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EDITOR'S COMMENTS

This is the second 2009 issue of *Clinical Thyroidology*. As you may know, each issue will be sent to you as a separate list of articles that can be downloaded separately or as the entire document.

You will notice that the articles contain figures with the ATA logo and a citation with the volume and issue numbers. We encourage you to continue using figures from *Clinical Thyroidology* in your lectures, which we hope will be useful to you and your students.

WHATS NEW The last page which lists new reviews has been expanded to REVIEWS & HOT ARTICLES The page now contains references to important reviews and very recent articles that look especially important to the editors

Articles designated as an EDITOR'S CHOICE are especially important articles that we recommend you read in their entirety.

We welcome your feedback and suggestions on these changes.

Beginning with the first review article for *Clinical Thyroidology* by Dr. Elaine Ron, authors can cite our CONCISE REVIEWS by using the electronic citation at the end of each review.

Ernest L. Mazzaferri, MD, MACP
Jennifer A. Sipos, MD

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Citations: Several of our readers have asked that we provide the correct citation for Concise Reviews and Editorials written for *Clinical Thyroidology*. Beginning with this issue, an electronic citation will be appended at the end of each Concise Review and each Editorial. If our readers wish to cite commentaries at the end of each article, we can format the journal to do this as well.

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Extensive prophylactic central and lateral neck lymph-node compartment dissections for patients with papillary thyroid cancers smaller than 2 cm modifies the indication for ^{131}I therapy

Bonnet S, Hartl D, Leboulleux S, Baudin E, Lumbroso JD, Al Ghuzlan A, Chami L, Schlumberger M, Travagli JP. Prophylactic lymph node dissection for papillary thyroid cancer less than 2 cm: implications for radioiodine treatment. J Clin Endocrinol Metab December 30, 2008. doi:10.1210/jc.2008-1931

SUMMARY

BACKGROUND Prophylactic cervical lymph-node dissection denotes removal of lymph nodes that are considered normal preoperatively or intraoperatively, and therapeutic dissection refers to removal of malignant lymph nodes identified before or during surgery. Although some advocate routine prophylactic cervical-lymph-node central-compartment dissection for patients with papillary thyroid cancer (PTC), this remains controversial. The aim of this retrospective study was to quantify the role of prophylactic central and lateral neck lymph-node compartment dissection, and to describe its role in staging small tumors and treating them with ^{131}I.

METHODS Patients selected for study had PTCs 1 to 1.9 cm designated as stage T1N0 according to the 6th edition of the American Joint Commission on Cancer (AJCC) TNM classification (T denotes tumor; N lymph node, and M distant metastases [https://www.protocols.fccc.edu/fccc/pims/staging/thyroid.html]).

All had negative results on neck ultrasonography preoperatively and had total thyroidectomy, prophylactic bilateral level VI, and ipsilateral level III and IV cervical-lymph-node compartment dissections (Figure 1) that were extended to levels II and V when tumor was found in the superior pole of the thyroid or when metastases were found in level III or IV. Radioiodine therapy was not administered when a patient had no adverse prognostic factors such as lymph-node metastases, no tumor extension beyond the thyroid capsule, vascular invasion, unfavorable histology such as tall-cell carcinoma, or T1 <10-mm tumors with lymph-node micrometastases or when the patient was 18 years of age or younger. The others were treated with 30 to 100 mCi of ^{131}I (1.1 to 3.7 GBq) after levothyroxine withdrawal or recombinant human thyrotropin (rhTSH) administration. All patients had follow-up for at least 1 year. Paralysis of the recurrent laryngeal nerve or hypoparathyroidism was considered permanent if it persisted for longer than 1 year. A serum thyroglobulin (Tg) ≤0.9 ng/ml was considered undetectable.

RESULTS A total of 115 patients were studied (99 women [86%], 16 men [14%]; mean age, 48.5 years; range, 18 to 73 years; median, 50 years). Mean PTC size was 13.1 mm (range, 1-19) on ultrasound and 12.5 mm (range, 1 to 19) on final pathology, and was smaller than 10 mm in 51 patients (44%). The tumor was unifocal in 73 patients (64%), multifocal and bilateral in 25 (22%), and multifocal but unilateral in 17 (15%), extended beyond the thyroid capsule (pT3) in 33 (29%), and showed vascular invasion in 7 (6%) (Figure 2). Two had diffuse sclerosing variant PTC. Bilateral prophylactic central neck dissection was performed in all of the patients; prophylactic ipsilateral dissections were performed in 96 (94%) and bilateral level III-IV dissections were performed in 6 (6%). Ipsilateral level II-III-IV-V dissections were performed in 13 patients, 10 of whom (77%) had ipsilateral and 3 (23%) bilateral tumors (Figure 3). The mean number of central lymph nodes dissected per patient was 12 (range, 2 to 26; median, 7) and the mean number of lymph nodes per patient was 5 (range, 1 to 11; median, 2). Among the metastatic lymph nodes, 14.8% had extracapsular extension. The

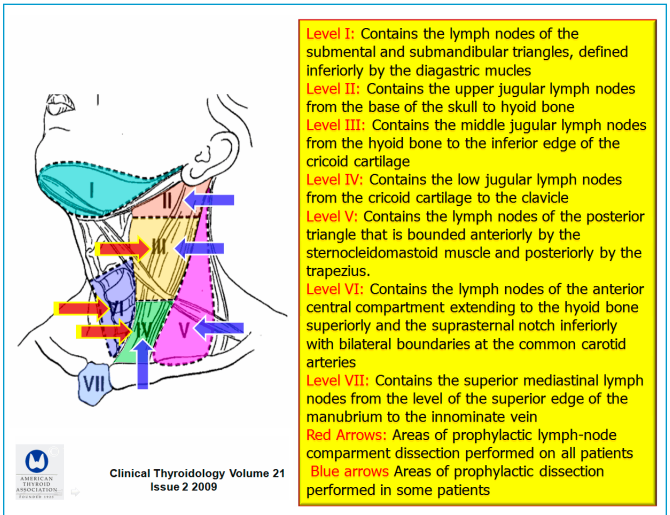

Figure 1. The cervical lymph-node compartments. Prophylactic ipsilateral cervical-lymph-node compartments III-IV and bilateral compartment VI dissections were performed in all patients (red arrows). Some underwent further prophylactic dissections in levels II-III-IV-V because of metastases in other neck compartments (blue arrows).

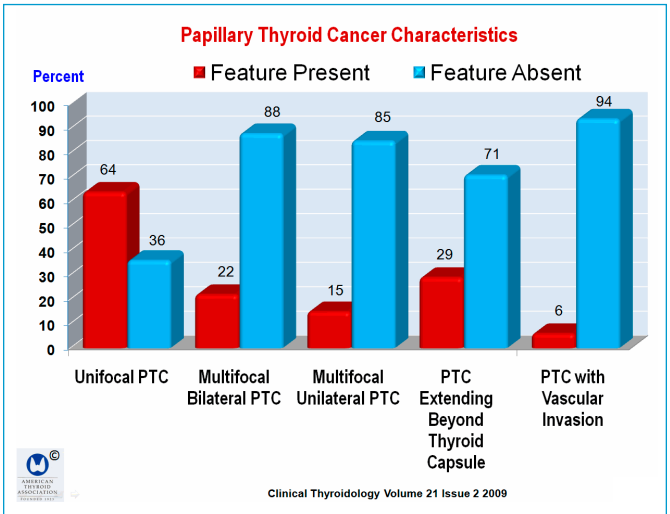

Figure 2. The characteristics of papillary thyroid cancers found at initial surgery.

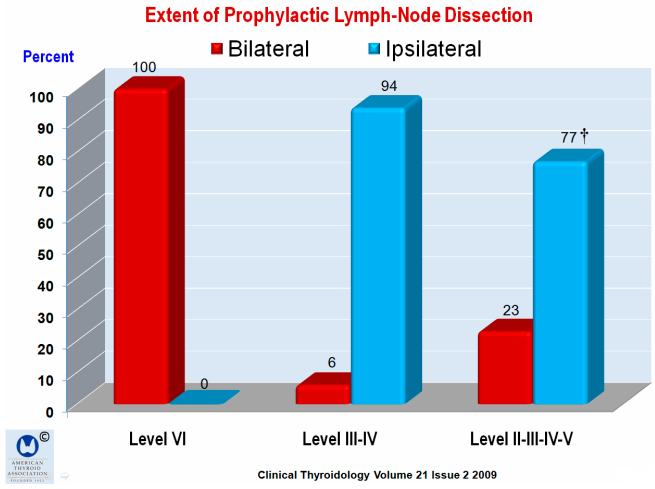

Figure 3. The extent of prophylactic lymph-node dissection. The indications for 10 patients with ipsilateral level II-III-IV-V dissections were PTC in the superior thyroid pole or metastatic lymph-node metastases in levels III-IV. Bilateral dissections in II-III-IV-V were performed in because of contralateral involvement in the same compartments. This figure is derived from data in Table 2 in Bonnet et al.

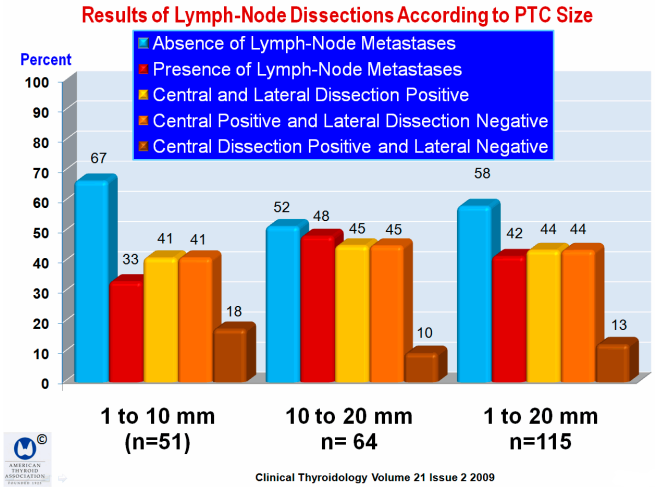

Figure 4. The results of lymph-node compartment dissections according to tumor size. This figure is derived from data in Table 3 in Bonnet et al.

results of lymph-node dissection according to PTC size are shown in Figure 4.

Univariate analysis identified the following prognostic factors for lymph-node involvement: age younger than 50 years (P = 0.001) and tumor extension beyond the thyroid capsule (P = 0.031), but multivariate analysis identified only age (odds ratio, 5.657; P<0.001) and tumor extension (odds ratio, 2.477; P = 0.48) as significant factors for lymph-node metastases.

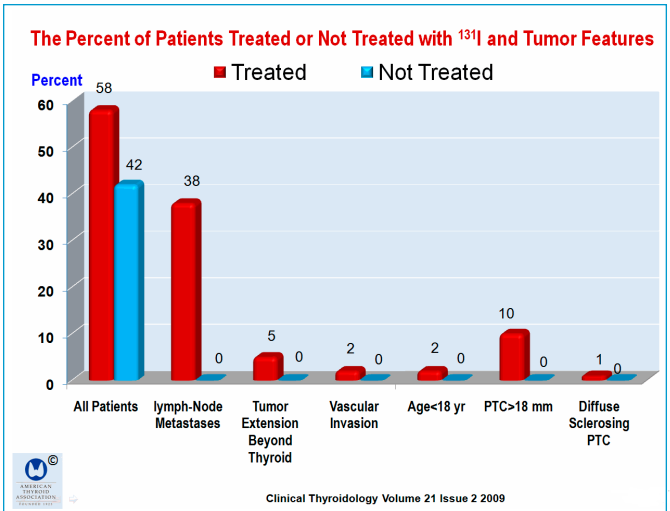

Figure 5. The indications for ^{131}I therapy.

In all, 48 patients (42%) were not treated with ^{131}I. Of this group, 44 (92%) had no lymph-node metastases or adverse prognostic factors, which included 31 tumors <10 mm and 13 >10 mm; 4 had a PTC <10 mm with micrometastases (Figure 5) In all, 67 patients (58%) had ^{131}I therapy for the following adverse prognosis factors: lymph-node metastases in 44 patients (38%), PTC >18 mm in 12 (10%), tumor extension beyond the thyroid capsule in 6 (5%), vascular invasion in 2 (2%), diffuse sclerosing variant of PTC in 1 (0.9%), and age <18 years in 2 (2%). Using the European consensus recommendations, lymph-node status modified the decision for postsurgical ^{131}I ablation for 25 of 115 patients (21.7%), 13 with T >10 mm and 12 with T <10 mm. Excluding the 33 patients with pT3 tumors, the indication for ^{131}I remnant ablation was modified in 25 of 82 patients (30.5%) with pT1 tumors. On the posttreatment whole-body scan, 59 patients (51%) had foci of ^{131}I uptake in the thyroid bed thought to be thyroid remnant. Radioiodine uptake was found in the central neck in 2 patients and in the lateral neck in 6, 1 of whom also had diffuse lung uptake.

One year after surgery, 1 patient (0.9%) had persistent laryngeal palsy and another (0.9%) had persistent hypoparathyroidism; no patients had suspicious cervical lymph nodes on ultrasound. Serum Tg levels during thyroid hormone suppression or rhTSH stimulation levels of Tg was undetectable (≤0.9 μIU/ml) on levothyroxine or after rhTSH stimulation in 97% of patients who had been treated postoperatively with ^{131}I.

CONCLUSION Prophylactic central and ipsilateral lateral neck dissection for PTC smaller than 2 cm facilitates the accurate selection of patients for ^{131}I ablation and modifies the indication for ^{131}I in 30% of patients with T1 tumors.

COMMENTARY

Slow growth and a favorable prognosis for survival characterize the clinical behavior of small PTCs with regional lymph-node metastases; however, the major challenge is to control locoregional recurrence, which happens with surprisingly high frequency. The rates of PTC lymph-node metastases in both low- and high-risk patients range from 25% to 60%, depending on the extent of surgery (1-3). Although lymph-node metastases are widely regarded to increase local recurrence rates without affecting survival, several studies suggest otherwise. A study of prophylactic lymph-node dissection in 342 patients with PTC found that systematic compartment-oriented dissection of lymph-node metastases improved recurrence ($P<0.0001$) and survival ($P<0.005$) especially in patients with T1 to T3 tumors (AJCC) (4). A study of almost 10,000 patient records maintained in the Surveillance, Epidemiology, and End Results (SEER) registry found that 14-year survival of patients with and without lymph-node metastases was 82% and 79%, respectively ($P<0.05$)(5). A more recent study (6) of the SEER registry records of 33,088 patients found that lymph-node metastases in patients 45 years or older with PTC, and patients of all ages with follicular thyroid cancer were associated with a 46% increased risk of death ($P<0.001$).

The ATA guidelines under revision suggest that prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with PTC with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4), which is a Grade C recommendation (Expert Opinion), and that near-total or total thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T2) noninvasive clinically node-negative PTCs and most follicular cancers (Grade C recommendation). The ATA guidelines also suggest preoperative cervical ultrasonography in all patients undergoing thyroidectomy. Although ultrasonography may identify suspicious cervical lymphadenopathy in up to half the cases, potentially altering the surgical approach in many patients, it has serious limitations in evaluating extracapsular invasion of the thyroid in deep locations in the neck and lymph-node metastasis in the central neck, which may lower the sensitivity of ultrasonography as much as 35%(7). There is controversy about prophylactic lymph-node dissections, especially in lymph-node compartment level VI. A systematic review of central lymph-node dissection by White et al. (8) found that systematic compartment-oriented central lymph-node dissection may decrease recurrence of PTC and likely improves disease-specific survival (Grade C recommendation) and that adding central lymph-node dissection to total thyroidectomy can significantly reduce serum Tg levels. They also concluded that there may be a higher rate of permanent hypoparathyroidism and unintentional permanent laryngeal nerve injury when compartment-oriented central lymph-node dissection is performed. Further, reoperation in the central neck compartment for recurrent PTC may increase the risk for hypoparathyroidism and unintentional nerve injury as compared with total thyroidectomy with or without central lymph-node dissection (Grade C recommendation) supporting a more aggressive initial operation (12).

The Bonnet study is a remarkable contribution that shows how meticulous lymph-node compartment dissection provides explicit information about initial tumor stage, which was far greater than T1N0 in a number of cases. The findings at surgery modified the decision for remnant ablation in 30% of the patients. No ^{131}I was administered to 42% of the patients, and 58% were treated with ^{131}I. The tumor was found to be unifocal in 64%, multifocal and bilateral in 22% and multifocal but unilateral in 17 (15%), and extended beyond the thyroid capsule (pT3) in 29%, and showed vascular invasion in 6%. None of this was suspected preoperatively. Prophylactic dissection resulted in unambiguous ^{131}I treatment of patients with lymph-node metastases while forgoing ^{131}I therapy for those without residual locoregional tumor. Whether patients will accept such extensive surgery for what is traditionally thought to be low-risk tumor remains to be seen.

Another important matter is that surgeons may not embrace this approach, as it likely prolongs the operative time for thyroidectomy. The surprising thing, however, is how prophylactic compartment dissection remarkably changed the stage of the disease, as compared with preoperative ultrasonography. Advocates of postsurgical radiation should recognize that the Bonnet study points the way to accurate selection of patients for ^{131}I therapy after surgery when tumors are metastatic or invasive.

Ernest L. Mazzaferri, MD MACP

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Simple clinical and laboratory features predict successful outcome of ^{131}I treatment of hyperthyroidism

Boelaert K, Syed AA, Manji N, Sheppard MC, Holder RL, Gough SC, Franklyn JA. Prediction of cure and risk of hypothyroidism in patients receiving ^{131}I for hyperthyroidism. Clin Endocrinol (Oxf) 2009;70:129-39.

SUMMARY

BACKGROUND There is no consensus concerning the most suitable amount of ^{131}I that should be administered to patients with hyperthyroidism. The aim of this study was to define the most effective fixed amount of ^{131}I that should be administered to patients with hyperthyroidism and to define the clinical and biochemical factors that predict outcome in individual patients.

METHODS This is a large retrospective study of patients with hyperthyroidism treated with a fixed amount of ^{131}I at Queen Elizabeth Hospital (University Hospital Birmingham England) from January 1984 through April 2006. The two outcomes assessed were the probability of curing hyperthyroidism and the risk of developing hypothyroidism following a single ^{131}I treatment. Patients were stratified into three diagnostic categories: (1) Graves' disease, (2) toxic nodular hyperthyroidism (TNH), and (3) indeterminate etiology (IDE). Graves' disease was defined as the presence of an elevated serum free thyroxine (T_4) level, with or without an elevated serum triiodothyronine (T_3), and an undetectable serum thyrotropin (TSH) level together with two of the following three conditions: Graves' ophthalmopathy, a palpably diffuse goiter, or elevated serum thyroid peroxidase antibodies (anti-TPOAb) with or without thyroglobulin antibodies. TNH was defined by a palpable nodular goiter, and patients who did not fulfill the criteria for Graves' disease or TNH were defined as having IDE, which comprised a mixture of Graves' disease and TNH. Goiter was assessed by neck palpation and classified as follows: none (normal size gland or impalpable) and medium (palpable) or large (visible) goiter. Graves' ophthalmopathy was defined according to the NOSPECS acronym (no signs or symptoms, only signs of lid retraction and stare, soft-tissue involvement, proptosis of 3 mm or greater, extraocular muscle involvement, corneal involvement and vision loss, and secondary optic-nerve disease). The following factors were defined at the time of diagnosis: Graves' ophthalmopathy; the presence, size, and type of goiter; anti-TPOAb titer, and serum free T_4 and TSH concentrations, which were available for analysis in 1165 patients. The protocol for selecting patients for ^{131}I therapy was unchanged for the duration of the study; however, in 1995 the ^{131}I dosage was increased from 5 to 10 mCi (185 to 370 MBq) until 2000, when it was increased again to 16 mCi (600 MBq) because a local audit demonstrated unacceptably low cure rates with 5 and 10 mCi of ^{131}I. If antithyroid drugs (ATDs) had been administered, they were withdrawn a week before ^{131}I therapy and were not restarted for a minimum of 1 week thereafter.

RESULTS The study group comprised 1278 patients, 543 (43%) with Graves' disease, 233 (18%) with TNH, and 502 (39%) with IDE. A total of 428 patients (79%) were female and 115 (21%) male. The mean(±SEM) patient age was 49.7±0.6 years, which was significantly higher in those with TNH (62.5±0.9) and IDE (51.5±0.8) as compared with Graves' disease (42.7±0.6) (P<0.0001). There were significantly more males in the Graves' disease group (21%) as compared with those with TNH (11.2%) (P<0.001).

The 485 patients treated with a single 16-mCi dose of ^{131}I had a greater cure rate (84%) as compared with those treated with either 5 mCi(63%) or 10 mCi (75%) (P<0.001) (Figure 1). Within

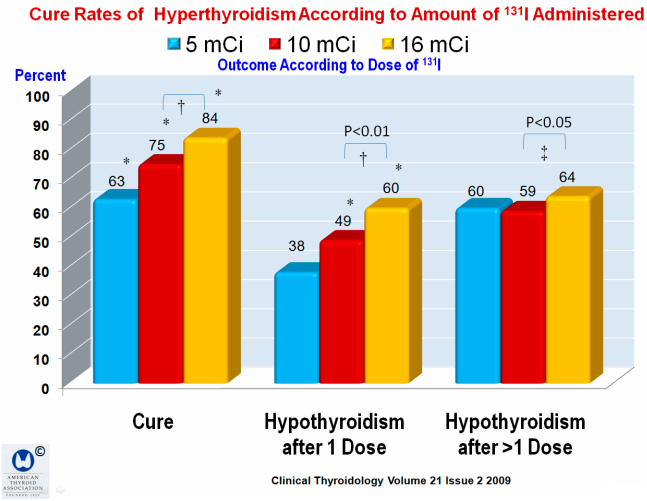

Figure 1. The prevalence and cure of hypothyroidism 1 year after a single fixed dose of ^{131}I. *P<0.001, comparing 5 vs. 10 mCi, and 5 vs. 16 mCi. †P<0.01, comparing 10 vs. 16 mCi. ‡P<0.05, comparing 10 and 16 mCi. Adapted from Figure 1 from Boelaert et al. Here and elsewhere percentages are rounded to a single integer.

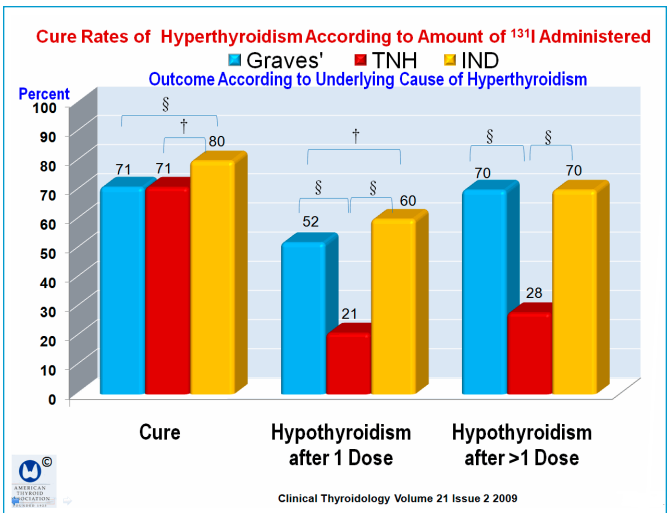

Figure 2. Outcome according to the underlying cause of hyperthyroidism. TNH is nodular hyperthyroidism, and IND is indeterminate cause of hyperthyroidism (features of both Graves' disease and nodular goiter). §P<0.0001. †P<0.01. Brackets show the comparisons that are statistically significant. Adapted from Figure 1 from Boelaert et al.

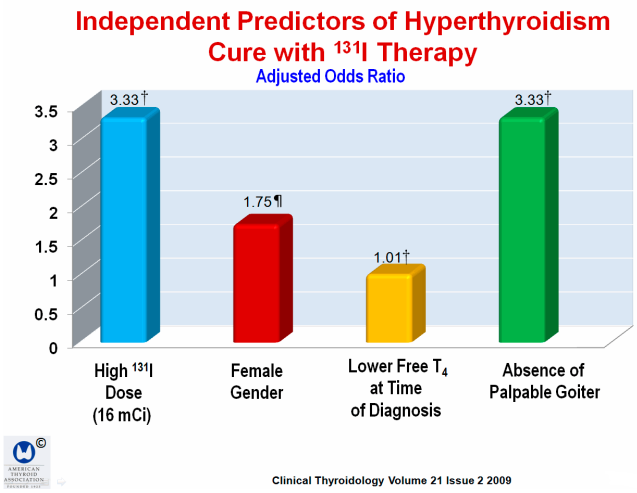

Figure 3. Independent predictors of hyperthyroidism cure according to binary logistic-regression analysis. Results are shown as adjusted odds ratios. †P<0.01. ¶P = 0.002.

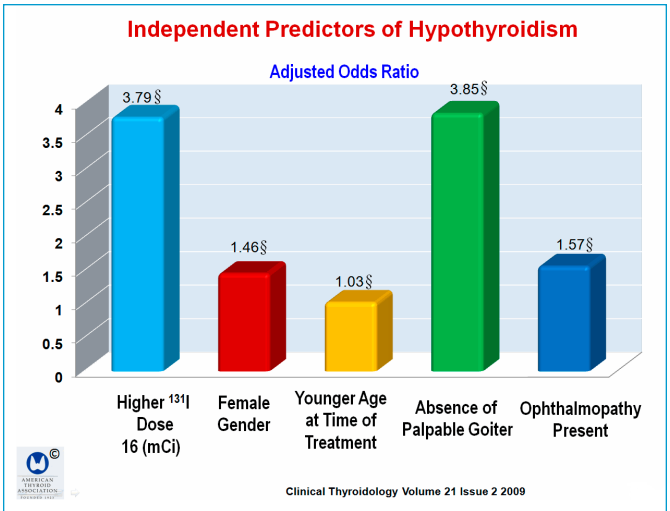

Figure 4. Independent predictors of hypothyroidism 1 year after initial therapy according to binary logistic-regression analysis. Results are adjusted odds ratios. §P<0.0001. ¶P = 0.002.

1 year, the incidence of hypothyroidism was significantly higher (60.4%) in patients treated with larger doses of ^{131}I (16 mCi) as compared with 38% of the patients treated with 5 mCi and 49.2% treated with 10 mCi (P = 0.001) (Figure 1).

The cure rates of hyperthyroidism were 71.3% in patients with Graves' disease and 71.2% in patients with TNH (P = not significant). However, 1 year after therapy there were significantly lower rates of hypothyroidism in patients with TNH (21%) as compared with Graves' disease (51.8%) (P<0.01) (Figure 2).

The use of ATDs 2 weeks before or after ^{131}I treatment (n = 845) was not associated with an increased risk for treatment failure, but was significantly associated with an increased risk for hypothyroidism, (adjusted odds ratio [AOR], 1.46; range, 1.16 to 1.85; P = 0.001), which was still present after correcting for the amount of ^{131}I administered or the underlying cause of hyperthyroidism.

Binary logistic-regression analysis found the following to be independent predictors of cure: a 16-mCi dose of ^{131}I (AOR, 3.33; range, 2.28 to 4.85; P<0.001); female gender (AOR, 1.75; range, 1.23 to 2.47; P = 0.002); lower serum free T_4 concentration at the time of diagnosis (AOR, 1.01; range, 1.01 to 1.02; P<0.001); and absence of a palpable goiter (AOR, 3.33; range, 2.00 to 5.56; P<0.001) (Figure 3). The independent predictors that identified hypothyroidism 1 year after therapy were as follows: 16 mCi of ^{131}I (AOR, 3.79; range, 2.66 to 5.38; P<0.001); female gender (AOR, 1.46; range, 1.05 to 2.02; P = 0.02); younger age (AOR, 1.03; range, 1.01 to 1.04; P<0.0001); absence of a palpable goiter (AOR, 3.85; range, 2.38 to 5.88; P<0.001); and presence of ophthalmopathy (AOR, 1.57; range, 1.06 to 2.31; P = 0.02) (Figure 4).

Based on the results from the binary logistic-regression analysis, the authors derived a formula to predict the probability of cure, which is summarized in Tables 2, 3 and 4 in the article, which they use in practice using a mathematical model available at http://medweb4.bham.ac.uk/websites/boelaert/index.asp.

CONCLUSION Successful treatment of hyperthyroidism with one dose of ^{131}I can be predicted by the administration of larger amounts of ^{131}I, and by female gender, younger age, low disease severity, and small goiter size. Independent predictors of ^{131}I-induced hypothyroidism are female gender, absence of palpable goiter, and larger amounts of ^{131}I.

COMMENTARY

Radioactive iodine (^{131}I) was first introduced as a novel treatment of hyperthyroidism in 1941 (1) and over the ensuing six decades became the preferred initial therapy in North America for patients with Graves' hyperthyroidism (2,3). Despite wide regional variations in its early use, ^{131}I has become first-line therapy for hyperthyroidism in many regions around the world (4-6). Yet its use continues to spark debate on a number of levels, including the amount of ^{131}I that is optimal for therapy(7) and the best technique to administer the treatment(4,7,8). In addition, there is concern about the efficacy of a single therapeutic dose of ^{131}I and the possibility of inducing hypothyroidism, thus precipitating the lifelong need for levothyroxine-replacement therapy. This is of special concern when larger amounts of ^{131}I are administered. The converse concern is persistent hyperthyroidism that may occur when smaller amounts of ^{131}I are administered. Indeed, it is highly unlikely that this dosage conundrum can be solved. There also is ongoing debate about administering ATDs shortly before or after ^{131}I has been administered.

A number of studies have shown that fixed doses of ^{131}I are as good as more elaborately calculated doses (9), which are clearly less cost-effective and more cumbersome for the patient than is the use of predetermined standard doses (5,7-9). In fact, most physicians prefer to give fixed doses of 5 to 15 mCi; yet doing this leaves little chance of accurately predicting the success rate or the probability

of inducing lifelong hypothyroidism (5). For example, the cumulative incidence of hypothyroidism may be as high as nearly 56% at 1 year and 86% at 10 years after initial ^{131}I therapy (10); the same study found that independent risk factors predicting hypothyroidism were the presence of thyroid autoantibodies, no ATD therapy prior to ^{131}I, and a high dose of ^{131}I.

The use of ATDs around the time that ^{131}I is administered seems to interfere with the effects of ^{131}I, although there is disagreement about the importance of this effect. A meta-analysis of 14 randomized, controlled trials with a total of 1306 participants found that ATD therapy was associated with an increased risk for ^{131}I treatment failure (relative risk, 1.28; P = 0.006) and a reduced risk of hypothyroidism (12). The study found no difference in summary estimates for different ATDs or for whether they were given before or after ^{131}I treatment.

Boelaert et al. address all of these issues. The main strengths of this study are the large number of patients and the completeness of follow-up. The study has a few limitations, namely that goiter size was determined by palpation and that routine ultrasound evaluation was not performed. It also is not clear why patients treated with ATDs 2 weeks before and after ^{131}I therapy did not have an adverse effect on therapeutic outcome, which is contrary to prospective randomized studies (11).

Boelaert et al. found that the independent factors predicting the highest cure rates were a single 16-mCi dose of ^{131}I, female gender, less severe hyperthyroidism, and an absence of palpable goiter. Conversely, the independent factors predicting the highest rates of hypothyroidism were a single 16-mCi dose of ^{131}I, female gender, younger age, an absence of a palpable goiter, and the presence of ophthalmopathy. The highest cure rates were in patients with IDE, comprising patients with both Graves' disease and TNH. Nearly half (49.8%) of this group had impalpable goiters.

In summary, a small number of simple clinical and biochemical factors can be used to identify patients who should receive doses of ^{131}I that are more likely to increase the chance of cure while identifying others at high risk for hypothyroidism. The authors developed a model to help identify patients who are likely to achieve a cure and those who are at risk for hypothyroidism. The model is on a website that provides an estimate of risk that may be useful to practitioners. However, the authors provide the caveat that the validity of the model must be evaluated in different patient populations, especially those living in environments affecting iodine intake. Nonetheless, this website model might facilitate thoughtful discussion for patients undergoing counseling concerning the pros and cons of ^{131}I therapy for hyperthyroidism.

In my view, this is an article that should be read by all who are administering ^{131}I to patients with hyperthyroidism.

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Neck compartment lymph-node dissection results in clinical benefit for the majority of patients with recurrent or persistent papillary thyroid cancer but may have complications.

Schuff KG, Weber SM, Givi B, Samuels MH, Andersen PE, Cohen JI. Efficacy of nodal dissection for treatment of persistent/recurrent papillary thyroid cancer. Laryngoscope 2008;118:768-75.

SUMMARY

BACKGROUND Papillary thyroid cancer (PTC) has a recurrence rate of up to 30%. The current American Thyroid Association (ATA) treatment guidelines recommend lymph-node compartment-directed surgery as the first line of therapy for patients with locoregional cervical metastases and no evidence of distant metastases. However, the likelihood of such repeat surgical interventions in rendering patients free of disease is unclear. The aim of this retrospective study was to determine the efficacy and safety of central or lateral neck-lymph-node dissection in patients with recurrent PTC.

METHODS This is a retrospective chart review of patients receiving central or lateral neck compartment dissections for persistent or recurrent PTC treated from January 2004 through March 2006. Seventy-five patients underwent 79 lymph-node dissections and were evaluated for safety of the procedure. Thirty-eight dissections from the safety group were excluded from the efficacy analysis because of any of the following features: distant metastases, presence of antithyroglobulin (Tg) antibodies, postoperative radioiodine therapy prior to Tg measurement, no prior radioiodine ablation, known residual macroscopic disease, or undetectable preoperative Tg. Of the 41 remaining dissections, 30 were evaluable for cure based on preoperative and postoperative stimulated Tg measurements. Patients were considered cured if their postoperative thyrotropin (TSH)-stimulated Tg was <2.0 μg/L. The clinical status of the remaining patients was stratified according to the following postoperative Tg reductions: near-complete (≥80%), major (50 to 79%), minor (20 to 49%), unchanged (within 20% of preoperative values), or increased (>20%). Patients who had a major or near-complete response were considered to be clinically improved.

RESULTS The study population comprised 75 patients with recurrent or residual PTC who underwent selective central compartment dissection with or without lateral lymph-node compartment neck dissections performed by a single surgeon at a university hospital. All patients were previously treated with total thyroidectomy; the majority (92%) received radioactive iodine for remnant ablation. Fifty-seven patients (72%) had undergone lymph-node surgery prior to the study period.

All but seven patients (9%) had lymph-node involvement of the central or lateral neck; however, five resections revealed no lymph-node involvement and two found tumor in other sites. The central neck compartments contained tumor in 80% of resections, performed alone or in combination with lateral dissections; only 11% of patients had lateral disease in the absence of central compartment involvement. The lateral compartments were found to have malignant lymph nodes in 63% of the patients. Bilateral disease was present in 46% of the lymph-node resections.

Of the 41 resections evaluable for efficacy, 30 had paired preoperative and postoperative stimulated serum Tg levels. Of the remaining 11 resections without stimulated Tg postoperatively, nine had paired preoperative and postoperative unstimulated Tg levels to assess the benefit of surgery. The two patients without paired Tg levels were not cured based on the detectable unstimulated postoperative serum Tg value.

Sixteen of the 30 patients with postoperative stimulated Tg levels were determined to be cured (Figure 1). There was evidence of a clinical benefit, defined by a near-complete or major Tg reduction, in an additional 12 resections. The two groups combined revealed a clinical benefit or cure in 28 of 39 (72%) resections. The Tg values for each group based on the response to surgery are shown in Figures 2 and 3.

A mean of 29 lymph nodes were removed in 79 resections. Of the removed lymph nodes, an average of 7 were positive for metastatic disease; more lymph nodes were positive for malignancy among resections that were not curative as compared with those that were curative (8 vs. 6, P = 0.02). There also was a tendency toward bilateral disease with noncurative resections, though this was not statistically significant (14 vs 5, P = 0.066).

There were 25 minor complications among the 79 resections (32%), including transient hypoparathyroidism (n = 12, 16%), hematoma/seroma/abscess (n = 9, 11%), cellulitis (n = 2, 3%), temporary recurrent laryngeal-nerve paresis (n = 1, 1%), and keloid (n = 1, 1%). In all, there were 7 major complications (9%):

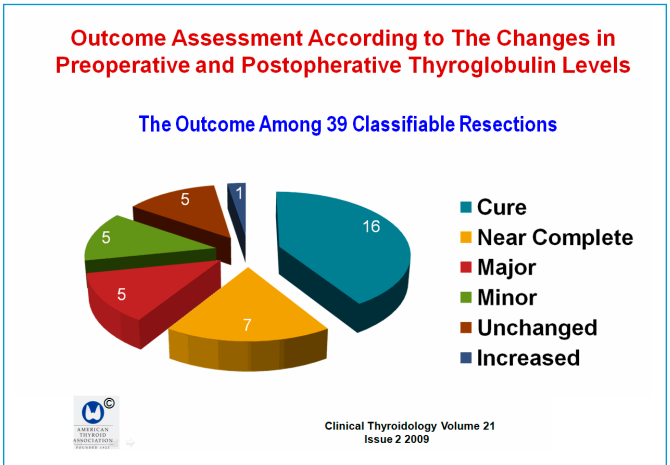

Figure 1. Outcome assessed according to thyroglobulin response to surgery. Patients were considered to be cured if postoperative TSH-stimulated Tg was <2.0 μg/L. The remaining patients were stratified by their postoperative Tg reductions as near-complete (≥80%), major (50–79%), minor (20–49%), unchanged (within 20% of preoperative values), or increased (>20%).

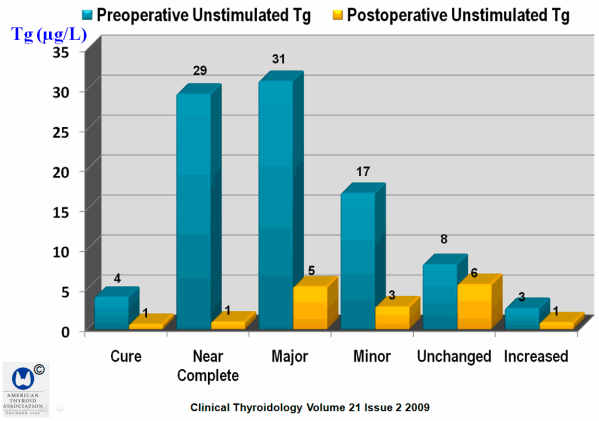

Figure 2. Tg responses to surgery based on unstimulated serum Tg levels Tg levels before and after surgery. (See legend for Figure 1.)

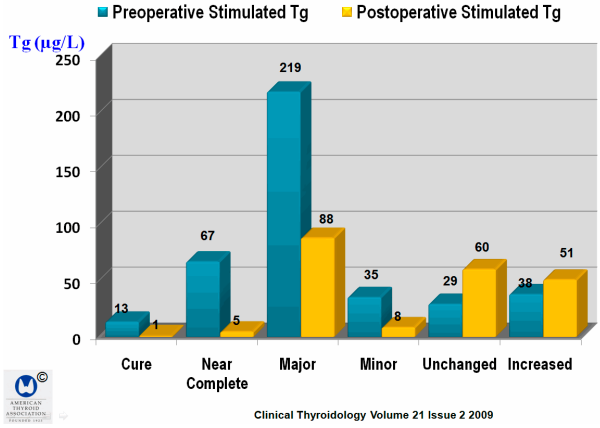

Figure 3. Tg responses to surgery based on TSH-stimulated serum Tg levels before and after surgery. (See legend for Figure 1.)

permanent hypoparathyroidism (n = 5, 7%), significant abscess requiring tracheostomy (n = 1), and deep venous thrombosis with subsequent pulmonary embolism (n = 1). There were no cases of permanent recurrent laryngeal-nerve damage.

CONCLUSION Lymph-node compartment dissection is not always a safe procedure for patients with recurrent or persistent PTC, even in the hands of an experienced surgeon, but it achieves some clinical benefit in almost 75% of patients.

COMMENTARY

The study by Schuff et al. addresses a very important question for the management of PTC: How often is repeat surgery likely to render a patient with recurrent or residual lymph-node metastases free of disease? The Schuff study found that resection of recurrent metastatic lymph nodes resulted in cure for 41% of patients and a clinical benefit in 72% of patients, as measured by a reduction in Tg of greater than 50%. An essential corollary to this issue is: How safe is the reoperation in terms of long-term morbidity? There are surprisingly little data to answer the first question when counseling a patient about reoperation for cervical lymph-node metastases. Most studies are limited by the concomitant use of radioiodine, lack of a unified definition for freedom from disease, and the retrospective nature of the studies (1-3). Current data support the findings of the Schuff study that only 20 to 40% of patients are deemed free of disease after a reoperation for recurrent or residual thyroid cancer in the form of cervical-lymph-node metastases (1-3). Likewise, the rate of postoperative complications in this patient population was in keeping with previous studies (4,5). Experience of the surgeon is a critical factor in determining the rates of postoperative hypocalcemia and vocal-cord paresis (6), and should be taken into account when counseling a patient for surgery. In the experienced hands of surgeons such as in this study, the likelihood of developing a permanent complication is low.

Patients with PTC have a high rate of lymph-node metastases at the time of initial surgery, ranging from 20 to 50% with standard pathology assessment (7), but are considerably higher when sophisticated molecular techniques are used to detect micrometastases (8). Many patients initially undergoing total thyroidectomy without central compartment dissection, with or without lateral neck compartment dissection, may present with macroscopic tumor years after initial treatment when lymph-node metastases have grown large enough to attract clinical attention. Many such patients will be considered for reoperation to render them free of disease. However, many questions remain concerning the optimal extent of surgery in this setting. A large retrospective study (9) of patients with untreated PTC found that those with one to five central compartment lymph-node metastases had a 69% chance of ipsilateral lateral neck lymph-node involvement. Of those with more than five central compartment lymph nodes, 100% had ipsilateral involvement, and 60 to 71% also had contralateral involvement. This and other studies of prophylactic neck dissection that yield high rates of previously undetectable lymph-node metastases highlight a major issue. The American Thyroid Association (ATA) guidelines suggest systematic neck lymph-node dissection, referring to en bloc dissection of anatomic neck compartments, as compared with selectively excising lymph nodes ("berry picking"), which is not recommended. Prophylactic dissection denotes removal of lymph nodes that are considered normal preoperatively or intraoperatively, and therapeutic dissection refers to removal of malignant lymph nodes identified before or during surgery. The revised ATA guidelines suggest that prophylactic central-compartment neck dissection (unilateral or bilateral) may be performed in patients with PTC with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T_3 or T_4) and that near-total or total thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T2) noninvasive clinically node-negative PTCs and most follicular cancers. The guidelines for lymph-node compartment dissection in patients who have previously undergone thyroidectomy are less clear, mainly because the risk for central compartment dissection is higher when patients undergo reoperation (10). Repeat surgery may result in low success rates because of the presence of large

and sometimes invasive lymph-node metastases in unexplored neck compartments.

Although studies of neck compartment dissection for recurrent or persistent disease yield high rates of positive lymph-node involvement, the long-term benefit of achieving a disease-free status is uncertain, making it difficult to advise central compartment reoperation. Radioactive iodine therapy may be a more useful approach providing the tumor is iodine-avid and bulky metastases have been surgically excised.

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Iron deficiency anemia in patients with subclinical hypothyroidism benefits substantially by the addition of low-dose levothyroxine to iron replacement, as compared with iron replacement alone

Cinemre H, Bilir C, Gokosmanoglu F, Bahcebasi T. Hematologic effects of levothyroxine in iron-deficient subclinical hypothyroid patients: a randomized, double-blind, controlled study. J Clin Endocrinol Metab 2009;94:151-6.

SUMMARY

BACKGROUND Patients with untreated overt hypothyroidism frequently have concomitant anemia. Treatment of the underlying thyroid disorder will typically improve the anemia, without any other specific hematologic intervention (1). Nearly 30% of patients with subclinical hypothyroidism (SH) may also have coexistent anemia (2). The anecdotal experience of the authors of the study under discussion is that there is a group of patients with anemia and SH who are resistant to oral iron supplementation. This study seeks to determine whether the addition of levothyroxine (L-T_4) to the standard iron replacement regimen will be more effective in ameliorating the hematologic condition.

METHODS Patients were selected from an Internal Medicine outpatient clinic at Duzce University in Turkey. New patients with anemia and SH who were seen from June through September 2007 were screened for underlying causes of anemia. Patients were excluded from the study if they had anemia due to other causes or other comorbid diseases, such as renal insufficiency, coronary heart disease, uncontrolled hypertension, or diabetes mellitus. To rule out other secondary causes of anemia, renal function was checked and peripheral-blood smears were performed. Each patient had three stool guaiac tests. Patients were also examined for signs and symptoms of malabsorption, colon cancer, and inflammatory bowel disease. In all, 51 patients who had iron deficiency anemia were eligible for the study and were randomly assigned to receive either 80 mg of ferrous sulfate (FeSO4) orally (iron-only group) or 80 mg of FeSO4 plus 25 μg of levothyroxine (L-T_4-plus-iron group) in identical capsules. Patients were instructed to take their capsules three times daily on an empty stomach 1 hour prior to meals. Diet instructions included 60 to 70 g/day of red meat and avoidance of excessive amounts of black tea. Four to six weeks after initiation of the intervention, hemoglobin (Hb) and hematocrit (Hct) were measured. After 12 weeks, ferritin, total iron-binding capacity (TIBC), transferrin saturation, fasting serum iron (Fe), thyrotropin (TSH), free T_4 (FT_4), Hb, Hct, and red-cell (RBC) levels were remeasured and the study was terminated.

RESULTS One of the 51 patients enrolled in the study was lost to follow-up. Among the remaining 50 patients, 25 were in the iron-only group, and 25 were in the L-T_4-plus-iron group. There were 22 men and 3 women in each group, with a mean age of 38 years (range, 27 to 50) and 35 (range, 29 to 55) in the iron group and L-T_4-plus-iron group, respectively. Baseline laboratory values were similar in the two groups. Patients did not have physical findings of hypothyroidism, and all but one patient reported no symptoms related to the anemia. There was no significant difference in the presence of serum antithyroid peroxidase or antithyroglobulin antibodies between the two groups. The two groups were similar in baseline hematologic status and thyroid-function indexes. Baseline mean (±SD) Hb was 10.4±1.58 and 12.9±0.93 g/dl, mean Hct 31.9±4.7 and 31.9±4.7%, mean RBC count 3.9±0.66 and 3.27±2.77 106 cells/μl, and mean serum TSH 6.5±1.24 and 7.4±1.65 μIU/ml in the iron-only group and L-T_4-plus-iron group, respectively (P = nonsignificant for all). There were no adverse effects of treatment in either group. Mean Hb increased by 0.4 in the iron-only group and by 1.9 g/dl in the LT_4-plus-iron group (P<0.0001). Likewise, the change in RBCs, Hct, iron, transferrin saturation, ferritin, and FT_4 were significantly

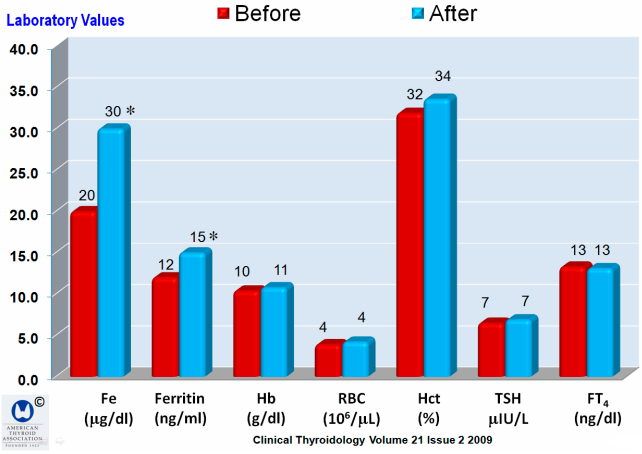

Figure 1. Change in blood parameters 3 months after iron treatment. *P <0.0001 for the change in iron levels between the iron only and L-T_4-plus-iron groups.

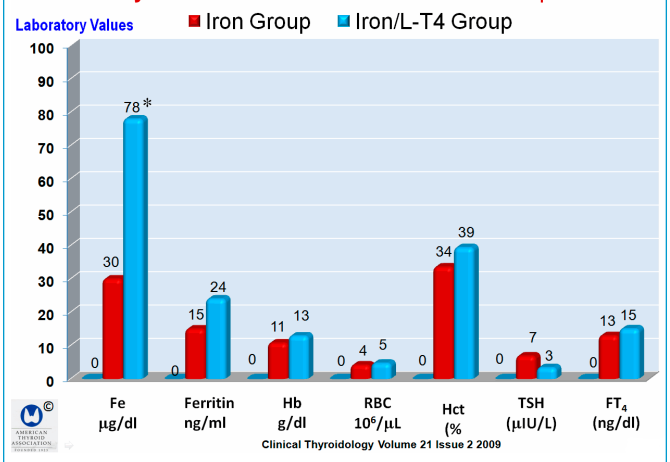

Figure 2. Change in blood parameters 3 months after iron and L-T_4-plus-iron treatment. *P <0.0001 for amount of change in hemoglobin between iron only and L-T_4-plus-iron groups.

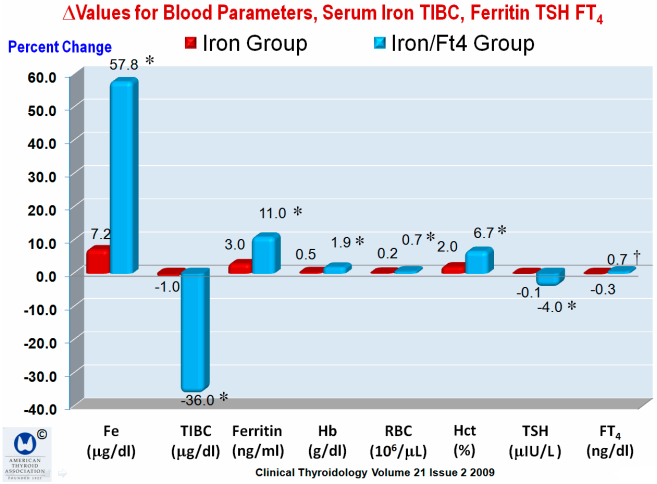

Figure 3. Incremental hematologic parameters before and after 3 months of treatment. *P <0.0001 for amount of change in hematocrit between iron-only and L-T_4-plus-iron groups. †P = 0.03.

higher in the L-T_4-plus-iron group than in the iron-only group. The decrease in TIBC and TSH after treatment was greater in the L-T_4-plus-iron group than in the iron-only group. There was a significant negative correlation between baseline Hb and the change in Hb in the L-T_4-plus-iron group, such that the more anemic patients were observed to have a greater hematologic response to the L-T_4-plus-iron than patients with higher starting Hb levels (Figures 2 and 3). Serum TSH normalized in 23 of the patients in the L-T_4-plus-iron group, and was reduced in 2.

CONCLUSION Iron deficiency anemia in patients with subclinical hypothyroidism benefits substantially by the addition of low-dose L-$T_4$to iron replacement, which yields greater improvement in hematologic parameters than iron replacement alone. Subclinical hypothyroidism should be treated in patients with iron deficiency anemia when the two conditions coexist. This would provide a desired therapeutic response to oral iron replacement and prevent ineffective iron therapy.

COMMENTARY

Subclinical hypothyroidism is a common endocrine disorder, affecting approximately 4.3% of the U.S. population (3). Significant controversy exists as to whether this condition should be treated with L-T_4 replacement therapy or simply followed expectantly until the development of overt hypothyroidism (4,5). This study by Cinemre et al. makes an argument in favor of early treatment for a subset of patients with SH. This is the first study to examine the effect of L-T_4 used jointly with iron supplementation on the hematologic parameters of patients with SH and iron deficiency anemia. It is interesting to note that FeSO4 has been shown to bind to and reduce the efficacy of L-T_4 when the medications are taken simultaneously (6). In spite of this well-recognized drug–drug interaction, the patients in the combination group had significant improvements in their TSH after 3 months of treatment. In addition, the combined intervention revealed significant improvement in levels of Hb over iron therapy alone, rendering the majority of patients euthyroid while simultaneously reversing the anemia. In fact, patients on combined therapy with the worse anemia achieved higher gains in Hb than patients with milder hematologic deficiencies within the same group. The majority of patients in the iron-only group also had significant improvements in Hb but they remained anemic upon completion of the trial.

An earlier study (7) found no change in Hb/Hct in patients with SH after 48 weeks of LT_4 therapy. Erythropoietin levels did increase, however. It is important to note that these patients were not anemic upon study entry, and as seen in the study by Cinemre et al., the greatest gains in Hb were made by those with lower baseline levels. It is thus conceivable that patients with a normal Hb at baseline would not see significant change in this particular hematologic parameter after L-T_4 therapy. The fact that the erythropoietin levels increased further supports the notion of a close association between thyroid dysfunction and hematopoiesis, though the exact mechanism of this relationship is not known. A recent study (8) showed that patients with subclinical hypothyroidism had significantly lower serum iron levels than euthyroid controls and L-T_4 replacement alone resulted in reversal of the iron deficiency. Taken together, these three studies suggest that iron deficiency and anemia are common among patients with subclinical hypothyroidism. Furthermore, treatment of the underlying thyroid disorder improves the hematologic profile. Though anemia is not identified as a potential consequence of untreated SH in the treatment guidelines (4,5), this study by Cinemre et al. expertly draws attention to this very important issue.

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Thyroid function during early pregnancy is similar in euthyroid women and in women with subclinical hypothyroidism treated with thyroid hormone

De Geyter C, Steimann S, Muller B, Kranzlin ME, Meier C. Pattern of thyroid function during early pregnancy in women diagnosed with subclinical hypothyroidism and treated with l-thyroxine is similar to that in euthyroid controls. Thyroid 2009;19:53-9.

SUMMARY

BACKGROUND Subclinical hypothyroidism (SCH) is defined as an elevation of serum thyrotropin (TSH) above the normal reference limit with normal serum free thyroxine (FT_4) or free triiodothyronine (FT_3) levels. When SCH occurs in pregnancy, there is an increased risk for miscarriage in both the first and second trimesters; however, there is uncertainty concerning how thyroid function during early pregnancy in women with SCH might differ from that in euthyroid pregnant women. The aim of this study was to determine the extent of thyroid secretory capacity and the regulation of thyroid function in women with SCH receiving levothyroxine ($L\text{-}T_4$) during early pregnancy as compared with pregnant euthyroid controls.

METHODS This cohort study was performed at Women's Hospital of the University of Basel, Switzerland, where thyroid function is routinely assessed in women undergoing an infertility workup during which ovulation was induced with 10,000 IU of human chorionic gonadotropin (hCG). Pregnant women with SCH—defined as a consistently elevated serum TSH greater than 4.5 μIU/ml in the presence of normal serum FT_4 and FT_3 levels—who agreed to participate in this prospective study had weekly serum samples collected until the 12th week of gestation for measurement of TSH, thyroglobulin, total T_4, FT_4, FT_3, estradiol, progesterone, hCG, and prolactin. Serum TSH was normalized with $L\text{-}T_4$ (50 μg/day) in women with SCH before infertility treatment and the establishment of pregnancy and was maintained until the 12th week of gestation. The control group comprised previously infertile pregnant women with normal thyroid function, defined as TSH levels ranging from 1 to 4 μIU/ml. This group took no medication other than folic acid and also had weekly serum samples taken during pregnancy until the 12th week of gestation.

RESULTS The study group comprised eight pregnant women with SCH taking $L\text{-}T_4$ and eight euthyroid controls in whom the clinical characteristics were not otherwise significantly different from those of the study group. The shortest interval between the beginning of treatment with $L\text{-}T_4$ and conception was 42 days and the longest was 3 years 10 months. Two women, one in each group, had a miscarriage at the 10th week of pregnancy. All the others delivered healthy children after uncomplicated pregnancies. Throughout the observation period, TSH levels remained higher among women with SCH taking $L\text{-}T_4$, as compared with euthyroid controls (Figure 1). Serum TSH levels in both groups increased during early pregnancy and reached peak levels at 6 weeks, with the most prominent differences occurring between study subjects and controls during weeks 6, ($P<0.06$) 7, ($P<0.03$) and 8 ($P<0.05$).) (Figure 1). Two of the eight patients diagnosed with SCH had TSH levels exceeding 4.5 μIU/ml during weeks 6 and 7 of their pregnancy. After week 7, serum TSH levels declined, reaching stable levels at week 9 and remaining parallel in the two groups thereafter (Figure 1). The amount of change in TSH, as compared with the TSH values at week 5, was comparable in the two study groups, except during week 12 when the drop in TSH was significantly greater in women with SCH as compared with the euthyroid group ($P<0.01$) (Figure 2).

Although the TSH levels were significantly higher among women with SCH as compared with euthyroid controls, the self-limited estrogen-induced increment of TSH during early pregnancy was

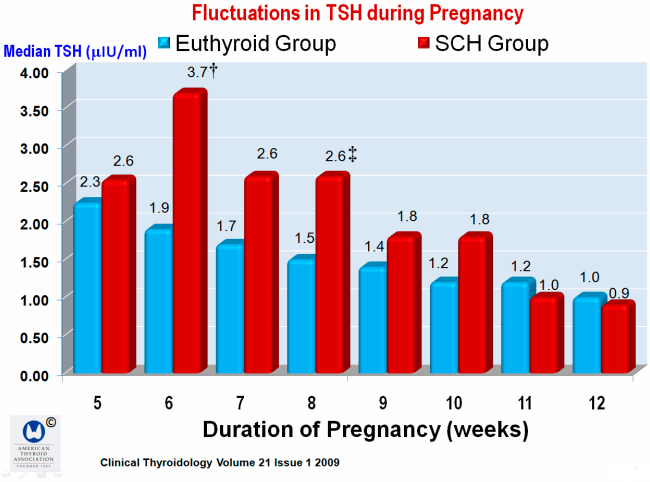

Figure 1. The fluctuations in TSH levels during pregnancy peak at month 6. *P<0.06. †P<0.006. ‡P <0.05. All P values are for comparisons of women with SCH and euthyroid controls. The figure was adapted from Figure 1a of De Geyter et al.

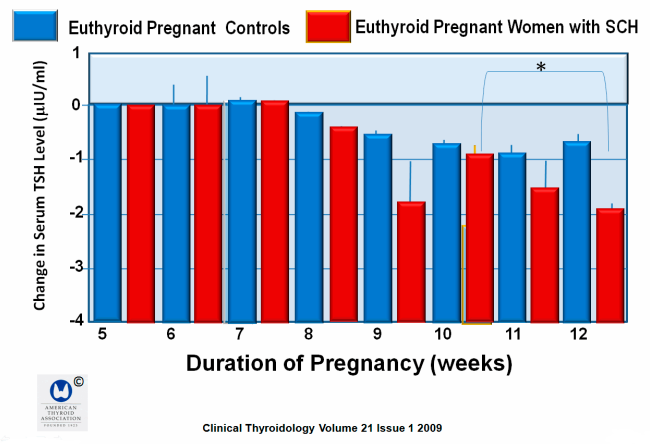

Figure 2. The TSH changes in months 5 to 12. TSH levels were calculated by subtracting the TSH level at week 5 in euthyroid controls and in women with subclinical hypothyroidism (SCH) taking $L\text{-}T_4$ (50μg). The height of each column represents the median value ±95%. The values were comparable in the two groups except during week 12 when the decline in the TSH was significantly greater in women with SCH compared with that in euthyroid women *P<0.01.

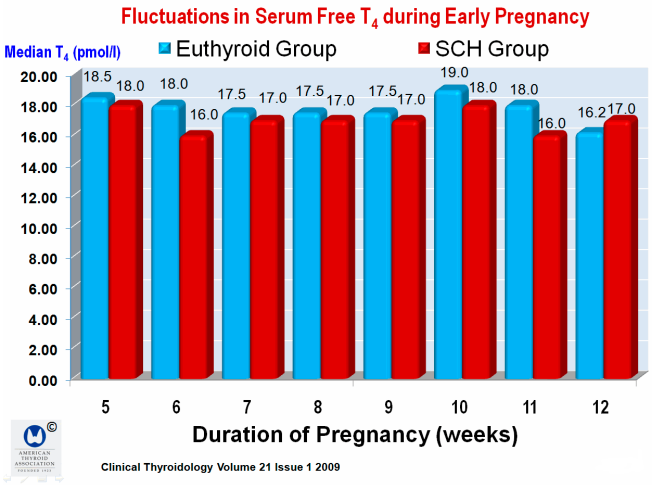

Figure 3. Fluctuations in Serum FT_4 in euthyroid and subclinically hyothyroid pregnant women Minor fluctuations in serum free T_4 and T_3 (T_3 not shown) occurred throughout pregnancy, without significant differences between euthyroid pregnant controls and women with SCH treated with L-T_4 during weeks 5 to 12 of gestation.

similar in the two groups. Serum hCG levels increased progressively during early pregnancy until week 9, remaining stable thereafter. In contrast, serum FT_4 and FT_3 remained unchanged throughout the sampling period both in women with SCH and in euthyroid controls (Figure 3). Prolactin levels increased in early pregnancy and continued to increase throughout pregnancy; however, by weeks 11 and 12 the levels were significantly lower in women with SCH treated with L-T_4 ($P<0.03$).

CONCLUSION The pattern of thyroid function during early pregnancy followed similar changes in euthyroid controls and women with SCH treated with 50 μg of L-T_4.

COMMENTARY

An evidence-based review by Stagnaro-Green confirmed that hypothyroidism and autoimmune thyroid disease in euthyroid women are associated with preterm delivery (1). This is of enormous concern, considering that preterm delivery, defined as birth occurring at or before 37 weeks of gestation, is the leading cause of perinatal fetal morbidity and mortality in the United States (2). Moreover, the rate of preterm delivery has been increasing significantly in the past two decades, rising from 8.8% of live births in 1989 to 10.2% in 1997, a relative increase of 15.6% (3), to about 12 to 13% in 2008 (2). Subclinical hypothyroidism, which appears to be an important component of this change, has been associated with miscarriage in both the first and second trimesters (1,4). A retrospective study by Casey et al. (5) found that among 17,298 pregnant women who presented for prenatal care to the University of Texas Southwestern Medical Center Parkland Hospital, 404 (2.3%) had SCH, a group whose pregnancies were 3 times as likely to be complicated by placental abruption (relative risk, 3.0) and an almost twofold rate of preterm birth (relative risk, 2.8). However, there is evidence that this might be avoided with L-T_4 therapy. Negro et al. (1) performed a prospective study in which 984 euthyroid women in the first trimester of pregnancy were screened for thyroid peroxidase antibodies (TPOAb). Of the 115 (12%) that were TPOAb-positive, 50% were treated with L-T_4 during pregnancy and 50% had no therapeutic intervention. The miscarriage rates were 3.5% in euthyroid woman who were TPOAb-negative and 2.4% (P = not statistically significant) in euthyroid women who were TPOAb-positive but were treated with L-T_4, as compared with a 22% miscarriage rate in women who were positive for TPOAb and were not treated with L-T_4 ($P< 0.01$). Maternal thyroid deficiency during pregnancy results in neuropsychological development in children (6), and there is evidence that low maternal serum FT_4 concentrations during early pregnancy are associated with impaired psychomotor development that is apparent in infancy and at least until the age of 3 years (7,8).

Thus, a number of studies implicate thyroid dysfunction in the form of overt or SCH, with or without autoimmune thyroid disease, in the high preterm delivery rates in the United States.

De Geyter et al. suggest that the clinical situations presented in their study are different from those observed with primary hypothyroidism, which are characterized by profound thyroid abnormalities that render the thyroid gland unresponsive to the compensatory stimulatory action of hCG. In their study, both SCH and ovarian hyperstimulation (a consequence of the infertility treatment) were associated with an intermediate rise then a decline in circulating TSH with normal FT_4 levels. The authors thus conclude that although both SCH and ovarian hyperstimulation were associated with an intermediate rise in circulating TSH, the pattern of thyroid function during early pregnancy followed changes similar to those observed in euthyroid controls. As a result, the authors believe that "…it is conceivable that the numerous reports on pregnancy-related complications observed in women with SCH, such as miscarriage and late obstetrical complications are not caused by hypothyroxinemia, but rather by additional contributing factors, such as age and antithyroid antibodies." However, it is difficult to reach this conclusion with any certainty as there were a limited number of subjects (n = 16) in the study, which was too small to reach appropriate statistical power. It is further limited by the supplementation of L-T_4 in women the group with SCH, which the authors suggest may have reduced possible differences between the two groups.

This study underscores how difficult it is to study thyroid function very early in pregnancy. This is undoubtedly an important contribution, but the interpretation of the data in terms of the pathophysiology of SCH in pregnancy is not immediately evident.

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Selenomethionine supplements may contain high levels of iodine as a result of an inactive ingredient in the tablet—kelp

Arum SM, He X, Braverman LE. Excess iodine from an unexpected source. N Engl J Med 2009;360:424-6.

SUMMARY

BACKGROUND This is a case report of a man with thyroid cancer and elevated body iodine concentrations from an unknown source.

METHODS A 55-year-old man with a large mass on the right side of his neck was found on fine-needle aspiration biopsy to have papillary thyroid cancer (PTC) in the right thyroid lobe. Total thyroidectomy and modified right neck dissection revealed a multifocal PTC, the largest mass being 1.8 cm in diameter, with thyroid capsular invasion without extrathyroidal extension. Lymph-node metastases were found in 26 of 78 cervical lymph nodes. After surgery, the patient was advised to have thyroid remnant ablation; however, he had undergone computed tomographic (CT) scanning with an iodine-rich contrast agent and was accordingly placed upon a low-iodine diet. Two months later, urinary iodine concentration was elevated to 394 μg/L (reference range, 42 to 350). The patient reported having ingested a large number of over-the-counter supplements, including selenium, vitamin C–bioflavonoid complex, calcium citrate, coenzyme Q10, α-lipoic acid, glucosamine–chondroitin complex, pygeum and saw palmetto, vitamin E, cellular forte, Pros-forte, green tea extract, methylsulfonylmethane, Vitamin B complex, glucosamine, Nettle, ß-carotene, vitamin D, Medizym, Bio zinc, folic acid, maitake mushroom extract, and L-threonine. The patient reported having reviewed the labels and finding no sources of iodine. As a result, the elevated iodine level was attributed to the CT.

RESULTS A 24-hour urine collection revealed an iodine content of 363 μg/L (optimal level, 94 to 360) according to spectrophotometric measurements in the authors' laboratory. After treatment with furosemide (20 mg daily) and a low-iodine diet, the 24-hour urinary iodine excretion remained elevated at 370 μg/L. As a result, the iodine content of 21 supplements the patient had been taking was measured (Figure 1). The selenium supplement was the source of the excess iodine (215 μg per tablet), with a total iodine ingestion of 29 μg, which was the result of an inactive ingredient in the supplement: kelp. When the patient stopped taking all supplements for 8 weeks and maintained a regular diet, his 24-hour urinary iodine excretion returned to a normal level (192 μg). After he stopped taking supplements and was placed on a low-iodine diet for 4 weeks, his 24-hour urinary iodine excretion fell to 36 μg/L.

CONCLUSION Excessive iodine intake came from an unexpected source: kelp-enriched selenium.

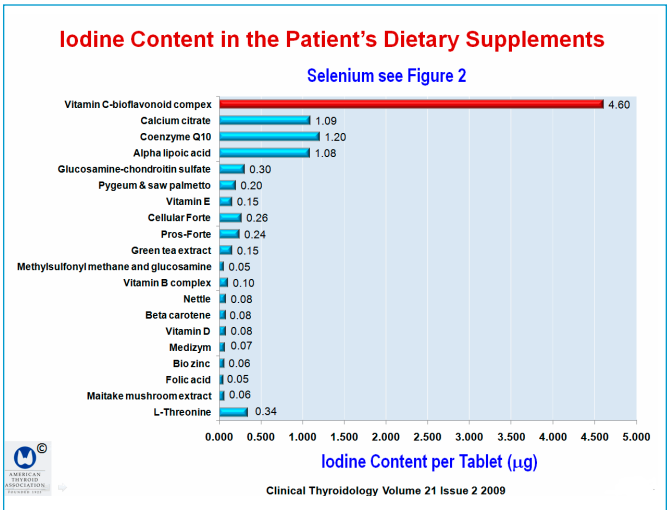

Figure 1. Iodine content in the patient's dietary supplements.

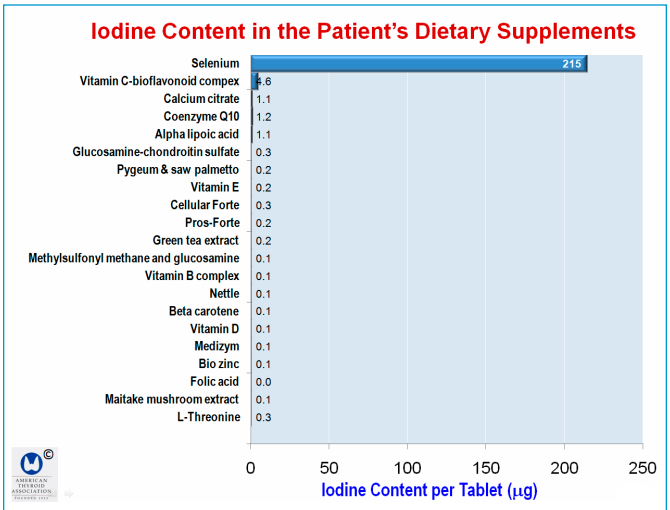

Figure 2. Urinary iodine content showing the disproportionately high iodine level in the Selenium tablets.

COMMENTARY

It is well known that excess exogenous iodine impairs the efficacy of ^{131}I therapy. In the patient under discussion, kelp-enriched selenium was the cause of the elevated urine iodine levels. The senior author of this study, Dr. L.E. Braverman is one of the leading worldwide authorities on iodine. As pointed out in this article, the iodine content of kelp is highly variable (1), and it is accordingly likely that the iodine levels are also variable in different batches of kelp-enriched selenium supplements. The key to this sleuthing was the accurate measurements of urinary iodine content performed by the standard, spectrophotometric measurements in Dr Braverman's laboratory.

A study that investigated whether urinary iodine levels change during the day found that 24-hour urinary iodine concentrations follow a circadian rhythm, with the lowest levels being between 8 and 11 hours and gradually peaking at about 24 hours (2). Urinary iodine returned to baseline levels between 21 and 22 hours in children only, peaking 4 to 5 hours after the main meals. The authors concluded that the existence of a circadian rhythm of urinary iodine is probably universal, but its profile depends on alimentation. As the nadir of urinary iodine is found in the morning, this might be an appropriate collecting period; the changes were small enough over a 24-hour period as to not interfere with spot-sample measurements of urine iodine levels throughout the day to assess adequacy of a low iodine diet for ^{131}I therapy. The iodine concentration for ^{131}I therapy is ideally <50 μg/L but without fastidious avoiding dietary iodine the level is more often around 100 μg/L. To regularly lower the urinary iodine level to <50 μg/day, patients should adhere to a low-iodine diet for 2 weeks (3).

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Disclosure

Dr. Mazzaferri receives honoraria from Genzyme for providing lectures.

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