher in SCH subjects compared with euthyroid participants from studies including those less than 65 years but not studies of subjects aged more than 65 years [Odds Ratio (95% CI)]: 1.57 (1.19 to 2.06) vs. 1.01 (0.87 to 1.18) and 1.68 (1.27 to 2.23) verses. 1.02 (0.85 to 1.22), respectively. All-cause mortality from CHD was also significantly higher in participants <65 years of age as compared with older people (OR, 1.37; 95% CI, 1.04 to 1.79 vs. OR, 0.85; 95% CI, 0.56 to 1.29). The prevalence of coronary artery disease was higher in both men and women with SCH, although this was statistically significant only in women. The conclusion of the study was that both the incidence and prevalence of SCH is associated with increased, CHD mortality, but only in younger subjects.

Boekholdt and associates suggest that the Razvi study is consistent with the Boekholdt study insofar as both found no statistically significant increased risk for CHD in patients with SCH. Boekholdt and associates point out that the results of their study cannot be applied to the general population because people with thyroid disease were excluded from the study, and their results are based on a single TSH and FT_4 measurement and cannot exclude the possibility that limited statistical power may have prevented identifying a moderately increased risk for SCH. Nonetheless, the Boekholdt study does not support an association between SCH and a substantial increase in the risk for CHD, although this has been reported in several small cross-sectional studies (5;6).

In conclusion, SCH is a common condition that has been associated with coronary artery disease in some, but not all studies, which may be due to differences in study design and the characteristics of the study participants. The study by Boekholdt offers important new information in a large study cohort.

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Complications of thyroid surgery in octogenarians are more likely caused by comorbidities than by age alone

Mekel M, Stephen AE, Gaz RD, Perry ZH, Hodin RA, Parangi S. Thyroid surgery in octogenarians is associated with higher complication rates. Surgery 2009;146:913-21.

SUMMARY

BACKGROUND

The frequency of thyroid nodules increases throughout life. As a consequence, a large number of people 80 years of age or older have thyroid nodules; many of them undergo thyroid surgery. Some suggest that there is neither ample information concerning the efficacy of thyroid surgery nor adequate information regarding the surgical complications in elderly patients. The aim of this study was to determine whether the complication rates of thyroid surgery are higher than usual in people 80 years of age or older.

METHODS

This is a retrospective study of the medical records of 3568 patients who had thyroid surgery at the Massachusetts General Hospital from July 2001 through October 2007. Patients selected for the study had a variety of surgical procedures, including excision of thyroid nodules, lobectomy, subtotal or near-total thyroidectomy, total thyroidectomy, and any other type of partial thyroidectomy. From this group, 90 patients 80 years of age or older (octogenarians) were selected for study. Also randomly selected from the 3568 patient records were 250 patients ages 18 through 79 years who comprised the control group. Excluded from this group were 8 patients, for whom major data were missing, leaving 242 patients in the control group. Data for analysis were obtained from preoperative and postoperative office records, electronic medical records, and anesthesia records. The following were collected as potential risk factors for the development of complications: patient age, sex, and preoperative diagnosis; presence of a substernal component of the thyroid; previous thyroid surgery and the extent of surgery; body-mass index (BMI) and Coumadin use, and the American Society of Anesthesiologists (ASA) score and the Charlson comorbidity index. The ASA scores were divided into I, II, III, and higher.

The indications for surgery were stratified into three categories: (1) presumed benign disease, (2) suspected or known malignant disease, and (3) microfollicular neoplasms. The final histopathology was also stratified into 3 categories: (1) benign, (2) significant malignancy (excluding incidentally found papillary microcarcinomas <1 cm), and (3) incidental papillary microcarcinoma.

The primary outcomes of interest were 30-day postoperative complications, including cardiovascular disease; respiratory, gastrointestinal, urologic, and central nervous system events such as stroke, metabolic and wound problems; and any other complications occurring within the 30-day time frame. Thyroid-specific complications such as hypoparathyroidism and vocal-cord dysfunction were based on the necessity of hospital readmission. Here and elsewhere in the text, percentages are reduced to an integer; in the figures the percentages are shown as reported.

RESULTS

Demographics of Octogenarians and Control Groups (Figures 1 and 2)

A total of 90 octogenarians were included in the study group, all of whom had thyroid surgery, comprising 2.5% of the thyroid operations performed during the study period. The mean age of

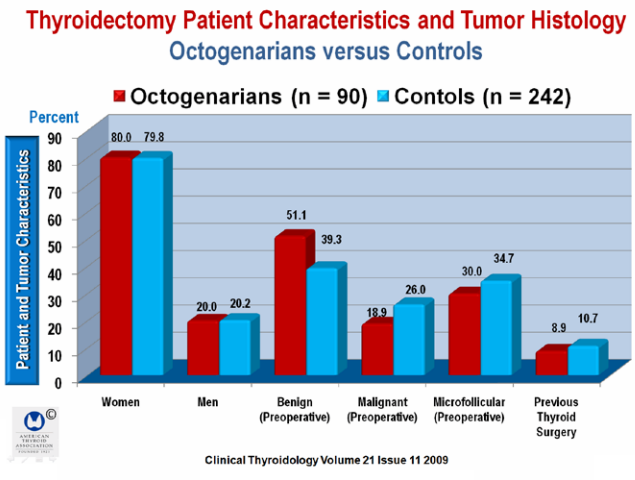

Figure 1. This figure shows the sex of the patients and histologic characteristics of the tumors and percent of patients who had previous thyroid surgery. The data for this figure are derived from Table 1 of Mekel et al.

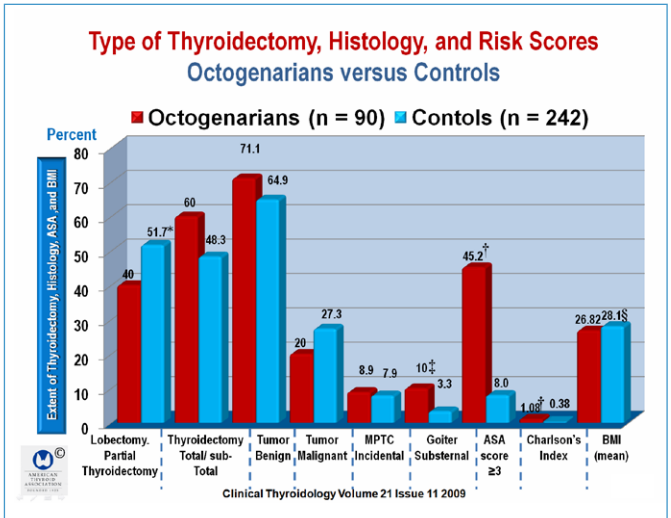

Figure 2. This figure shows the type of thyroid surgery, tumor characteristics, substernal goiter, ASA score, Charlson's index and mean BMI (the weight in kilograms divided by the square of the height in meters). *P<0.059, †P<0.001, ǂP = 0.014, and §P = 0.25 comparing octogenarians with younger controls. The data for this figure are derived from Table 1 of Mekel et al. MPTC = microscopic papillary thyroid carcinoma .

octogenarians was 83.2 years (range, 80 to 94); 72 were women (80%) and 18 were men (20%) (Figure 1). Of the 242 patients in the control group, 193 were women (80%) and 18 were men (20%), with a mean age of 50.1 years (range, 18 to 79). There was no significant difference between the study and control groups in terms of sex, preoperative diagnosis, previous thyroid surgery, or final histopathology. Overall, there were 161 lobectomies or partial thyroidectomies (40%) and 171 total or subtotal thyroidectomies (60%). More octogenarians had a substernal goiter as compared with the control group (10% vs. 3%, P = 0.014). There were no significant differences in the mean BMI among octogenarians and controls. More octogenarians had total or subtotal thyroidectomy as compared with the control group; however, the difference was not statistically significant (Figure 2).

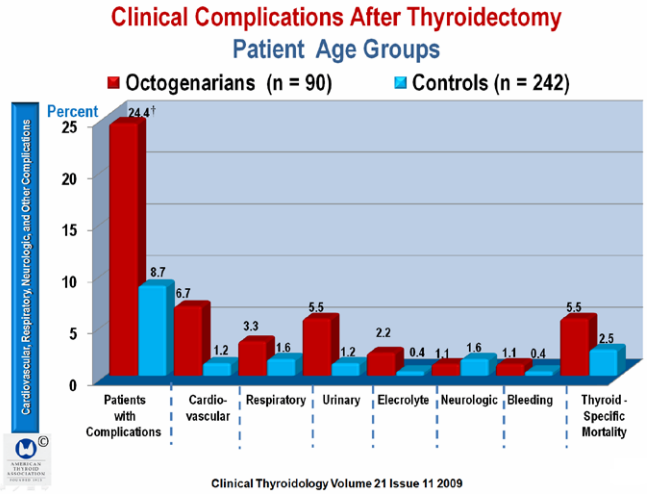

Figure 3. This figure shows that the clinical complications after thyroidectomy are almost threefold for octogenarians as compared with controls. †P<0.001 (octogenarians vs. controls). The data for this figure are derived from Table 2 of Mekel et al.

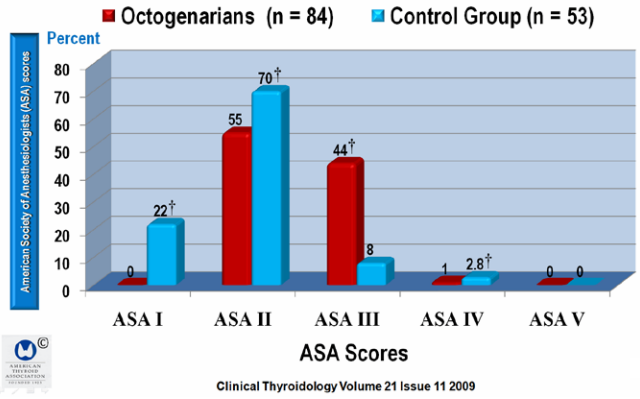

Figure 4. This figure shows the ASA scores, which are summarized as follows: ASA I = patients considered to be normal and healthy and having little or no risk for surgery. ASA II = patients with mild-to-moderate systemic disease that poses minimal risk during treatment. ASA III = patients with severe systemic disease that limits activity and represents a "yellow flag" for treatment. ASA IV = patients with severe systemic disease that limits activity and is a constant threat to life. ASA V = moribund patients not expected to survive more than 24 hours with or without an operation. ASA VI = patients who are clinically dead, being maintained for harvesting of organs. †P<0.001 for octogenarians versus controls.

Comorbidity and Charlson and ASA scores (Figures 2 and 3)

The Charlson index score was significantly higher (worse) in the octogenarians as compared with the control group. The mean (±SD) score was 1.08±1.38 (range, 0 to 6) versus 0.38±0.89 (range, 0 to 8) in octogenarians and controls (P< 00.1) (Figure 2). In the octogenarian group, 45% had an ASA score ≥3 (45%) and a comorbidity index of 0; 37% had a score of 1 or 2. In the control group, 76% had a comorbidity index of 0, 22% had a score of 1 or 2, and only 8% had a score ≥3. Cerebrovascular disease was the most prevalent comorbid condition in the octogenarians, 14% of whom had this at the time of surgery, and pulmonary disease was the most common comorbidity (12%) in the controls (Figure 3).

The American Society of Anesthesiologists (ASA) scores (Figure 4)

The ASA scores, which were available in 84 octogenarians (93%), were ASA I (0), ASA II (55%), ASA III (44%), ASA IV (1%), and ASA V (0%). ASA scores, which were available in 53 people in the control group (22%), were ASA I (22%), ASA II (70%), and ASA III (8%). The ASA scores were significantly higher in the octogenarians as compared with the control group (P<0.001) (Figure 4). The mean length of hospital stay for octogenarians was significantly longer than that for the control group: 1.67±2.19 days (range, 1 to 18) versus 1.23±2.85 days (range 1 to 43) (P<0.01). The overall complication rate was 13%; it was 24% in the octogenarians versus 9% in the younger group (P<0.01).

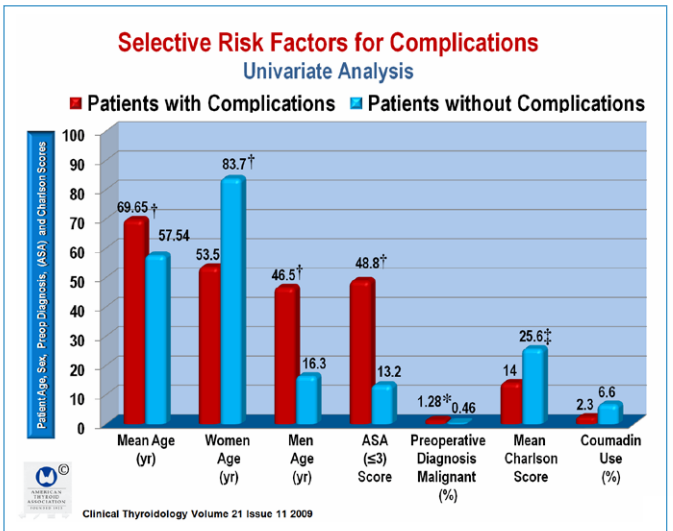

Figure 5. This figure shows the results of univariate analysis of selected risk factors that pose complications at the time of thyroid surgery. American Society of Anesthesiologists (ASA) score, Charlson's index and mean BMI. *P<0.203, †P<0.001, ǂP = 0.005, comparing octogenarians with younger controls. The data for this figure are derived from Table 4 of Mekel et al.

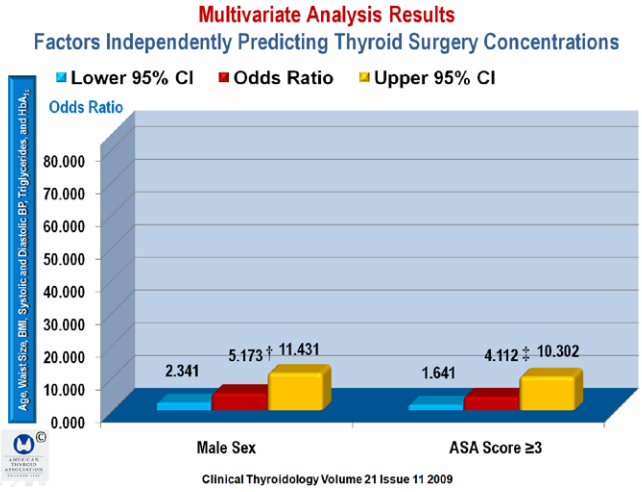

Figure 6. The two variables independently predicting complications are male sex and ASA score ≥3. †P<0.001. ‡P = 0.03. BP = blood pressure.

Univariate and Multivariate Analyses (Figures 5 and 6)

Univariate analysis found that age, male sex, ASA score ≥3, and the Charlson comorbidity index were significantly associated with postoperative complications after thyroidectomy (Figure 5). Multivariate analysis found that male sex independently increased the risk of complications after thyroid surgery by fivefold and an ASA score ≥3 increased the risk of complications fourfold. Age alone was found not to be an independent risk factor for complications after thyroid surgery (Figure 6).

CONCLUSION

Although an age of 80 years or older is associated with higher complication rates for thyroid surgery, this is independently related to other factors, such as underlying illnesses and male sex.

COMMENTARY

The study by Mekel and associates is one of the larger studies to address the complication rates of thyroid surgery in patients 80 years of age or older. The main conclusion of the study was that two independent risk factors predicted postoperative complications in the 30-day postoperative period under study—male sex and a high American Society of Anesthesiologists (ASA) risk score. Of considerable importance, advanced age was not an independent factor predicting postoperative complications. This is a key point that might be overlooked from the title of this article. It is important to separate the effects of age from the disorders that increase with age. It is the latter that predict postoperative complications, not patient age per se. The importance of this distinction is underscored by census studies indicating that there were approximately 5 million people 80 years of age or older in the United States in 2005, a number that is steadily rising. Obviously, the people in this group range from healthy to extremely ill, which impacts preoperative decisions, such as the decisions in this study.

Patients in the Mekel study had a variety of benign and malignant thyroid disorders that were treated by the authors, who are high-volume thyroid surgeons. There were some fairly large differences among the preoperative thyroid diagnoses in the two study groups: the thyroid disease was benign in approximately half the 90 octogenarians and in one-fourth of the 242 members of the control group 18 through 79 years of age, and approximately one-third of both groups had microfollicular lesions. Substernal goiter was found in 10% of the octogenarians and 3% of the younger control group, a difference that was statistically significant, and in some of the cases, clinically quite important. For example, an especially prolonged hospitalization occurred in an 83-year-old woman who had a sternotomy for a large substernal goiter complicated with reintubation, tracheostomy, and sternal wound infection, requiring an 18-day hospitalization. The mean hospital stay was about the same: <2 days in both octogenarian and younger controls, with a range of 1 to 18 days in octogenarians and 1 to 43 days in controls. These diagnoses were not found to be independent variables affecting postoperative complications, yet as a practical matter, each thyroid diagnosis likely posed unique surgical challenges. Likewise, the list of comorbidities is long, including a large number of major health problems such as cardiovascular complications, stroke, congestive heart failure, arrhythmias, pneumonia, and acute renal failure, to mention a few. Each of these disorders predicts high postoperative complications as confirmed by the high ASA scores. Although the authors suggest that the octogenarians seemed to have a significantly greater comorbidity burden, as reflected by the mean Charlson index score—which was less predictive than the ASA score—the authors thus recommend that the ASA status should be part of the routine preoperative decision-making process. The authors also advise that more individualized strict criteria be applied before fine-needle aspiration biopsy (FNAB) is performed, suggesting that it may be delayed in octogenarians if the nodules are very small and of little clinical significance. They also suggest that performing FNAB on all clinically suspicious thyroid nodules and nodules >1 cm increases operations for benign disease that might be avoided. The current American Thyroid Association guidelines provide strong evidence that performing FNAB in multiple large nodules >1 cm is very likely to avoid missing a diagnosis of thyroid cancer unless there is ultrasound evidence that reliably indicates the nodule is benign.

Comorbidity is known to be an important contributory factor to poor outcomes in patients with thyroid cancer, especially in elderly patients. For example, a population-based observational study from the Netherlands (1) found that hypertension was the most frequent comorbidity with thyroid cancer (18%), followed by

other serious conditions such as cardiovascular diseases (6%) and diabetes mellitus (6%). The prevalence of hypertension was twice as high as expected in all age groups, yet comorbidity was not independently associated with overall survival up to 5 years, which might be insufficient follow-up to fully evaluate the effect of comorbidity.

Similar to the study by Mekel and associates, a study of 242 patients 70 years of age or older by Sanabria et al. (2) assessed the predictive effect of preoperative clinical factors on postoperative complications in patients undergoing head and neck surgery. Comorbidities were present preoperatively in almost 90% of patients, and approximately half had some type of local or systemic complication. Male sex, bilateral neck dissection, the presence of two or more comorbidities, reconstruction, and clinical stage IV tumors were significantly associated with postoperative complications. After analysis of risk factors, the authors concluded that it is possible to predict postoperative complications using preoperative clinical variables in older patients with head and neck tumors who had oncologic surgery.

A recently published study by Matsuyama and associates (3) that compared the clinical characteristics of thyroid cancers in 85 elderly patients 75 years of age or older, with those of 37 patients <30 years of age found that the elderly patients with papillary thyroid carcinoma had a significantly worse cumulative 5-year survival rate than that of the young patients with papillary thyroid carcinoma (92% vs. 100%, P = 0.03). Still, there was no significant difference in the survival rates of patients with low-risk tumors in the two age groups. Yet, with high-risk tumors the cumulative 2-year survival rate of elderly patients was significantly lower in patients not treated surgically than in those treated surgically (80% vs. 100%, P = 0.02). The quality of life was severely impaired in 67% and 6% of the patients treated nonsurgically and surgically, respectively; demonstrating that surgery for thyroid cancer increases the survival rate and promotes the quality of life in elderly patients if they are well enough to tolerate the operation. In the Matsuyama study of elderly patients with recurrent papillary thyroid carcinoma, there were no statistically significant differences in survival among patients with locoregional metastases when patients had metastases found on the initial surgery or were secondarily identified as locoregional recurrences later in the course of follow-up. Although outcome tended to be worse in patients undergoing a second surgery for recurrent metastases, the difference was not statistically significant as compared with patients who had metastases at the time of initial surgery.

The Mekel study found that men had a significantly higher complication rate than women. Why this is so is not entirely clear. However, it is well recognized that men use the health system differently than woman do, seeking medical attention later than women and presenting with more advanced disease.

The conclusion is that patients 80 years of age or older have a higher complication rate with thyroid surgery that is more closely related to comorbidities than to age per se. Mekel and associates recommend providing more stringent preoperative evaluation using ASA scores and caution in prescribing therapy before it is clear that thyroid surgery is the most effective means of treating elderly patients after counseling the patient and their families concerning expectations and risk.

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www.thyroid.org/patients/ct/index.html

After a median follow-up of 3.7 years, patients with low-risk thyroid cancer prepared for postoperative remnant ablation with either L-T_4 withdrawal or rhTSH stimulation have comparable rates of thyroid remnant ablation and tumor recurrence or persistent disease.

Elisei R, Schlumberger M, Driedger A, Reiners C, Kloos RT, Sherman SI, Haugen B, Corone C, Molinaro E, Grasso L, Leboulleux S, Rachinsky I, Luster M, Lassmann M, Busaidy NL, Wahl RL, Pacini F, Cho SY, Magner J, Pinchera A, Ladenson PW. Follow-up of low-risk differentiated thyroid cancer patients who underwent radioiodine ablation of postsurgical thyroid remnants after either recombinant human thyrotropin or thyroid hormone withdrawal. J Clin Endocrinol Metab 2009;94(11):4171-9.

SUMMARY

BACKGROUND

This international group previously demonstrated in a prospective, randomized study that thyroid remnant ablation rates with 100 mCi of ^{131}I were comparable after patients with low-risk tumors were prepared with either thyroid hormone withdrawal (THW) or recombinant human thyrotropin-α (rhTSH). A posttherapy evaluation of the efficacy of thyroid remnant ablation was performed at a mean (±SD) of 8±1 months after the treatment, at which time patients were studied with rhTSH-stimulated ^{131}I whole-body diagnostic scans (DxWBS) and measurement of serum thyroglobulin (Tg) levels. The aim of the current study was to compare outcomes of the original patients 3.7 years later.

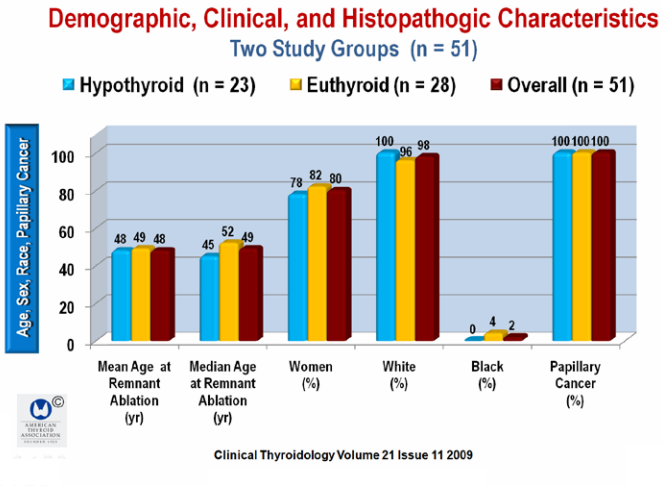
Patients and Methods

In the original study, 63 patients—61 with papillary thyroid cancer and 2 with follicular thyroid cancer—were randomly assigned postoperatively to either thyroid hormone withdrawal (hypothyroid group) or rhTSH stimulation (euthyroid group) in preparation for thyroid remnant ablation with 100 mCi of ^{131}I. Ten of the 61 patients were ineligible for the current follow-up study for several reasons, such as the inconvenience of further testing or recent extensive diagnostic evaluation during follow-up. The current study cohort thus comprised 51 (81%) of the original 63 patients, 28 of whom were in the euthyroid group (55%) and 23 in the hypothyroid group (45%). An ^{131}I DxWBS was performed in 43 of the 51 patients (84%). Successful remnant ablation was defined by the same criteria used in the previous study, which was no visible uptake in the thyroid bed, or if uptake was visible, then radioiodine uptake <0.1%. The secondary criterion was an rhTSH-stimulated serum Tg <2 ng/ml. The current study compared the rhTSH-stimulated serum Tg levels and the neck ^{131}I uptake at the 8-month evaluation in the first study, with the 3-to 4-year testing results in the present study. Here and elsewhere percentages have been rounded to an integer.

RESULTS

The Demographic Characteristics of the Study Patients (Figures 1 and 2)

The demographic characteristics, clinical and histopathologic features of the study group are summarized in Figures 1A and 1B. The mean (±SD) ages of the cohort were 48±13, 49±12, and 48±12 years in the hypothyroid, euthyroid, and combined groups, respectively. The tumor–node–metastasis (TNM) status of the patients ranged from T1 through Mx and was approximately the same in the hypothyroid and euthyroid groups (Figure 1B) The characteristics of the patients in the first trial who were not enrolled and those in the current follow-up study were comparable (Figure 2).



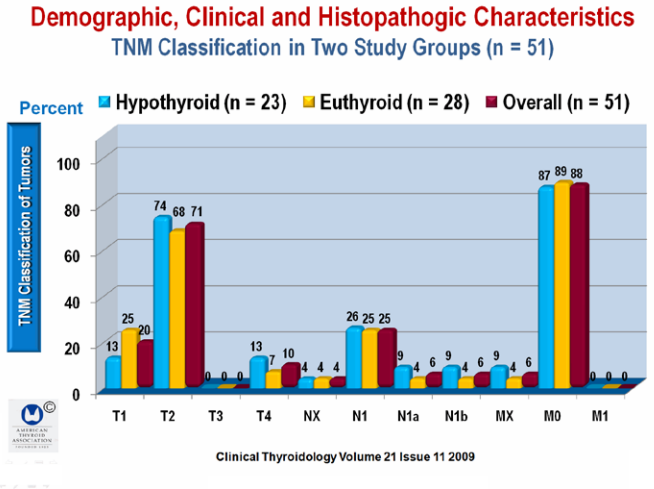


Figure 1. (a) This figure shows the comparison of patient and tumor characteristics in the current follow-up study of 51 patients prepared for remnant ablation with either thyroid hormone withdrawal or recombinant human TSHα (rhTSH), **(b)** This figure shows the TNM stage in this group. Figures are derived from data in Table 1 of Elisei et al. THW = thyroid hormone withdrawal.

Characteristics of the Nine Study Patients Requiring Further Therapy (Figure 3)

None of the 63 patients who participated in the first trial had died by the time of the second follow-up study; however, 9 of the 51 patients (18%) in the second study group (5 hypothyroid and 4 euthyroid) had received additional ^{131}I therapy, 2 of the 9 (1 hypothyroid and 1 euthyroid) also had further surgery, and 1 (euthyroid) had surgery without further ^{131}I treatment; none of them had iodine-avid disease. These data are summarized in Figure 3.

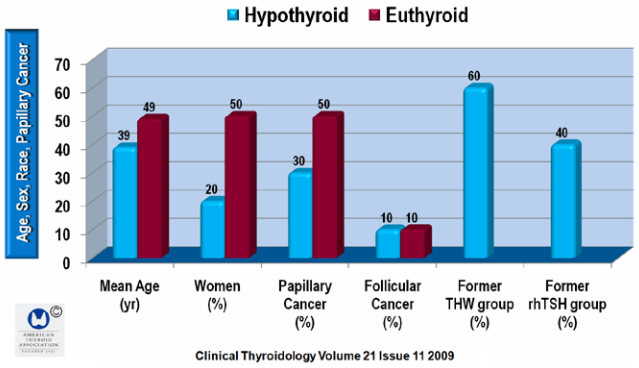


Figure 2. This figure shows the patient and tumor characteristics of those from the original study cohort who were not enrolled in the current follow-up study. There are no significant differences between the two groups. rhTSH = recombinant human thyrotropin-α; THW = thyroid hormone withdrawal. Figures are derived from data in Table 2 of Elisei et al.

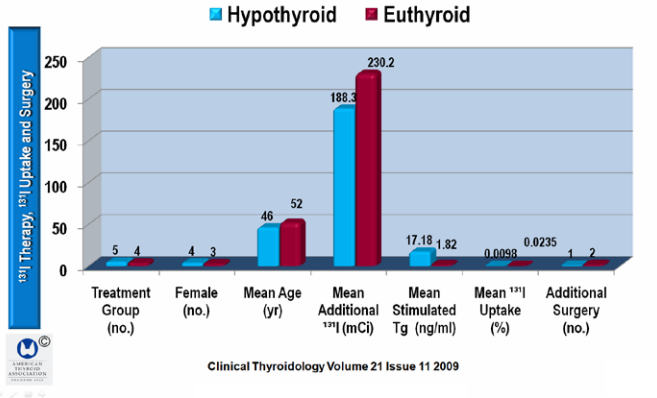


Figure 3. This figure shows the details of the nine patients in the current cohort who were treated with ^{131}I and surgery after the 8-month evaluation of outcome in the original study group. Mean values are shown for serum recombinant human thyrotropin-α (rhTSH)-stimulated serum thyroglobulin, the amount of ^{131}I used for therapy for the patients with recurrences, and the mean ^{131}I uptake. *P <0.004 and †P = 0.015 comparing mean ^{131}I uptake in the two study groups. The mean values were calculated and figures derived from Table 3 by Elisei et al.

The nine patients who required further therapy were judged to have had successful remnant ablation based on the absence of ^{131}I uptake in the neck, but none had unequivocal serum Tg evidence of being free of disease or without thyroid tissue, but instead had persistent elevation of the TSH-stimulated serum Tg levels (n = 4) or uninterpretable Tg measurements because of serum anti-Tg antibodies (TgAb). One patient had a small thyroid remnant found

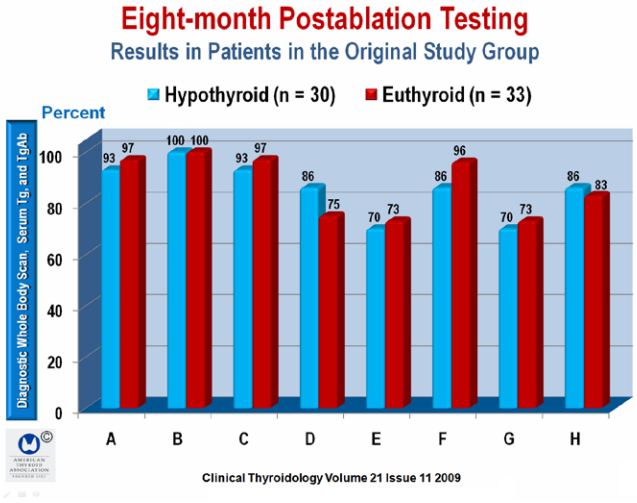


Figure 4A. This figure shows the 8-month postablation testing in the evaluable patients in the original study group, comparing hypothyroid and euthyroid groups. A = patients included in scan analysis divided by all original patients; B = patients with no visible uptake or <0.1% divided by patients in scan analysis; C = patients included in DxWBS analysis divided by all original patients; D = patients with no visible ^{131}I uptake divided by patients in DxWBS analysis; E = patients with serum Tg measurement and no interfering TgAb divided by all original patients; F = patients with serum Tg <2 ng/ml divided by all patients with Tg analysis; G = patients with serum Tg measured and no interfering TgAb divided by all original patients; H = patients with serum Tg <1 ng/ml divided by all patients with Tg analysis. TgAb = thyroglobulin antibody. Figures 4A and B are derived from data in Table 4 of Elisei et al.

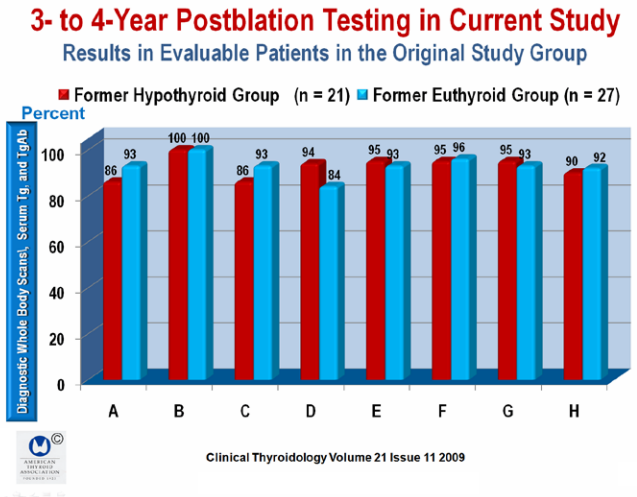


Figure 4B. This figure shows the 3-to 4-year postablation testing in the current study group comparing the former hypothyroid group with the former euthyroid group. See Figure 4A legend for definitions of A through H.

by neck ultrasonography, and 4 others had persistent thyroid-bed ^{131}I uptake or cervical lymph-node metastases detected on the initial posttherapy whole-body scan. All three of the patients who required additional surgery had a negative DxWBS, but all had elevated serum Tg values or serum TgAb levels and ultrasound evidence of suspicious cervical lymph nodes. Seven of the 9 study patients who required further therapy (78%) had a negative rhTSH-stimulated DxWBS but 2 (1 hypothyroid and 1 euthyroid) still had an rhTSH-stimulated serum Tg >2 ng/ml reflecting persistent cervical lymph-node metastases. None of the 51 patients in the follow-up study who had been thought to be free of disease on the basis of undetectable rhTSH-stimulated serum Tg levels subsequently had tumor recurrence.

Comparison of 8-Month and Current Study Results for Evaluable Patients (Figures 4A, 4B, and 5)

Because 3 of the 51 patients enrolled in the second study could not be given rhTSH for various reasons, diagnostic testing was done in 48 patients (21 hypothyroid and 27 euthyroid). Among the 48 patients, 43 agreed to receive 4 mCi for a DxWBS. Serum Tg measurements were completed in 47 of the 48 patients, but were uninterpretable in 3 because of serum anti-Tg TgAb levels >30 U/ml, reducing the number of patients from 48 to 45 with reliable serum Tg measurements.

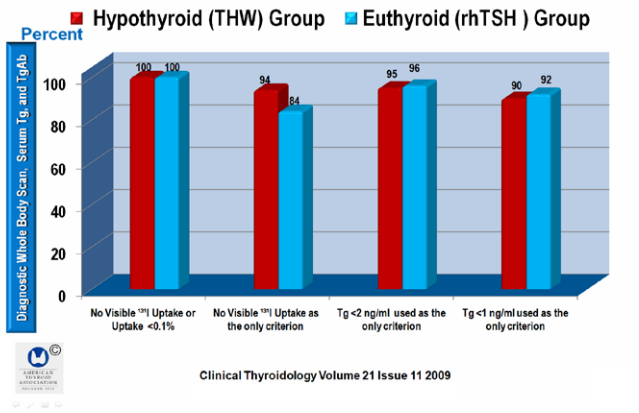


Figure 5. This figure compares the rate of successful ablation using the criteria in the original study with only the criterion of <0.1% ^{131}I uptake in the thyroid bed, in which case 100% of the hypothyroid and euthyroid groups had an ablation rate of 100%. When no visible uptake was used instead of <0.1% ^{131}I uptake, fewer patients were regarded as having successful ablation. When TSH-stimulated Tg <2 ng/ml levels were compared with <1 ng/ml as the only criterion for remnant ablation, there was little difference in the rates of successful ablation between the two Tg cutoffs.

Thus, the long-term efficacy of the original ^{131}I ablation procedure was evaluated in 43 patients who completed both an rhTSH-stimulated WBS and rhTSH-stimulated Tg measurement in the current follow-up study. Also, this group included 9 patients who had received further therapy after the original study, thus confounding the evaluation of efficacy in the original ablation study. As a consequence, 100% of the patients in both the hypothyroid and euthyroid groups continued to meet the initial criteria of no visible ^{131}I uptake or less than 0.1% uptake in the thyroid bed, which interfered with calculation of the confidence intervals (Figure 4A). When no visible ^{131}I uptake was used as the only criterion, five patients (one hypothyroid and four euthyroid) had minimally visible ^{131}I activity, making the successful ablation rates 94% and 84% in the two groups, respectively (Figure 4B).

When TSH-stimulated Tg was used to evaluate outcome, 45 patients could be assessed, and all but two (one hypothyroid and one euthyroid) had an rhTSH-stimulated serum Tg <2 ng/ml, making the ablation rates 95% and 96% (95% confidence interval [CI], –11.3 to 13.3) in the two groups, respectively. Using the even more stringent criterion of an rhTSH-stimulated Tg <1 ng/ml, all but four patients (two hypothyroid and two euthyroid) were considered to have had successful ablation, thus making the ablation rates 90% and 92%, respectively (95% CI, –14.9 to 18.9. in the two groups, respectively) (Figure 5).

After a median of 3.7 years, patients prepared with thyroid hormone withdrawal or recombinant human TSHα, have similar rates of remnant ablation, tumor recurrence, and persistent disease.

Two patients with serum TgAb >30 U/ml were excluded from the main Tg follow-up analysis (one hypothyroid and one euthyroid), and nine were excluded (four hypothyroid and five euthyroid) when the more stringent criterion of TgAb <5 U/ml was used. When the rhTSH-stimulated serum Tg levels were <1 ng/ml 8 months after the original ^{131}I ablation study, the Tg values remained at this level in the current follow-up study.

In the eight cases (four hypothyroid and four euthyroid) in which the rhTSH-stimulated serum Tg levels were >1 ng/ml 8 months after the original ^{131}I ablation (five >2 ng/ml and three >1 ng/ml), three had elevated Tg levels, but also had high anti-TgAb levels that potentially interfered with the Tg results. As a result, comparison of ^{131}I efficacy for remnant ablation in the two study groups could not be assessed because six of the patients had been retreated after the initial therapy. Only one patient had not been treated with ^{131}I during the interim and had no interfering anti-TgAb. However, this did not change the Tg evidence for ablation with rhTSH and THW.

CONCLUSION

After a median follow-up of 3.7 years, patients with low-risk thyroid cancer prepared for postoperative remnant ablation with either L-T_4 withdrawal or rhTSH stimulation have comparable rates of thyroid remnant ablation and tumor recurrence or persistent disease.

COMMENTARY

The study by Elisei et al. strengthens our understanding of how patients can be prepared for ^{131}I remnant ablation. It is a follow-up of an important study reported in 2006, by Pacini et al. (1), who published the results of a randomized, controlled, international, multicenter trial aimed at assessing the efficacy and safety of rhTSH in a cohort of patients with low-risk thyroid cancers, 97% of which were papillary thyroid carcinoma, with the others being follicular thyroid cancers. In the clinical trial, patients

receiving levothyroxine therapy were prepared for thyroid remnant ablation with 100 mCi (3.7 GBq) of ^{131}I using rhTSH (euthyroid) or levothyroxine withdrawal (hypothyroid) to stimulate uptake of ^{131}I by postoperative thyroid remnants. The study was also designed to assess the quality of life and the rate of ^{131}I clearance from blood and thyroid remnants and to evaluate the extent of whole-body irradiation in patients prepared with rhTSH as compared with those using thyroid hormone withdrawal. The study protocol defined the primary criterion for successful ablation as "no visible uptake in the thyroid bed, or if visible, ^{131}I uptake <0.1%" on a diagnostic neck scan performed 8 months after therapy. The goal of remnant ablation was achieved in 100% of both groups. A secondary criterion for assessment of ^{131}I remnant ablation in the two groups was an rhTSH-stimulated serum Tg <2 ng/ml, which was fulfilled in 23 of 24 (96%) euthyroid patients and 18 of 21 (86%) hypothyroid patients (P = 0.2). The study also found that patients prepared with rhTSH maintained a substantially better quality of life and received significantly less radiation exposure to the blood as compared with hypothyroid patients.

At the time of the current follow-up study, none of the 63 patients who had participated in the 2006 trial had died. Moreover, the current study found that patients prepared with rhTSH and THW continue to have comparable rates of successful remnant ablation after approximately 4 years of follow-up. This is of considerable importance since it is within the first year after surgery that recurrence rates are highest (2) and typically have the worst outcomes (3). Nine of the patients in the original trial (five hypothyroid and four euthyroid) received additional ^{131}I therapy and two, along with another patient who did not receive ^{131}I therapy, were surgically treated for cervical lymph-node metastases. The patients treated with ^{131}I were all found to have non–iodine-avid tumors. The patients considered to have successful remnant ablations at 8 months after ^{131}I therapy all were confirmed to have an absence of visual ^{131}I uptake in the neck or <0.1% ^{131}I uptake, and were subsequently found to have a negative rhTSH-stimulated DxWBS a median of 3.7 years later. This confirms that repeat diagnostic scanning is not necessary in most patients who have a negative postoperative scan.

All the patients in this study had low-risk tumors of stage T2 or T4 with minor invasion of the thyroid capsule, N0 to N1, and M0, or T0 to T1, N1, and M0. The authors provide the caveat that T4 tumors were considered ineligible later in the initial study, because certain centers routinely treated such patients with more than 100 mCi of ^{131}I or were treated with external-beam radiotherapy, which might apply to patients with higher stages of disease.

The other important finding in this study relates to the diagnostic differences of serum Tg levels and visible uptake of ^{131}I on a DxWBS. An rhTSH-stimulated serum Tg measurement in the absence of anti-TgAb has a greater sensitivity, in the range of 80%, when the Tg is rising (4, 5). In contrast, an rhTSH-stimulated DxWBS has a much lower sensitivity in detecting tumor recurrence (6), which is best done with neck ultrasonography and rhTSH-stimulated serum Tg measurements (7).

Tuttle et al. (8) retrospectively assessed tumor recurrence a median of 2.5 years after ^{131}I remnant ablation in 394 consecutive patients with thyroid cancer (93% papillary) treated with a median of 108 mCi ^{131}I for remnant ablation (3996 MBq). The study found similar ablation and tumor recurrence rates after preparation with rhTSH and thyroid hormone withdrawal (4% and 7%, respectively; P = not statistically significant for both tumor and remnant ablation) in 320 patients prepared with rhTSH and 74 by THW. When the definition of no clinical evidence of disease included a suppressed Tg <1 ng/mL and a stimulated thyroglobulin level <2 ng/mL, rhTSH-assisted remnant ablation was found to be associated with significantly higher rates of no clinical evidence of disease (74% rhTSH vs. 55% THW, P = 0.02) and significantly lower rates of persistent disease (19% rhTSH vs. 32% THW, P = 0.02) than was remnant ablation after THW. The conclusion of the study was that rhTSH-assisted remnant ablation is associated with rates of clinically evident disease recurrence and persistent uptake in the thyroid bed that are similar to those for traditional THW.

Elisei et al., in an even longer follow-up study, confirm that ^{131}I remnant ablation performed with rhTSH stimulation, over a median of nearly 4 years of follow-up, is a safe and effective means of preparing for remnant ablation as compared with THW in patients with low-risk tumors and is superior to ^{131}I DxWBS.

Ernest L. Mazzaferri, MD, MACP

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Prophylactic central neck dissection with total thyroidectomy in familial medullary thyroid cancer with codon 634 mutations is safe and results in high cure rates

Schellhaas E, König C, Frank-Raue K, Buhr H, Hotz H. Long-term outcome of "prophylactic therapy" for familial medullary thyroid cancer. Surgery 2009;146-906-12.

SUMMARY

BACKGROUND

Patients with medullary thyroid carcinoma (MTC) should be tested for genetic mutations in the RET proto-oncogene. Such testing provides information about the clinical behavior of the tumor and at the same time determines the risk of genetic susceptibility in first-degree relatives. Identification of gene carriers can prevent the development of invasive MTC at a premalignant stage by leading surgeons to perform prophylactic total thyroidectomy, the timing of which is dependent upon the type of mutation. The most common mutation at codon 634 is associated with progression from C-cell hyperplasia to MTC at an early age. Total thyroidectomy by 5 years of age is therefore recommended by the American Thyroid Association guidelines to reduce the likelihood of invasive MTC developing. However, the role and timing of prophylactic central neck dissection in patients with codon 634 mutations is less clear. The present study thus seeks to ascertain whether central neck dissection is beneficial for asymptomatic patients with codon 634 mutations.

METHODS

The study subjects were 17 patients with codon 634 mutations who underwent total thyroidectomy with central neck dissection from 1992 through 1999. All patients were asymptomatic genetic carriers undergoing prophylactic surgery. Fourteen had multiple endocrine neoplasia 2A (MEN2A) and 3 had familial MTC. The median age of the patients under study was 13 years (range, 4 to 36). Prior to surgery, ultrasonography (US) was performed on 15 patients, and basal serum calcitonin levels were obtained on all patients. Follow-up phone calls were made to the patients and their physicians to determine the subsequent course of the patient's disease. Inquiries were made about additional treatments as well as basal and stimulated calcitonin levels. The median follow-up was 147 months (range, 90 to 181).

RESULTS

Tumor Stages in Patients Who Underwent Prophylactic Thyroidectomy (Figure 1)

Surgical pathology revealed C-cell hyperplasia in 3 patients, invasive MTC (T1 tumor) <1 cm in 12 patients, and MTC from 1 to 2 cm (T2 tumor) in 2 patients. A mean of 10 lymph nodes were removed. Only two patients, ages 9 and 36 years, had lymph-node involvement, with T1 and T2 tumors, respectively. The preoperative serum calcitonin levels correlated with tumor size ($P = 0.012$) but not the presence of lymph-node metastases. Preoperative stimulated calcitonin levels did not correlate with tumor size or the extent of lymph-node metastases.

Pathology in 15 Patients with Ultrasound Findings (Figure 2)

Fifteen patients underwent preoperative US; nine did not reveal abnormalities. Six of these patients had invasive MTC, and one had lymph-node involvement. The remaining three patients had C-cell hyperplasia. Six patients were found to have thyroid nodules on US, all of whom had invasive MTCs.

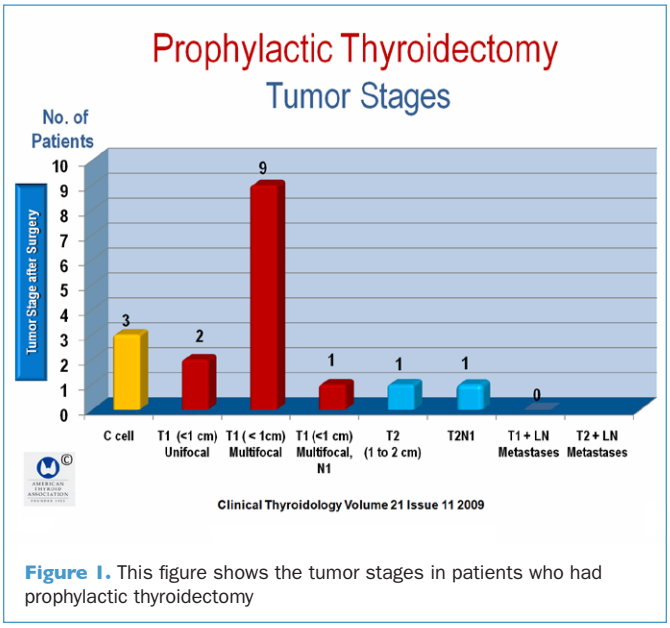

Figure 1. This figure shows the tumor stages in patients who had prophylactic thyroidectomy

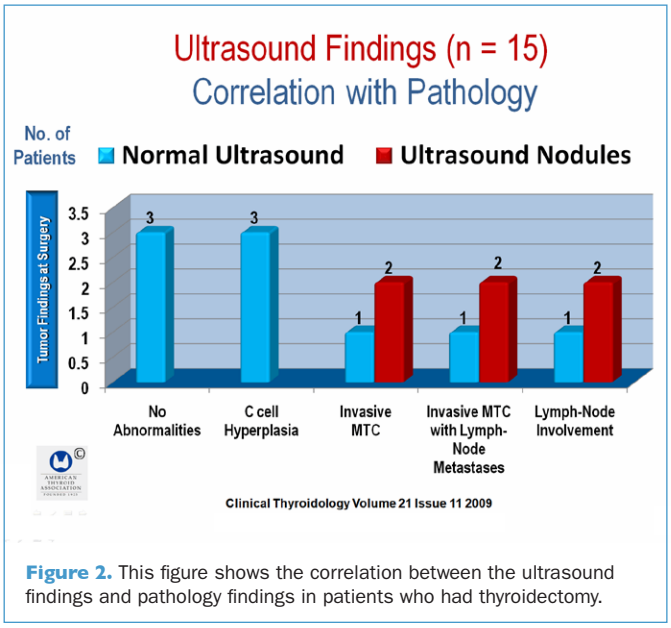

Figure 2. This figure shows the correlation between the ultrasound findings and pathology findings in patients who had thyroidectomy.

Postoperative Morbidity (Figure 3)
The incidence of permanent postoperative morbidity was low; only one patient (5.9%) had permanent hypoparathyroidism, requiring oral calcium supplementation. Five patients experienced transient hypoparathyroidism that resolved with long-term follow up. One patient had temporary recurrent laryngeal nerve injury, but repeat examination after the initial surgery revealed bilateral normally functioning nerves.

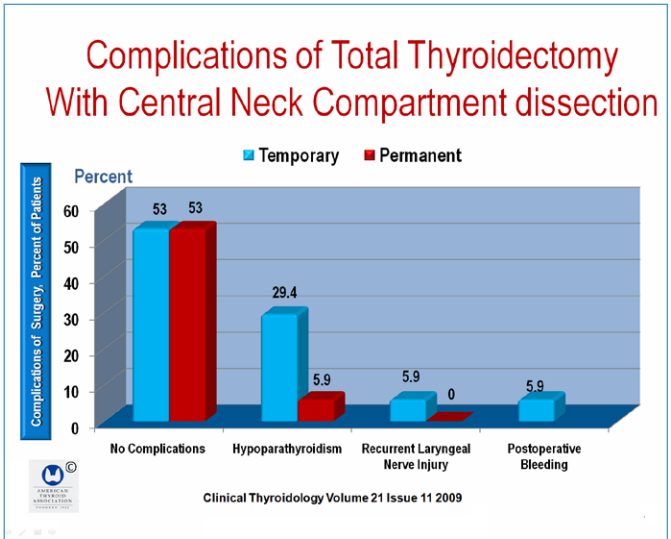

Figure 3. This figure shows the complications of total thyroidectomy with central neck compartment dissection

Recurrent disease was found in the two patients with lymph-node metastases at initial surgery. In the 36=year-old, calcitonin levels failed to normalize after initial surgery and 3 months later, he underwent a lateral neck dissection. Repeat calcitonin levels normalized after surgery and the patient remains free of disease. The 9-year-old patient, who had a T1 tumor, had malignant nodes removed 2 and 5 years after initial surgery as a result of persistently elevated calcitonin levels. At present, the patient's calcitonin remains elevated but there is no clinical evidence of disease.

CONCLUSION In the hands of experienced surgeons, prophylactic central neck dissection in conjunction with total thyroidectomy may be safely performed with minimal morbidity and results in high cure rates. However, the incidence of lymph-node metastases in patients with asymptomatic MTC was low in this patient population with codon 634 mutations; therefore, no general conclusion can be made about whether prophylactic central neck dissection is beneficial.

COMMENTARY

Medullary thyroid cancer, although difficult to treat once it becomes clinically evident, is unique in that it can be prevented with prophylactic thyroidectomy in patients with genetic mutations of the RET proto-oncogene. It has become the standard of care to perform genetic testing of all individuals diagnosed with MTC (1). A positive test becomes important for evaluation of the MEN syndromes in the patient, but also is significant for first-degree relatives who should determine their genetic susceptibility to the disease. Once clinically evident disease develops, the cure rate declines significantly (2, 3). Therefore, it is generally accepted that prophylactic thyroidectomy should be performed in patients testing positive for a RET mutation and may be recommended as early as the first year of life, depending on the specific codon involved (1).

However, the question of whether prophylactic lymph-node dissection should accompany the total thyroidectomy is more controversial. Lymph-node metastases are rare before the age of 11 years; in one large study of 50 children with MEN2A undergoing prophylactic total thyroidectomy and central-compartment dissection, only one patient was found to have lymph-node metastases before this age (4). Once present, however, these lymph-node metastases reduced the rate of biochemical cure to approximately 33% (4).

None of the patients in this study by Schellhaas et al. had clinical evidence of MTC before thyroidectomy. Only 3 of 17 patients had C-cell hyperplasia; the remaining 14 already had invasive MTC. The authors rightly contend that these 14 patients underwent therapeutic rather than prophylactic thyroidectomies. All but 2 patients had preoperative US to determine the extent of disease, and neither of the patients with metastatic disease at surgery were found to have abnormalities on US exam. The authors thus argue that because the majority of patients with codon 634 mutations already have invasive disease, which cannot readily be detected preoperatively, central cervical lymphadenectomy should be performed at the time of the initial thyroidectomy. This decision is justified by the fact that there were very few complications in their patients; only one patient had permanent hypoparathyroidism. The authors also maintain that such extensive surgery provides a more accurate method of staging and that removal of involved nodes decreases tumor mass, thereby improving outcome.

Schellhaas et al. measured serum calcitonin levels in addition to performing cervical US for preoperative staging. As expected, there was a direct correlation between serum calcitonin levels and tumor size. However, the calcitonin levels did not correlate with the presence of lymph-node metastases. Nevertheless, conclusions about the futility of measuring calcitonin for preoperative detection of lymph-node metastases should not be made from this study because of the small number of patients with metastatic disease. In fact, several studies have shown that a basal calcitonin of <40 pg/ml is only rarely associated with lymph-node metastases (5-7). A basal calcitonin of <40 pg/ml thus provides a reasonable cutoff below which prophylactic central-neck dissection may not be necessary (1). When prophylactic central-neck dissection is deemed necessary, it is critical that it be performed at a facility with experienced and highly skilled surgeons such as those in the study by Schellhaas et al.

This study provides valuable insight into the frequency of lymph-node metastases in patients with the codon 634 mutation.

Although it tends to be a more aggressive phenotype requiring thyroidectomy by age 5, it is reassuring that only 2 patients with codon 634 mutations had metastatic disease at the time of their initial surgery. Further, both of these patients had surpassed the recommended timeframe for thyroidectomy (ages 9 and 36 years). Because lymph-node metastases are uncommon before the age of 11 years, it may be beneficial to consider the patient's age in addition to the preoperative basal serum calcitonin levels and cervical US in order to decide on the extent of surgery needed for an individual patient rather than recommend prophylactic central-neck dissection for all patients with codon 634 mutations (1).

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

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