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EDITORS' COMMENTS

This is the 12th 2009 issue of *Clinical Thyroidology*. As we end the first year that the journal has been published on a monthly basis, we wish to thank our readers for providing positive feedback about changing the journal to monthly issues in 2009.

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

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

SEARCH FOR PREVIOUS ISSUES OF *Clinical Thyroidology* Many of our readers have asked for a quick way to find articles published in this journal over the past years. Now you can access previous issues using key words, author names, and categories such as thyroid cancer, or other terms. You will find this by simply clicking the following: 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.

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There is a high rate of tumor multifocality and lymph-node metastases in papillary thyroid cancers that arise in a thyroglossal duct cyst, including a relatively high rate of "skip" metastases

Hartl DM, Al Ghuzlam A, Chami L, Leboulleux S, Schlumberger M, Travagli JP. High rate of multifocality and occult lymph node metastases in papillary thyroid carcinoma arising in thyroglossal duct cysts. Ann Surg Oncol 2009;16:2595-601.

SUMMARY

BACKGROUND

Thyroglossal-duct cyst carcinoma (TDC) is uncommon, and its management remains controversial. The object of this study was to examine the rate of tumor multifocality, lymph-node metastases, and long-term results with TDC.

METHODS

Records from 1979 through 2008 were reviewed for cases of differentiated thyroid cancer in a TDC discovered during a Sistrunk procedure, on preoperative cytology, or on frozen-section diagnosis. Data were collected on patient demographics, tumor size and stage, thyroid tumor multifocality, lymph-node metastases, radioiodine (^{131}I) therapy, and follow-up with neck ultrasound and thyroglobulin (Tg) levels.

RESULTS

Patient Demographics and Initial Presentation (Figure 1)

The study subjects were 18 patients, 13 women (72%) and 5 men (28%), with an average age of 41.5 years (range, 15 to 68) who were treated for papillary thyroid TDC (Figure 1). Five patients were initially treated at the authors' institution, and 13 were referred from other hospitals after the diagnosis of TDC had been established. Only one patient had a history of thyroid disease with ^{131}I treatment for Graves' disease 1 year prior to the diagnosis of TDC. Another patient had a history of external-beam pelvic radiation at age 34 for a testicular seminoma, 13 years before the diagnosis of TDC, which at the time of this study was in complete remission. For 17 patients, the initial presentation of the problem was that of a typical TDC that appeared from several months to years before surgery with no clinical signs of malignancy. Another patient who had TDC diagnosed during pregnancy had TDC surgery after delivery. Preoperative ultrasonography was performed in all patients but only two had thyroid abnormalities. One had two 5-mm right-lobe thyroid nodules and the other had one 25-mm nodule in the right thyroid lobe and two 5-mm nodules in the left lobe. The tumors in the left thyroid lobe were 4 to 27 mm (average, 15.2). Four patients treated at the authors' hospital had fine-needle aspiration biopsy (FNAB). The cytology was insufficient in 1 patient, suspicious in 2 patients, and malignant in 1 patient.

The Initial Surgery and the Extent of Malignancy (Figures 2 to 5)

Total thyroidectomy was performed in 15 of the 18 patients (83%) as a secondary procedure to the Sistrunk procedure (Figure 2). Further surgical procedures were isthmusectomy in addition to the Sistrunk procedure in 1 patient, and Sistrunk procedure alone in 2 patients and central neck dissection with or without lateral compartment dissection in 16 patients (89%) (Figure 3). Other tumor foci were found in the thyroid lobes in 9 of 16 patients (56%), 15 of whom had thyroidectomy (83%) and 1 isthmusectomy. In addition to the TDC, three patients had 1- to 2-mm tumors in both thyroid lobes. Lymph-node metastases were found in 12 of 16 patients (75%) who had prophylactic neck dissection. Lymph-node metastases were found in 6 of 15 (40%) of the central (level VI) neck-compartment dissections, and in 9 of 15 lateral neck

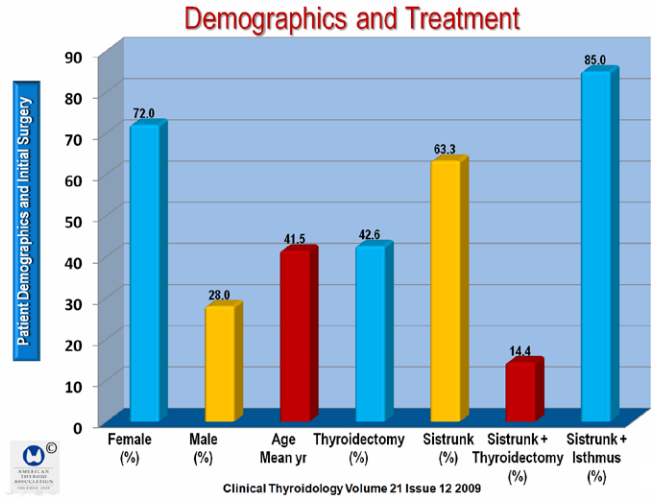


Figure 1. This figure shows the demographic characteristics in the 18 patients in this study, and the percent of patients who had Sistrunk procedures either alone, or with total thyroidectomy, or thyroid isthmusectomy

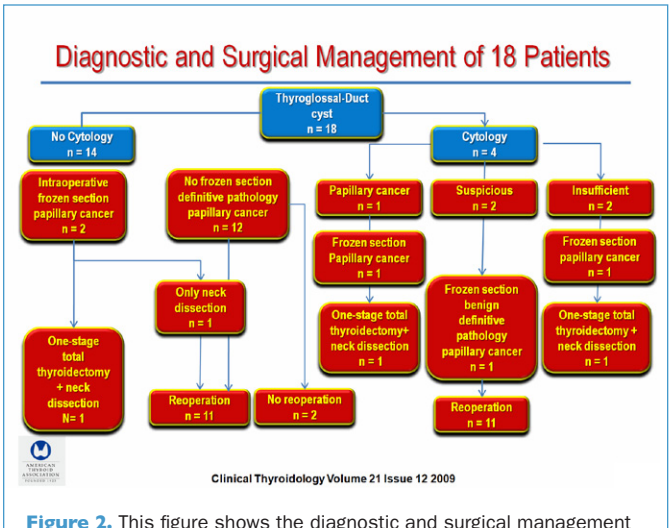


Figure 2. This figure shows the diagnostic and surgical management of the 18 patients who had papillary thyroid carcinoma in a thyroglossal duct remnant. Only four of the patients had FNA cytology, and the diagnosis of cancer was made on frozen section studies, reoperation and one-stage total thyroidectomy.

dissections (60%). The lateral neck metastases were bilateral in 4 patients (22%), on the left side only in 3 (5%), and on the right side only in 2 (13%). "Skip" metastases were found in lateral levels III and IV without central compartment metastases in 6 of 15 patients (40%). Level II (subdigastric) lymph nodes were found in 2 patients, 1 of whom had only level II lymph-node metastases. Of the 12 of 18 patients (67%) with lymph-node metastases, 6 (50%) had tumor foci in the thyroid whereas the other 6 had no tumor foci (Figure 4).

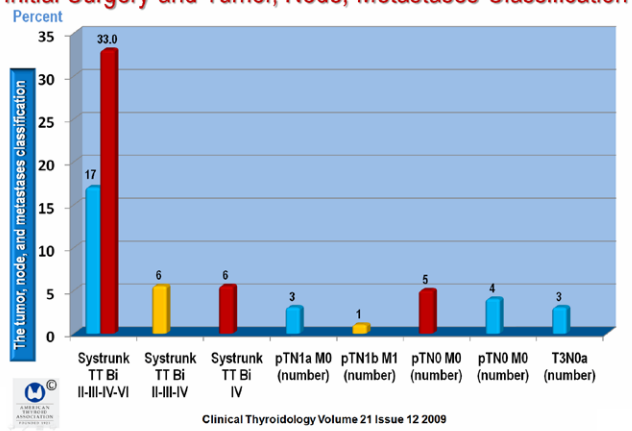


Figure 3. This figure shows the initial thyroid surgery and the TNM classification of tumors found in this group of patients. Not shown in this figure is the one patient with pulmonary metastases with a thyroglossal duct remnant.

The tumor stage was pT1 in 15 patients (83%), pT3 in 3 (17%), pN0 in 4 (22%), PN1a in 3 (17%), and PN1b in 9 (50%), M0 in 17 (94%) and M1 in 1 patient (6%). Nine of the T1N0 tumors were upgraded to N1a or N1b after prophylactic neck dissection. Twelve patients (67%) were treated with 100 mCi or more of ^{131}I. Eight of 18 (44%) received 100 mCi because of lymph-node metastases and 11 (92%) had multifocal tumors with or without lymph-node metastases (Figure 3).

After a mean follow-up of 11 years (median, 12), no patient was lost to follow-up and none had evidence of disease, including neck ultrasonography and thyrotropin-stimulated thyroglobulin levels of <1 µg/L in 11 patients and 2 µg/L in 2 patients. None of the patients had permanent recurrent laryngeal-nerve paralysis or hypoparathyroidism.

CONCLUSION

There is a high rate of tumor multifocality and lymph-node metastases in papillary thyroid cancers that arise in a thyroglossal duct, including a relatively high rate of skip metastases.

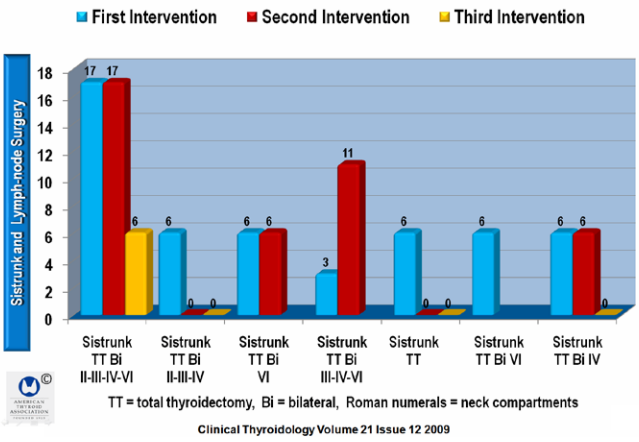


Figure 4. This figure shows the multiple procedures done in this group of patients. TT = total thyroidectomy, Bi = bilateral tumors. The Roman numerals are the lymph-node compartments.

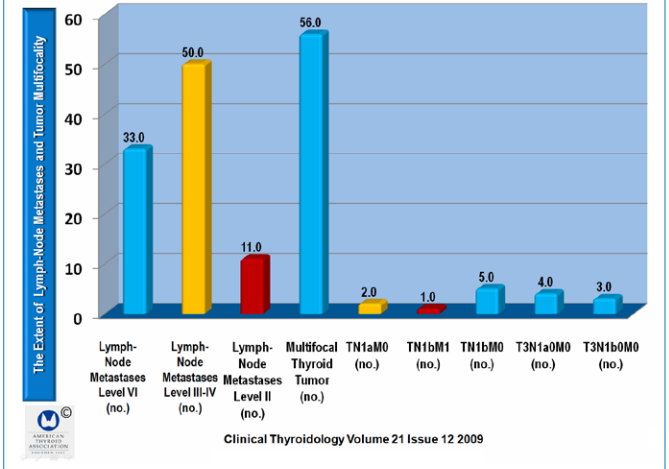


Figure 5. This figure shows the neck compartments in which of lymph-node metastases were found and the Tumor node, metastases (TNM) classification of the tumors.

COMMENTARY

In 2004, I suggested that thyroid cancer occurring in a thyroglossal cyst is a thorny problem that amplifies many of the controversial issues that swirl around the management of small well-differentiated thyroid carcinomas (1). The problem is that thyroglossal cysts are very common, yet they rarely contain tumors. However, when they do, there are myriad diagnostic and therapeutic problems. The diagnostic accuracy of fine-needle aspiration biopsy is low, especially in large cystic lesions with a small mural tumor. Moreover, thyroglossal-duct remnants are ubiquitous, comprising more than 75% of midline neck tumors in children, and they are even found in about 7% of adults (1). Still, only a very small number of people have thyroglossal-duct cancers. Although some report a higher incidence of thyroid cancers (2), the largest study from California (3) found only 14 thyroid cancers in thyroglossal-duct remnants. Luna-Ortiz and associates (4) found only 215 cases in the world literature in 2004. It is thus not surprising that not many exceptional studies of this problem have been published in the past decade. As a

consequence, the key question remains, "Should thyroidectomy be done when malignant tumor is identified in a thyroglossal-duct remnant?" Another key question that is asked less often is: "Should prophylactic neck compartment dissection be performed in this setting and when if ever should ^{131}I be administered?" (1).

The study by Hartl and associates shines a bright light on this hazy problem. The study is unique insofar as the surgical approach that was taken in this group of 18 patients. Although the Sistrunk procedure was performed on all of the 18 patients, 15 (83%) also had total thyroidectomy as a secondary procedure, and 1 had an isthmusectomy in addition to the Sistrunk procedure, and two had only a Sistrunk procedure. In addition, prophylactic neck dissection in the central compartment with or without lateral-compartment dissection was performed in 16 patients (89%) as part of a surgical protocol used by the authors to optimize tumor staging to facilitate selection of patients for ^{131}I therapy. As a consequence, tumor foci were found in the thyroid in 9 of the 16 patients (56%) who had a total thyroidectomy or in one case, isthmusectomy. In addition to tumor in the thyroglossal-duct remnant, 3 of the 16 patients (19%) were found to have bilateral tumor foci. Lymph-node metastases were found in 12 of the 16 patients (75%) who had prophylactic neck dissections.. Lymph-node metastases were found in 6 of 15 central compartment (level VI) dissections (40%) and in 9 of 15 lateral neck dissections (60%). Furthermore, lateral lymph-node metastases were bilateral in 4 patients, on the left side only in 3 patients and on the right side only in 2 patients. A striking finding was skip metastases to the lateral compartments (levels III and IV), without central compartment metastases, which were found in 6 of 15 patients (40%), which is a much higher than the usual rate of skip metastases, which was approximately 20% in several large studies (5;6). Also, level II (subdigastric) lymph nodes were positive in two patients, one of whom had only two isolated level II lymph-node, and the other had levels III and IV lymph-node metastases. Of the 12 patients with lymph-node metastases, 6 (50%) also had tumor foci in the thyroid gland and the other 50% had no thyroid tumors.

A total of 12 patients (67%) were treated with 100 mCi or more of ^{131}I, 11 of whom (92%) had multifocal thyroid tumors with or without lymph-node metastases, and 8 of the 18 patients (44%) were treated with ^{131}I on the basis of lymph-node metastases found as a result of tumors being upstaged to N1a or N1b after prophylactic neck dissection.

Unlike most studies of thyroglossal-duct cancers, the average follow-up was 11 years, with a median of 12 years and a range of 1 to 22. None were lost to follow-up and no patient had physical evidence of persistent or recurrent disease. All had negative neck ultrasonography and 11 of the 18 patients (61%) had thyrotropin-stimulated serum thyroglobulin measurements, 10 of whom had levels <1 µg/L. Of importance, none of the patients had either temporary or permanent recurrent laryngeal-nerve paralysis or hypoparathyroidism.

The findings of this study are very similar to those by Bonnet and associates, also from the Institut Gustave Roussy, Villejuif (7), in which 115 patients with 10- to 20-mm papillary thyroid cancers, all of whom had negative preoperative neck ultrasonography, had prophylactic central- and lateral-compartment lymph-node dissection. The aim of the study by Bonnet, as in the present study, was to determine the effect of lymph-node staging on the indication for ^{131}I treatment. In that study, 42% of the patients with tumors <20 mm without lymph-node metastases were not treated with ^{131}I. On the other hand, 58% were treated with ^{131}I because they had lymph-node metastasis, extracapsular thyroid tumor invasion, or an unfavorable histologic subtype. Similar to the Hartl study, after 1 year the neck ultrasonography was normal in all patients, and recombinant human TSH-stimulated thyroglobulin was undetectable for 97% of the patients.

Thus, both studies from the same group in Paris found that precise lymph-node staging by prophylactic neck dissection for tumors initially staged T1N0 modified the indication for ^{131}I ablation in 30% of the patients in the Bonnet study and over twice as many patients (67%) with thyroglossal-duct papillary cancers in the Hartel study.

Hartl and associates point out that prophylactic neck dissection is controversial but that routine central-compartment (level VI) dissection allows staging of the extent of the disease in lymph nodes and is performed by many surgeons to reduce the incidence of reoperation in this region. They also note that prophylactic lateral neck dissection is not part of the current management guidelines for differentiated thyroid cancer.

I thought the Bonnet study was one of the most important studies reported in 2009 (8) and find the present study to be just as important. Hartl and associates reach the conclusion that "Because the rationale for total versus less-than-total thyroidectomy and for elective neck dissection mirrors that for papillary carcinoma arising in the thyroid lobes, we believe that current guidelines for treatment of differentiated thyroid cancer should be followed in treating papillary thyroid cancer arising in thyroglossal duct remnants." This is a well-reasoned conclusion based on important studies that will help further focus the debate over the routine use of prophylactic lymph-node compartment dissection and will facilitate the selection of ^{131}I therapy only in patients with metastases. It perhaps goes without saying that lymph-node level VI compartment dissections must be performed by well trained and highly experienced surgeons as those in the Institut Gustave Roussy

Ernest L. Mazzaferri, MD, MACP

References

1. Mazzaferri E.L. Thyroid cancer in thyroglossal duct remnants: a diagnostic and therapeutic dilemma. Thyroid 2004;14:335-6.

2. Tew S, Reeve TS, Poole AG et al. Papillary thyroid carcinoma arising in thyroglossal duct cysts: incidence and management. Aust N Z J Surg 1995;65:717-8.

3. Doshi SV, Cruz RM, Hilsinger RL, Jr. Thyroglossal duct carcinoma: a large case series. Ann Otol Rhinol Laryngol 2001;110:734-8.

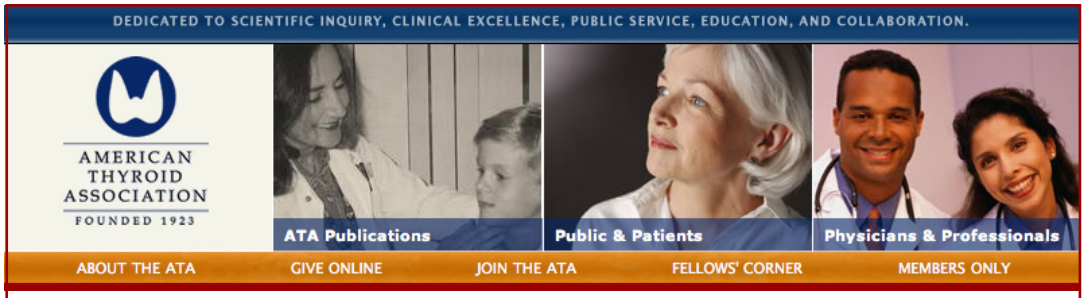
4. Luna-Ortiz K, Hurtado-Lopez LM, Valderrama-Landaeta JL et al. Thyroglossal duct cyst with papillary carcinoma: what must be done? Thyroid 2004;14:363-6.

5. Machens A, Holzhausen HJ, Dralle H. Skip metastases in thyroid cancer leaping the central lymph node compartment. Arch Surg 2004;139:43-5.

6. Mirallie E, Visset J, Sagan C et al. Localization of cervical node metastasis of papillary thyroid carcinoma. World J Surg 1999;23:970-3.

7. Bonnet S, Hartl D, Leboulleux S et al. Prophylactic lymph node dissection for papillary thyroid cancer less than 2 cm: implications for radioiodine treatment. J Clin Endocrinol Metab 2009;94:1162-7.

8. Mazzaferri EL. A vision for the surgical management of papillary thyroid carcinoma: extensive lymph node compartmental dissections and selective use of radioiodine. J Clin Endocrinol Metab 2009;94:1086-8.



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A short course of lithium is safe and significantly increases the cure rate of Graves' hyperthyroidism

Bogazzi F, Giovannetti C, Fessehatsion R, Tanda ML, Campomori A, Compri E, Rossi G, Ceccarelli C,Vitti P, Pinchera A, Bartalena L, Martino E. Impact of lithium on efficacy of radioactive iodine therapy for Graves' disease: a cohort study on cure rate, time to cure, and frequency of increased serum thyroxine after antithyroid drug withdrawal. J Clin Endocrinol Metab 2009. 11-11-2009. doi: 10.1210/jc.2009-16559.

SUMMARY

BACKGROUND

Although Graves' hyperthyroidism is commonly treated with radioactive iodine (^{131}I), its effect might be improved by lithium pretreatment. Still, whether this is safe and can increase the cure rate of hyperthyroidism is uncertain, the examination of which is the aim of this study.

SUBJECTS AND METHODS

This is a retrospective cohort study of the medical records of patients who were prospectively evaluated during follow-up in the authors' clinic. Because patients were not randomly assigned to treatment with ^{131}I or with ^{131}I plus lithium, the propensity score was used to reduce selection bias by adjusting for confounding variables. This provides a more accurate estimate of the effect of treatments that differ in several groups. In addition, multivariate analysis was performed using both the propensity score and significant covariates to control for possible bias from the nonrandomized assignment of patients to treatment.

How Study Subjects Were Selected

The study subjects were 651 patients with Graves' disease, 508 women (78%) and 143 men (22%) referred to the University of Pisa in Italy from January 2004 through June 2007. Patients 18 years of age or older who had Graves' disease with mild or absent Graves' ophthalmopathy were selected for study unless they had moderate to severe ophthalmopathy, had previously undergone ^{131}I treatment or partial thyroidectomy, or had contraindications to treatment with glucocorticoids.

The Treatment Paradigm (Figure 1)

Methimazole (MMI) was started 3 to 6 months before ^{131}I therapy to restore euthyroidism and was discontinued 5 days (T-5) before ^{131}I was initiated. On the same day, lithium, 900 mg/day was started. Seven days after ^{131}I was administered (day T0), lithium was withdrawn, comprising 12 days of lithium, and oral prednisone was started at 0.5 mg/kg daily to avoid ^{131}I-associated Graves' ophthalmopathy. Prednisone was gradually tapered from 0.1 to 0.3 mg/kg every 7 to 17 days and was withdrawn after 2 months. (Figure 1). Radioactive iodine (^{131}I) was given at a dose of 260 µCi/g of estimated thyroid tissue, corrected for the 24-hr radioactive iodine uptake (RAIU).

The Baseline Evaluation, Follow-up, and Definition of Cure (Figure 2)

The baseline evaluation included thyroid function tests, 3 and 24 hours after RAIU, and a battery of other tests such as blood counts, measurements of blood urea nitrogen and creatinine, urinalysis, and electrocardiography. Serum free thyroxine (FT_4), free triiodothyronine (FT_3), and thyrotropin (TSH) measurements were obtained on days T-5, T-3, T-0 , and days T+1, T+3 T+5,

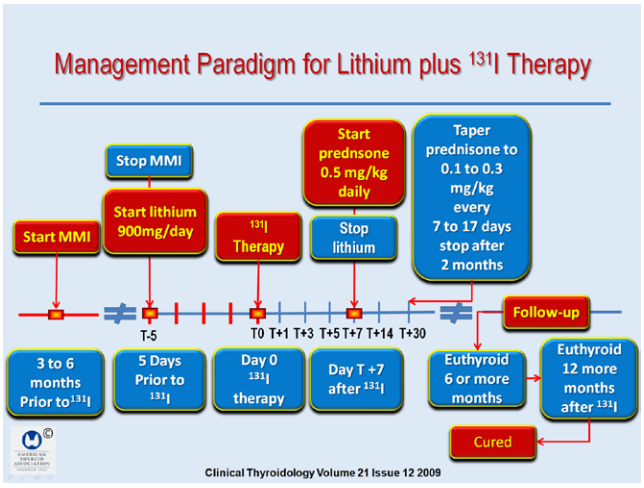

Figure 1. This figure shows the management paradigm for lithium therapy in conjunction with ^{131}I therapy for Graves' hyperthyroidism. The data for this figure are derived from the methods section in Bogazzi et al. MMI = methimazole.

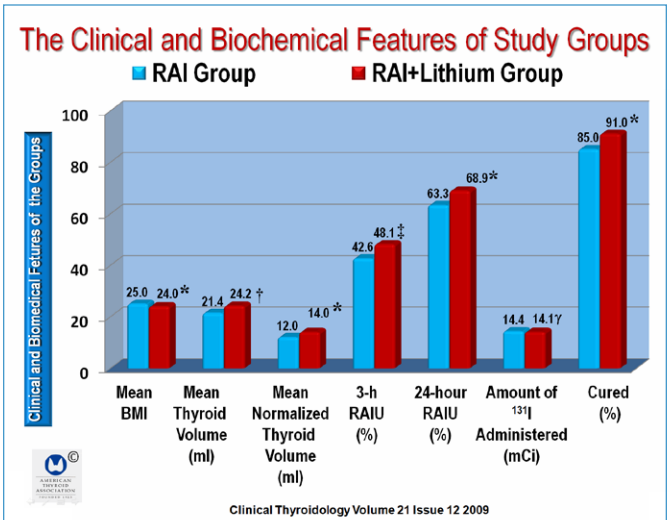

Figure 2. This figure shows the baseline clinical and biochemical findings that differed slightly between the two treatment groups. Patients who were treated with ^{131}I plus lithium were slightly thinner, had a slightly larger goiter, and received a slightly smaller dose of ^{131}I as compared with the group treated with ^{131}I. *P = 0.002. †P = 0.005. ‡P = 00001. §P = 0.028. The other clinical and biochemical features were approximately the same in the two groups. BMI = body-mass index (the weight in kilograms divided by the square of the height in meters); RAI = radioactive iodine; RAIU = radioactive iodine uptake. This figure and Figure 3 are drawn from the data in Table 1 of Bogazzi et al.

T+7, T+14, and T+30, and then every month during a 1-year follow-up period (Figure 1).

Patients were considered to be cured when permanent hypothyroidism developed or they had stable euthyroidism, defined as serum FT_4, FT_3, and TSH within the normal range and confirmed during the entire 12-month follow-up. Thus, a patient who became euthyroid 6 months after ^{131}I therapy was finally considered cured if euthyroidism continued during the ensuing 12 months. A second ^{131}I treatment was given to patients with persistent hyperthyroidism after the 1-year follow-up (Figure 1). Side effects of ^{131}I were evaluated by a patient questionnaire 1 month after the administration of ^{131}I.

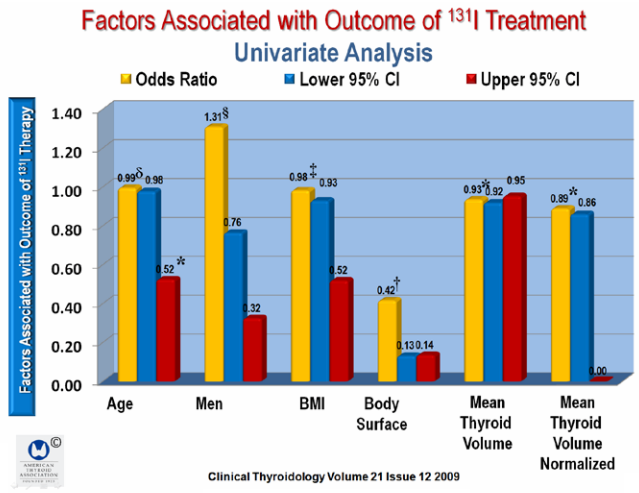

Figure 3. This figure shows the factors associated with the outcome of ^{131}I therapy by univariate analysis. BMI = body-mass index (the weight in kilograms divided by the square of the height in meters); OR = odds ratio. *P = 0.0001. †P = 0.135. ‡P = 0.158. §P = 0.327. δP = 0.528. γP = 0.028. P = 0.846. ¶P>0.5.

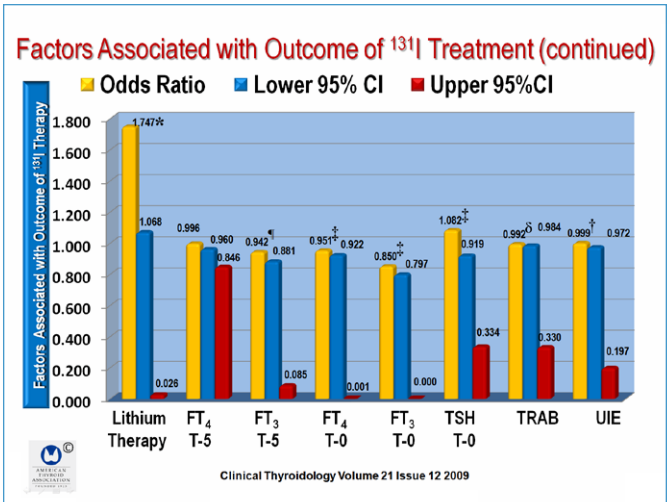

Figure 4. This figure shows the variables associated with outcomes of ^{131}I therapy that were significantly associated with a cure rates on univariate analysis. FT_3 = free triiodothyronine; FT_4 = free thyroxine; TRAb = thyroid receptor antibody; TSH = thyrotropin; UIE = urinary iodine excretion. *P = 0.026. †P = 0.001. ‡P = 0.001. §P = 0.000. δP = 0.033.

RESULTS

The Baseline Clinical and Biochemical Findings (Figure 2)

Among the 651 patients, 353 (54%) were treated with ^{131}I and 298 (46%) were treated with ^{131}I plus lithium. The clinical and biochemical features did not differ between the two treatment groups, except patients treated with ^{131}I plus lithium were slightly thinner, had a larger goiter, and received a slightly smaller dose of ^{131}I as compared with the group treated with ^{131}I. A larger number of patients in the ^{131}I-plus-lithium group were cured of hyperthyroidism as compared with the ^{131}I group (91% vs. 85%, P = 0.03) (Figure 2).

The Determinants of Cure by Univariate and Propensity-Adjusted Analysis (Figures 3, 4, and 5)

At 1 year, factors associated with the probability of cure by univariate logistic regression were a higher cure with lower thyroid receptor antibody (TRAb) levels (P = 0.03), lithium treatment, lower thyroid volume (P = 0.0001), lower thyroid hormone levels (P = 0.001) and higher TSH concentrations at T0 (Figures 3 and 4).

However, when the difference in the cure rate in the two groups was adjusted for covariates on meta-analysis, only lithium, TRAb, and thyroid volume maintained a significant effect on outcome (Figure 5). The odds ratio (OR) with lithium use was 2.618 (95% confidence interval [CI], 1.444 to 4.749).

After adjusting for the propensity score for lithium treatment and for TRAb values, the variables significantly affecting the propensity score were age (P = 0.005) and normalized thyroid volume (P = 0.007). Even when adjusting for the propensity score and TRAb values, the effect of lithium on cured patients was highly significant (OR, 2.459; 95% CI, 1.383 to 4.374; P = 0.002), even after adjusting for the propensity score and TRAb values (Figure 5).

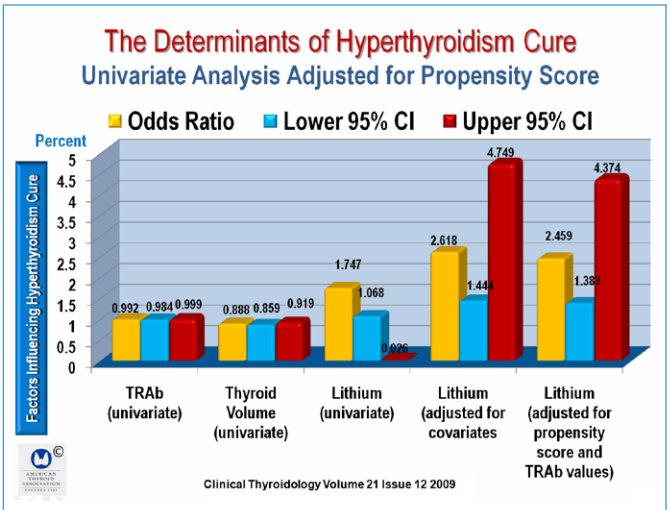

Figure 5. This figure shows the determinants of hyperthyroidism in univariate analysis, and after adjusting for the propensity score for lithium treatment and for thyroid receptor antibody (TRAb) values, the variables significantly affecting the propensity score were age (P = 0.005) and normalized thyroid volume (P = 0.007). Even when adjusting for the propensity score and TRAb values, the effect of lithium on cured patients was highly significant, even after adjusting for the propensity score and TRAb values. CI = confidence interval. The data for this figure are from Table 2 of Bogazzi et al.

The Time Required to Cure Hyperthyroidism with Lithium

The median time for cure of hyperthyroidism was 60 days in the ^{131}I-plus-lithium group and 90 days in the ^{131}I group (P = 0.0001). Control of hyperthyroidism was more rapid in the ^{131}I-plus-lithium group during the first months after ^{131}I. The hazard ratio of a favorable effect of lithium on median cure time was 1.512 (95% CI, 1.220 to 1.875), even when adjusted for the covariates that were significantly associated to the median cure time as shown by Cox univariate analysis (TRAb = 0.007; normalized thyroid volume P = 0.0001; and FT_3 P = 0.046

The Effect of Serum Lithium Levels on Cure Rate

The mean serum lithium level was 0.56±0.23 mEq/L; only four were >1, and one was >1.5 mEq/L. A receiver operating curve found that the optimal lithium cutoff was 0.45 mEq/L, with a sensitivity of 70% and specificity of 56%. The cure rate was higher with lithium levels ≥0.45 mEq/L (OR, 2.97; 95% CI, 1.04 to 8.81; P = 0.042). The cure rate was 93% when the lithium level was 0.45 mEq/L and 83% when it was <0.45 mEq/L.

The Time Trend of Serum Thyroid Hormone Levels

Mean serum FT_4 levels, which initially did not differ in the two ^{131}I groups, increased significantly in both groups after MMI withdrawal, reaching a peak between days T+3 to T+5 in the ^{131}I group, (P<0.001 for both times). However, in the group treated with ^{131}I and lithium, the serum FT_4 levels increased after both MMI withdrawal and ^{131}I therapy but remained within the normal range, with peaks at day T+3 (P = 0.0138) and T+5 (P = 0.050). The mean serum FT_4 levels at days T+3 and T+5 were significantly higher in the ^{131}I group (P = 0.0139) as compared with the ^{131}I-plus-lithium group (P = 0.0373). Serum FT_4 levels declined, reaching the normal range between days T+14 and T+30. The mean serum FT_3 levels had a similar trend.

The Outcome of Thyroid Volume and Graves' Ophthalmopathy (Figure 6)

Thyroid volume decreased significantly after ^{131}I in both groups but was greater in the ^{131}I-plus-lithium group, which decreased from a mean of 14.0±7.0 to 4.8±4.5 ml (P<0.0001), as compared with the ^{131}I group, which changed from 12.0 ± 6.3 to 5.0 ± 3.9(P<0.0001); still, by the end of follow-up, thyroid volume did not differ in the two groups (P = 0.762). No patient in the study had worsening of eye disease after ^{131}I therapy.

Symptoms Attributed to ^{131}I plus Lithium versus ^{131}I (Figure 7)

Although 25% of patients in both groups had mild symptoms, which lasted 2 to 3 days, 15% in both groups had gastrointestinal symptoms, which did not differ in the two groups. Patients reported no toxic effects of lithium, including the four patients with lithium concentrations of >1mEq/L.

CONCLUSION

The short course of lithium is safe and of considerable benefit for patients who are treated with ^{131}I. It increases the cure rate for hyperthyroidism, shortens the time for cure, and prevents an abrupt increase in thyroid-hormone levels immediately after ^{131}I therapy.

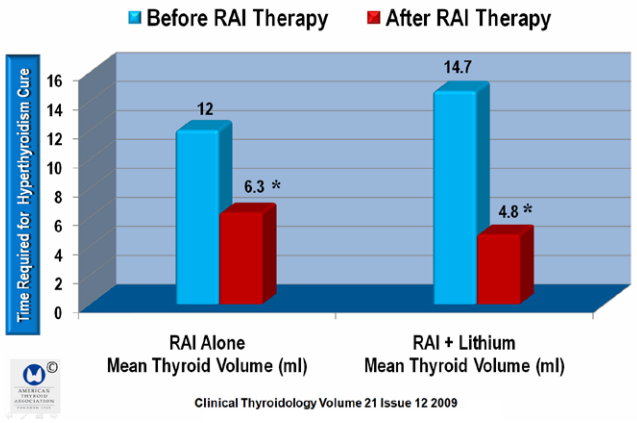

Figure 6. This figure shows that thyroid volume decreased after ^{131}I therapy with or without lithium; however, in the ^{131}I-plus-lithium group, volume decreased from 14 to 4.8 ml after therapy, as compared with 6.3 to 5.0 ml in the ^{131}I group. *P<0.0001 for both groups. The thyroid volumes were not significantly different at the end of the follow-up period. *P<0.0001, comparing thyroid volume before and after ^{131}I therapy in the two treatment groups. RAI = radioactive iodine.

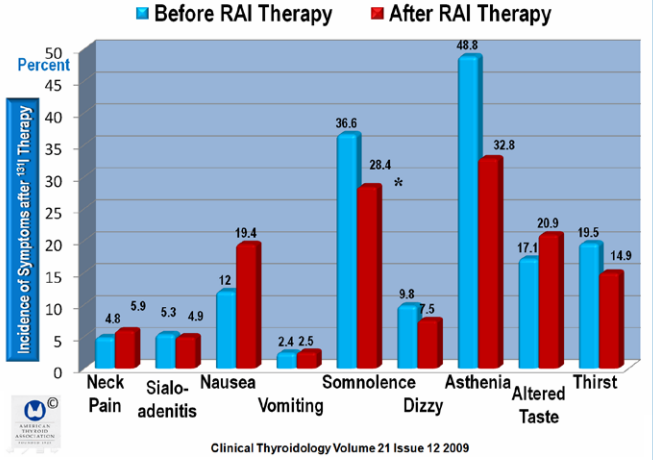

Figure 7. This figure shows some of the symptoms in both treatment groups. Fifteen percent of both groups had symptoms of gastrointestinal symptoms, but otherwise there were no serious symptoms and no toxic effects of lithium. RAI = radioactive iodine. *P = 0.04.

COMMENTARY

Although Graves' hyperthyroidism may be treated with surgery, antithyroid drugs, or ^{131}I, none of the three has yet emerged as the best form of therapy. A prospective, randomized study by Torring et al. (1) that analyzed the risks and benefits of the three forms of treatment found after a follow-up of at least 48 months that all three treatments normalized the mean serum thyroid hormone levels within 6 weeks. The risk of relapse was highest in the young and old adults (42% vs. 34%) treated with

antithyroid drugs, intermediate in those treated with ^{131}I (21%), and lowest in the surgically treated young and old adults (3% vs. 8%). Moreover, there is little consensus regarding the most appropriate regimen for ^{131}I in the treatment of hyperthyroidism; with some suggesting that 100 mCi may be the most appropriate amount of ^{131}I for patients with Graves' hyperthyroidism (2). Still, this is an amount of ^{131}I in the range usually selected for patients with thyroid cancer. Some physicians use a fixed dose of ^{131}I without measuring uptake in order to prevent recurrence of Graves' hyperthyroidism. However, there is conflicting evidence about whether giving a fixed dose of ^{131}I for this purpose is better than a more elaborate calculation of the dose based on goiter size, and iodine uptake and turnover (3). Also of concern is the substantial rise in thyroid hormone levels that occur when antithyroid drugs are withdrawn just before ^{131}I therapy is initiated (4). Another concern is that simultaneous antithyroid drug therapy interferes with the outcome of ^{131}I therapy. However, a relatively recent randomized trial found that withdrawal of an antithyroid drug 3 days before ^{131}I treatment does not diminish the therapeutic effect of ^{131}I (5).

Some have failed to find a favorable effect of lithium as an adjuvant in ^{131}I therapy for patients with hyperthyroidism. A randomized study by Bal and associates (6) examined the role of lithium in 350 patients treated with ^{131}I for hyperthyroidism. The study patients were treated with 300 mg of lithium three times a day for 3 weeks starting on the day that ^{131}I was administered at an initial ^{131}I dose of approximately 6 mCi, which was the same in the control group that was treated with ^{131}I alone. The overall cure rate at the end of the study was the same in both groups (96.7% and 96.3%) and the authors concluded that lithium as an adjuvant in ^{131}I treatment of hyperthyroidism is insignificant after a mean follow-up of 33.3 ± 9.8 months. The fact that lithium was started on the same day that ^{131}I was administered is a major difference from the studies by Bogazzi et al that likely account for the negative results in the study by Bal and associates.

The Bogazzi protocol, which is shown in Figure 1, was meticulously designed to avoid interference with antithyroid drugs, and to deliver lithium at the most favorable time. In the current study, lithium was given for only 9 days, beginning 5 days before ^{131}I therapy was initiated, and maintained for 7 days thereafter. This is a shorter protocol (12 vs. 19 days) than that of a previous pilot study by Bogazzi and associates (7) that found that the effect of lithium on serum thyroid hormone concentrations occurred 3 to 5 days after ^{131}I was administered.

Although this is a retrospective study, the scrupulous statistical analysis takes into account the possibility of selection bias by adjusting for confounding variables. Multivariate analysis was performed using both the propensity score and significant covariates to control for possible bias from the nonrandomized assignment of patients to treatment. The main findings of the study were that patients treated with ^{131}I plus lithium had a higher cure rate (91%) than those treated with ^{131}I alone. Treatment with lithium also prevented an increase in serum free T_4 and T_3 levels after withdrawal of MMI, which had been given for 3 to 6 months prior to ^{131}I therapy. Side effects of lithium were mild and transient and were not different in the two study groups with and without lithium pretreatment for ^{131}I therapy. None of the patients had ophthalmopathy, and the thyroid volume decreased much more rapidly in the patients pretreated with lithium as compared with the group treated with ^{131}I alone. Lastly, and of considerable importance, the study found that serum lithium concentrations of 0.7 mEq/L or greater were not associated with a higher cure rate, indicating that lithium increases ^{131}I efficacy at blood levels far lower than those considered risky for the occurrence of side effects.

This large well-analyzed robust study shows that lithium is of substantial benefit in the treatment of patients with Graves' hyperthyroidism. The authors suggest that a short course of lithium is safe and beneficial for patients treated with ^{131}I, increasing the cure rate for hyperthyroidism and shortening the time for cure, and preventing an abrupt increase in thyroid hormone levels.

It is highly likely that this important study will provide a strong impetus for a change in practice paradigms for patients with Graves' hyperthyroidism. It must be kept in mind, however, that all the positive effects of lithium found in this study rely upon careful adherence to a meticulous treatment protocol described in this article. The utilization of the protocol described in this study may well emerge as the dominant treatment of Graves' hyperthyroidism.

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References

1. Torring O, Tallstedt L, Wallin G et al. Graves' hyperthyroidism: treatment with antithyroid drugs, surgery, or radioiodine–a prospective, randomized study. Thyroid Study Group. J Clin Endocrinol Metab 1996;81:2986-93.

2. Allahabadia A, Daykin J, Sheppard MC et al. Radioiodine treatment of hyperthyroidism-prognostic factors for outcome. J Clin Endocrinol Metab 2001;86:3611-7.

3. Leslie WD, Ward L, Salamon EA et al. A randomized comparison of radioiodine doses in graves' hyperthyroidism. J Clin Endocrinol Metab 2003;88:978-83.

4. Burch HB, Solomon BL, Cooper DS et al. The effect of antithyroid drug pretreatment on acute changes in thyroid hormone levels after 131-I ablation for Graves' disease. J Clin Endocrinol Metab 2001;86:3016-21.

5. Walter MA, Christ-Crain M, Schindler C et al. Outcome of radioiodine therapy without, on or 3 days off carbimazole: a prospective interventional three-group comparison. Eur J Nucl Med Mol Imaging 2006;33:730-7.

6. Bal CS, Kumar A, Pandey RM. A randomized controlled trial to evaluate the adjuvant effect of lithium on radioiodine treatment of hyperthyroidism. Thyroid 2002;12:399-405.

7. Bogazzi F, Bartalena L, Campomori A et al. Treatment with lithium prevents serum thyroid hormone increase after thionamide withdrawal and radioiodine therapy in patients with graves' disease. J Clin Endocrinol Metab 2002;87:4490-5.

Children with Graves' hyperthyroidism may have a poor therapeutic response to ^{131}I if it is delayed or if they have recently been treated with antithyroid drugs or have Graves' ophthalmopathy

McCormack S, Mitchell DM, Woo M, Levitsky LL, Ross DS, Misra M. Radioactive iodine for hyperthyroidism in children and adolescents: referral rate and response to treatment. Clin Endocrinol (Oxf) 2009. CEN3565 [pii];10.1111/j.1365-2265.2009.03565.x[doi]

SUMMARY

BACKGROUND

Antithyroid drugs are usually the first-choice therapy for children and young adults with hyperthyroidism. However, minor and major complications may occur with antithyroid drugs, making surgical or radioiodine (^{131}I) therapy necessary. Yet there is controversy concerning the merits of each treatment, which may make this decision difficult. Also, it is not entirely clear what patient or therapeutic features predict a response to ^{131}I in children and adolescents. The aims of this study were to describe current referral practices in an academic pediatric center and an adolescent endocrine practice, to assess the responses of hyperthyroidism to ^{131}I therapy, and to further identify the factors predicting outcome in this group of patients.

METHODS

This was a retrospective electronic chart review of 720 consecutive patients treated in the Pediatric Endocrine Unit of the Mass General Hospital for Children (MGH) or the Thyroid Unit of the Massachusetts General Hospital.

How Patients Were Selected

Patients were selected from the 720 cases in the hospital database that had had any thyroid-function test abnormality and ranged in age from 30 days to 21 years. Among this group were 131 patients who had thyroid-function tests diagnostic of hyperthyroidism and a follow-up of at least 6 months. Also included in the search were medical records of pediatric patients who were treated during the same period with methimazole (MMI) or propylthiouracil (PTU) or had a diagnosis of thyroiditis, thyrotoxicosis, or postablative hypothyroidism. Among the latter group, the medical records of adolescent patients with hyperthyroidism treated with ^{131}I and had follow-up in the adult endocrinology clinic were selected for study. Excluded from the study were asymptomatic children with mild laboratory evidence of hyperthyroidism that spontaneously resolved.

How the Patient Data Were Collected

Data collected included patient sex and Tanner stage at the time of diagnosis, thyroid size estimated by palpation, prior use of MMI or PTU, with or without β–blockers, and the administration of ^{131}I. Tanner stage I was considered prepubertal, whereas other Tanner stages were considered pubertal or postpubertal. A diagnosis of Graves' disease was made if there was laboratory evidence of hyperthyroidism and at least two of the following: goiter, thyrotropin (TSH) receptor–binding immunoglobulins (TSHR-Ab) or thyroid-stimulating immunoglobulins, Graves' eye disease, and significantly increased thyroidal ^{131}I uptake. Patients with benign thyroid nodules and hyperthyroidism were assigned to a separate diagnostic category.

What Were the Indications for ^{131}I Therapy?

The major indication for ^{131}I therapy was identified from the primary clinician's electronic notes. Other possible indications were an adverse reaction to antithyroid drugs, poor control of

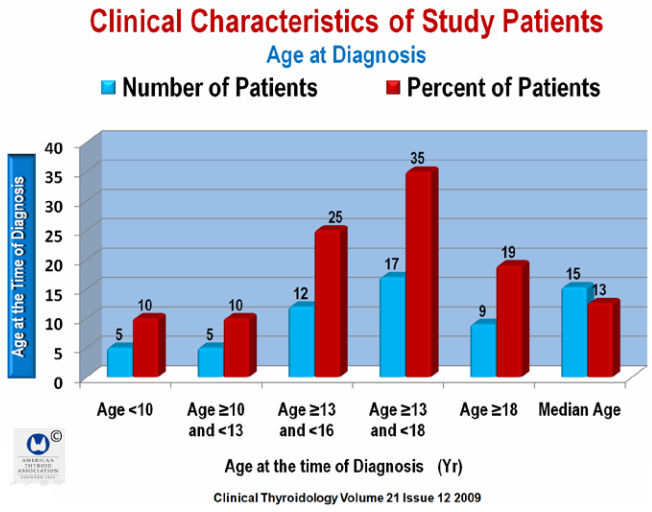

Figure 1. This figure shows the age of patients in this study. The data in this figure and Figures 2 through 4 and 6 are derived from Table 1 of McCormack et al.

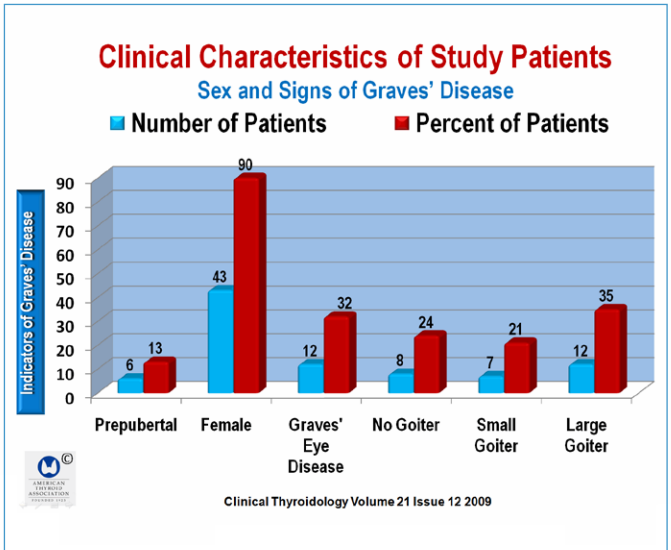

Figure 2. This figure shows the number of patients who were prepubertal and female and the number with signs of Graves' disease (ophthalmopathy and goiter).

hyperthyroidism on antithyroid drugs, or patient preference.

A single primary indication for ^{131}I was assigned using an iterative process. First, if an adverse reaction to antithyroid drugs was cited, then this was considered the primary indication; second, if poor control of hyperthyroidism was found, as defined by clinical signs of hyperthyroidism with or without persistent TSH suppression and with or without persistent elevation of free thyroxine (FT_4) while the patient was taking antithyroid drugs, despite attempts to optimize therapy, and without adverse reaction to the drugs, then poor control was considered the primary indication; third, if nonadherence was found in the record, excluding other reasons such as adverse effects of antithyroid drugs, then this was considered as the primary indication; and lastly, if evidence of patient preference was found in the clinical notes, then this was cited as the primary indication for ^{131}I therapy unless the report was incomplete, in which case it was labeled as unknown.

How Radioiodine Therapy Was Administered

All patients treated at MGH who received ^{131}I were treated by one of two endocrinologists. Antithyroid drugs were discontinued 3 to 5 days before ^{131}I was administered, using 160 μCi per gram of thyroid tissue as estimated by palpation.

How Outcome Was Determined during Follow-up

All patients had follow-up for at least 6 months after ^{131}I therapy was administered or until hypothyroidism occurred. This typically included laboratory studies every 2 weeks and at least monthly clinic visits or more as required until hypothyroidism occurred. Time to development of hypothyroidism was defined from the initiation of therapy to the first visit at which hypothyroidism was diagnosed without antithyroid drugs or when thyroid-hormone replacement was necessary to treat hypothyroidism. However, if hypothyroidism did not occur well after 6 months, then this was used to identify patients who had a poor response to ^{131}I. If hyperthyroidism recurred or persisted after ^{131}I, then a second ^{131}I treatment was given to some patients, depending on the patient's and family's wishes.

How the Possible Predictors of a Poor Response to ^{131}I Therapy Were Determined

The following were considered possible predictors of a poor therapeutic response to ^{131}I: diagnosis before the onset of puberty, thyroid size, presence of ophthalmopathy, preceding antithyroid drug therapy, very elevated FT_4 or total triiodothyronine (T_3) at the time of diagnosis, previous β-blocker therapy and the time to administer ^{131}I therapy. These variables were largely chosen from the existing literature on children treated with ^{131}I for hyperthyroidism. Proxy measures of the severity of hyperthyroidism were thyroid-gland size, very elevated serum

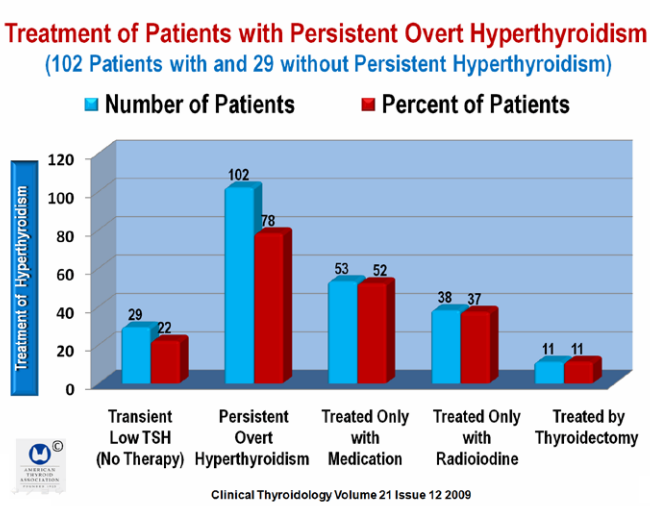

Figure 3. This figure shows the treatment of 102 patients with persistent overt hyperthyroidism and 29 other patients with transient low serum TSH for less than 6 months that spontaneously returned to normal without therapy.

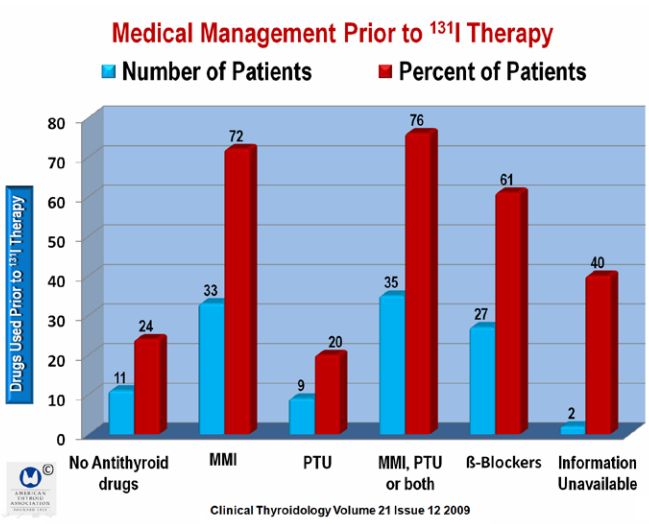

Figure 4. This figure shows the indictions for ^{131}I in 47 of the 48 patients treated with ^{131}I for whom the indications were known. Poor control of hyperthyroidism was the indication for ^{131}I in 9 patients, 4 of whom had poor control as the result of poor adherence to therapy.

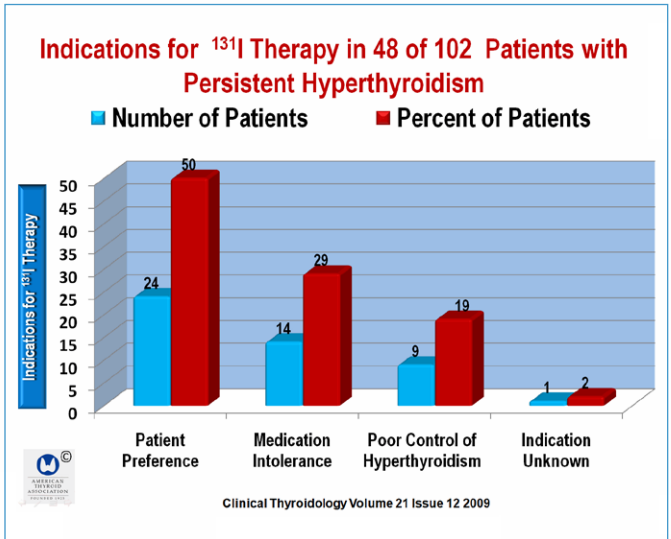

Figure 5. This figure shows the indictions for thyroidectomy in 11 of the 131 patients who had hyperthyroidism.

FT_4 or T_3, defined as threefold the upper limit of normal (69 mol/L for T_4 and 8.36 nmol/L for T_3). However, FT_4 and T_3 test results were not available for all patients because the tests were performed elsewhere. Also assessed was the effect of ^{131}I therapy after waiting more than 12 months from the time of diagnosis.

RESULTS

Clinical Characteristics and Course of Patients with Hyperthyroidism (Figures 1 to 3)

Of the 720 cases reviewed, 131 (18%) met the study criteria for hyperthyroidism. The primary clinical characteristics of this group are shown in Figures 1 and 2. Of these 131 cases, 29 (22%) had transient TSH suppression for less than 6 months that spontaneously resolved without additional therapy (Figure 3). Follow-up thyroid-function tests in this group disclosed normalization of the tests with or without subsequent hypothyroidism, which occurred in patients with subacute or silent thyroiditis or chronic lymphocytic thyroiditis. Persistent overt hyperthyroidism was found in 102 patients (78%), 53 (52%) of whom were treated only with medication; 38 (37%) were treated with ^{131}I, and 11 (11%) had thyroidectomy (Figure 3). Ten adolescent patients who had follow-up in the adult endocrinology clinic also were treated with ^{131}I and were included in this study.

The Preparation and Indications for ^{131}I Therapy (Figures 4 and 5)

Medical management before ^{131}I therapy comprised no antithyroid drugs in 11 patients (24%), MMI in 33 (72%), PTU in 9 (20%), MMI, or PTU, or both in 35 (76%), β-blockers in 27 (61%), and incomplete information in 2 (40%). (Figures 4 and 5)

The Indications for Thyroidectomy (Figure 6)

The indication for ^{131}I therapy was judged as patient preference (50%) followed by intolerance to medications (29%) and poor control while taking medications (19%), which was due to poor adherence to therapy in 4 of the 9 patients (44%). (Figure 6) All 48 patients who were treated with ^{131}I had Graves' disease.

Thyroidectomy was performed in patients with hyperthyroidism and thyroid nodules; it was also performed in 4 of 11 patients with persistent overt hyperthyroidism (36%), in 1 (9%) with a palpable thyroid >80 g, in 1 (9%) with ophthalmopathy, in 2 (18%) with significant ophthalmopathy, in 2 (18%) with intolerance to medical therapy in 2 (18%), and in 1 (9%) because of patient preference.

Predictors of a Poor Response to ^{131}I Therapy (Figure 7)

Thirteen of the 48 patients treated with ^{131}I (27%) had a poor response to ^{131}I or required a second treatment with ^{131}I. The main indicators that portended a poor response were the use of antithyroid drugs prior to ^{131}I, poor control of hyperthyroidism, the presence of ophthalmopathy, and a delay of ^{131}I treatment of more than 12 months after the diagnosis of hyperthyroidism (Figure 7). However, a poor therapeutic response to ^{131}I was not associated with a diagnosis of hyperthyroidism before puberty, prior use of β-blockers, goiter size, or a very elevated serum FT_4 or T_3. A Kaplan–Meier analysis of 46 patients for whom information was available on the use of antithyroid drugs showed that the median time to hypothyroidism was 2.2 months (95% confidence Interval [CI], 1.9 to 2.4 months) for those who did not take antithyroid drugs before ^{131}I as compared with 4.2 months (95% CI, 2.7 to 4.4 months) for those who did take antithyroid drugs before ^{131}I therapy ($P<0.01$)

CONCLUSION

Children with Graves' hyperthyroidism may have a poor therapeutic response to ^{131}I if treatment is delayed or if they were recently treated with antithyroid drugs or have Graves' ophthalmopathy.

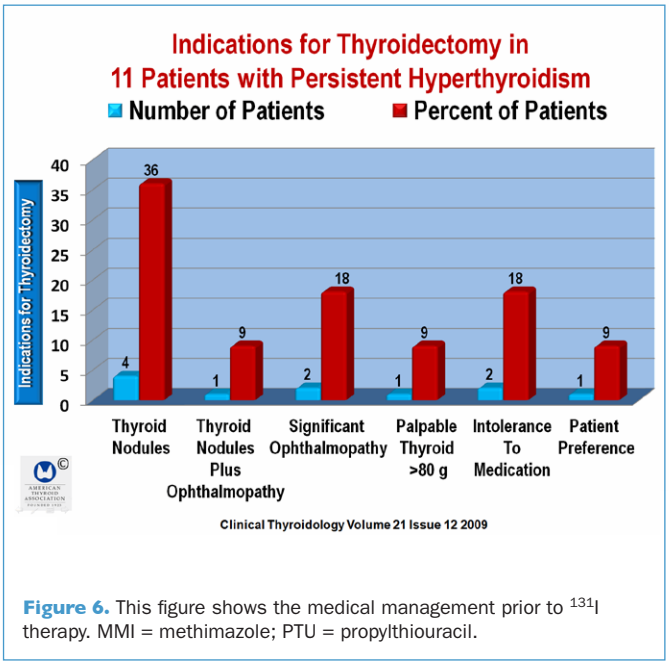

Figure 6. This figure shows the medical management prior to ^{131}I therapy. MMI = methimazole; PTU = propylthiouracil.

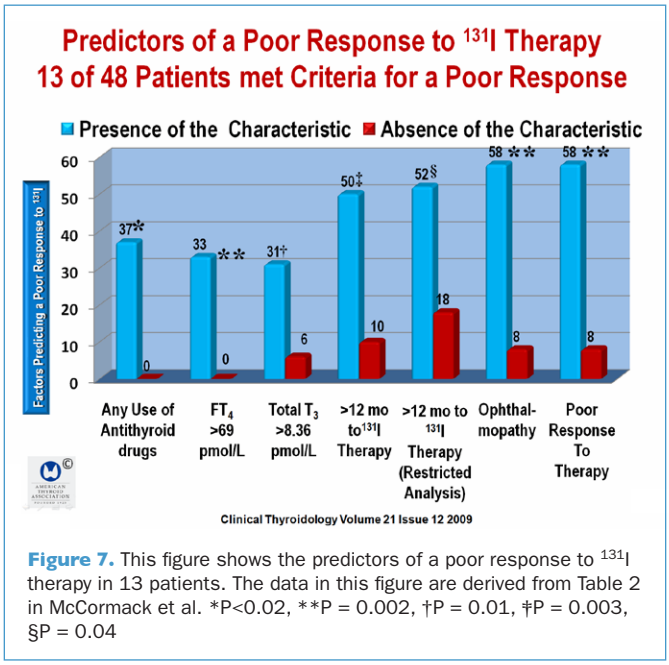

Figure 7. This figure shows the predictors of a poor response to ^{131}I therapy in 13 patients. The data in this figure are derived from Table 2 in McCormack et al. *P<0.02, **P = 0.002, †P = 0.01, ‡P = 0.003, §P = 0.04

COMMENTARY

Antithyroid medications, surgery, and ^{131}I have been widely used for more than five decades for the treatment of Graves' hyperthyroidism in children and adolescents, (1) yet children often require prolonged courses of antithyroid drugs to achieve remission, and long-term compliance is often challenging (2). For example, a study by Glaser et al. (2) of 191 patients with Graves' disease who were younger than 19 years old found that patients achieving early remission were older (mean, 12.5 vs. 10.9 years; P = 0.039) and had a higher BMI (19.0 vs. 16.6, P = 0.002), lower heart rates (110 vs. 121, P = 0.023), and smaller goiters (60% with moderate goiter versus 83%, with larger goiters; (P = 0.050), and lower serum T_4 and T_3 concentrations (18 vs 22.5 μ g/dL P = 0.008).

Controversy still exists concerning the merits of each of the three therapies in children, especially the use of ^{131}I. This is particularly important as long-term spontaneous remission of Graves' disease occurs in less than 30% of children (1), but may rise incrementally over the ensuing years (3). Still, most children with Graves' disease require definitive treatment, mainly because there is little evidence that the use of antithyroid drugs beyond 1 year enhances outcome. For example, Greer et al(4) found that the lasting remission rate in children is as good when antithyroid drugs are stopped as soon as the patient is euthyroid as when they are continued for 1 year or more. Nonetheless, Barrio et al.(5) found that the implementation of a long-term antithyroid drug protocol achieved 40% long-term remissions in pediatric patients with Graves' disease.

The goal of ^{131}I therapy in both children and adults is to induce hypothyroidism in order to prevent a recurrence of Graves' disease, which is achieved in approximately 80% of patients, regardless of the approach to ^{131}I dosing, although calculated dosimetry may have an efficacy similar to that of fixed dosing, but with less radiation exposure (1;6).

Graves' disease is associated with few acute side effects, and the potential long-term adverse side effects, including thyroid cancer and genetic damage, have yet to be observed in individuals treated with ^{131}I as children or adolescents (1). In support of this observation, a 36-year retrospective study by Read et al. (7) of the efficacy and safety of ^{131}I treatment of young patients with Graves' disease, including 6 who were younger than 6 years of age, 11 who were between 6 and 11, and 45 who were between 11 and 15, and 45 who were between 16 and 19 years of age at the time of ^{131}I treatment. After an average length of follow-up of 36 years in 2001 to 2002, none of the patients had cancer of the thyroid or leukemia. Early on in this study, when the objective of treatment was euthyroidism, the dose of ^{131}I was low, and retreatment was frequently needed, but the ^{131}I doses were subsequently increased. The authors concluded that treating young people with Graves' disease with ^{131}I is safe and effective over the long term.

Rivkees et al. (8), assessed the dose response of ^{131}I in children with hyperthyroidism treated with one of three doses: 80 to 120 μCi/g (72 to 108 Gy), 200 to 250 μCi/g (180 to 225 Gy), and 300 to 405 μCi/g (270 to 364 Gy), in 31 patients ranging in age from 7 to 18 years. When thyroid status was assessed >1 year after therapy, the ^{131}I doses of 110, 220, and 330 μCi/g resulted in hypothyroidism in 50%, 70%, and 95% of treated individuals, respectively. The authors concluded that 300 μCi/g of thyroid is needed for ^{131}I treatment of hyperthyroidism, especially when the thyroid is large.

A meta-analysis of randomized, controlled trials by Walter et al,(9) found that, antithyroid medication was associated with an increased risk of treatment failure (relative risk, 1.28; 95% CI, 1.07 to 1.52; P = 0.006) and a reduced risk for hypothyroidism (relative risk, 0.68; 95% CI, 0.53 to 0.87; P = 0.006) after ^{131}I treatment. The main conclusion was that antithyroid drugs increase the rates of ^{131}I failure and reduce rates of hypothyroidism if they are given in the week before or after radioiodine treatment, respectively. Similar observations were found by Tuttle et al. (10).

The main conclusions of the study by McCormack et al. were that high success rates of ^{131}I therapy are achievable in children and adolescents with hyperthyroidism but may be hindered by preexisting eye disease and a prolonged time from diagnosis to ^{131}I therapy and that pretreatment use of antithyroid drugs may confer resistance to ^{131}I therapy.

The authors mention several limitations of this study. The main problems are the limits in statistical power for subgroup analysis, which impaired the performance of multivariate analysis. Also, some patients did not have thyroid-function tests, and data were missing in the primary indications for ^{131}I. Lastly, the estimation of thyroid volume by palpation leaves some room for error that may have altered the amounts of ^{131}I chosen for therapy.

Nonetheless, there is robust information that ^{131}I is highly effective and safe for the treatment of children and young adults with Graves' hyperthyroidism, providing antithyroid drugs are not given prior to therapy and delay in ^{131}I therapy is minimized.

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References

1. Rivkees SA, Dinauer C. An optimal treatment for pediatric Graves' disease is radioiodine. J Clin Endocrinol Metab 2007;92:797-800.

2. Glaser NS, Styne DM. Predictors of early remission of hyperthyroidism in children. J Clin Endocrinol Metab 1997;82:1719-26.

3. Lippe BM, Landaw EM, Kaplan SA. Hyperthyroidism in children treated with long term medical therapy: twenty-five percent remission every two years. J Clin Endocrinol Metab 1987;64:1241-5.

4. Greer MA, Kammer H, Bouma DJ. Short-term antithyroid drug therapy for the thyrotoxicosis of Graves's disease. N Engl J Med 1977;297:173-6.

5. Barrio R, Lopez-Capape M, Martinez-Badas I et al. Graves' disease in children and adolescents: response to long-term treatment. Acta Paediatr 2005;94:1583-9.

6. Brent GA. Clinical practice. Graves' disease. N Engl J Med 2008;358:2594-605.

7. Read CH, Jr., Tansey MJ, Menda Y. A 36-year retrospective analysis of the efficacy and safety of radioactive iodine in treating young Graves' patients. J Clin Endocrinol Metab 2004;89:4229-33.

8. Rivkees SA, Cornelius EA. Influence of iodine-131 dose on the outcome of hyperthyroidism in children. Pediatrics 2003;111:745-9.

9. Walter MA, Briel M, Christ-Crain M et al. Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials. BMJ 2007;334:514.

10. Tuttle RM, Patience T, Budd S. Treatment with propylthiouracil before radioactive iodine therapy is associated with a higher treatment failure rate than therapy with radioactive iodine alone in Graves' disease. Thyroid 1995;5:243-7.

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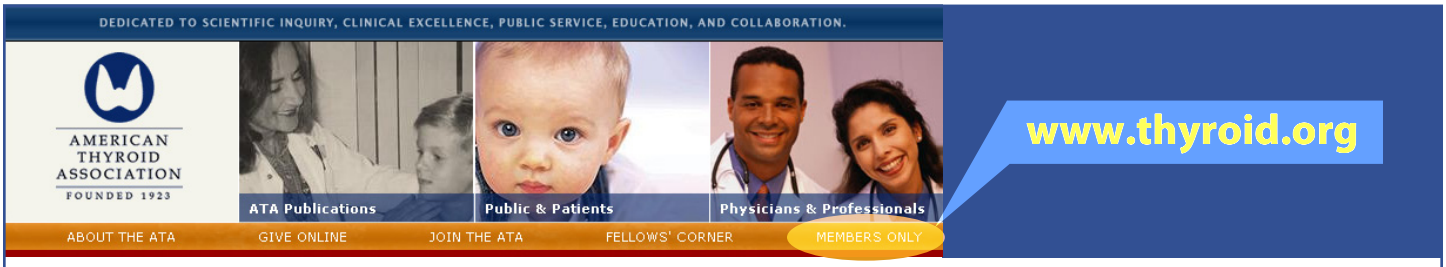

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The new National Cancer Institute classification system for fine-needle aspiration cytology is an excellent standard for reporting cytology results

Theoharis CG, Schofield KM, Hammers L, Udelsman R, Chhieng DC.The Bethesda thyroid fine-needle aspiration classification system: year 1 at an academic institution. Thyroid 2009;19:1215-23. DOI: 10.1089=thy.2009.0155

SUMMARY

BACKGROUND

On October 22 and 23, 2007, the National Cancer Institute (NCI) hosted the "NCI Thyroid Fine Needle Aspiration State of the Science Conference" which brought together a group of national experts in the field who reviewed the literature and attended the meeting. Among the many important features of the meeting was the general acceptance of a classification scheme for FNA cytology. The aim of the study by Theoharis and associates was to report their experience with this new NCI six-tier cytology classification and to analyze the distribution of diagnostic categories in their patients and to evaluate the diagnostic accuracy of the NCI conference recommendations for the classification for FNA cytology.

METHODS AND PATIENTS

In January 2008, the authors' institution adopted the NCI classification for reporting thyroid FNA cytology results as suggested at the NCI conference. This prospective study extended over a 12-month period, during which the incidence and histologic outcomes of each diagnostic category was examined. The study comprised 3207 consecutive FNA thyroid cytology specimens evaluated at the Yale-New Haven Hospital from January 1st, 2008 through December 31, 2008, some of which were submitted by outside laboratories for a second opinion. The majority of the FNAs were performed under ultrasound guidance.

The surgical histology report was the standard for confirming the accuracy of the diagnostic FNA cytology classification. The specificity of the FNA cytology was estimated using two approaches. One was to consider the FNA as a diagnostic test if the FNA specimens were interpreted as suspicious of malignancy or positive for malignancy, and the remaining categories were classified as negative. The other approach was to consider the FNA as a screening test if the FNA cytology specimens were diagnosed as benign or negative, and the remaining FNA cytology categories were classified as positive. Cases classified as unsatisfactory or indeterminate were excluded from calculations for both approaches because they indicate the absence of diagnostic material and the need for additional sampling rather than the presence of malignancy or benign cytology. Also excluded from calculations in the first approach—FNA as a diagnostic test—were follicular or Hürthle cell adenomas because cytology does not distinguish this group from their malignant counterparts.

RESULTS

A total of 3207 thyroid FNAs obtained from 2468 patients were evaluated at the authors' institution during the 12-month study, and FNA specimens from 271 patients (11%) were submitted by outside laboratories for a second opinion. Of the 3207 thyroid

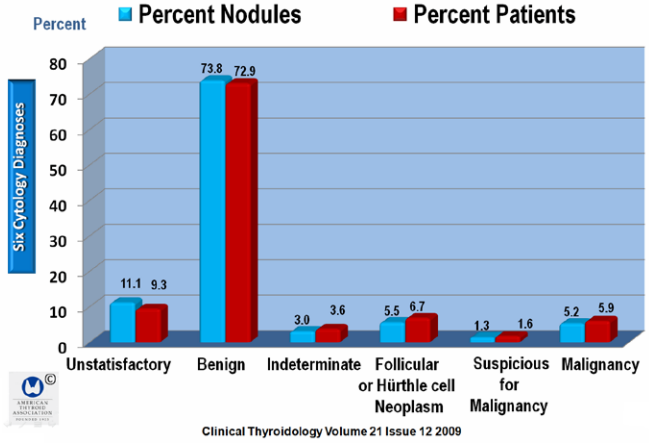

Figure 1. This figure shows the correlation of six cytology diagnoses with the histology diagnosis. The six diagnostic cytology categories are (1)Unsatisfactory/ (2) Benign/negative, (3) Indeterminate/cells of undetermined significance, (4) follicular neoplasms/Hürthle cell neoplasms or (5) suspicious for malignancy and (6) malignant. The benign histologic categories are (1) multinodular goiter, Hashimoto's thyroiditis, follicular and Hürthle cell adenoma. The malignant categories are papillary thyroid carcinoma, follicular thyroid carcinoma, medullary carcinoma and squamous cell carcinoma of the head and neck. The number of patients shown in this figure represents a consolidation of the malignant and benign histology groups. The data for this figure is derived from Table 2 of Theoharis et al.

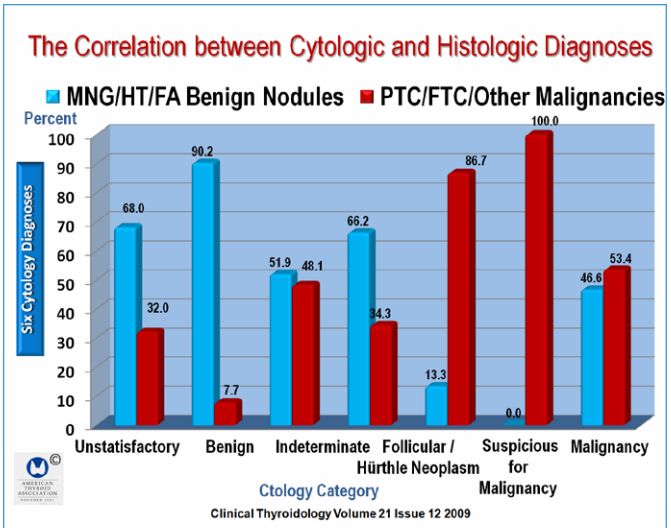

Figure 2. This figure shows the correlation between the cytology and histologic diagnoses. MNG = multinodular goiter; HT = Hashimoto's thyroiditis; FA = follicular adenoma; PTC = papillary thyroid carcinoma, FTC = follicular thyroid carcinoma; Other = other thyroid cancers.

nodules, 2386 (74%) were negative for malignancy. Of the 2468 patients, 378 (15%) had a thyroidectomy. Of this group of 2468 patients, 82 had thyroidectomy (3%) because of other clinical considerations such as the size of the nodules, a family history of thyroid cancer or a history of neck irradiation, and the majority (75%) had nodular goiters, followed by lymphocytic thyroiditis and colloid nodules (74%), and 13 (16%) had follicular adenoma and 8 had papillary thyroid carcinoma (10%). All of the papillary thyroid carcinomas that were discovered in a histologic specimen in patients with benign cytologic diagnosis had tumors ≤10 cm, 6 of which were 0.5 cm or less. Among the patients who had FNA, 89 had indeterminate FNA cytology, 58 of which (65%) were further subclassified as low cellularity with microfollicular architecture and absence of colloid and, and 31 (35%) had nuclear features not characteristic of benign cytology. Seventeen of the 89 (19%) patients had a repeat FNA, which was unsatisfactory in 3, negative for malignancy in 11, indeterminate in 1, follicular neoplasm in 1, negative for malignant in 11, indeterminate in 1 and positive for papillary thyroid carcinoma in 1.

Of the 230 patients with an unsatisfactory diagnosis, repeat FNA was performed in 34 (15%) patients. Repeat FNA diagnoses were unsatisfactory in 14 patients, negative for malignancy in 19, and positive for papillary thyroid carcinoma in 1 patient. Of the 230 patients, 25 (11%) with an unsatisfactory FNA had a surgical resection, which revealed a benign goiter in 9 patients, follicular adenoma in 8, and papillary thyroid carcinoma in 7 patients.

The distribution of six-tier FNA cytology diagnoses in nodules (Figure1)

This figure shows the cytology diagnosis in terms of nodules and patients. The six cytology diagnoses were: (1) unsatisfactory in 357 of 3207 nodules, (11.%), (2) benign or negative in 2368 (74%), (3) indeterminate or cells of undetermined significance (3%), (4) follicular or Hürthle cell neoplasms (6%), (5) suspicious for malignancy (1%), and malignant (5%). (Percentages are rounded to an integer in the text but shown in full in the figures). Of the 3720 thyroid nodules in the study, the cytology interpretation was negative for malignancy in 357 (11%), benign or negative in 2368 (74%), indeterminate or cells of undetermined significance in 95 (3%), follicular nodules or Hürthle cell neoplasm in 176 (6%), or suspicious for malignancy in 43 (1%), and malignant in 168 (5%). (Figure 1)

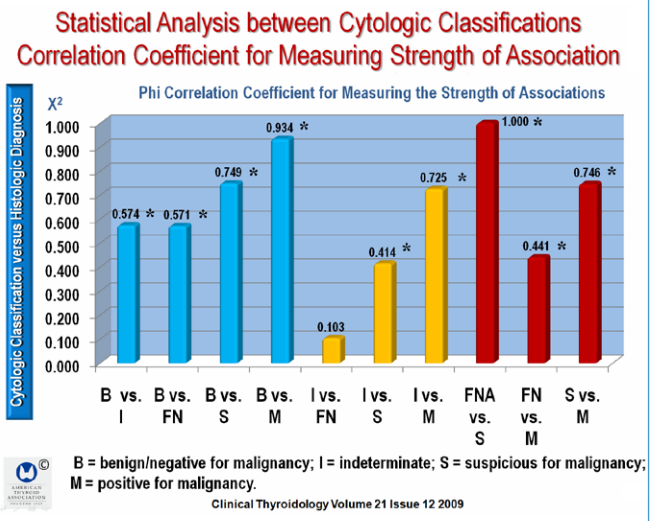

Figure 3. This figure represents the Phi correlation coefficient for measuring the strength of association between categorical data. The values range from +1 to -1. +1 denotes a strong positive association and -1 a strong negative correlation. B = benign/negative for malignancy; I = indeterminate; S = suspicious for malignancy; M = positive for malignancy; *P <0.001. This figure is derived from Table 5 of Theoharis et al.

The correlation between FNA cytology and histology diagnoses (Figure2)

The study found excellent correlations between the FNA diagnostic categories and the histologic outcomes in predicting nonneoplastic versus neoplastic thyroid nodules and benign vs. malignant thyroid nodules.

Statistical analysis of the cytologic classification system (Figure3)

Overall, 378 (15%) of the patients

Comparing each individual cytologic diagnostic category against the other four categories included in the analysis (without follicular or Hürthle cell adenomas) found statistically significant differences between benign and indeterminate, benign and follicular neoplasms, benign and suspicious, indeterminate and malignant, follicular neoplasms and malignant as well as suspicious and malignant. On the other hand, there was no statistically significant difference between indeterminant and follicular neoplasms.

The risk of malignancy per diagnosis (Figure 4)

There was an excellent association between the FNA categories and in predicting benign versus malignant thyroid nodules ($p<0.0001$). The cytology diagnosis in five of the thyroid FNA categories was compared with the histology findings in 82 patients who had surgery. Among the benign/negative for malignancy cytology group that comprised 82 of the 2468 patients (3%), 8 of the 82 had malignant tumors (9.8%) on histology; of the Indeterminate/cells of undetermined

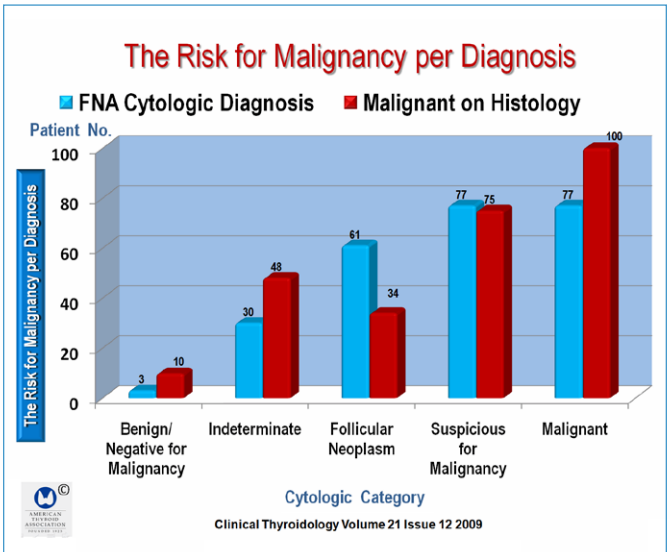

Figure 4. This figure shows the accuracy of FNA cytology. The sensitivity and negative predictive values could not be calculated.

significance cytology group that comprised 27 of 89 patients (30%), 13 of 27 (48%) had malignant tumors; of the follicular neoplasm cytology group that comprised 102 of 166 patients (61%), 35 of 102 patients (34%) had malignant histology; of the suspicious for malignancy cytology group, which comprised 30 of 39 patients (77%), 26 of 30 (75%) had malignant histology; and lastly, among the positive for malignancy cytology group, which comprised 112 of 145 patients (77%), 112 of 112 (100%) had malignant histology (Figure 4).

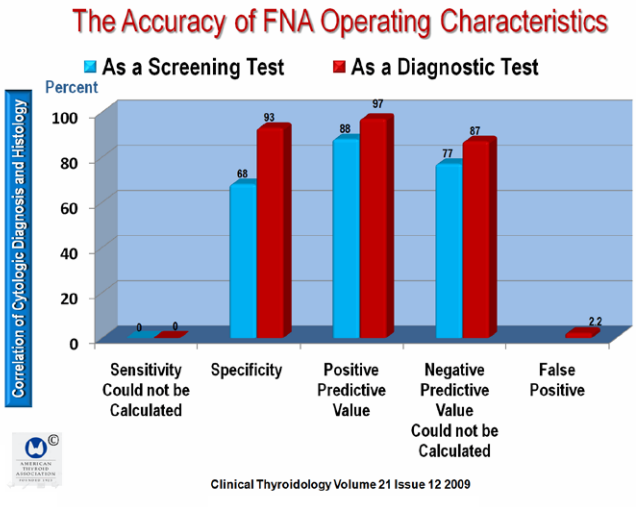

Figure 5. The false-negative rate could not be calculated because of the small number of patients with benign diagnosis who underwent surgery. The false-positive rates were 2.2%, but the FNA cytologies were all categorized as suspicious. Because only 15% of the patients underwent surgery, the sensitivity of thyroid FNA for diagnosing malignant thyroid nodules could not be calculated, nor could the sensitivity of thyroid FNA cytology be accurately assessed as a screening test for all neoplasms.

The accuracy of cytology (Figure 5)

Based on the small number of patients with benign diagnoses, the false-negative rate could not be calculated. The false-positive rate was 2.2%, all of which were diagnosed as suspicious cytology. Because only 15% of the patients had surgery, the FNA sensitivity for diagnosing malignant thyroid nodules could not be accurately calculated, nor could the sensitivity of thyroid FNA as a screening test for all neoplasms be accurately estimated. The specificity for a diagnosis of malignant thyroid nodules was 93%, whereas the specificity as a screening test for all neoplasms was 68%. The positive predictive values for a follicular neoplasm, suspicious, and positive cytologic diagnoses were 34%, 87%, and 100%, respectively. (Figure 5)

CONCLUSION

This study demonstrates that the recently proposed NCI classification system for FNA cytology is an excellent standard for reporting thyroid FNA results. Each diagnostic category conveys specific risks of malignancy, which offers guidance for patient management.

COMMENTARY

Several recent clinical guidelines address the evaluation of thyroid nodules, many of which suggest that a tiered system for classifying thyroid FNA cytology provides the most accurate diagnostic approach(1) (2). The NCI conference has proposed diagnostic categories for the classification of (FNA) cytology, comprising the following categories: (1) Nondiagnostic, Benign, (2) Atypia of Undetermined Significance, (3) Follicular Neoplasm or suspicious for a follicular neoplasm, (4) Follicular Neoplasm or Suspicious for a Follicular Neoplasm, (5) Suspicious for Malignancy, and (6) Malignant. The contents of this very important meeting are available on the National Cancer Institute website (http://thyroidfna.cancer.gov/ and has been reviewed by several authors. (1;3;4) Cibus et al. point out that it is critical that the cytopathologist communicate thyroid FNA interpretations to the referring physician in terms that are succinct, unambiguous, and clinically helpful. This is especially important considering that the terminology for thyroid FNA has varied significantly in recent years from one laboratory to another, creating confusion in some instances and hindering the sharing of clinically meaningful data among multiple institutions.

The study by Theoharis CG, and associates is one of the early studies of the accuracy of the National Cancer Institute Thyroid Fine-Needle Aspiration State-of-the-Science Conference that opens new avenues of information for the biopsy and interpretation of FNA cytology.

Theoharis and associates found an excellent association between the FNA categories and the predictions of benign versus malignant thyroid nodules ($p<0.0001$). However, the false-negative rate could not be calculated because of the small number of patients with benign diagnosis who underwent surgery. The false-positive rates were 2.2%, but the FNA cytologies were all categorized as suspicious. Because only 15% of the patients underwent surgery, the sensitivity of thyroid FNA for diagnosing malignant thyroid nodules could not be calculated, nor could the sensitivity of thyroid FNA cytology be accurately assessed as a screening test for all neoplasms. However, of considerable importance, the specificity for diagnosing malignant thyroid nodules was 93%, whereas the specificity as a screening test for all neoplasms was 68%. The positive predictive values for a follicular neoplasm, suspicious, and positive cytologic diagnosis were 34%, 87%, and 100%, respectively. The authors' conclusion that their data demonstrate the recently proposed NCI classification system is excellent for reporting thyroid FNAs is well supported by this study.

Yang et al(5) reported their experience with a similar FNA cytology classification from 2 institutions in which cytology diagnoses were classified as unsatisfactory, benign, atypical cellular lesion (ACL), follicular neoplasm (FN), suspicious for malignancy, and positive for malignancy. Of 4703 FNA samples, 10.4% were classified as unsatisfactory, 64.6% were classified as benign, 3.2% were classified as ACL, 11.6% were classified as FN, 2.6% were classified as suspicious, and 7.6% were classified as

malignant. At least 1 repeat FNA was necessary in 512 patients, mainly for results in the unsatisfactory and ACL categories. Of this group, 1252 patients had surgical follow-up, including 14.9% with unsatisfactory FNA results, 9.8% with benign results, 40.6% of with ACL results, and 63.1% with FNA results, 86.1% with suspicious results, and 79.3% with malignancy results. Sources of errors were diagnoses on inadequate specimens, sampling errors, and overlapping cytologic features between hyperplastic nodules and follicular adenoma. The sensitivity and specificity of thyroid FNA for the diagnosis of malignancy were 94% and 98.5%, respectively. The authors concluded that FNA provides an accurate diagnosis of thyroid malignancy, and that 6 diagnostic categories were beneficial for triaging patients for either clinical follow-up or surgical management

This relatively new evidence supports the NCI recommendations for the interpretation of FNA cytology.

Ernest L. Mazzaferri, MD, MACP

References

1. Baloch ZW, Cibas ES, Clark DP et al. The National Cancer Institute Thyroid fine needle aspiration state of the science conference: a summation. Cytojournal 2008;5:6.

2. Guidelines of the Papanicolaou Society of Cytopathology for fine-needle aspiration procedure and reporting. The Papanicolaou Society of Cytopathology Task Force on Standards of Practice. Diagn Cytopathol 1997;17:239-47.

3. Cibas ES, Alexander EK, Benson CB et al. Indications for thyroid FNA and pre-FNA requirements: A synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagn Cytopathol 2008;36:390-9.

4. Cibas ES, Sanchez MA. The National Cancer Institute Thyroid Fine-Needle Aspiration State-of-the-Science Conference: Inspiration for a uniform terminology linked to management guidelines. Cancer 2008.

5. Yang J, Schnadig V, Logrono R et al. Fine-needle aspiration of thyroid nodules: A study of 4703 patients with histologic and clinical correlations. Cancer 2007.

Elderly patients with differentiated thyroid cancer not treated with total thyroidectomy and radioiodine have higher mortality rates than elderly patients treated more aggressively

Park HS, Roman SA, Sosa JA.Treatment patterns of aging Americans with differentiated thyroid cancer.Cancer 2009.

SUMMARY

BACKGROUND

The incidence of differentiated thyroid cancer (DTC) increases with age and is more aggressive in patients ≥45 years, a group that is more likely to have biologically aggressive tumors and a poor outcome as compared with that of younger patients. This is of considerable importance as elderly individuals comprise a steadily increasing segment of the US population. Park et al. emphasize that in 2000, Americans ≥65 years of age constituted slightly more than 12% of the population, which is projected to increase to 20% by 2050. This group requires careful study, as there are more than 30,000 new cases of thyroid cancer diagnosed annually in the United States.

PATIENTS AND METHODS

The National Cancer Institutes' Surveillance, Epidemiology, and End Results (SEER) program was used to identify patients with papillary, follicular and Hürthle cell thyroid cancer. This retrospective cohort study identified all patients who had histologically confirmed differentiated thyroid cancer. Excluded from study were patients <45 years of age who were missing data regarding surgery, tumor stage, and diagnoses established by autopsy or only or by death certificate, and patients with tumors < 1 cm.

Included in this study were patient demographics, primary tumor site, histology, tumor stage at diagnosis, and the first course of treatment, including surgery and radiation therapy. Independent demographic variables included age at diagnosis, sex, race/ethnicity, including white, black Asian/Pacific Islander, Other, and Hispanic origin, and the year of diagnosis, from 1988 to 1991, 1992 to 1995, 1996 to 1999, and 2000 to 2003. Clinical variables studied included the number of primary tumors, and surgical therapy described as none, lobectomy/isthmusectomy, or total/near-total thyroidectomy. Data for lymph-node dissection were available only from 1998 through 2002. It was assumed that radioactive isotopes were ^{131}I for all patients with thyroid cancer. Other study variables were disease stage at the time of diagnosis, tumor size, and extension/thyroid capsular invasion and lymph-node metastases. The 6th edition of the American Joint Commission on Cancer (TNM) classification was used to stage the tumors in this study.

RESULTS

The study data (Figure 1)

The study initially focused on 43,657 adults who had a diagnosis of DTC in 1988 through 2003. Of this group, 24,055 (55%) were >45 years of age, and 11,394 (47%) had tumors ≥1 cm. Complete surgical data were available on 10,896 patients (96%), and staging data were available on 9377 patients (83%), including information on tumor size, tumor extension, lymph-node metastases and TNM data. Thus a total of 8899 patients had complete surgery and staging data; 2271 patients (26%) were age 65 to 79 years and 444 (5%) were ≥80 years of age. (Figure 1). Analyses were performed on three age groups: 45 to 64, 65 to 79, and ≥80 years of age.

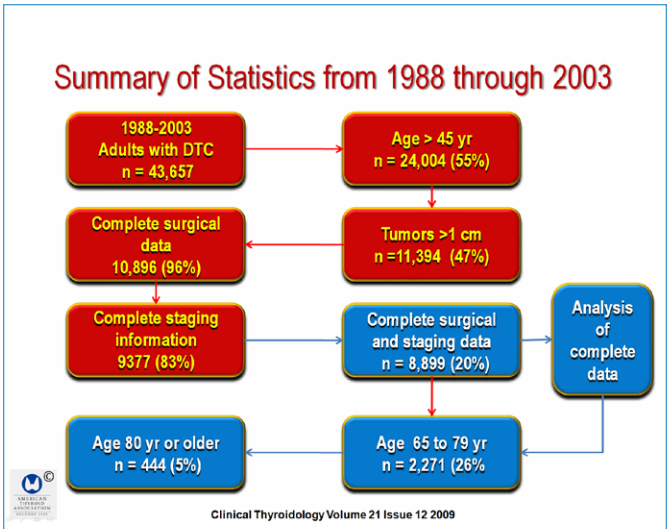

Figure 1. This figure shows the progression of SEER data from 24,044 patients with DTC who had tumors >10 mm and complete surgical and staging information, 2271 of whom were 65 to 79 years.

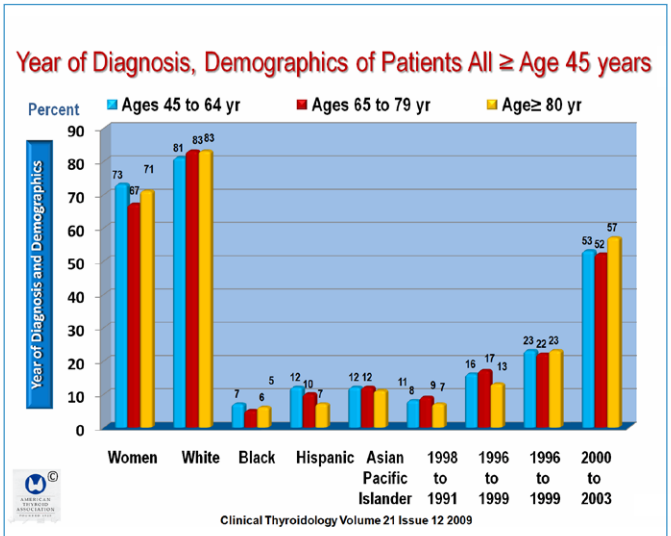

Figure 2. This figure shows the key patient and tumor demographics in this study; 71 % of the patients were women, 81% were white, 89% were non-Hispanic and 70% were married. The figure shows the differences in three age groups: 45 to 64, 65 to 79, and ≥80 years of age. The data for the all figures are derived from Tables 1 to 4 of Park et al. The differences in among the three age are significantly different (P<0.001 for women vs. and among the ethnic groups and race).

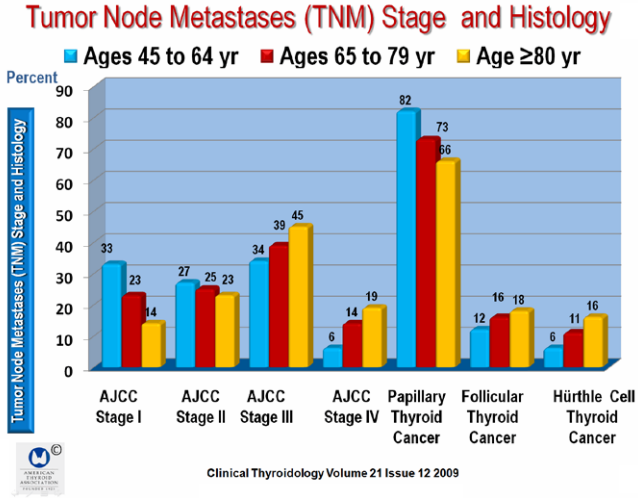

Figure 3. This figure shows the TNM stages (P<0.01) the tumor histology among the age groups (P <0.01) for both histology and TNM stages, comparing the difference in three age groups.

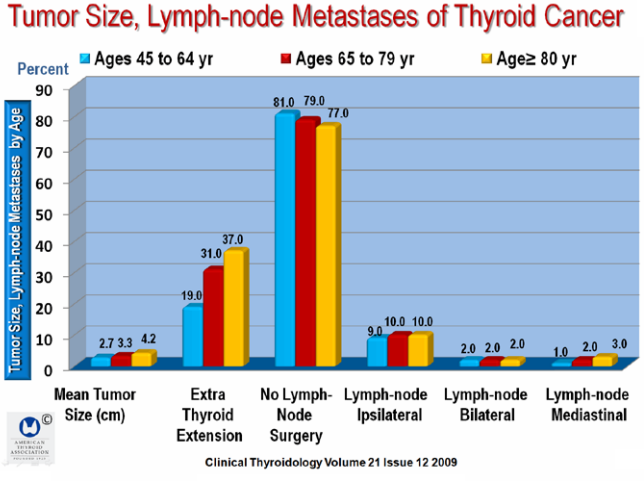

Figure 4. This figure shows tumor size, the location of lymph-node metastases, and the degree of extrathyroid tumor extension in the three age groups (P<0.001 for all three variables).

Patient sex, race and ethnicity (Figure2)

From 1988 to 2003, for all study patients combined, the cohort comprised 71% women; however, with age this changed to 73%, 67% and 71% for the three age groups, respectively. (Figure 2) Also, the ethnicity and race for all patients was 81% white, 6% black, 12% Asian/Pacific Islanders, 11% Hispanic, and 1% Others; however, this changed to 81% 83% and 83% for the three age groups, respectively, during the years shown in Figure 2.

Tumor features (Figures 3 and 4)

Tumor stage increased significantly with increasing age. For all patients combined, 30% of the tumors were stage I, but the rate decreased with advancing age to 33%, 23% and 14% in the three age groups, respectively. For all patients combined, 26% were stage II, but this changed to 27%, 25% and 23% in the three age groups. For all patients combined, 9% of tumors were stage IV; but this also changed with advancing age to 6%, 14% and 19% in patients in the three age groups (P<0.001). (Figure 3)

The rates of papillary thyroid cancer became less frequent with advancing age and other types of thyroid cancer became more common. For all patients combined, the tumor histology was papillary thyroid cancer in 79%, but this changed to 82%, 73%, and 66% of the three patient age groups, respectively. (Figure 3) Tumor size increased with age. Mean tumor size±SD was 3±2.2 cm for all patients combined, but was 2.7±1.9, 3.3±2.1cm and 4.2±5.1 cm for patients in the three age groups, respectively (P< 0.001). (Figure 4) Tumor extension beyond the thyroid capsule was found in 23% of all patients combined, but occurred in 19%, 31%, and 37% in the three age groups. (Figure 4)

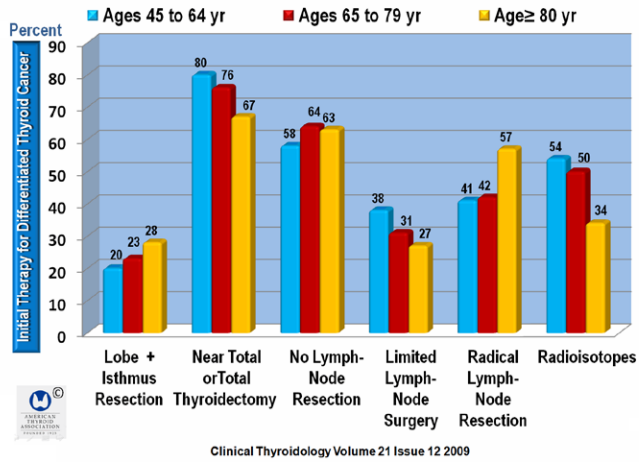

Figure 5. This figure shows the initial surgical and ^{131}I therapy in the three age groups P< 0.001) comparing the differences among age groups in both variables.

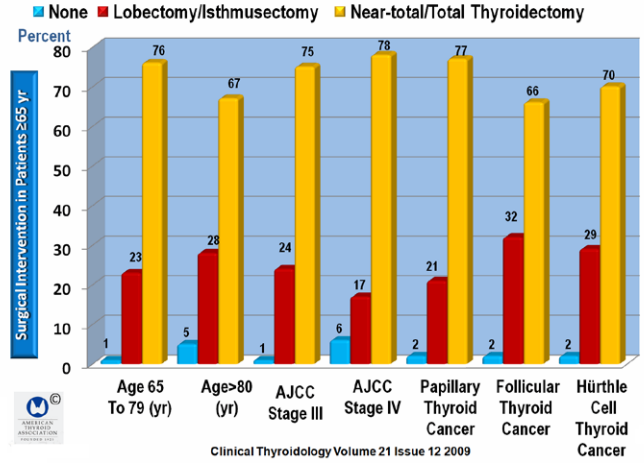

Figure 6. This figure shows the surgical interventions among patients ≥ 65 years of age and the tumor histology in this group, the TNM tumor stage and histology P<0.001) comparing differences among age in all variables.

Initial surgical findings in the primary tumor site (Figures 5 and 6)

In all patients combined, no lymph-node metastases were found in 80% of the patients, but this declined to 82%, 79%, and 77%, in the three age groups; and the rate of ipsilateral cervical lymph-node metastases was 9% for all patients, which changed to 9%, 10% and 10% in the three age groups. The same trend with advancing age was found in bilateral/contralateral/midcervical, mediastinal, and regional metastases (Figure 5)

The surgical intervention among elderly patients ≥ 65 years of age are shown in Figure 6, In all patients combined, no thyroidectomy was performed in 1% (87 patients); and this remained at 1%, 1% and 5% in the three age groups, respectively. (Figure 5) Thyroidectomy in all patients combined, was lobectomy/isthmusectomy in 21%, and this remained approximately the same at 20%, 23% and 28% in the three age groups, respectively. In all patients combined, near-total or total thyroidectomy was performed in 78% of all patients combined; but this changed to 80%, 76% and 67%, in the three groups, respectively. (Figure 5) Among the 87 patients who did not have surgery, it was contraindicated in 15%, was not recommended in 37%, and was refused by the patient or guardian in 24%, and the reason was unknown in 30%. (Figure 5)

No lymphadenectomy was performed in 60% of all patients combined, and in 58%, 64% and 63% of the three age groups, respectively (Figure 5). Limited lymphadenectomy was performed in 36% of all patients combined, and in 38%, 31% and 27% of the three age groups. (Figure 5) Limited lymph-node surgery was done in 36% of all patients combined, and in 38%, 31% and 27%, in the three age groups, respectively.

Initial radioiodine therapy for the primary tumor site (Figure7)

Adjuvant Radioisotope therapy (^{131}I) was administered to 52% of all patients combined, and to 54%, 50%, and 34% of all three age groups, respectively (Figure 5). Of elderly patients 65 to 79 years of age, (50%) received ^{131}I and (50%) did not; of patients ≥80 years of age 34% received ^{131}I and 66% did not. Of patients with ipsilateral cervical lymph-node metastases, 57% received ^{131}I and 43% did not. Of patients with bilateral/contralateral/midcervical lymph-node metastases, 61% received ^{131}I and 31% did not, and of patients with mediastinal lymph node metastases, 56% received ^{131}I and 44% did not, and of patients with distant metastases 50% received ^{131}I and 50% did not. (Figure 7)

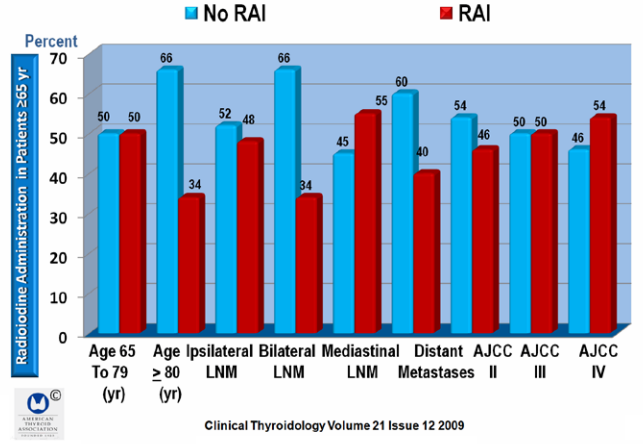

Figure 7. This figure shows the difference in ^{131}I therapy according to patient age, tumor stage and tumor histology. P< 0.001) comparing the differences in variables among the three age groups. LNM = Lymph-Node Metastases.

Second primary tumors

One primary malignancy was found in 83% of all patients combined, but was found in 86%, 75% and 75% in the three age groups, respectively; two primary malignancies were found in 15% of all patients combined, but were found in 12%, 20% and 19% in the three age groups, respectively; three or more primary malignancies were found in 3% of all patients combined, but >3were found in 2%, 5% and 6% of the three age groups.

Bivariate Analysis

Patients ≥65 years who had total or near-total thyroidectomy were more likely to have advanced tumor stage (P<0.05) and nonpapillary histology (P<0.001), and those who were treated with ^{131}I were more likely to have advanced-stage disease (P<0.001)

Multivariate Analysis (Figure 8)

Three variables associated with not undergoing total thyroidectomy were (1) ages 69 to 79 years, odds ratio (OR) 1.27, P<0.001; (2) age≥ 80 years, OR, 2.32, P< 0.001; and (3) stage IV disease OR, 1.35, P<0.05.

The four variables associated with not being treated with^{131}I were (1) ages 65 to 79 years OR, 1.16, P<0.01; (2) age≥80

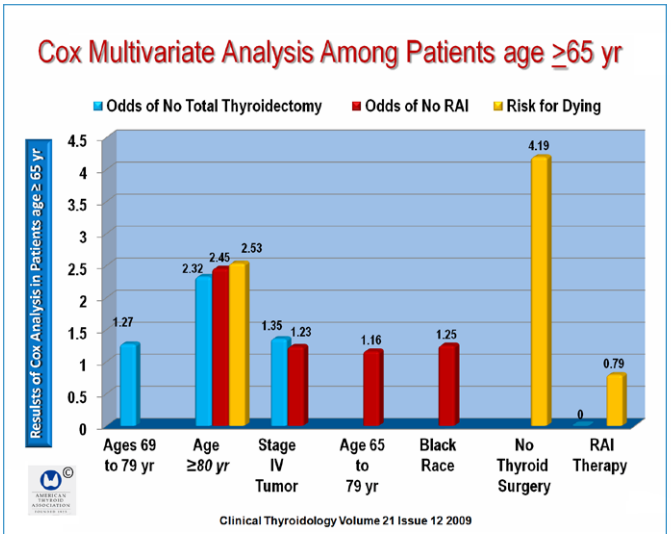

Figure 8. This figure shows the results of a Cox proportional hazards regression module, that found age at the time of diagnosis was a strong predictor of survival; patients aged ≥80 years had a 2.53-fold greater risk for dying than that of patients of ages 65 to 79 years. Not undergoing surgery was associated with a 4.19-fold greater risk for dying as compared with patients undergoing surgery. Stage III and IV disease also was associated with decreased survival (P<0.01 for both no surgery and disease stage). Radioiodine therapy significantly reduced the risk for dying. (OR 0.79)

years, OR, 2.45, P<0.001,(3) stage IV disease, OR, 1.23, P<0.05; and (4) black race, OR, 1.25, p<0.05)

A Cox proportional hazards regression module found age at the time of diagnosis was a strong predictor of survival; patients aged ≥80 years had a 2.53-fold greater risk for dying than that of patients of ages 65 to 79 years. Not undergoing surgery was associated with a 4.19-fold greater risk for dying as compared with patients undergoing surgery. Stage III was associated with and IV disease also was associated with decreased survival (P<0.01 for both no surgery and disease stage). (Figure 8)

CONCLUSION

Elderly patients with differentiated thyroid cancer often fail to receive total thyroidectomy and radioiodine therapy and have higher mortality as compared with patients treated more aggressively.

COMMENTARY

This important study shows that elderly Americans ≥65 years of age with differentiated thyroid cancer larger than 1 cm receive, as a population, less aggressive treatment with total or near-total thyroidectomy and radioiodine therapy as compared with younger patients. This trend is even more evident among patients age 80 years or older and has persisted throughout the 16-year study period encompassed by the Park study. Although the number of patients treated with total or near-total thyroidectomy and radioiodine was increased in older patients with stage IV tumors, older age was still associated with a lower likelihood of being treated with total or near-total thyroidectomy and radioiodine. Yet the elderly population had tumors that were larger, more invasive and more often metastatic than those in younger patients. This all underscores the aggressive tumor behavior in older patients that requires optimal therapy.

The 2009 American Thyroid Association (ATA) management guidelines for differentiated thyroid cancer (1) recommends that patients with thyroid cancer >1cm should be treated with total or near-total thyroidectomy unless there are contraindications to this surgery. This A recommendation is supported by a number of studies, including a study by Bilimoria et al. (2) of over 50,000 patients with papillary thyroid cancer that found on multivariate analysis that total thyroidectomy significantly improved recurrence and survival rates for tumors >1.0 cm. Even patients with 1 to 2 cm tumors were found to have a 24% higher risk of recurrence and a 49% higher risk of thyroid cancer mortality with lobectomy as compared with total or near-total thyroidectomy (P< 0.04 and p<0.04, respectively). Other large studies also have found that recurrence and mortality rates in low-risk patients are significantly reduced by total or near total thyroidectomy (3;4). Despite these findings, the Park study found that older patients are often treated with less than total thyroidectomy without radioiodine therapy for reasons that remain elusive.

In another study by Bilimoria et al. (5) that examined the use of total thyroidectomy in over 90,00 patients, found that the its use increased from approximately 71% in 1985 to 90% in 2003 (P< .0001). Patients were less likely to have total thyroidectomy if they were black, older than 45 years, had Medicare, had lower household incomes, or had less education (P< .0001). Patients treated at high-volume or academic centers were more likely to receive total thyroidectomy than were patients treated at low-volume or community hospitals (P <0.0001). The disparities in access to care and the use of total thyroidectomy were thus related to several factors, including the patient, the tumor, and the hospital.

Park et al. found that among 87 patients who did not undergo surgery, the procedure was contraindicated in 15%, was not recommended in 37%, was refused by the patient or guardian in 24%, and the reason was unknown in 30%. This small sample does not provide a full understanding of this problem. Even less data were available to know why elderly patients failed to receive radioiodine.

Recommendation 32 of the ATA guidelines advises RAI for remnant ablation for all patients with known distant metastases, gross extrathyroidal extension of the tumor regardless of tumor size, or primary tumor size >4 cm, even in the absence of other higher risk features, and is recommended for selected patients with 1 to 4cm thyroid cancers confined to the thyroid with documented lymph-node metastases or other higher risk features. Radioiodine ablation is recommended when the combination of age, tumor size, lymph-node status, and individual histology predicts an intermediate to high risk of recurrence or death from thyroid cancer. This is a C Recommendation (expert opinion). Most elderly patients meet the criteria for radioiodine remnant ablation. The conundrum remains as to why elderly patients in the Park study were not treated with surgery and radioiodine. One possible reason for the omission of radioiodine therapy is that large thyroid cancer databases are derived from hospitalized patients that often miss therapies such as radioiodine provided in an outpatient setting (6).

Comorbidities contribute to poor outcomes in the elderly. For example, a population-based observational study from the Netherlands (7) found that hypertension was the most frequent comorbidity with thyroid cancer (18%), followed by other serious conditions such as cardiovascular diseases (6%) and diabetes mellitus (6%). The prevalence of hypertension was twice as high as expected in all age groups, yet comorbidity was not independently associated with overall survival up to 5 years, which might be insufficient follow-up to fully evaluate the effect of comorbidity.

The observations from the Netherlands are similar to those in a recent study by Masuyama et al. (8) that compared the clinical characteristics of thyroid cancers in 85 elderly patients ≥75 years of age with those of 37 patients <30 years of age. Elderly patients with papillary thyroid carcinoma had a significantly worse cumulative 5-year survival rate with papillary

thyroid cancer than that of young patients (92% vs. 100%, P = 0.03). The cumulative 2-year survival with high-risk tumors was significantly lower in elderly patients treated surgically compared with those who were not so treated (80% vs. 100%, P = 0.02). Furthermore, the quality of life was severely impaired in 67% and 6% of the patients treated with and without surgical therapy, respectively. This study demonstrated that surgery for thyroid cancer increases the survival rate and promotes the quality of life in elderly patients if they are well enough to undergo surgery.

A study of octogenarians by Mekel et al (9) found that the two independent risk factors predicting postoperative complications in patients undergoing thyroid surgery were male sex and a high American Society of Anesthesiologists risk score. Of importance, advanced age by itself was not an independent factor predicting postoperative complications; instead it was comorbidities that predicted complications. This is similar to the Park study in which elderly patients who did not have surgery did not report higher rates of contraindications to surgery. Moreover, there was no significant difference among age groups with regard to the contraindication rates cited as the primary reason for not undergoing surgery.

Park et al. clearly demonstrated that many elderly patients with DTC received less aggressive surgery and RAI therapy, despite having more advanced disease, and had improved survival with aggressive therapy. This study, along with others, suggests a careful preoperative evaluation and consultation with the patient should be performed before recommending limited therapy for elderly patients with thyroid cancer.

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References

1. Cooper DS, Doherty GM, Haugen BR et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.

2. Bilimoria KY, Bentrem DJ, Ko CY et al. Extent of Surgery Affects Survival for Papillary Thyroid Cancer. Ann Surg 2007;246:375-84.

3. Mazzaferri EL, Young RL. Papillary thyroid carcinoma: a 10 year follow-up report of the impact of therapy in 576 patients. Am J Med 1981;70:511-8.

4. DeGroot LJ, Kaplan EL, McCormick M et al. Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 1990;71:414-24.

5. Bilimoria KY, Bentrem DJ, Linn JG et al. Utilization of total thyroidectomy for papillary thyroid cancer in the United States. Surgery 2007;142:906-13.

6. Hundahl SA, Cady B, Cunningham MP et al. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the United States during 1996. U.S. and German Thyroid Cancer Study Group. An American College of Surgeons Commission on Cancer Patient Care Evaluation study. Cancer 2000;89:202-17.

7. Kuijpens JL, Janssen-Heijnen ML, Lemmens VE et al. Comorbidity in newly diagnosed thyroid cancer patients: a population-based study on prevalence and the impact on treatment and survival. Clin Endocrinol (Oxf) 2006;64:450-5.

8. Matsuyama H, Sugitani I, Fujimoto Y et al. Indications for thyroid cancer surgery in elderly patients. Surg Today 2009;39:652-7.

9. Mekel M, Stephen AE, Gaz RD et al. Thyroid surgery in octogenarians is associated with higher complication rates. Surgery 2009.

REVIEWS & GUIDELINES

1. Kloos MBq, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, Moley JF, Pacini F, Ringel MD, Schlumberger M, Wells SA, Jr.Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.

2. Cooper MBq, Doherty GM, Haugen BR, Kloos MBq, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM.Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.

3. Baloch ZW, Cibas ES, Clark DP, Layfield LJ, Ljung BM, Pitman MBq, Abati A.The National Cancer Institute Thyroid fine needle aspiration state of the science conference: a summation. Cytojournal 2008;5:6.

4. Wells SA, Jr., Santoro M.Targeting the RET pathway in thyroid cancer. Clin Cancer Res 2009;15:7119-23.

HOT ARTICLES

1. Hoftijzer H, Heemstra K, Morreau H, Stokkel M, Corssmit E, Gelderblom AJ, Weijers K, Pereira A, Huijberts M, Kapiteijn E, Romijn J, Smit J.Beneficial effects of sorafenib on tumor progression, but not on radioiodine uptake, in patients with differentiated thyroid carcinoma. Eur J Endocrinol 2009.

2. Mills SC, Haq M, Smellie WJ, Harmer C.Hurthle cell carcinoma of the thyroid: Retrospective review of 62 patients treated at the Royal Marsden Hospital between 1946 and 2003. Eur J Surg Oncol 2009;35:230-4.

3. Machens A, Dralle H.Age disparities in referrals to specialist surgical care for papillary thyroid cancer. Eur J Surg Oncol 2009;35:1312-7.

4. Nikiforov YE, Steward DL, Robinson-Smith TM, Haugen BR, Klopper JP, Zhu Z, Fagin JA, Falciglia M, Weber K, Nikiforova MN.Molecular Testing for Mutations in Improving the Fine Needle Aspiration Diagnosis of Thyroid Nodules. J Clin Endocrinol Metab 2009.

5. Nikiforova MN, Nikiforov YE.Molecular Diagnostics and Predictors in Thyroid Cancer. Thyroid 2009.

6. Svare A, Nilsen T, Bjoro T, Forsmo S, Schei B, Langhammer A.Hyperthyroid Levels of TSH correlate with low bone mineral density: The HUNT 2 -Study. Eur J Endocrinol 2009.

7. Tierney K, Delpachitra P, Grossmann M, Onwude J, Sikaris K, Wallace EM, Hamilton EJ, Tong S. CEN3569 [pii];10.1111/j.1365-2265.2009.03569.x [doi]

8. Boas M, Forman J, Juul A, Feldt-Rasmussen U, Skakkebaek N, Hilsted L, Chellakooty M, Larsen T, Larsen J, Petersen J, Main K.Narrow intra-individual variation of maternal thyroid function in pregnancy based on a longitudinal study of 132 women. Eur J Endocrinol 2009. EJE-09-0579 [pii];10.1530/EJE-09-0579 [doi]

Disclosures

Dr Mazzaferri receives honoraria from Genzyme for providing lectures

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

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

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