

CLINICAL THYROIDOLOGY

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FEBRUARY 2010

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EDITORS' COMMENTS

This is the second 2010 issue of *Clinical Thyroidology*. As of January 25, 2010 there were 4408 members of the opt-in *Clinical Thyroidology* Notification email list. In addition, there were a total of 81,184 pdf article downloads and web page views for *Clinical Thyroidology* Volume 21 Issues 1–12 from January through December 2009. Our viewers listed a total of 202 specialties from 122 countries. Thank you all for your participation.

We wish to thank Dr. Kenneth Burman for his contribution to this issue of *Clinical Thyroidology* that will be very useful to our recipients.

IN MEMORIAM — DAVID V. BECKER MD



We are sorry to inform you that David V. Becker MD passed away on January 31, 2010. Dr. Becker was professor of radiology and medicine at Weill Cornell Medical College in Manhattan, and an attending radiologist and physician at New York Presbyterian Hospital/Weill Cornell Medical Center.

An internationally recognized expert and pioneer in the use of radioactive materials, Dr. Becker was an early leader in the use of radioactive materials for imaging and therapy. Among his countless achievements, Dr. Becker was an expert on the thyroid damage caused by the Chernobyl nuclear reactor accident in 1986, and later led a team for the National Cancer Institute that investigated the effects of radioactive iodine on the thyroid. Dr. Becker's international reputation is widely recognized. He went to Micronesia in the postwar years, where he studied the people who had been exposed to radiation fallout from atmospheric testing of nuclear bombs, including the crew of a Japanese fishing trawler that was in the vicinity of the fallout. On a personal level, Dr. Becker's many dear friends at the American Thyroid Association will deeply miss his friendship and countless contributions to medicine and the ATA.

EDITOR'S CHOICE ARTICLES are particularly important studies that we recommend you read in their entirety. This month we have two important Editors' choice articles. Both address the management of papillary microcarcinoma from a widely different view, providing an excellent format to delve into the complex features of treating these small tumors from two different perspectives.

SEARCH FOR PREVIOUS ISSUES OF *Clinical Thyroidology* Many of our readers have asked for a quick way to find articles published in this journal over the past years. Now you can access previous issues using key words, author names, and categories such as Hyperthyroidism, Thyroid cancer, or other terms pertaining to thyroidology. You will find this by simply clicking the following URL: <http://thyroid.org/professionals/publications/clinthy/index.html>.

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

WHATS NEW On the last page of the journal, in addition to the section **HOT ARTICLES AND REVIEWS**, we have added **CURRENT GUIDELINES** that have relevance to thyroidologists, endocrinologists, surgeons, oncologists, students, and others who read this journal. We hope you will find this useful.

We welcome your feedback and suggestions 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
Jennifer A. Sipos, MD

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Prophylactic Neck Dissection in Differentiated Thyroid Cancer

Differentiated thyroid cancer is increasing in incidence, and the frequency of cervical-lymph-node metastases is common, occurring in approximately 40 to 60% of patients (1-5). The basic tenets of treatment for differentiated thyroid cancer typically include a thyroidectomy, radioactive iodine therapy, and close monitoring with periodic serum thyroid-function tests, measurements of thyroglobulin levels, and neck sonography (6). However, following surgery and radioactive iodine therapy, many patients will still have detectable serum thyroglobulin levels with cervical adenopathy detected on sonography. The aspect of this issue on which we have chosen to focus relates to whether prophylactic cervical- or lateral-lymph-node dissection at the time of the original thyroidectomy is beneficial and will reduce the likelihood of the patient having residual disease when monitored. The definition of compartments and surgery type is as defined by Carty et al (7). Although cervical-lymph-node metastasis may occur in as many as 40 to 60% of patients (8, 9), preoperative sonography, even when meticulously performed, will detect only perhaps 50% of central-node involvement, and even less frequently detects disease in the lateral compartments (10, 11). Given these observations, it is hypothesized that a more thorough neck dissection at the time of the original thyroidectomy will decrease the likelihood of cervical disease remaining (or occurring).

These studies must be considered in relationship to the recently revised ATA guidelines (6). These guidelines recommend, unless there is a specific contraindication, that an initial near-total or total thyroidectomy be performed when the thyroïdal papillary thyroid cancer is larger than 1 cm. A patient with a smaller tumor and no worrisome risk factors (e.g., history of head and neck irradiation) may have a lobectomy alone (Recommendation level A). Many (but not all) studies have suggested that the presence of cervical-node metastases, especially in patients over 45 years of age, portends a higher risk of recurrence and even mortality. They also note that if central-compartment pathologic adenopathy is identified by the prophylactic removal of nodes, the pathologic classification may increase from N0 to N1a, thus increasing the stage in patients older than age 45 from 1 to 3 (6). It is controversial whether prophylactic central- or lateral-compartment dissection decreases the risk of cervical recurrences. The ATA guidelines recommend that a prophylactic central-compartment neck dissection (ipsilateral or bilateral) "may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4). Recommendation rating: C" (6). Of relevance to our discussion, the ATA guidelines note that patients with papillary thyroid cancer with T1 or T2 lesions without apparent invasion and negative cervical nodes (and most follicular thyroid cancers) may not require prophylactic central neck dissection (Recommendation rating: C) (6). Similar recommendations are made for lateral-compartment dissection. If there is evidence of adenopathy then surgical dissection is recommended (Recommendation rating: B). There is no specific comment regarding prophylactic lateral neck dissection (6).

Bonnet et al. (12) performed a retrospective review of 115 patients who had a small focus of differentiated thyroid cancer less than 2 cm without apparent cervical adenopathy on preoperative ultrasound. Specifically, patients were selected for neck compartment surgery only if the primary tumor was <1 to 2 cm and had no obvious lymph-node metastases on neck ultrasonography. Surgery consisted of a total thyroidectomy, level VI central neck dissection, and ipsilateral jugulocarotid supraclavicular and supraomohyoid compartment dissection (levels III and IV). Baseline demographic analysis revealed that the mean age was 48.5 years and the mean tumor size on ultrasound was 13.1 mm (range, 1 to 19). The mean tumor size pathologically was 12.5 mm (range, 1 to 19), with 44.3% of patients having tumor sizes less than 10 mm; 63.5% of tumors were single, 21.8% were bilateral multifocal, 14.8% were unilateral multifocal, 28.7% extended beyond the capsule, and 6.1% had vascular invasion. Thyroid tumor sizes of 1 to 10 and 10 to 20 mm in 66.7% and 51.6% of patients, respectively, had no evidence of tumor in both their central and lateral compartments. Papillary cancer adenopathy in both central and lateral compartments was present in 43.7% of patients with tumor sizes of 1 to 20 mm, whereas only 12.5% had negative central nodes with positive lateral adenopathy. Younger age (<50 years) and tumor extension beyond the capsule were both associated with cervical-node metastases, whereas sex, tumor size larger or smaller than 10 mm, and vascular invasion were not significantly associated with cervical-lymph-node pathology. It should also be mentioned that the size of the lymph-node metastases was not reported, and it is currently believed that patients with microscopic lymph-node metastases have an improved outcome as compared with macroscopic lymph-node metastases (13,14).

This study seems contradictory to the present guidelines, which indicate that prophylactic central- and lateral-compartment dissections are not indicated in patients with small papillary thyroid cancers without evidence of cervical-node involvement on sonography or at the time of surgery. In the study by Bonnet et al. (12), cervical-node metastasis was observed in approximately 42% of patients who had thyroid cancers 1 to 20 mm. They make the argument that the detection of previously unrecognized positive cervical adenopathy frequently changes the tumor stage and also increases the frequency of 131I therapy. More than 97% of their patients had an undetectable baseline or recombinant human thyrotropin-stimulated thyroglobulin level 1 year after surgery.

Machens et al. (15) have recently published their retrospective analysis of 251 patients with thyroid cancer who underwent surgery, 69 of whom had a total thyroidectomy with central-neck cervical-node dissection performed for confirmed or suspected central-compartment disease. A total of 88 patients had their initial total thyroidectomy performed in conjunction with central ipsilateral-compartment dissection because of

evidence of disease on preoperative or intraoperative analysis. These patients also had a lateral-neck dissection. A total of 56 of these patients had only an ipsilateral lateral-compartment dissection, and 43 (77%) had lateral-neck involvement with papillary thyroid cancer. A total of 32 patients had a bilateral lateral-neck dissection, and 24 of these (75%) had evidence of node involvement. In addition, the greater the number of involved central-compartment nodes the more likely there were positive nodes in the ipsilateral and contralateral areas. In fact, if there were more than five positive nodes in the central compartment, positive nodes were also identified in the ipsilateral compartment 100% of the time and approximately 70% in the contralateral neck.

Counterbalanced against the view of Bonnet et al. (12) are the potential complications of original central- and lateral-neck dissections (16). Roh et al. (8) observed temporary or permanent hypocalcemia in 23.6% and 1.4% of patients, respectively, and transient vocal-fold paralysis in 1.4%. Inadvertent incision of the thoracic duct may cause a chyle leak; other rare complications include development of a seroma, Horner's syndrome, and brachial plexus or accessory-nerve injury or local infection (17). It is possible that the complication rates may even be higher in less experienced hands.

Shaha (16,17) suggests that in most patients with differentiated thyroid cancer, an elective node dissection is not indicated if the surgeon does not identify pathology in this compartment at the time of surgery. However, if there is obvious pathologic adenopathy, especially if confirmed on frozen section, then a careful dissection of the involved compartment is indicated. It is generally agreed, however, that the surgeon's intraoperative impression may not be as accurate as the detection of cervical adenopathy by preoperative or intraoperative radiologic techniques.

Sadowski et al. (18) performed routine prophylactic central-compartment dissection in 169 patients with differentiated thyroid cancer (average tumor size, 1.26 cm); 25.5% had positive ipsilateral and contralateral adenopathy, while 4.7% had positive contralateral adenopathy and negative ipsilateral adenopathy. Davidson et al. (19) observed that pathologic adenopathy occurred in 12 of 19 patients (63.2%) with a central-compartment neck dissection, in 61 of 73 (83.6%) with a lateral-neck dissection, and in 11 of 14 (78.6%) with combined central and lateral dissections. Sywak et al. (20) studied patients with papillary thyroid cancer (>1 cm) who did not have clinical evidence of adenopathy. A total of 56 patients had an initial total thyroidectomy with central-compartment dissection (average tumor size, 20 mm) and 391 had a total thyroidectomy alone (average tumor size, 23 mm). Following surgery and subsequent 131I therapy at approximately 6 months of follow-up, the average serum thyroglobulin level during levothyroxine withdrawal was lower (0.4 ng/ml vs. 9.3 ng/ml), and more patients had an undetectable serum thyroglobulin level (72% vs.

43%) in the patients who had a total thyroidectomy and central-compartment dissection as compared with a total thyroidectomy alone. The rate of recurrence between the two groups, although not statistically significant, was 3.6% versus 5.6%. White et al. (21) reviewed the literature regarding the utility of routine prophylactic neck dissection in patients with papillary thyroid cancer and concluded that a systematic central-compartment dissection may decrease the chance of recurrence, but there are very limited data suggesting a survival benefit. However, as noted above, this procedure may increase the likelihood of the patient having a lower serum thyroglobulin level when monitored.

It is, therefore, controversial, whether central and ipsilateral lateral-compartment dissection should be performed at the time of the original thyroidectomy, especially in patients with thyroid nodules less than 2 cm and in whom thyroid ultrasound does not reveal cervical adenopathy. Moreover, the controversy extends to whether the surgeon can accurately identify tumor and pathologic adenopathy at the time of surgery. Given the often subjective nature of being able to identify pathologic adenopathy during surgery, it then becomes problematic that central- and lateral-compartment dissections should be performed only when there are abnormalities noted during the operation.

My view is that the high frequency of cervical-node pathologic adenopathy even in small original thyroid cancers suggests that there is utility of prophylactic central dissection for all tumors. Patients with small thyroid cancers may have their treatment plan modified by identifying positive cervical nodes, and older patients will have their stage changed. Central-neck dissection, performed during the initial thyroidectomy, may increase the likelihood of hypocalcemia, but, in general, is a relatively safe procedure. Reoperation in a central compartment may be more problematic than when performed during the initial procedure. Lateral dissection is a more complex, potentially serious issue. Additional complications possibly associated with lateral dissection include neck discomfort, recovery time, and cosmetic issues. Based on the studies noted, it seems reasonable to perform a prophylactic central-neck dissection with the initial thyroidectomy in patients with known papillary thyroid cancer, but further studies are warranted prior to routinely recommending a prophylactic lateral-neck dissection. Of course, individual recommendations must be tempered by the experience of the surgeon in the context of the entire clinical and surgical situation.

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CLINICAL THYROIDOLOGY FOR PATIENTS
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Initial near-total or total thyroidectomy and central compartment lymph-node metastases has the greatest impact on recurrence in children with papillary thyroid cancer treated at the Mayo Clinic

Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. *World J Surg* 2010; January 20. [Epub ahead of print].

SUMMARY

BACKGROUND

Thyroid cancer is a relatively uncommon disorder in children, making it difficult to perform meaningful studies because the cohorts are usually very small and follow-up is generally short. As a consequence, there is considerable debate concerning the most effective treatment of children and young adults with differentiated thyroid cancer. This study of children and young adults with papillary thyroid cancer reports the efficacy of therapy in one institution. One of the objectives of the study was to determine the efficacy of surgical therapy and radioactive remnant ablation (RRA) in this group of patients.

METHODS

This is a retrospective study of 215 patients younger than age 21 years who had surgery for papillary thyroid carcinoma (PTC) at the Mayo Clinic during a 68-year period from January 1, 1940, through December 31, 2008. The data concerning this cohort were retrieved from the hospital database, from which details of the patient's initial presentation, treatment, and pathology records were reviewed, and for this study, the histologic diagnosis was reconfirmed by the pathology department. Follow-up information was obtained by a review of death certificates in 22 patients and by reexamination or correspondence with the patients, family, or attending physicians in the other 193 patients, who were alive, up to June 2009.

RESULTS

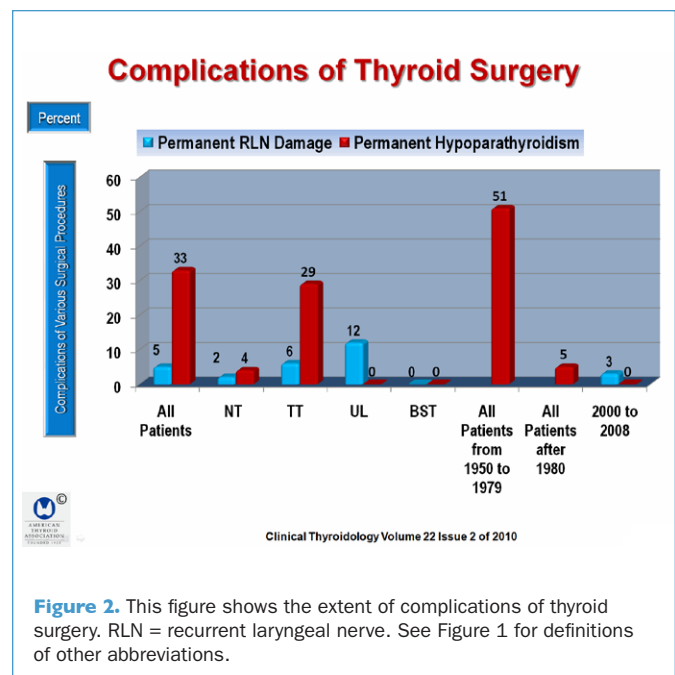
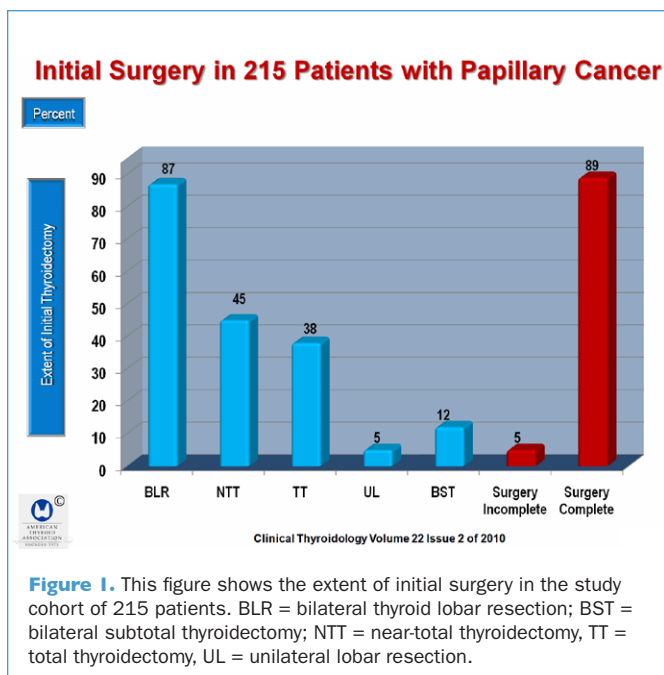
The study subjects were 215 patients, 152 of whom were women (70%) with a median age of 16 years at the time of initial diagnosis. Thirty-six patients had a history of head or neck irradiation, which occurred during 1936 through 1957. Mean tumor size was 2.65 cm (median, 2.20; range, 1 to 9.5). Of the 190 reexamined histologic specimens, 55 (29%) were multifocal and 39 (6%) were locally invasive.

Initial Surgery (Figure 1)

Of the 215 patients who had thyroid surgery, bilateral lobar resection (BLR) was performed in 188 (87%). The most frequently performed primary surgical procedure was near-total thyroidectomy (NTT) in 96 patients (45%); total thyroidectomy (TT) was performed in 82 patients (38%). Bilateral subtotal thyroidectomy (BST) was performed in 10 patients (5%). Unilateral lobectomy (UL) was performed in 25 patients (12%). Lesser procedures were performed in the remaining 1% of patients. A total of 11 patients (5%) had incomplete initial tumor resection, 185 patients (86%) had lymph nodes removed at the time of initial surgery, and 168 (78%) had lymph-node metastases. In addition, 11 patients (5%) had incomplete tumor excision, and 192 (89%) had complete thyroid resection with no distant metastases at the time of initial examination or within 30 days of the operation.

Complications of Surgery (Figure 2)

Permanent unilateral recurrent laryngeal-nerve damage occurred



in 10 patients (5%): in 3 (12%) after UL, in 5 (6%) after TT, and in 2 (2%) after NTT.

Permanent hypoparathyroidism requiring long-term calcium and vitamin D therapy occurred in none of the 35 patients treated with either BST or UL. However, permanent hypothyroidism occurred in 9 patients (4%) after NT and in 28 after TT (29%), but in no patients who underwent UL or BST.

During 1950 through 1979, permanent hypoparathyroidism developed in 22 of 43 patients who had TT (51%) but since 1980, only 2 of 30 patients (5%) have had permanent hypoparathyroidism. However, during 2000 through 2008 there have been no cases of permanent hypoparathyroidism and only 1 case of permanent unilateral recurrent laryngeal-nerve damage.

Neck Lymph-Node Surgery (Figure 3)

A total of 185 of the 215 patients (86%) had cervical lymph-node surgery as part of the initial surgery. In the early decades, “node-picking” in the central lymph-node compartment (CLNC) was performed unilaterally in 51 of the 215 patients (24%) and bilaterally in 13 (6%). Only 27 patients (13%) had bilateral modified neck central neck lymph-node dissection (CLND), while 29 of 215 (13%) had unilateral CLND modified neck dissection as part of the initial surgery. A combination of “berry picking” and lateral-compartment dissection was performed in 25 patients (12%). Since 1995, CLND was performed routinely with BLR in 40 of the 215 patients (19%)

Postoperative Thyroid RRA (Figures 4 and 5)

A total of 192 of the 215 patients (89%) had tumor that was confined to the neck and completely resected. Only the 192 patients with no evidence of residual thyroid tissue were deemed eligible to receive RRA. Of this group, 68 (35%) were treated with ¹³¹I RRA; 54 (79%) received one ¹³¹I treatment, 9 had two treatments (13%), 4 had 3 (6%) and 1 had 4 (6%). The cumulative ¹³¹I activity varied greatly, from 29 to 400 mCi, averaging 79 mCi.

There was enough information in 64 of the 68 patients (86%) to evaluate the efficacy of the ¹³¹I treatment; 55 of 64 ¹³¹I treatments (86%) were judged to be successful according to a diagnostic whole-body scan using ¹³¹I or ¹²³I, showing no residual disease ¹³¹I and no uptake higher than background ¹³¹I uptake.

Figure 5 shows the trend in RRA ablation at the Mayo Clinic from 1960 to 2008, which reflects the change in surgery during this period.

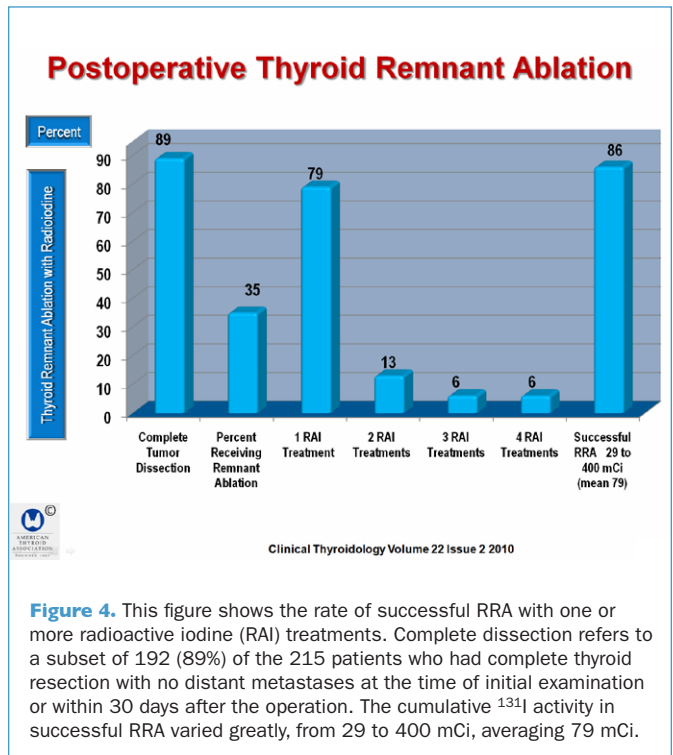


Figure 4. This figure shows the rate of successful RRA with one or more radioactive iodine (RAI) treatments. Complete dissection refers to a subset of 192 (89%) of the 215 patients who had complete thyroid resection with no distant metastases at the time of initial examination or within 30 days after the operation. The cumulative ¹³¹I activity in successful RRA varied greatly, from 29 to 400 mCi, averaging 79 mCi.

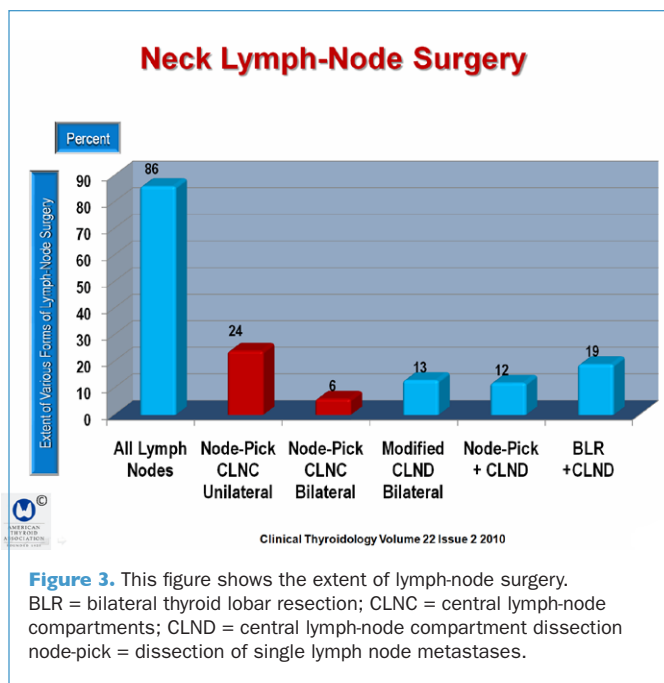


Figure 3. This figure shows the extent of lymph-node surgery. BLR = bilateral thyroid lobar resection; CLNC = central lymph-node compartments; CLND = central lymph-node compartment dissection node-pick = dissection of single lymph node metastases.

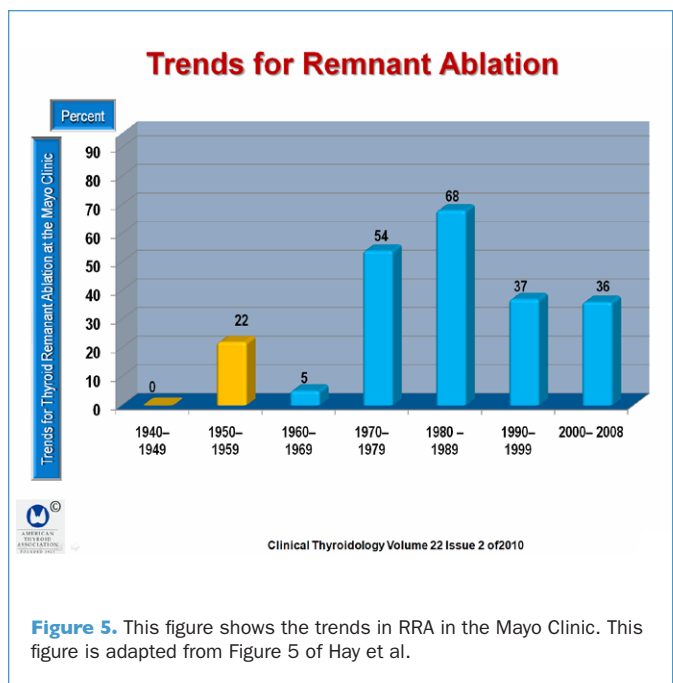


Figure 5. This figure shows the trends in RRA in the Mayo Clinic. This figure is adapted from Figure 5 of Hay et al.

Postoperative Recurrence Rates (Figures 6 and 7)

Postoperative recurrence was considered only for the 192 patients who had complete thyroid resection with no distant metastases within 30 days after the initial surgery. The recurrence rates at 5, 10, 20, and 30 years were 20, 22, 27, and 30% (Figure 6).

After 40 years of follow-up, neck or distant metastases were found in 61 patients (32%). Among the 192 patients, recurrences were found in the thyroid bed in 12 patients (6%), in regional neck metastases in 38 (20%), and in distant metastases in 13 (7%). After 5, 10, and 20 years of follow-up, the postoperative local recurrence rates were 3, 4, and 7%, respectively, and the rates of distant metastases were 4, 4, and 5% (Figure 7).

Cause-Specific Mortality

After a median follow-up of 28.7 years, there were no deaths from PTC during the first 20 years of follow-up, including 12 patients (5%) who had distant metastases at the time of initial diagnosis. After 25 years, there were two deaths from distant metastases (0.09%), both of which were associated with localized disease at the time of initial treatment that comprised bilateral lobar resection performed with curative intent. The cause-specific survival rates since 1951 were 100% at 20 years and 98% from 30 through 50 years.

Comparison of Surgical Outcome after UL or BLR (Figure 7)

During the first three decades of the study period from 1940 through 1970, UL was performed in 24 of the 25 patients who had surgery (96%). During 1940 through 1969, UL comprised 24% and BLR 73% of the primary surgeries; however, there were only two deaths during this period, making the difference between UL and BLR statistically insignificant.

After 40 years of follow-up, the rates of local recurrences were 6% with BLR and 35% with UL (P<0.001). The rates of regional recurrence were 13% after BLR and 60% after UL (P<0.0001).

From 1970 through 2008, most of the BLR surgeries (94%) were near-total (n = 59) or total (n = 51) thyroidectomy.

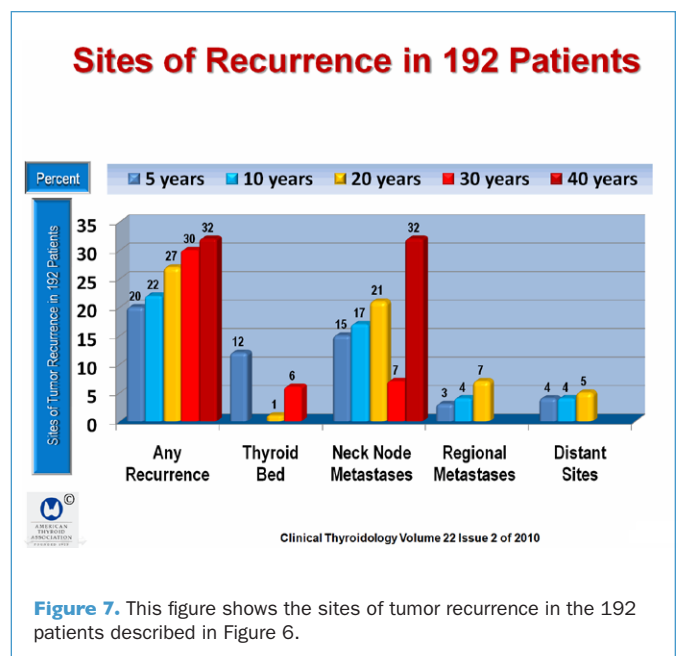
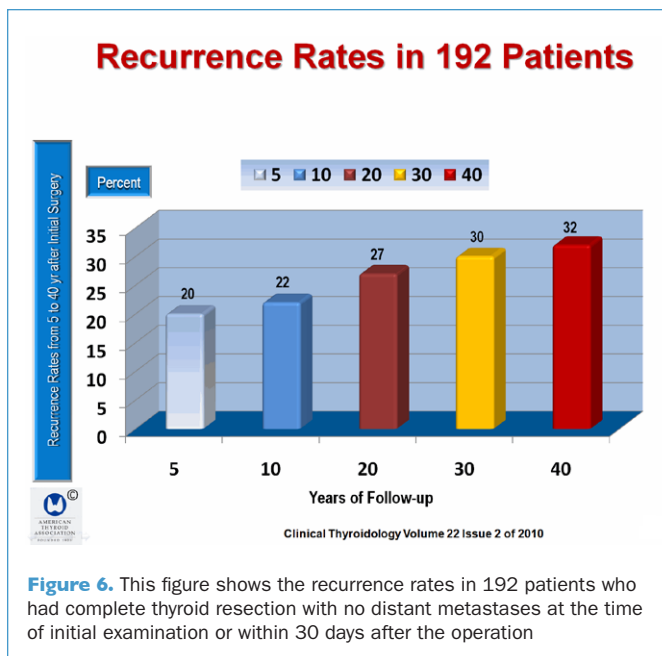
Outcome of Thyroid RRA

From 1950 through 2008, 169 patients had BLR surgery with the intent of curing the patient, which in 53 patients (31%) was followed by ¹³¹I RRA within 6 months of surgery. There was only one death in the group without ¹³¹I and no deaths in those who received ¹³¹I, which was not statistically significant (P = 0.62). Lower recurrence at both local and distant sites were found in the 53 patients who had been treated with ¹³¹I as compared with surgery alone, but the difference was not statistically significant (n = 116) (P = 0.018, and P = 0.013, comparing the two treatments respectively).

Using similar data from 1950 through 2008 in which 161 patients were treated with either near-total or total thyroidectomy, there were no deaths due to PTC. The differences between survival after surgery alone versus surgery plus ¹³¹I was not significantly different for multiple end points, including local recurrence (P = 0.18), regional neck lymph-node metastases (P = 0.61), locoregional recurrence (P = 0.37), distant metastases (P = 20), and recurrence at all disease sites (P = 0.27).

Death from Malignancy

During 1941 through 1950, there were 24 patients with PTC treated at the Mayo Clinic, ranging in age from 7 to 20 years (average, 14). Fourteen survived and, to date, 10 of them (42%) have died from malignancy, 2 of whom died from metastatic PTC and 8 died from nonthyroidal second malignancies (NSPM). This preceded the approval of ¹³¹I as a radiopharmaceutical. Of the eight who died from NSPM, seven (87%) had been treated with radium-seed application or a course of external-beam radiation and 4 of the 7 were additionally treated with ¹³¹I in amounts ranging from 175 to 200 mCi. The number and sites of radiation-associated NSPM were lung (three patients) trachea (one patient) pleura (one) and liver (one) and the seventh had grade 4 adenocarcinoma, and the eighth patient, who was 7 years old



at diagnosis and did not receive adjunctive radiation therapy died from cervical cancer 40 years after the diagnosis of PTC.

During 1951 through 2008, 12 of the 191 patients died of causes other than PTC. Five of the seven who died of NSPM each died from one of the following tumors: acute myelogenous leukemia (AML), duodenum, lung, breast, and brain, and two had adenocarcinoma of uncertain origin. The patient with AML had been treated with 95 mCi and the patient with lung cancer had received 200 mCi. Of the 15 patients who died of NSPM, 11 (73%) had received postoperative therapeutic irradiation.

Expected versus Observed Mortality Rates

A total of 22 patients died during the study period. The expected and observed death rates were not significantly different during the first 30 years; however, in the interval from 30 through 50 years of follow-up, there was an unexpected excessive death rate in the juvenile patients with PTC as compared with the control population of identical age and sex, in which 11 deaths would have been expected. This difference is highly significant (P = 0.00045). Of the 22 patients who died, 17 (77%) died from malignancy, 2 of which were PTCs and the remaining 15 (88%) were NSPMs and 5 fatalities were attributed to causes other than malignancy.

Of the 24 children ranging in age from 7 to 20 years during the period from 1941 through 1950, 10 (42%) died from malignancy, two from PTC and 8 from NSPMs. Of the eight with NSPMs seven (87%) had been treated with radium-seed application or a course of external-beam radiation and four were treated with ¹³¹I in amounts ranging from 95 to 200 mCi. Of the seven who died from nonthyroidal malignancies, one died of acute myelocytic leukemia (AML), and one each died from duodenal tumor, lung cancer, breast cancer, and brain tumor, and two others died of adenocarcinoma of uncertain origin. Four of the seven patients had received ¹³¹I in amounts from 95 through 200 mCi. The patient with AML had received 95 mCi, and the others were treated with ¹³¹I for RRA, a few with relatively high amounts of ¹³¹I for RRA. The remaining five fatalities were unrelated to malignancy and five were attributed to cardiovascular disease.

CONCLUSION

The authors of this study suggest that initial near-total or total thyroidectomy and routine central compartment lymph-node metastases has the greatest impact on recurrence and is not further influenced by RRA.

COMMENTARY

This retrospective study from the Mayo Clinic reports their experience in the treatment of PTC in children and young adults over a span of almost seven decades. The cause-specific mortality rate was 2% and the tumor recurrence rate was 32% after a 40-year followup. The main conclusion was that the initial surgical approach has the greatest impact on recurrence and is not further influenced by ¹³¹I RRA. The authors link various forms of adjuvant ionizing radiation to the occurrence of nonthyroidal second primary malignancies that appeared 30 to 50 years after the initial diagnosis. As a consequence, the authors recommend radioiodine only for high-risk patients, such as those with distant metastases or incomplete surgical resection. They reject ¹³¹I RRA, which is still performed in over 30% of the patients treated at the Mayo Clinic.

Children with PTC pose a particularly difficult problem because they generally have low cause-specific mortality rates and consequently have a long life expectancy during which adverse effects of therapy may develop, including the complications of surgery, radioiodine treatment, or external-beam radiotherapy. As compared with adults, children have a greater degree of extrathyroidal tumor extension and more lymph-node and lung metastases at the time of initial diagnosis. Still, they responded to total thyroidectomy and postoperative ¹³¹I RRA (1), which is particularly relevant, as up to 90% of children with PTC have lymph-node metastases (2). Yet there is evidence that the response to ¹³¹I therapy is not always prompt and may require more than one ¹³¹I treatment to destroy residual thyroid tissue or tumor. Also, the child's age plays an important role in outcome, which in the Hay study ranged from 7 to 20 years, with a mean of 14 years

Lazar et al. (1) found that total thyroidectomy with or without lymph-node dissection had similar effects in both prepubertal and pubertal patients, but the amount of weight-adjusted radioiodine for RRA was significantly greater in the prepubertal group as compared with the pubertal group (P = 0.004). Also, a family history of thyroid cancer was more prevalent in the prepubertal children (P = 0.037), who had a greater degree of extrathyroid tumor extension (P = 0.012), lymph-node metastases (P = 0.009), and lung metastases (P = 0.009). Still, after a median follow-up of 5 years after initial therapy with surgery and RRA, there were no significant differences in the extent of residual or recurrent tumor in prepubertal or pubertal children. The authors concluded that differentiated thyroid cancer has a more aggressive presentation in prepubertal children, but that rigorous initial surgical and ¹³¹I therapy and thyrotropin suppression resulted in an outcome similar to that achieved in the pubertal group who ranged in age up to 17 years.

The Mayo Clinic patients were treated with a spectrum of different surgical procedures that changed over time, including both the extent of thyroid surgery and surgical techniques for lymph-node metastases. The study group for RRA comprised 192 patients who had tumor confined to the neck that was completely resected with a potentially curative operation with no postoperative gross residual disease. Node-picking was performed in 28% of patients who had RRA and 27% of those not treated with RRA, while compartment dissection was performed in 41% of the patients who had RRA and 40% of without RRA (chi-square P=0.48) (personal communication with Dr. Hay)

Still, over a 40-year span, 32% had a recurrence in the thyroid bed or regional neck area or had distant metastases. Of the 192 patients, only 68 (35%) were treated with RRA that was given as

one treatment in 54 patients (79%) and up to four treatments in the others, with a cumulative amount of ^{131}I ranging from 29 to 400 mCi, and a mean of 79 mCi.

The study does not provide data concerning how disease status was ascertained at the end of follow-up, including thyroglobulin measurements. Modern evaluations of the outcome of PTC require stringent analyses to identify patients with no evidence of disease. The American and European Thyroid Associations both recommend the following triad to identify patients who are free of disease: (1) no clinical evidence of tumor, (2) no imaging evidence of tumor (no uptake outside the thyroid bed on the initial posttreatment whole-body scan, or, if uptake outside the thyroid bed had been present), no imaging evidence of tumor on a recent diagnostic radioiodine scan and neck ultrasound, and (3) undetectable serum Tg levels during thyrotropin (TSH) suppression and stimulation in the absence of interfering antibodies. Without this information, it is difficult to accurately assess the final outcome in this group of patients.

The authors of this study are understandably concerned about the fact that observed and expected death rates, which were not significantly different during the first 30 years of follow-up, unexpectedly increased after 30 to 50 years of follow-up. Seven (87%) had been treated with radium-seed application or a course of external-beam radiation and four were treated with ^{131}I . Four of the seven patients who died from nonthyroidal tumors had received radioiodine in amounts ranging from 95 through 200 mCi. The patient with AML had received 95 mCi, and some of the others were treated with larger amounts of ^{131}I for RRA. The authors conclude that these results strongly highlight the necessity to carefully delineate the indication for ^{131}I therapy, particularly in a population of young patients.

There is little question that second nonthyroidal malignancies are related to the cumulative amount of ^{131}I therapy. The study by Rubino et al. (3) was quoted by Hay et al. to emphasize the caveat concerning the potential risk for treating young patients with ^{131}I . The Rubino study of 6841 patients found an increased risk of both solid tumors and leukemias with the administration of larger cumulative amounts of ^{131}I . The study found an excess absolute risk of 14.4 solid cancers and of 0.8 leukemia per 1 GBq (27 mCi) of ^{131}I during 100,000 person-years follow-up. The risk for nonthyroidal malignant tumors increased with a cumulative amount of ^{131}I >400 mCi for solid tumors and ≥ 500 mCi for leukemia. The authors estimated that 100 mCi of ^{131}I will induce an excess of 53 solid malignant tumors and 3 leukemias in 10,000 patients during 10 years of follow-up (100,000 patient-years). The Hay study found that of after 5838 patient-years follow-up, 15 patients who died of NSPM, 11 (73%) had received postoperative therapeutic irradiation, 4 of whom had been treated with ^{131}I . The patients had been treated with 29 to 400 mCi of (mean, 79), and thus some may have been treated with amounts of ^{131}I that fall into the worrisome range described by Rubino et al.

A comprehensive review of the management of childhood thyroid cancer is the evidence-based study by Rachmiel et al. (4). The definition of the types of evidence and grading of data,

which followed the recommendations of the U.S. Agency for Health Care Policy and Research, were as follows: Ia = obtained from meta-analysis of randomized, controlled trials (RCTs); Ib = obtained from at least one RCT; IIa = obtained from at least one well-designed controlled study without randomization; IIb = obtained from at least one other type of well-designed quasi-experimental study; and III = obtained from a well-designed non-experimental, descriptive study, or case controlled studies. Data were obtained from a literature search using PubMed, Cochrane databases, guidelines from various international groups, and studies pertaining to pediatric differentiated thyroid cancer (DTC) management and outcome in order to answer pertinent questions concerning the management of pediatric thyroid cancer. Several of the recommendations deserve brief mention. The first question addressed was: What is the most appropriate initial therapy?

Recommendation 1a is: It is important to diagnose and initiate therapy as early as possible, as initiation of therapy more than 1 year after the appearance of symptoms is associated with an increased mortality and is probably attributable to more diffuse and progressive disease.

Recommendation 1b is: Pediatric patients with DTC should have total or near-total thyroidectomy with selective lymph-node dissection (when involved) as the initial treatment. The goal should be to achieve complete surgical remission (Grade B, Level III). The authors identified similar guidelines in the adult population with tumors larger than 5 cm (Level IV). The recommendations in children were based on registry data, historical uncontrolled data, and retrospectively attained data in various groups of children and adolescents with DTC. They found a significant amount of evidence to support total or near-total thyroidectomy for children with DTC. Children had a high rate of local tumor recurrence, either in the thyroid bed or in regional cervical lymph nodes in 4.6 to 30% of cases (Level III). They found that children have a high rate of extrathyroidal invasion and cervical involvement at initial presentation, which have been reported as significant negative predictive factors for progression-free survival in children (Level III). They recommend initial removal of as much tumor tissue as possible and found that total thyroidectomy or near-total thyroidectomy may increase disease-free survival as compared with lobectomy (Level III). Jarzab et al. (5) found that radical surgery was the most significant factor for disease-free survival, and others have found that it may increase cancer-specific survival (6;7).

Recommendation 2a is: All pediatric patients with DTC should undergo radioiodine RRA within 4 to 6 weeks after the initial thyroidectomy (Grade B, Level III). This approach is similar to that in adults with intermediate-to-high-risk disease (Level IV [guidelines]). This was based on a report of 1510 patients (adults and children) without distant metastases at diagnosis showed ^{131}I RRA to be an independent variable that reduced relapse and disease-related mortality in patients with tumors larger than 1.5 cm (6). A meta-analysis (8) in high-risk adults and adolescents demonstrated that RRA was associated with a decrease in relative risk of 0.3 for local relapse and 3% decrease (from 4%) in the absolute risk for recurrent distant metastases

at 10 years. However, the decrease in cancer-related mortality has not been a consistent finding, and the benefit of RRA was less clear in low-risk patients treated with total thyroidectomy and suppressive levothyroxine therapy (Level IIb). However, a recent multivariate analysis of predictive factors for progression-free survival in children demonstrated that RRA decreased the relative risk of relapse, but with borderline significance (Level III) (9). In still another study (10), ¹³¹I RRA was associated with a decreased risk for distant metastases recurrence in two adjusted analysis, as well as the pooled unadjusted analysis (pooled risk difference, -2% for DTC). RRA was associated with a statistically significant reduction in risk of distant metastatic recurrence with a risk difference of -2% (95% confidence interval, -4 to -1) (Z = 3.49, P = .0005, pooled data from 2263 patients). Rachmiel et al. recommend ¹³¹I administration according to risk stratification. A child was regarded as low risk if age was >10 years, the nodule <1.5 cm, and there was no residual disease, capsular invasion, or lymph-node metastases. If a child does not meet these criteria, he or she is deemed as high risk. Rachmiel et al. also recommend ¹³¹I RRA with 30 to 50 mCi.

The risk for ¹³¹I in children is an especially important issue. The risk for ¹³¹I of radiation to body tissues is dependent on the serum concentration of ¹³¹I. New therapy paradigms in the administration of ¹³¹I for RRA show that total-body radiation can be significantly reduced (35%) when patients are prepared with recombinant human TSH, which reduces bone-marrow and other tissue radiation. Body radiation can be lowered even more

by administering smaller amounts of ¹³¹I, as little as 30 to 50 mCi of ¹³¹I, which in prospective, randomized studies have been shown to be as effective as 100 mCi of ¹³¹I (11;12).

The Hay study shows that lymph-node compartment dissection has a favorable effect on outcome; however, whether this alone with total thyroidectomy is sufficient therapy remains uncertain. Two recent studies suggest that ¹³¹I is still necessary after extensive neck-compartment dissection in patients with lymph-node metastases (13;14).

Hay et al. emphasize the importance of central lymph-node metastases, although it is not clear that these are all prophylactic dissections or therapeutic dissections, or a mixture of both. Although the efficacy of prophylactic lymph node compartment dissection is currently under intense debate, it is an intriguing aspect of initial surgery that will continue to spark important debate. Whether this alone can suffice as the full extent of initial therapy remains unresolved. The studies by Schlumberger's group suggest that ¹³¹I may play a selective role in treatment of patients with lymph-node compartment dissection, when lymph-node metastases and tumor invasion are discovered.

It is likely that this debate will extend for decades before consensus is reached. , Nothing short of randomized studies will quell the disparate views.

— Ernest L. Mazzaferri, MD, MACP

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Risk factors predicting hypothyroidism with autoimmune thyroid disease are female sex and baseline TSH levels combined with thyroid antibodies

Walsh JP, Bremner AP, Feddema P, Leedman PJ, Brown SJ, O'Leary P. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. *J Clin Endocrinol Metab* 2010; January 22 [Epub ahead of print].

SUMMARY

BACKGROUND

Autoimmune hypothyroidism is a common disorder that is largely defined by the population being studied. The most sensitive diagnostic marker of the disease is a high serum thyrotropin (TSH) concentration. However, there is an ongoing debate concerning the upper reference limit for TSH. It is generally based on the 95% confidence interval of log-transformed TSH concentrations in healthy individuals, which usually places the upper TSH reference limit at approximately 4.0 to 4.5 mU/L, although some believe that this should be lowered to 2.5 to 3 mU/L. The authors of this study suggest that the main arguments in favor of maintaining the upper reference limit around 4.0 to 4.5 are the increased prevalence of antibodies and the risk for hypothyroidism in people with TSH levels in the upper reference range and that longitudinal studies of risk factors for hypothyroidism are required to address the debate regarding the upper TSH range, including the predictive value of thyroid antibodies measured by automated immunoassay, as compared with using older semiquantitative methods.

METHODS

In surveys conducted in 1981 and 1994, sera were analyzed for TSH, free thyroxine (FT₄), antithyroid peroxidase antibodies (TPOAb), and antithyroglobulin antibodies (TgAb) using the Immulite platform on sera from the 1184 participants. The two surveys were conducted in Busselton, Western Australia, an iodine-sufficient area with a

predominantly white population. The main outcome in the 1994 survey was hypothyroidism, defined as a serum TSH level greater than 4.0 mU/L or treatment with levothyroxine (L-T₄). The following were excluded from the study: subjects with raised serum TSH with low FT₄, treatment with L-T₄ or antithyroid drugs, hyperthyroidism, missing serum TSH values, and discordant thyroid-function test results suggesting pituitary disease or antibody interference and subjects on amiodarone or lithium. As the rationale for routine L-T₄ replacement is uncertain for individuals with mildly elevated TSH concentrations up to 10 mU/L, this large group was also excluded from the study. Receiver-operating-characteristic (ROC) curve analysis was used to determine optimal cutoffs for baseline TSH, TPOAb, and TgAb as predictors of hypothyroidism. The characteristics of the study cohort at baseline (1981) and follow-up (1994) surveys were compared.

RESULTS

A total of 1804 of the 1981 subjects (86%) were alive in 1994, but some chose not participate in the follow-up study; however, those who died before the 1994 survey were significantly older than those in the 1994 follow-up survey. After exclusions, 1184 subjects met the criteria for the study. The mean time between the two study visits was 13 years (range, 12.3 to 14.0)

The Baseline Demographics of the Study Cohort in 1981 and 1994 (Figure 1)

The original 1981 survey cohort and those in the 1994 follow-up survey had serum TPOAb concentrations that increased

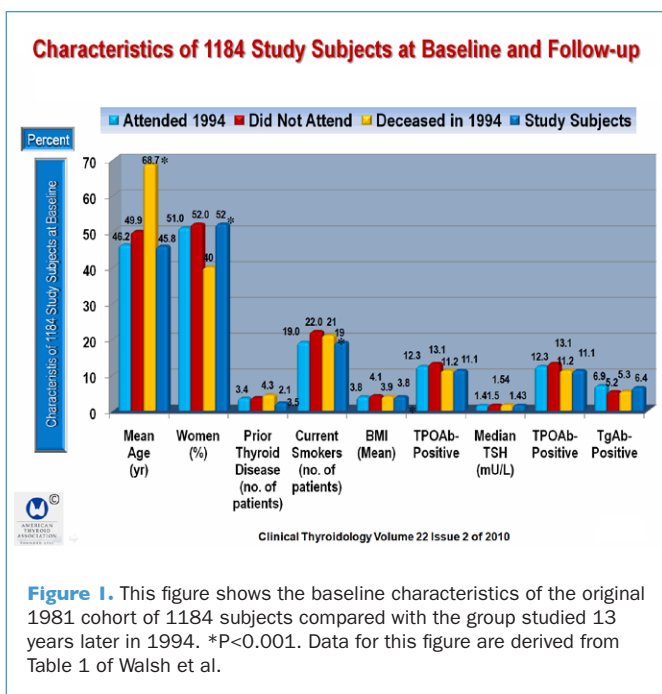


Figure 1. This figure shows the baseline characteristics of the original 1981 cohort of 1184 subjects compared with the group studied 13 years later in 1994. *P<0.001. Data for this figure are derived from Table 1 of Walsh et al.

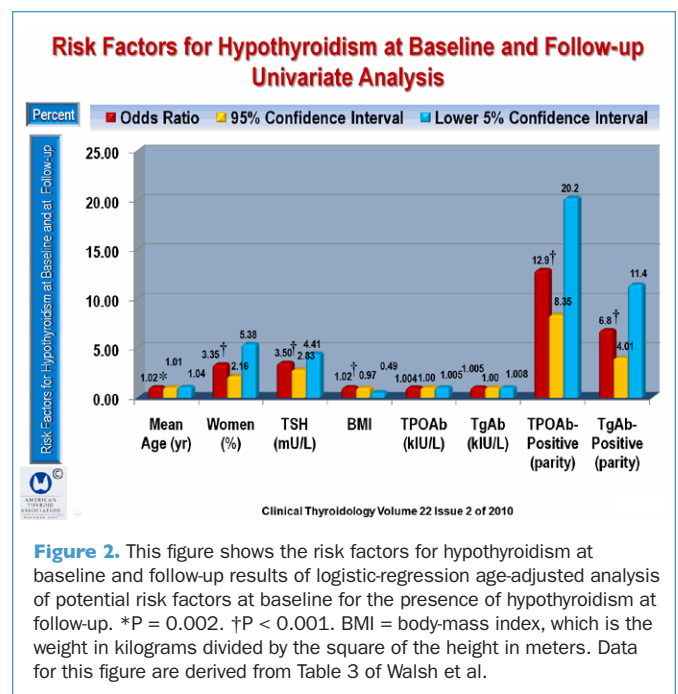


Figure 2. This figure shows the risk factors for hypothyroidism at baseline and follow-up results of logistic-regression age-adjusted analysis of potential risk factors for the presence of hypothyroidism at follow-up. *P = 0.002. †P < 0.001. BMI = body-mass index, which is the weight in kilograms divided by the square of the height in meters. Data for this figure are derived from Table 3 of Walsh et al.

from 11.1% in 1981 to 15.1% in 1994 ($P < 0.001$), and the TPOAb status changed from negative to positive in 5.2% and from positive to negative in 1.3% of the participants. The baseline group of 1110 subjects (93.7%) had serum TSH concentrations between 0.1 and 4.0 mU/L, and none were taking L-T₄; however, 13 years later, 29 subjects (2.4%) were taking L-T₄ and another 81 (6.8%) had elevated serum TSH concentrations, 3 of whom also had low FT₄ concentrations. Thus, of the 1110 subjects in the 1981 cohort with normal serum TSH concentrations, 110 (9.3%) had overt hypothyroidism, defined as a TSH >4 mU/L, or were on L-T₄ therapy; 84 of these were women (76%). Thus, of the 1110 subjects with normal TSH levels, 42 (3.5%) had overt hypothyroidism, 38 of whom (91%) were women

Univariate Analysis (Figure 2)

The baseline variables associated with overt hypothyroidism were age; female sex; TSH, TgAb, and TPOAb concentrations; TPOAb-positive status; and TgAb-positive status. Of the 76 subjects with positive TgAb, 26 (34%) were TPOAb-negative, 4 of whom (15.4%) had overt hypothyroidism at follow-up. Thus, TgAb was not a significant risk factor for hypothyroidism as compared with TPOAb-negative and TgAb-negative subjects (odds ratio, 1.80; 95% confidence interval, 0.52 to 4.82).

Risk Factors at Baseline for the Presence of Hypothyroidism Multivariate Analysis

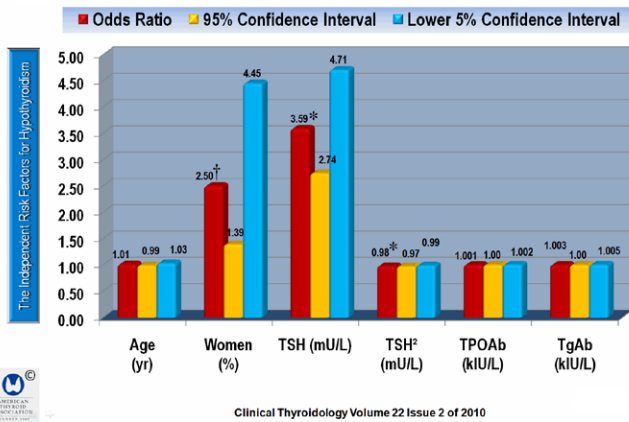


Figure 3. This figure shows that the independent risk factors for hypothyroidism, are a TSH above 2.5 mU/L and a TPOAb above 29 kIU/L in women positive for thyroid antibodies. The prevalence of hypothyroidism at follow-up was 12%, with a baseline TSH of 2.5 mU/L, and 87.5% for TSH above 4.0 mU/L. * $P < 0.001$ for odds ratio. † $P = 0.002$ for the odds ratio. Data for this figure are derived from Table 3 of Walsh et al. Functional forms of covariates (e.g. TSH², in case of a quadratic relationship) and interactions were explored, and TSH² was included because it significantly improved goodness of fit.

Multivariate Analysis (Figures 3 to 5)

The strongest independent predictors of hypothyroidism were female sex and baseline TSH, whereas the predictive value of thyroid antibodies was not significant in the multivariate model, although TgAb as a continuous variable remained significant. The odds ratios for baseline TPOAb and TgAb are shown in Figures 3 to 5.

Outcomes Analyzed by Baseline TPOAb Odds Ratio

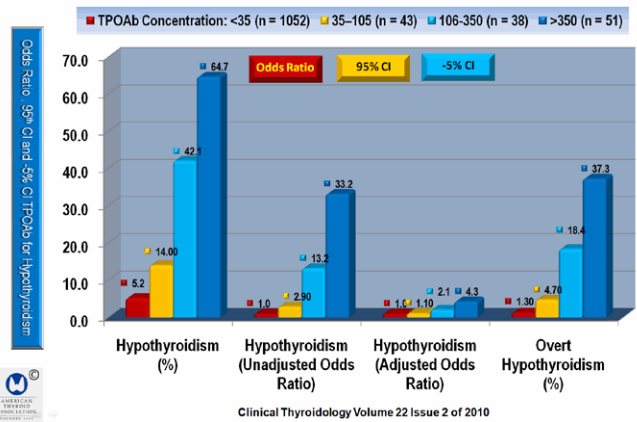


Figure 4. This figure shows the outcomes analyzed by baseline TPOAb concentration. The data for this figure are derived from Table 5 of Walsh et al, which shows odds ratio (red) 95% CI = confidence interval (gold), and -5% CI (light blue).

Outcomes Analyzed by Baseline TgAb Odds Ratio

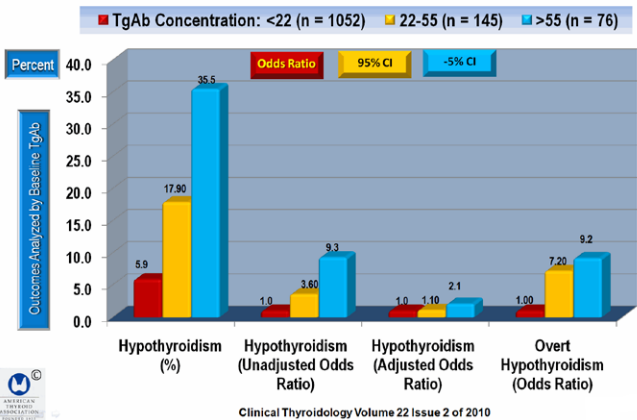


Figure 5. This figure shows the outcomes analyzed by baseline TgAb concentration. The data for this figure are derived from Table 5 of Walsh et al. See Figure 4 legend.

Optimal Cutoffs for TSH, TPOAb, and TgAb (Figures 6 and 7)

The best predictor of hypothyroidism was associated with a baseline TSH of 2.6 mU/L, with a sensitivity of 76% and a specificity of 90% using a ROC curve analysis. Using these data, the sensitivity, specificity, positive predictive value, and negative predictive value of baseline serum TSH of 2.5 mU/L versus 4

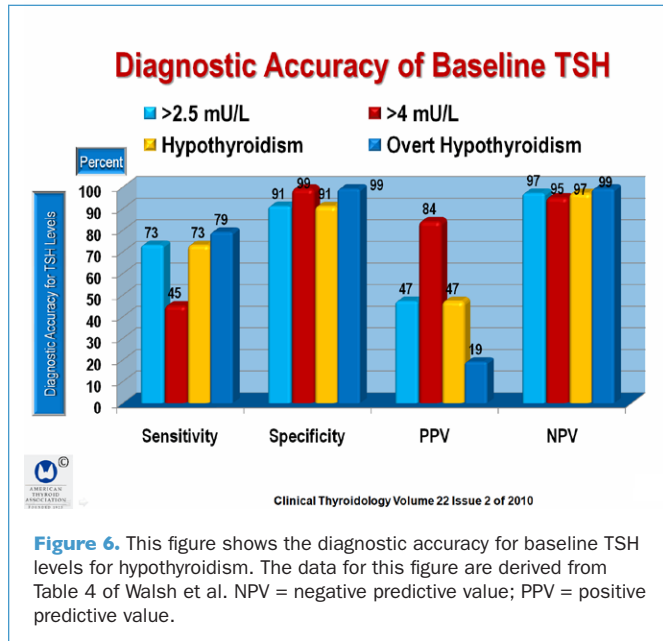


Figure 6. This figure shows the diagnostic accuracy for baseline TSH levels for hypothyroidism. The data for this figure are derived from Table 4 of Walsh et al. NPV = negative predictive value; PPV = positive predictive value.

mU/L is shown in Figure 6. The study outcomes analyzed by baseline TSH and antibody concentrations are shown in Figure 7.

CONCLUSION

Female sex and baseline TSH levels, combined with thyroid antibodies are the strongest risk factors predicting the development of hypothyroidism during an extended follow-up.

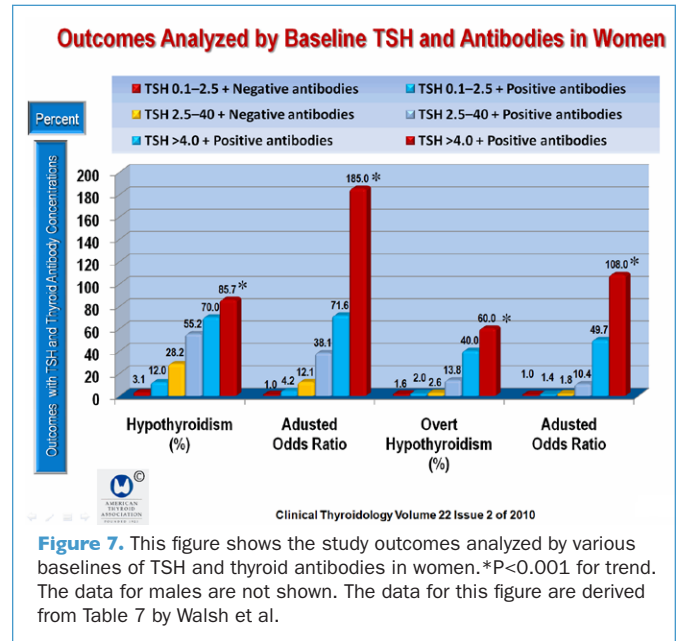


Figure 7. This figure shows the study outcomes analyzed by various baselines of TSH and thyroid antibodies in women. *P<0.001 for trend. The data for males are not shown. The data for this figure are derived from Table 7 by Walsh et al.

COMMENTARY

This study provides data concerning hypothyroidism over a 13-year period, using current methods for the determination of TSH and thyroid antibodies. The authors opine that the results will provide information concerning the upper reference range for TSH that provides a means for clinicians to estimate the long-term risk for hypothyroidism, based on sex, TSH, and thyroid antibody status. Still, multivariate analysis found that female sex and TSH were the strongest independent predictors of hypothyroidism, while age was of no significance and thyroid antibodies were of borderline importance. The ROC analysis identified a TSH threshold of 2.5 mU/L as the optimal cutoff for predicting hypothyroidism, which was associated with optimal diagnostic sensitivity and specificity. The authors suggest that this finding is broadly consistent with several other studies. The Wickham study (1) found that increasing values of serum TSH above 2 mU/L at the first survey increased the probability of hypothyroidism developing, which was further increased in the presence of antithyroid antibodies. Other studies, by Teng et al. (2) and Li et al. (3), found that subjects who were TPOAb- and TgAb-positive at baseline had thyroid dysfunction more frequently than seronegative subjects. The authors concluded that patients with TSH concentrations of 2.5 to 4 mU/L are at increased risk for hypothyroidism; however, the risk is small at 12% (range, 3 to 21%) over 13 years. For this reason, the authors do not support lowering the upper limit of the TSH reference range, but suggest

that these individuals be regarded as being at intermediate risk for developing hypothyroidism. However, the role of antithyroid antibodies altered this risk. For example, with a baseline TSH less than 2.5 mU/L, the risk for hypothyroidism was approximately 1% per year and the risk of overt hypothyroidism was 0.2% per year, whereas in women who were antibody-positive with a baseline TSH between 2.5 and 4.0 mU/L, the risks were much higher, at 4 and 1% per year, respectively. The strength of this study is based on its duration and large number of participants, and probably is one of the largest of its kind. However, there are a few weaknesses in the study, such as the attrition rate due to death and failure to attend the 1994 survey; still, 81% of the survivors participated in the study. The Walsh study essentially confirms the 20-year follow-up study by Vanderpump et al. (1) of the Wickham cohort that provides 20-year risks for the development of hypothyroidism as a function of age, antibody status, and initial TSH in 1-ml increments of TSH from 1 to 5 mU/L.

Recent recommendations to decrease the upper reference range of the TSH from 4.5 to 2.5 mU/liter, based on the high proportion of healthy people whose serum TSH is less than 2.5 mU/liter and the observation that those with a serum TSH between 2.5 and 4.5 mU/L (upper reference range) have an increased risk of progression to overt hypothyroidism.

A study by Surks, Goswami, and Daniels (4) challenged the notion of lowering the TSH upper reference range from 4.5 to

2.5 mIU/L. Using the reference group of the National Health and Nutrition Examination Survey (NHANES) III, the authors found that 85% of 14,333 people 12 years of age or older without thyroid disease or antithyroid antibodies had TSH levels below 2.5 mIU/liter and that 2.3% had subclinical hypothyroidism. They also found that if the upper TSH limit were decreased, an additional 9.7% had an upper reference range for TSH, representing 20.6 million Americans who would also be identified as having subclinical hypothyroidism, many of whom do not have thyroid disease. They opined that about half of those with a TSH at upper reference range probably have thyroid disease, but most with thyroid disease and antithyroid peroxidase antibodies have a TSH below 2.5 mIU/liter.

The distribution of serum TSH shifts progressively to higher concentrations with age. A study by Atzmon et al. (5) found that serum TSH was significantly higher in Ashkenazi centenarians than in Ashkenazi and NHANES controls (median, 2.5th and 97.5th centiles)—1.97 mIU/L (0.42 and 7.15), 1.55 (0.46 and 4.55), and 1.61 (0.39 and 6.29), respectively ($P < 0.001$). The TSH distribution curve of the NHANES control group was superimposable on and not significantly different from the Ashkenazi controls. This is of some importance in the Welsh

study. The mean age at follow-up was 58.8 ± 14.4 years. Thus, there were many people in the study 70 years of age or older, suggesting that this group would have higher TSH levels due to advancing age, which might increase the number of individuals with a diagnosis of hypothyroidism.

The Walsh study has one relatively important shortcoming: the definition of hypothyroidism included physician-prescribed L-T₄ replacement, and the authors had no access to serum TSH concentrations at the time of diagnosis for independent verification, which is a potentially serious shortcoming insofar as it relates to the serum TSH level, the standard for the diagnosis of hypothyroidism. A study from Israel by Meyerovitch et al. (6) found that nearly 5000 patients with normal TSH levels were treated with L-T₄ for reasons that could not be determined. Thus, the authors have no idea how many of those treated with L-T₄ actually had hypothyroidism.

The Walsh study thus will likely join the debate concerning the optimal upper reference range to establish a diagnosis of hypothyroidism with or without antithyroid antibodies.

— Ernest L. Mazzaferri, MD, MACP

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Patients with a primary diagnosis of autoimmune thyroid disease are at significantly increased risk for additional autoimmune diseases

Boelaert K, Newby PR, Simmonds MJ, Holder RL, Carr-Smith JD, Heward JM, Manji N, Allahabadia A, Armitage M, Chatterjee KV, Lazarus JH, Pearce SH, Vaidya B, Gough SC, Franklyn JA. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med* 2010;123:183.e1-9.

SUMMARY

BACKGROUND

Autoimmune thyroid diseases are common, manifested most commonly as autoimmune thyroiditis (AITD) or Hashimoto's thyroiditis and Graves' disease. The prevalence of spontaneous hypothyroidism is as high as 2% in iodine-replete areas such as the United States and Europe. In addition, autoimmune thyroid diseases are associated with a variety of other disorders such as type 1 diabetes mellitus, Addison's disease, systemic lupus erythematosus, and pernicious anemia, and also appear as a family trait that tends to be associated with many other autoimmune disorders. The object of this cross-sectional multicenter study was to systematically quantify the prevalence of coexisting autoimmune disorders.

METHODS

Data were obtained from a protocol in the national U.K. collection of DNA for studies of genetic susceptibility to autoimmune thyroid diseases, including prospective and systematic collection of clinical data regarding the coexistence of other common autoimmune disorders in index cases and their parents. Patients were recruited from February 2002 through July 2007. The diagnosis of autoimmune disorders was based on patient recall, with confirmation in the index case through verification

of current medical records and medications by recruiting physicians. Records confirming the evidence of coexisting autoimmune diseases were considered positive. All subjects completed a structured questionnaire seeking a personal and parental history of common autoimmune disorders, as well as a history of hyperthyroidism or hypothyroidism among parents.

RESULTS

The Prevalence of Coexisting Autoimmune Diseases in Men and Women (Figures 1 and 2)

The study cohort comprised 3286 individuals, 2791 (85%) of whom were white subjects with Graves' disease, 2317 women (83%) and 474 men (17%), and 495 white subjects with Hashimoto's thyroiditis (15%), 427 women (86%) and 68 men (14%) who were recruited from specialist referral thyroid clinics in the United Kingdom. Approximately 90% of the eligible patients participated in the study. The mean age at the time diagnosis was 43 years for the index cases of Graves' disease, and 42.5 years for Hashimoto's thyroiditis (P = not significant [NS]). The mean age at the time of recruitment in the study was not different in the index cases of Graves' disease (47.3 years) or Hashimoto's thyroiditis (47.5 years, P = NS) (Figures 1 and 2). There also were no significant differences in age at the time of diagnosis or recruitment to the study in patients with Graves' disease or Hashimoto's thyroiditis with no coexisting autoimmune disease or for those with an additional autoimmune disorder (Figures 1 and 2).

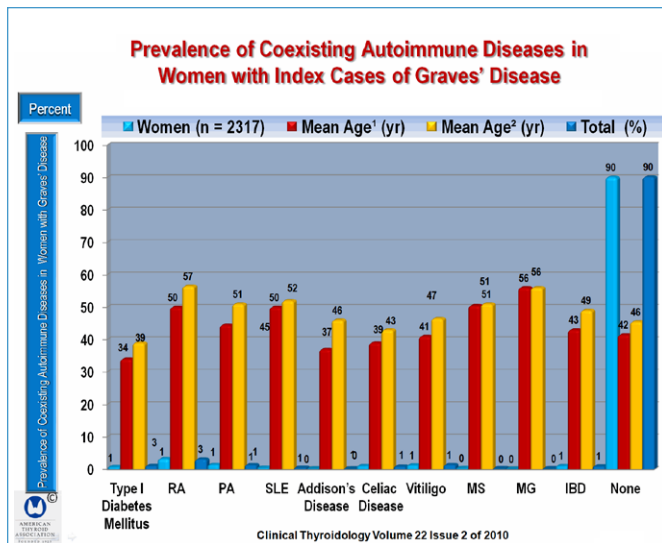


Figure 1. This figure shows the prevalence of coexisting autoimmune diseases in the index cases of women with Graves' disease. Age¹ = age at the time of diagnosis of Graves' disease or Hashimoto's thyroiditis; Age² = age at recruitment to the study; celiac = celiac disease; IBD = inflammatory bowel disease; MG = myasthenia gravis; MS = multiple sclerosis; PA = pernicious anemia; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus. This figure is drawn from data in Table 2A in Boelaert et al.

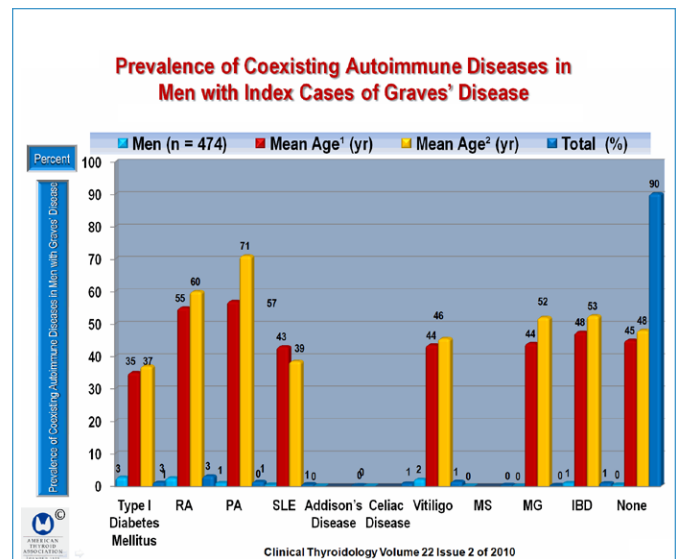


Figure 2. This figure shows the prevalence of coexisting autoimmune diseases in the index cases of men with Graves' disease. (See Figure 1 for definitions of the abbreviations.) This figure is drawn from data in Table 2B in Boelaert et al.

The Prevalence of Coexisting Autoimmune Diseases in the Index Cases with Graves' disease or Hashimoto's Thyroiditis (Figures 3 to 6)

Almost 10% of the 2791 subjects with Graves' disease and 14% of the 495 with Hashimoto's thyroiditis had another autoimmune disorder (P = 0.005). The most common autoimmune disease associated with the index cases of Graves' disease or Hashimoto's thyroiditis was rheumatoid arthritis (Figures 1 and 2). Those with Hashimoto's thyroiditis had a 10-fold higher risk for Addison's disease (P<0.001) and a 3-fold higher risk for pernicious anemia (P = 0.004), as compared with index cases of Graves' disease (Figures 1 and 2). Comparing index cases

of Graves' disease, there were significantly higher prevalence rates of type 1 diabetes mellitus (P = 0.011) and myasthenia gravis (P = 0.001) in men as compared with women; however, Addison's disease, celiac disease, and multiple sclerosis were exclusively associated with the index cases of Graves' disease in women. There were no significant differences in the prevalence rates of other autoimmune disorders in men and women with index cases of Hashimoto's thyroiditis (Figures 4 to 6). Comparing male and female patients, there were no significant differences in age at either diagnosis or recruitment. When comparing age at diagnosis of Graves' disease between index cases with different autoimmune diseases (Figure 1 to

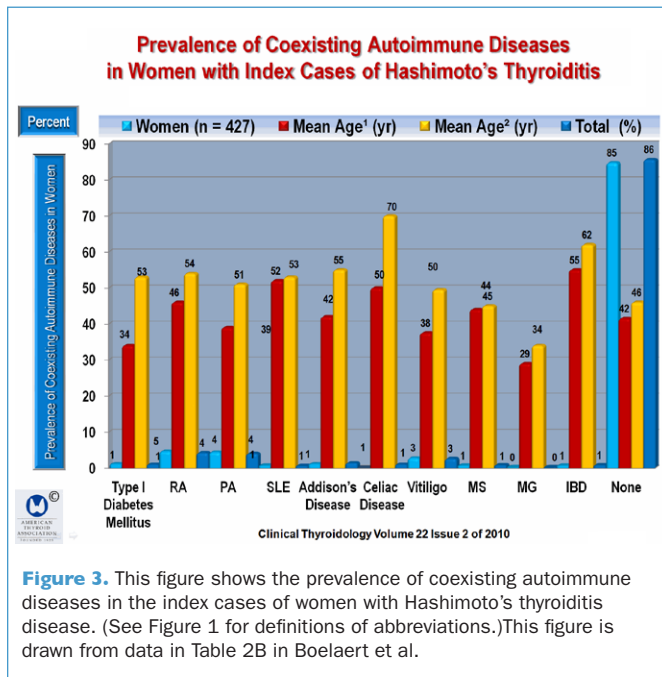


Figure 3. This figure shows the prevalence of coexisting autoimmune diseases in the index cases of women with Hashimoto's thyroiditis disease. (See Figure 1 for definitions of abbreviations.) This figure is drawn from data in Table 2B in Boelaert et al.

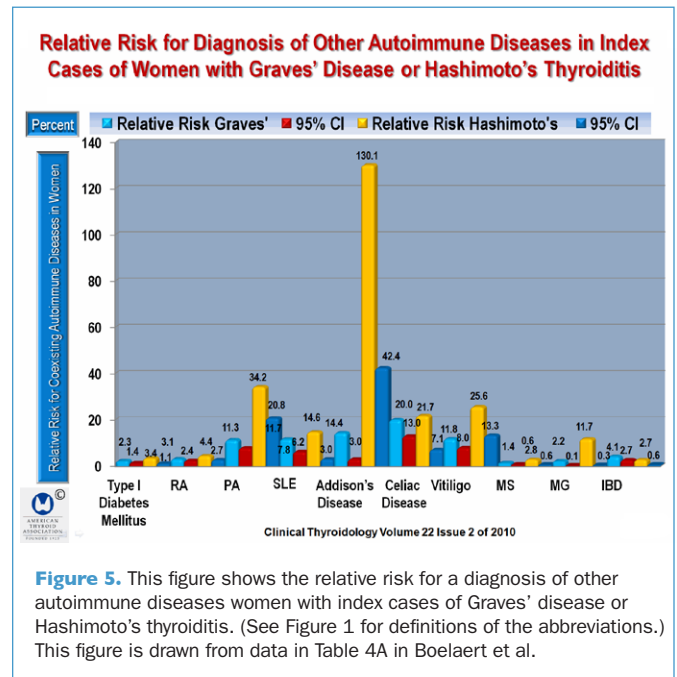


Figure 5. This figure shows the relative risk for a diagnosis of other autoimmune diseases women with index cases of Graves' disease or Hashimoto's thyroiditis. (See Figure 1 for definitions of the abbreviations.) This figure is drawn from data in Table 4A in Boelaert et al.

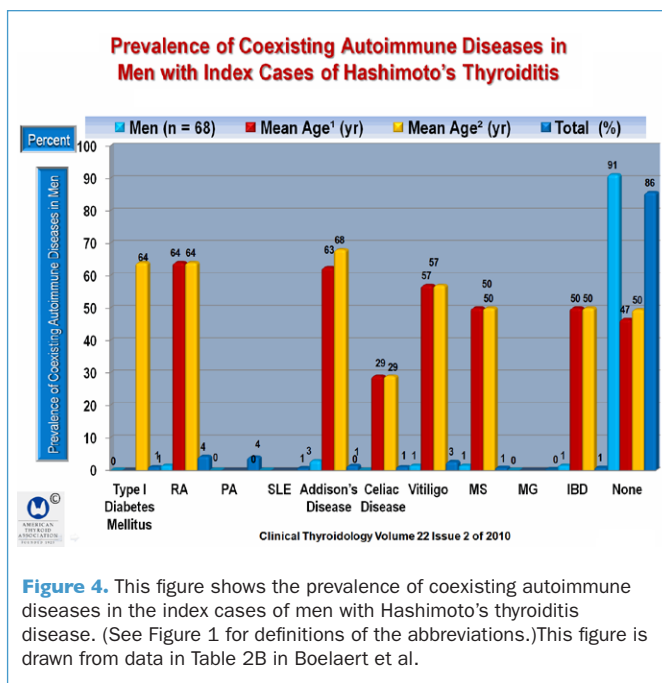


Figure 4. This figure shows the prevalence of coexisting autoimmune diseases in the index cases of men with Hashimoto's thyroiditis disease. (See Figure 1 for definitions of the abbreviations.) This figure is drawn from data in Table 2B in Boelaert et al.

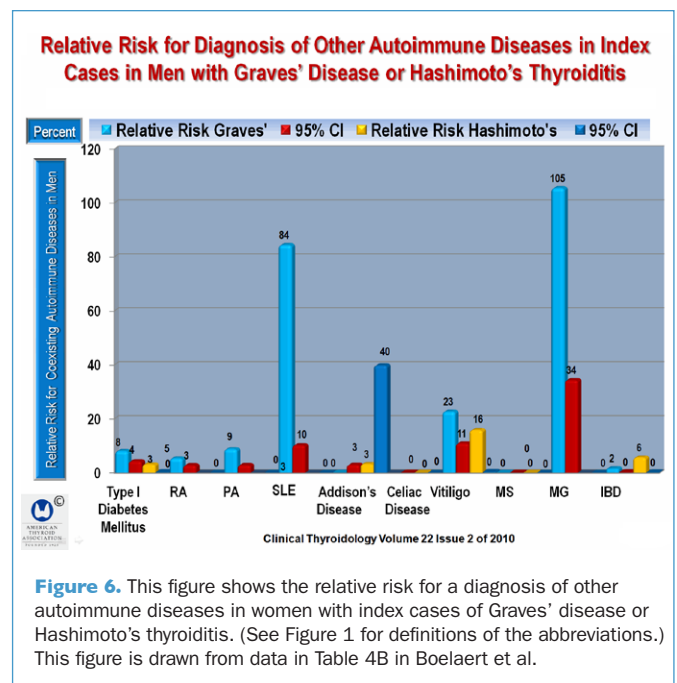


Figure 6. This figure shows the relative risk for a diagnosis of other autoimmune diseases in men with index cases of Graves' disease or Hashimoto's thyroiditis. (See Figure 1 for definitions of the abbreviations.) This figure is drawn from data in Table 4B in Boelaert et al.

4), those with coexisting rheumatoid arthritis were significantly older as compared with patients with no coexisting autoimmune diseases ($P < 0.001$), which was also the case in patients with type 1 diabetes ($P < 0.001$), vitiligo ($P < 0.001$), or inflammatory bowel disease ($P = 0.003$). Also, subjects with coexisting pernicious anemia were older as compared with index cases with no associated autoimmune disease ($P = 0.04$) and those with coexisting type 1 diabetes ($P = 0.03$).

The Prevalence of Coexisting Autoimmune Diseases in parents of Patients with Graves’ disease and Hashimoto’s Thyroiditis

A total of 17.5% of the mothers of the index cases with Graves’ disease and 23.6% of the mothers of the index cases of Hashimoto’s thyroiditis had a history of thyroid dysfunction. The mothers of index cases with Graves’ disease were reported to have hyperthyroidism and hypothyroidism with similar frequency ($P = NS$); however, the mothers of index cases with Hashimoto’s thyroiditis had a higher frequency of hypothyroidism than hyperthyroidism ($P < 0.001$). Furthermore, the mothers of index cases with Graves’ disease were more likely to have hyperthyroidism ($P < 0.001$) as compared with the mothers of those with Hashimoto’s thyroiditis ($P < 0.001$). Hypothyroidism was

more common in mothers of patients with Hashimoto’s thyroiditis than in mothers of those with Graves’ disease ($P < 0.001$).

A total of 3.1% and 5.7% of the fathers of index cases with either Graves’ disease or Hashimoto’s thyroiditis, respectively, had thyroid dysfunction. Fathers of the index cases with Graves’ disease were more likely to have hyperthyroidism than hypothyroidism ($P = 0.017$), while fathers of the index cases with Hashimoto’s thyroiditis more frequently had hyperthyroidism than hypothyroidism ($P = 0.007$). In all of the autoimmune diseases investigated, except myasthenia gravis, Graves’ disease and Hashimoto’s thyroiditis and inflammatory bowel disease in Hashimoto’s thyroiditis were more commonly found in parents of patients with autoimmune thyroid disease than that in the background U.K. population.

CONCLUSION

Patients with a primary diagnosis of autoimmune thyroid disease are at significantly increased risk for additional autoimmune diseases. The authors of the study suggest that these risks highlight the importance of screening for other autoimmune diagnoses if patients with autoimmune thyroid disease present with new or nonspecific symptoms.

COMMENTARY

This is perhaps the largest study to quantify the risk for coexisting autoimmune diseases in more than 3000 index cases with well-characterized Graves’ disease or Hashimoto’s thyroiditis. The authors point out that this study demonstrated the high relative risks for the diagnosis of several organ-specific autoimmune disorders, particularly pernicious anemia, Addison’s disease, and celiac disease. In addition, they demonstrated parental clustering of index cases of hyperthyroidism and hypothyroidism. The authors indicated that the higher prevalences and relative risks of rheumatoid arthritis in parents as compared with index cases suggest a strong disease association in the two. The index cases with coexisting rheumatoid arthritis were older at diagnosis of Graves’ disease, and the authors suggest that it is possible that the same age-related autoimmune mechanisms contribute to the pathogenesis of both of these autoimmune diseases. There also was a striking association between autoimmune thyroid diseases and Addison’s disease, although the authors caution that this apparent association may have been exaggerated by the influence of Addison’s disease on thyroid function caused by a well-described phenomenon of increasing serum thyroid-stimulating hormone in untreated glucocorticoid deficiency that might lead to an incorrect diagnosis of hypothyroidism. One of the main findings in this study was that the frequency of coexisting autoimmune disorders was nearly 10% in the index cases of Graves’ disease and almost 15% in the index cases of Hashimoto’s thyroiditis ($P = 0.005$). Rheumatoid arthritis was the most common autoimmune

disorder, found in over 3% of patients with Graves’ disease and over 4% of patients with Hashimoto’s thyroiditis.

The authors provide the caveat that screening for other autoimmune diagnoses might be indicated if patients with autoimmune thyroid disease present with new or nonspecific symptoms. They further propose additional investigation of susceptibility genes common to more than one autoimmune disorder.

Several years ago, Allen et al. (1) studied autoimmune thyroiditis in a homogeneous founder white population, the Old Order Amish of Lancaster County in Pennsylvania, and found that circulating antimicrosomal antibodies were relatively common in the Amish, with a prevalence of almost 23%, and the prevalence of autoimmune hypothyroidism was nearly 10%. The authors found suggestive evidence of linkage of autoimmune thyroid disease confined to a locus on chromosome 5q11.2-q14.3 that was previously reported to be linked to AITD–hypothyroidism in a Japanese study. The authors suggested that this gene is likely to contribute to the susceptibility to autoimmune thyroiditis in the Amish. Other studies (2) have found subclinical autoimmune thyroid disorders in patients with systemic sclerosis, type 1 diabetes mellitus, celiac disease (3-6), and other diseases (3-9).

The study by Boelaert et al. is a significant contribution that provides important new information on this problem

— Ernest L. Mazzaferri, MD, MACP

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The diagnosis of differentiated thyroid cancer during pregnancy or in the first year post partum is a significant indicator of persistent disease

Vannucchi G, Perrino M, Rossi S, Colombo C, Vicentini L, Dazzi D, Beck-Peccoz P, Fugazzola L. Clinical and molecular features of differentiated thyroid cancer diagnosed during pregnancy. *Eur J Endocrinol* 2010;162:145-51.

SUMMARY

BACKGROUND

It has long been recognized that during pregnancy thyroid nodules or cancer may develop and that those with cancer may experience growth of their tumor. Though several theories have been proposed, the exact mechanism of this mitogenic effect is unknown. Estrogen has been an attractive candidate for this follicular growth because numerous studies have documented its neoplastic tendencies in thyroid tissues. The authors of this study sought to examine the role of estrogen in thyroid cancers during pregnancy by analyzing tumor immunohistochemical staining for estrogen receptor alpha (ER α). Patients were stratified into three groups based on timing of the diagnosis of thyroid cancer in relation to pregnancy to determine whether there was a relationship between patient outcomes and pregnancy.

METHODS

This is a retrospective study of 123 women followed between 1995 and 2006 at one institution in Italy. Patients were excluded if they were >45 years old at diagnosis, had a family history of thyroid cancer, or had a personal history of neck irradiation. All patients had been treated with total thyroidectomy; if clinically warranted, they also had cervical-

lymph-node dissection. Patients were divided into three groups based on the time of diagnosis of their thyroid cancer. Patients in group 1 were at least 1 year postdelivery (n =7). Group 2 patients had a diagnosis of thyroid cancer during pregnancy and underwent thyroidectomy during the second trimester (n = 11) or in the first year after pregnancy (n = 4). One patient was counted twice in this group, as she had a follicular carcinoma and was initially treated with lobectomy after her first pregnancy. Subsequently, papillary thyroid carcinoma (PTC) was diagnosed in the contralateral lobe during her second pregnancy. Group 3 patients were either nulliparous or their PTC was diagnosed and treated before pregnancy (n = 61).

Freedom from disease was based on the guidelines of the European and American Thyroid Associations for the management of differentiated thyroid cancer. Patients were deemed free of disease if they met all of the following criteria: undetectable thyroglobulin (Tg) while on levothyroxine therapy and after stimulation with recombinant human thyrotropin (rhTSH). In addition, patients had a negative thyroglobulin antibody (TgAb) level and a negative neck ultrasound (US). Persistent or recurrent disease was defined by a basal Tg >2 μ g/L on consecutive measurements or Tg >2 μ g/L after rhTSH stimulation, Tg >1 μ g/L after rhTSH stimulation on two consecutive measurements, neck US findings of malignancy, and/or uptake outside the thyroid bed on radioiodine scans, TgAb positivity for >4 years, or a rise in the TgAb levels.

Immunohistochemical analysis of 38 paraffin-embedded tissues (16 in group 1, 8 in group 2, and 14 in group 3) was performed to determine the presence of ER α in the PTC tumors. The tumors were classified as negative, weakly positive if there was a single area of positivity, or positive if there were multiple areas of positivity seen. Eleven tumors from patients in group 2 were evaluated for the presence of BRAF mutations.

RESULTS

Tumor–Node–Metastasis Tumor Staging, Patient Age, Treatment, and Follow-up in the Three Groups (Figures 1 and 2)

There were no significant differences between the groups in patient age at diagnosis, duration of follow-up, tumor size, or the presence of extrathyroidal invasion. Group 2 had a higher likelihood of lymph-node involvement, though this did not reach statistical significance. There was a significantly higher proportion of follicular carcinoma in group 2 as compared with the other two groups. There was no difference between the groups in terms of the use of remnant ablation or the amount of ¹³¹I administered (Figures 1 and 2).

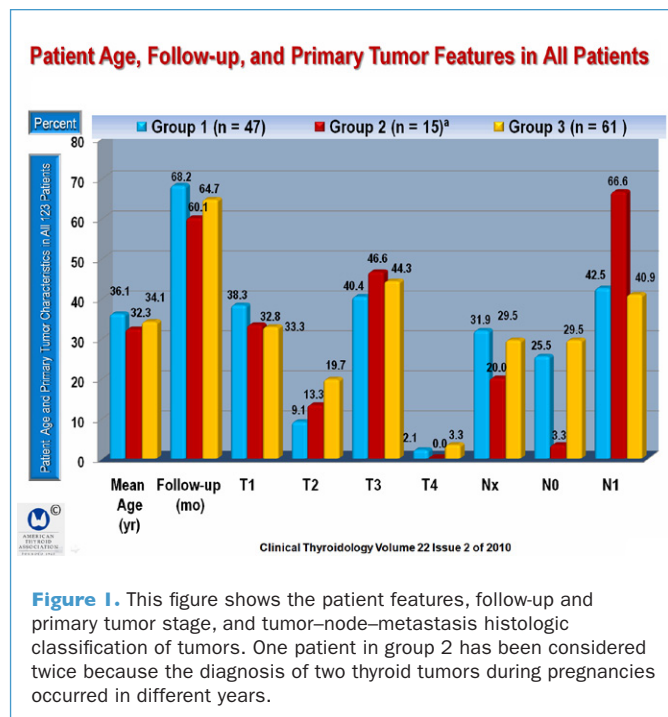


Figure 1. This figure shows the patient features, follow-up and primary tumor stage, and tumor–node–metastasis histologic classification of tumors. One patient in group 2 has been considered twice because the diagnosis of two thyroid tumors during pregnancies occurred in different years.

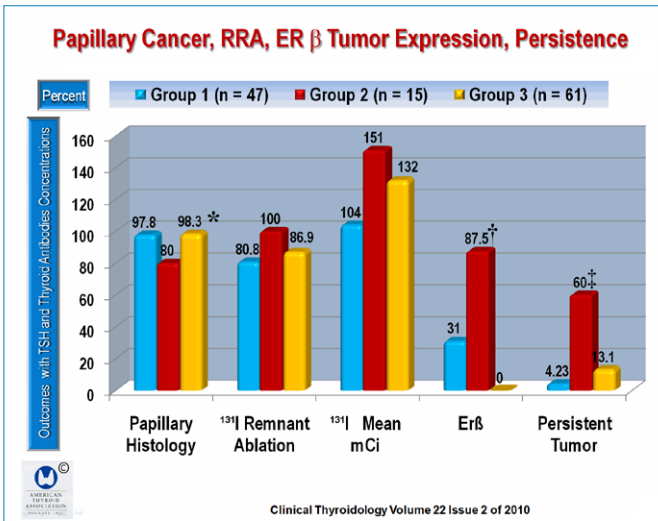


Figure 2. This figure shows the extent of papillary histology, remnant ablation, mean ¹³¹I mCi, ERβ, and persistent tumor. *P = 0.66. †P = 0.048. ‡P = 0.001. The following analyses were also made: group 1 versus group 2, P = 0.01; group 1 versus group 3, P = 0.85; group 2 versus group 3, P = 0.004; †group 1 versus group 2, P = 0.009; group 1 versus group 3, P = 0.11; group 2 versus group 3, P < 0.0001; ‡group 1 versus group 2, P < 0.0001; group 1 versus group 3, P < 0.02; group 2 versus group 3, P < 0.001. All patients without a papillary histology had a follicular carcinoma.

Tumor Features, Remnant Ablation, and ERα (Figure 2)

There was a significant difference in the expression of ERα among the three groups; it was identified in 31% of group 1 tumors, 87.5% of group 2 tumors, and none of the group 3 tumors (P = 0.01). The receptor was detected in multiple areas of the tumors in 35 to 40% of patients in groups 1 and 2 (Figure 2).

Analysis of Outcomes in the Three Groups (Figure 3)

Clinical outcomes varied significantly among the three groups. Persistent or recurrent disease was significantly more frequent in group 2 (60%) as compared with group 1 (4.2%) or group 3 (13.1%) (P < 0.0001). To rule out the possibility that the delay in surgery during pregnancy in group 2 patients was responsible for their worse outcome, a univariate analysis was performed. The variables of time until thyroidectomy and delay in remnant ablation after surgery were taken into account. Neither of these variables was significantly correlated with disease persistence or recurrence. Likewise, the increased incidence of follicular tumors in group 2 was not responsible for the worse prognosis, as two of these three patients are in remission. On stepwise logistic-regression analysis, pregnancy and the presence of lymph-node metastases were independent predictors of recurrent or persistent disease. Extrathyroidal invasion was not a statistically significant predictor of outcome, as the confidence interval of this association crossed unity (Figure 3). Neither the presence of a BRAF mutation nor follicular histology was responsible for the worse prognosis of group 2. All three patients with BRAF were in remission at the end of the study. Likewise, two of the three patients with follicular thyroid carcinoma were free of disease at the end of the study.

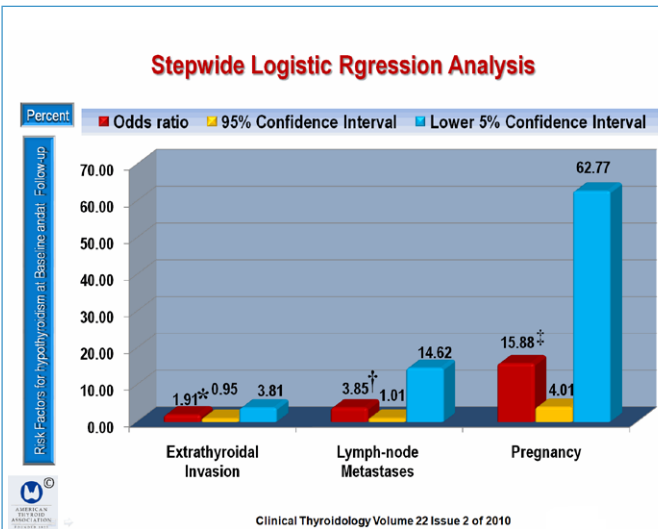


Figure 3. This figure shows a stepwise logistic-regression analysis for indicators of persistent disease. *P = 0.66. †P = 0.048. ‡P = 0.001.

CONCLUSIONS

Patients with thyroid cancer detected during pregnancy are more likely to have persistent or recurrent disease as compared with women whose tumors were diagnosed before pregnancy or more than a year after pregnancy. Estrogen may play a role in these poorer outcomes; immunohistochemical staining for ERα was significantly more prevalent in the tumors diagnosed during pregnancy.

COMMENTARY

Although it has been routinely reported that both thyroid nodules and cancer may grow or develop during pregnancy (1,2), there is a relative paucity of data regarding the long-term outcome of patients diagnosed with thyroid cancer during pregnancy. This important study by Vannucchi et al. seeks to clarify this cloudy picture. Two prior studies have examined the outcome of patients diagnosed with thyroid cancer during pregnancy (3,4). The study by Moosa and Mazzaferri (4) determined that outcomes were similar when surgery was performed during or shortly after pregnancy. This study was important in that lengthy follow-up (median, 22.4 years) was available and that there was no difference in overall survival or recurrence rates between women diagnosed during pregnancy and age-matched controls. The limitation of the study, however, was that diagnostic whole-body scans were the norm for detection of residual disease at the time and there were no data on thyroglobulin. Armed with the knowledge that these scans are burdened with a high false negative rate (5), Vannucchi et al. sought to investigate whether patients will fare equally well when using the modern criteria for determination of remission (6). The higher recurrence rates in pregnant women seen in the study by Vannucchi et al. are in contrast with those of Moosa and Mazzaferri. It is likely that this difference reflects the modern use of more sensitive testing for recurrent disease with thyroglobulin assays and

cervical ultrasonography. However, it should be noted that with the long follow-up in the study by Moosa and Mazzaferri, one would expect the latent small tumors unable to be seen initially with diagnostic scans would eventually come to clinical detection after so many years. Additional long-term studies may be beneficial in clarifying this discrepancy.

In an attempt to explain this poorer prognosis among women diagnosed with thyroid cancer during pregnancy, the authors performed immunohistochemical studies of ER α expression in tumors from all three groups. Thyroid cancer is three times more common in women than in men. This sex difference, coupled with the findings of increased tumor growth during pregnancy prompts the question of the etiologic mechanism of these phenomena. Estrogen is the logical culprit; it has been implicated in the growth of benign and malignant thyroid tissue through the activation of the mitogen-activated protein kinase pathway (7). Indeed, the cell proliferation appears to be mediated through estrogen-mediated upregulation of ER α levels in thyroid cells (8). Thus, the findings by Vannucchi et al. of increased ER α in tumors diagnosed during pregnancy reinforce these conclusions of cell-line studies and add further evidence that estrogen may be at least partially responsible for the increased growth of thyroid tumors during pregnancy.

— Jennifer A. Sipos, MD

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A summary of the abundant data on the growing literature on the management of thyroid cancer during pregnancy

Holt EH. Care of the pregnant thyroid cancer patient. *Curr Opin Oncol* 2010;22:1-5.

SUMMARY

BACKGROUND

The incidence of differentiated thyroid cancer, especially papillary thyroid cancer in women, has been steadily increasing for the past three decades, peaking in women during their mid-40s. As a consequence, thyroid cancer and thyroid nodules are an especially important problem during the reproductive years in women. In fact, about 10% of thyroid cancers occurring during the reproductive years are diagnosed during pregnancy or the first year after delivery. A study by Vannuchi et al. that is highlighted in this issue of *Clinical Thyroidology* shows that pregnancy has a negative impact on the outcome of thyroid cancer, and is associated with especially high levels of estrogen receptor α (ER α) during pregnancy as compared with the levels before and after pregnancy. ER α appears to have an important impact on follicular cell growth, and numerous studies have documented its neoplastic tendencies in thyroid tissues.

The main finding of the Vannuchi study is that pregnancy has a negative impact on the outcome of thyroid cancer, almost all of which were papillary thyroid cancers. This leads to a number of new and important questions concerning the clinical management of thyroid cancer in pregnant women. Holt's review of the current care of pregnant women with thyroid cancer is propitious, considering the timing of events linking pregnant women with more aggressive papillary thyroid cancers. This set of events is important to obstetricians, internists, and endocrinologists.

METHODS

Holt summarized the recommendations of the Endocrine Society in late 2007 and the data in a symposium on thyroid dysfunction and pregnancy hosted by the American Thyroid Association (ATA) in April 2009. In addition to the problem of thyroid cancer, hypothyroidism was addressed by the ATA and the Endocrine Society. Moreover, recent studies have addressed the consequences of thyroid cancer and hypothyroidism on the fetus and the impact of surgery, radioiodine, and levothyroxine therapy in both mother and fetus.

RESULTS

Guidelines for Thyroid Cancer during Pregnancy

The Holt study summarizes the Endocrine Society's guidelines for the care of pregnant patients with thyroid nodules or thyroid cancer, highlighting the following six features: [1] Thyroid nodules ≥ 1 cm should be evaluated with fine-needle aspiration biopsy. [2] Women with malignant or rapidly growing thyroid nodules should be offered surgery in the second trimester. [3] As thyroid nodules and thyroid cancer are not expected to progress rapidly, the risk of surgery might outweigh the benefits of immediate surgery, and it thus might be appropriate for women to wait until postpartum for thyroidectomy. This latter recommendation will have to be regarded in light of the Vannuchi study. [4] Women with

thyroid cancer should have a consistently low but measurable levothyroxine (L-T₄) level during pregnancy. [5] Women who are breast-feeding should wait 6 to 12 months before becoming pregnant. [6] Women should wait 6 to 12 months after ¹³¹I therapy before becoming pregnant.

Guidelines for Hypothyroidism

[1] During pregnancy, women who have had lobectomy should be screened for hypothyroidism. [2] As a consequence of physiologic changes on thyroid function during pregnancy, the Endocrine Society recommends that the interpretation of thyroid-function tests should be as follows: for the total thyroxine (TT₄), multiply the upper and lower limits of the laboratory-specific adult normal range for TT₄ by 1.5 to bring it into the normal range during the second and third trimester; keep the free T₄ (FT₄) results in the laboratory-specific normal range during pregnancy; keep the thyrotropin (TSH) below 2.5 mU/L; and keep TSH in the trimester-specific normal range as determined by the laboratory determining the TSH concentration.

Thyroid Surgery during Pregnancy

[3] The Endocrine Society guidelines recommend that patients found to have thyroid cancer during pregnancy be considered for thyroidectomy during the second trimester, when the fetus is viable but after organogenesis is complete. Holt indicates that that this guideline was based on limited evidence.

Perhaps the most important study is a retrospective one by Kuy et al. (1) that was aimed at performing the first population-based measurement of clinical and economic outcomes in pregnant women who had thyroid and parathyroid surgery and to identify the characteristics of this population in the Health Care Utilization Project Nationwide Inpatient Sample (HCUP-NIS), a 20% sample of nonfederal U.S. hospitals. All pregnant women were compared with age-matched nonpregnant women who had thyroid and parathyroid procedures from 1999 through 2005. A total of 201 pregnant women had thyroid (165 patients) and parathyroid (36 patients) surgery and were examined together. The study subjects' mean age was 29 years; 60% were white and 46% had thyroid cancer. As compared with 31,155 nonpregnant women, pregnant patients had a higher rate of endocrine complications (15.9% vs. 8.1%, $P < 0.001$) and general complications (11.4 vs. 3.6%, $P < 0.001$), longer unadjusted lengths of stay (2 days vs. 1 day, $P < 0.001$), and higher unadjusted hospital costs (\$6,873 vs. \$5,963, $P = 0.007$). Fetal and maternal complication rates were 5.5% and 4.5%, respectively. On multivariate regression analysis, pregnancy was an independent predictor of higher combined surgical complications (odds ratio, 2; $P < 0.001$), longer adjusted length of stay (0.3 day longer, $P < 0.001$), and higher adjusted hospital costs (\$300, $P < 0.001$). Other independent predictors of outcome were surgery volume, patient race or ethnicity, and insurance status. Pregnant women thus had worse clinical and economic outcomes following thyroid and parathyroid surgery

than nonpregnant women, with disparities in outcomes based on race, insurance, and access to high-volume surgeons. These data will help physicians and patients to deal with thyroid cancer during pregnancy, particularly for women who are advised to wait until the postpartum period for surgery.

Hypothyroidism or Hyperthyroidism during Pregnancy

A study by Cleary-Goldman et al. (2) was aimed at estimating whether maternal thyroid hypofunction is associated with complications. The study subjects were 10,990 patients who had first- and second-trimester serum assayed for TSH, FT₄, and antithyroglobulin antibodies (TgAb) and antithyroperoxidase antibodies (TPOAb). Subclinical hypothyroidism was defined as TSH levels above the 97.5th percentile, and FT₄ between the 2.5th and 97.5th percentiles. Hypothyroxinemia was defined as a TSH between the 2.5th and 97.5th percentiles and FT₄ below the 2.5th percentile. Patients with subclinical hypothyroidism were compared with euthyroid patients who had TSH and free FT₄ between the 2.5th and 97.5th percentiles. Also, patients with and without antibodies were compared. Subclinical hypothyroidism was found in 240 of 10,990 (2.2%) women in the first trimester and in 243 of 10,990 women (2.2%) in the second trimester. Hypothyroxinemia was found in 232 of 10,990 women (2.1%) in the first trimester and in 247 of 10,990 women (2.3%) in the second trimester. Subclinical hypothyroidism was not associated with adverse outcomes. Hypothyroxinemia was associated with preterm labor in the first trimester, (adjusted odds ratio [aOR], 1.62; 95% confidence interval [CI], 1.00 to 2.62) and macrosomia (aOR, 1.97; 95% CI, 1.37 to 2.83). In the second trimester, hypothyroxinemia was associated with gestational diabetes (aOR, 1.7; 95% CI, 1.02 to 2.84). A total of 1585 of 10,990 women (15%) in the

first trimester and 1491 of 10,990 women (14%) in the second trimester had TgAb. When both TPOAb and TgAb were positive in either trimester, there was an increased risk for preterm premature rupture of membranes (P = 0.002 and P<0.001, respectively). The authors concluded that maternal thyroid hypofunction is not associated with a consistent pattern of adverse outcomes.

Thyroid Function Testing in Pregnancy

Although there are a number of studies describing normal ranges for serum TSH and T₄, the largest is from the National Health and Nutrition Examination Survey (NHANES III) from 1988 through 1995. Soldin et al. (3) used the NHANES III data to determine trimester-specific levels of serum T₄ and TSH in the U.S. population and compared these data with published trimester-specific T₄ and TSH means and medians obtained in other countries. The mean serum T₄ levels for the U.S. population were 141.35 mIU/L in the first trimester, 152.95 in the second, and 142.65 in the third, whereas mean serum TSH levels were 0.91, 1.03, and 1.32 mIU/L, respectively. The study concluded that gestation-specific mean T₄ and TSH levels for the representative U.S. population are well within the trimester-specific reference intervals. T₄ and TSH measured during pregnancy in longitudinal and cross-sectional studies of populations worldwide demonstrate that, in some populations, serum T₄ and TSH levels are outside the normal trimester-specific reference intervals.

CONCLUSION

There is a growing literature on the management of thyroid cancer during pregnancy, and this study is a major contribution that summarizes the abundant data on this problem.

COMMENTARY

This review by Dr. Holt was placed in *Clinical Thyroidology* adjacent to the study by Vennuchi et al., which reported that a diagnosis of differentiated thyroid cancer during pregnancy or in the first year postpartum is a harbinger of persistent disease. This is an even greater problem than usual, given the fact that the rate of papillary thyroid cancer in women has been steadily rising over the past three decades. Thyroid cancer poses a wide spectrum of problems for pregnant women with thyroid cancer. In addition to the problems summarized in this issue of *Clinical Thyroidology*, a pregnant woman must make important decisions not only about the timing and extent of initial surgery, she must maintain euthyroidism to protect the fetus from serious developmental defects and must make important decisions

concerning radioiodine and its effect on gonadal function and follow-up to mention a few.

This is a unique problem in which endocrinologists, surgeons, gynecologists, and primary care physicians often are involved, and all these providers must be cognizant of the myriad issues to properly advise the patient in making a decision that is best for her and the fetus. The short summary of the Holt study in this issue of *Clinical Thyroidology* does not fully cover the wide spectrum of information that is found in the study. This is a powerful source of information that will help physicians assist in the treatment and education of patients with this serious problem. The Holt article should be read in its entirety.

— Ernest L. Mazzaferri, MD, MACP

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DISCLOSURE

Dr. Mazzaferri is a consultant to Genzyme.

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

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6:45 AM - 8:00 AM	FELLOWS CONFERENCE (7:00 AM-4:30 PM)	EARLY RISER SYMPOSIUM	EARLY RISER SYMPOSIUM	EARLY RISER SYMPOSIUM
8:00 AM - 8:15 AM		WELCOME	BREAK	
8:15 AM - 9:15 AM		PLENARY LECTURE (8:15-9:00)	PLENARY LECTURE (8:15-9:00)	SYMPOSIUM (8:00-9:30)
9:15 AM - 9:45 AM	ADVANCED ULTRASOUND WORKSHOP (9:30 AM-1:30 PM)	COFFEE BREAK (9:15-9:45)	COFFEE BREAK (9:15-9:45)	SYMPOSIUM (9:30-11:00)
9:45 AM - 11:15 AM		SYMPOSIUM (9:45-11:15)	SYMPOSIUM (9:45-11:15)	<i>Program subject to change</i>
11:15 AM - 12:45 PM		SYMPOSIUM (11:15-12:45)	SYMPOSIUM (11:15-12:45)	
12:45 PM - 1:30 PM	ATA BOARD MEETING (12:30-5:00 PM)	LUNCH BREAK	LUNCH BREAK	
1:30 PM - 2:30 PM	INTRODUCTORY ULTRASOUND WORKSHOP (12:45-6:00)	ATA COMMITTEE MEETINGS (12:45-1:30)		 AMERICAN THYROID ASSOCIATION FOUNDED 1923 www.thyroid.org
2:30 PM - 4:00 PM		MEET THE PROFESSOR WORKSHOPS (3) (1:30-2:30)	MEET THE PROFESSOR WORKSHOPS (3) (1:30-2:30)	
4:00 PM - 4:30 PM		SYMPOSIUM (2:30-4:00)	SYMPOSIUM (2:30-4:00)	
4:30 PM - 6:00 PM	WOMEN IN THYROIDOLOGY MEETING (4:30-6:00)	COFFEE BREAK (4:00-4:30)	COFFEE BREAK (4:00-4:30)	
6:00 PM - 7:30 PM	WELCOME RECEPTION (6:00-7:30)	SYMPOSIUM (4:30-6:00)	PLENARY LECTURE (4:30-5:30)	
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