

# CLINICAL THYROIDOLOGY

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# CLINICAL THYROIDOLOGY

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## EDITORS' COMMENTS

This is the first 2010 issue of *Clinical Thyroidology*. As we begin the second 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 MEMORIAM** We are sorry to inform you that Constance Shen Pittman passed away on January 15, 2010 at age 81. She was a graduate of Wellesley College and Harvard Medical School. She was an accomplished investigator of thyroxine metabolism and its relationship to carbohydrate metabolism. Connie was active in NIH study sections and was appointed to the Council of the NIH and became the first female President of the American Thyroid Association in 1991. She was a popular teacher of endocrinology to medical students at the University of Alabama in Birmingham where she was Professor of Medicine. Alarmed at the severity of iodine deficiency in her native China, she became active in the International Council for Control of Iodine Deficiency Disease, working tirelessly for the organization and becoming a member of its Board of Directors. She is survived by her husband, James A. Pittman, Jr., retired Dean of the UAB Medical School, and their two sons Clinton Pittman and John Pittman.

On a personal level, Connie was a compassionate physician who always inspired her students and colleagues, and she will be missed by all of her friends at the ATA.

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

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

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

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

We welcome your feedback and suggestions on these changes.

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

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

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# The need for radioiodine ablation and follow-up for patients with papillary thyroid microcarcinoma should be based on patient- and tumor-related prognostic variables

Lombardi CP, Bellantone R, De Crea C, Paladino NC, Fadda G, Salvatori M, Raffaelli M. Papillary thyroid microcarcinoma: extrathyroidal extension, lymph node metastases, and risk factors for recurrence in a high prevalence of goiter area. *World J Surg* 2010. 10.1007/s00268-009-0375-x [doi]

## SUMMARY

### BACKGROUND

The optimal therapy for papillary thyroid microcarcinoma (PTMC) and the follow-up for these small tumors remain controversial despite the fact that they comprise a large group of tumors that are commonly diagnosed with ultrasound-guided fine-needle aspiration biopsy. This retrospective study of PTMC was aimed at determining the risk factors for tumor recurrence in an area with a high prevalence of goiter.

### METHODS

This is a study from the Division of Endocrine Surgery, in the Università, Policlinico, Rome, Italy, in which medical records from October 2002 through June 2007 were searched for patients who had thyroidectomy with a final pathology report of PTMC. The retrieved data were as follows: patient age, sex, type of diagnosis, including incidental or nonincidental tumors, autoimmune thyroid disorders, including Graves' disease and thyroiditis, the extent of thyroid resection, type of lymph-node dissection, thyroid weight, tumor size, tumor multifocality, extrathyroidal tumor extension and tumor-node-metastases (TNM) staging, and follow-up results. Patients who completed the follow-up evaluation were included in the study.

PTMC was defined as incidental when it was found on the surgical histology specimens from patients who had thyroid surgery for non-malignant thyroid disorders and was described as nonincidental when the tumor was diagnosed preoperatively on the basis of fine-needle aspiration biopsy, or the patient was preoperatively proven or suspected of having cervical lymph-node metastases or distant metastases. Hemithyroidectomy was defined as complete extracapsular resection of a thyroid lobe containing more than half of the isthmus including the pyramidal lobe. Total thyroidectomy was defined as total bilateral extracapsular thyroidectomy. Completion thyroidectomy was defined as resection of all residual thyroid tissue after previous partial thyroidectomy performed within 6 months after hemithyroidectomy or other partial resection, which was considered as a one-step thyroidectomy. Completion thyroidectomy performed more than 6 months after partial thyroid resection was considered surgery for a local recurrence.

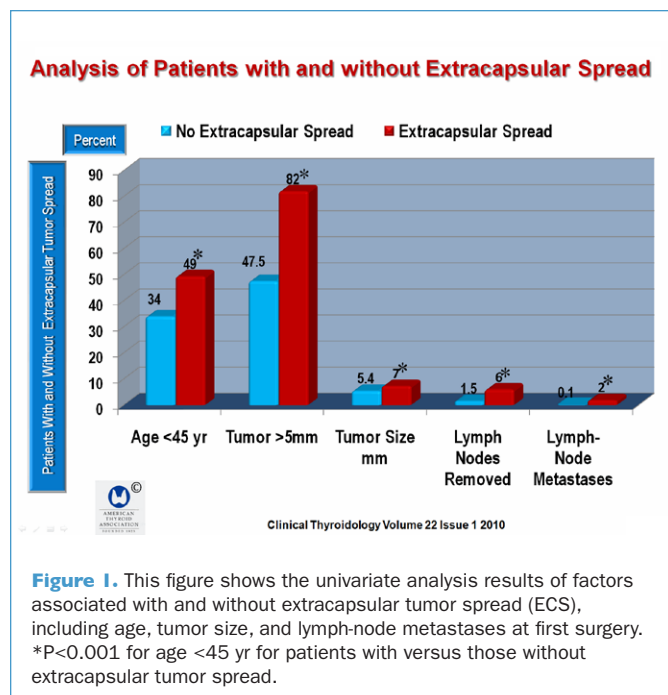
The term node picking was defined as the selected removal of enlarged or suspicious lymph nodes in the central (level VI) or lateral (level II to V) neck compartments, in which case, the lymph nodes were usually sent for frozen-section analysis. When metastases were identified intraoperatively, systematic compartment-oriented lymph-node dissection was performed. Central compartment lymph-node dissection is defined by complete level VI dissection, and lateral neck lymph-node dissection is a level II to level V dissection. The need for any lymph-node dissection was established on the basis of the preoperative or intraoperative evidence of enlarged, suspicious, or malignant nodes. Tumors were defined as multifocal if two or more tumor foci were found in one (unilateral) or both (bilateral) thyroid lobes, and the largest tumor dimension was used for statistical analysis.

The criteria for successful <sup>131</sup>I thyroid remnant ablation were defined as the disappearance of any visible area of radioiodine uptake in the thyroid bed, and a radioiodine neck uptake <1%, and undetectable serum thyroglobulin off levothyroxine and a serum thyrotropin (TSH) ≥30 IU/ml

## RESULTS

### Comparative Analysis of Patients with and without Extracapsular Tumor Spread (Figure 1)

During the study period, a total of 5355 patients had thyroidectomy, 2220 of whom (41%) had thyroid malignancy and 933 of whom had PTMC (17%). Of the patients with PTMC, 197 were men (21%) and 736 were women (79%), with a mean (±SD) age of 49.4±1.3 years (range, 9 to 81). The diagnosis was incidental in 704 patients (75.5%) and nonincidental in 229 (24.5%). Among



the nonincidental group, 225 patients (88%) had a preoperative fine-needle aspiration biopsy (FNAB) that was suspicious for or diagnostic of a malignant thyroid nodule, and the remaining 4 had lateral lymph-node metastases. The indications for thyroidectomy in patients with an incidental diagnosis were compressive goiter symptoms in 458 of 704 (65%) and toxic goiter in 246 (35%).

Univariate analysis showed that patients with extracapsular tumor spread (ECS) were significantly younger than those without ECS (44.6±13.8 vs. 49.9±12.9 yr, P<0.001), had larger tumors (7.7±2.3 vs. 5.2±3.0 mm, P<0.001), had a greater number of lymph nodes removed (5.9±11.7 vs. 1.5±4.9, P<0.001), and had a greater number of metastases at first surgery (1.8±6.3 vs. 0.1±1.4, P<0.001).

Multivariate analysis showed that the independent variables for ECS were tumor size, diagnosis of nonincidental PTMC, and cervical lymph-node metastases at the time of diagnosis.

**Comparative Analysis of Patients with and without Lymph-Node Metastases (Figure 2)**

Univariate analysis showed that patients who had lymph-node metastases at the time of diagnosis (pN1) or within 6 months after initial surgery were significantly younger (42.3±16.4 vs. 49.9±12.6 yr, P<0.001), had larger tumors (7.3±2.4 vs. 5.4±3.1 mm, P<0.001), and had a larger number of lymph nodes removed at first surgery (15.1±16.9 vs 1.0±2.5, P<0.001).

Multivariate analysis showed that nonincidental diagnosis, ECS, multifocal disease, and the number of excised lymph nodes were independent risk factors for lymph-node metastases at the time of diagnosis.

**Comparative Analysis of Patients with and without Tumor Recurrence (Figure 3)**

Follow-up evaluation was completed in 287 of all patients with PTMC (30.8%), comprising 52 men and 235 women with a mean age of 49±13.9 years (range, 11 to 81); 105 of the 287 patients (36.6%) had <sup>131</sup>I therapy, and successful ablation was achieved after the first <sup>131</sup>I treatment in 91 (86.7%). Nine of the 287 patients had a tumor recurrence (3.1%), 7 in regional lymph nodes, 1 in regional lymph nodes and multiple bone metastases, and 1 with lung metastases. The mean time between the first operation and diagnosis of recurrence was 17.1±15.7 months (range, 7 to 51). After a mean follow-up of 35.5 months, all of the patients were alive, 4 with (1.4%) recurrent disease in lateral neck lymph-node metastases, 2 in lung, and 1 in bone.

Univariate analysis showed that risk factors for recurrence were multifocal disease (P<0.05), ECS (P<0.01), lymph-node metastases at the time of diagnosis (P<0.001), and the number of removed and metastasized lymph nodes (P<0.05 and P<0.001, respectively). Patients who required lymph-node dissection at first surgery frequently had recurrence (P<0.005). Also, follow-up was significantly longer in patients in whom a recurrence developed (48.9±24.7 vs. 34.9 ± 20.0 months, P<0.05). The mean tumor size did not differ significantly different among patients who experienced a recurrence and those who did not.

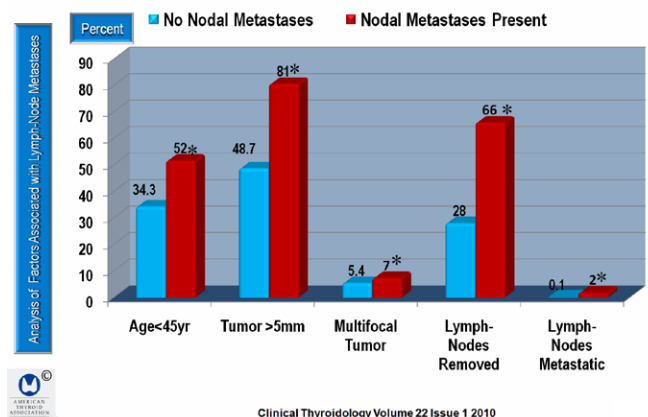
Multivariate analysis showed that the independent risk factors for recurrent disease were the number of removed and metastasized

nodes at first operation and the length of the follow-up (time elapsed from the first surgery).

**CONCLUSION**

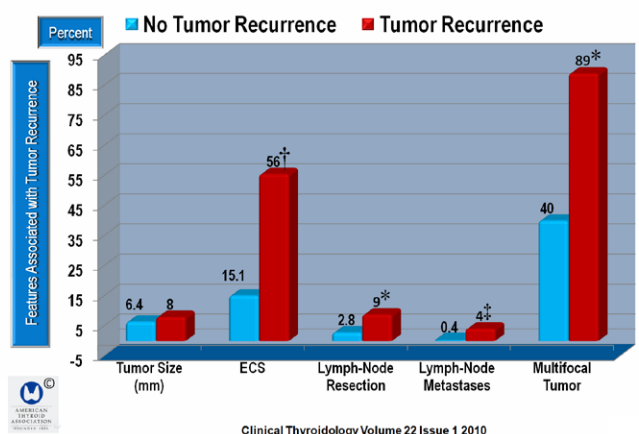
The need for radioiodine ablation and the follow-up protocol for patients with PTMC should be based on patient- and tumor-related prognostic variables, similar to that in patients with larger papillary thyroid cancers.

**Analysis of Patients with and without Lymph-Node Metastases**



**Figure 2.** This figure shows the factors associated with pN1 lymph-node metastases at the time of diagnosis \*P<0.001 comparing patients with versus those without lymph-node metastases, and P<0.001 comparing patients who did and did not require lymph-node dissection at initial surgery.

**Analysis of Patients with and without Tumor Recurrence**



**Figure 3.** This figure shows that risk factors for recurrence were multifocal disease (\*P<0.05), extracapsular spread (ECS) (†P<0.01), lymph-node metastases at the time of diagnosis (P<0.001), and the number of removed and metastasized lymph nodes (\*P<0.05 and †P<0.001, respectively). Patients who required lymph-node dissection at first surgery frequently had recurrence (\*P<0.005). Not shown is that follow-up was significantly longer in patients in whom recurrence developed (P<0.05).

**COMMENTARY**

Although it is widely recognized that the incidence of PTMC has more than doubled worldwide over the past three decades, its management has been a matter for global debate. The reason for this rests solely on the fact that at the time of diagnosis we cannot clearly determine whether a patient's PTMC is a potentially aggressive tumor or a biologically benign tumor that requires little or no management. As a direct consequence, at one end of the spectrum, management protocols range from simply performing extended follow-up without therapy to protocols that are essentially the same as those for the treatment of larger papillary thyroid cancers. Nonetheless, it is clear that some patients with PTMC die from this tumor, while others go without therapy for decades without consequences. Lombardi et al. make the point that this problem is clearly reflected in the large number of recently published reviews, guidelines, and meta-analyses that have failed to find any compelling evidence on which to base management protocols for PTMC (1-5).

The aim of the study by Lombardi et al. was to determine the best therapeutic option based on risk factors in a cohort with a high prevalence of goiter. The majority of tumors (75%) were incidental findings in patients who had surgery for goiters causing suppression (65%) or thyrotoxic goiters (35%). Multivariate analysis showed that tumor size, nonincidental diagnosis, and cervical lymph-node metastases at the time of diagnosis were independent risk factors for ECS, whereas ECS, multifocal disease, and the number of resected lymph nodes were independent factors for lymph-node metastases at

the time of diagnosis. Lastly, multivariate analysis showed that the independent risk factors for recurrent disease were the number of removed and metastasized nodes at first operation and the length of follow-up (time elapsed from the first surgery). Diagnosis of tumor was incidental in 704 cases (75.5%) and nonincidental in the remaining 229 patients (24.5%). Among the nonincidental cases, 225 had a preoperative FNAB consistent with a suspicious or malignant thyroid nodule and the remaining 4 had a preoperative diagnosis of lateral neck node metastases. Contrary to other studies, patients with lymph-node metastases and ECS were younger than those with PTMC confined to the thyroid. In short, these findings show that patients with clinically evident tumors have a more advanced stage of disease that requires more aggressive therapy than incidentally diagnosed tumors.

The authors point out that the study has several limitations; namely, follow-up was completed in only about one third of the patients, and mean follow-up was only about 3 years, with the longest being 7 years. This is a relatively short follow-up considering that it may take several decades to identify residual tumor (6). Nonetheless, in spite of these limitations the recurrence rates are in keeping with most published reports and reviews (7).

In conclusion, although other factors likely impact recurrence of PTMC, this carefully crafted study provides information that is unique and likely to influence future protocols for the management of PTMC.

— Ernest L. Mazzaferri, MD, MACP

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# Papillary microcarcinomas without unfavorable features may be candidates for observation alone

Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, Tomoda C, Takamura Y, Kobayashi K, Miya A. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg* 2010;34:28-35.10.1007/s00268-009-0303-0 [doi]

## SUMMARY

### BACKGROUND

Neck ultrasonography and ultrasound-guided fine-needle aspiration biopsy has substantially altered the approach to the diagnosis of thyroid cancer, which has facilitated the identification of a large number of papillary microcarcinomas (PTMC) of uncertain long-term risk. This has prompted some to forgo surgery for PTMC unless there are unfavorable tumor features portending a poor prognosis. This is a prospective follow-up study of patients with PTMC who selected to forgo surgery. The authors started this observational trial in 1993, and in 2003 published their first report on 162 patients with PTMC who had observation alone, in whom 70% had no change in their tumors and 1.2% developed lymph-node metastases. The present study reports the most recent data on patients who participated in this trial.

### METHODS

Between 1993 through 2004, a diagnosis of PTMC was made after ultrasound screening and fine-needle aspiration biopsy in 1395 patients, 1055 of whom had immediate surgery, and 340 of whom were enrolled in the observation group after being given the option of not having surgery. Postoperative follow-up included ultrasonography and chest roentgenography or computed tomography scan more than once per year, and 52 patients had radioiodine a whole-body scan using 3 to 13 mCi, none of whom had abnormal <sup>131</sup>I uptake except in the thyroid bed. Tumor enlargement was defined as an increase in tumor size of 3 mm or more from the time of diagnosis.

However, when tumors developed unfavorable features such as tumor adjacent to the trachea or the dorsal surface of the thyroid, possible tumor invasion of the recurrent laryngeal nerve, clinically apparent lymph-node metastasis, high-grade malignancy on fine-needle aspiration biopsy or signs of tumor progression were recommended to have surgery.

### RESULTS

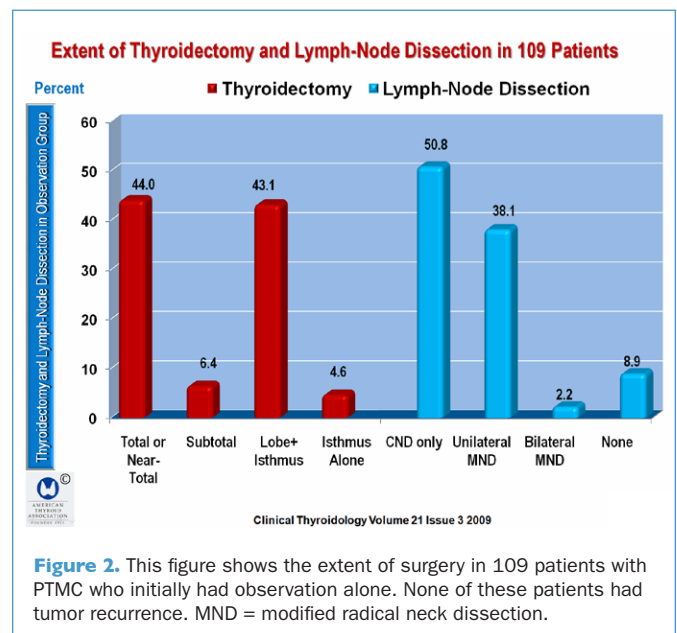
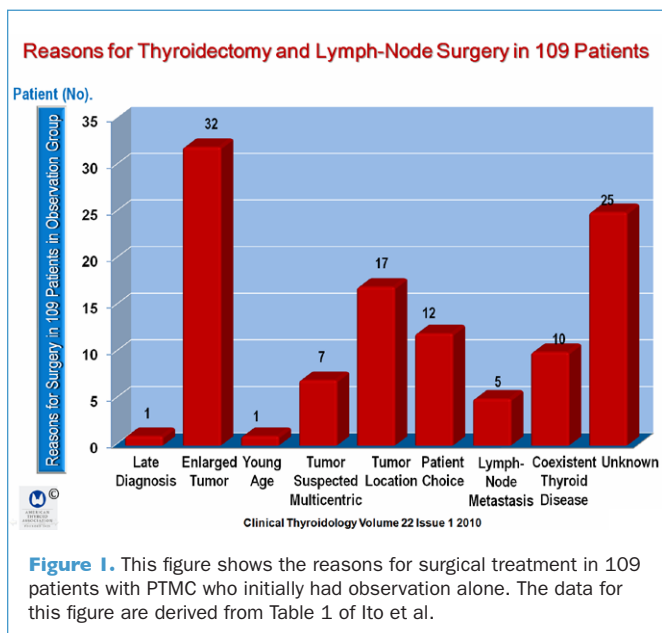
#### The immediate surgery and the long-term observation groups

In the immediate surgery group, 2 patients were found to have distant metastases at the time of initial diagnosis and were excluded from the study. The final immediate surgery group comprised 1059 patients, 964 women (91%) and 95 (9%) men whose mean age was 52 years (range 15 to 84).

In the observation group, 340 patients, 314 women (92%) and 26 men (8%) had follow-up for periods ranging from 18 through 187 months, during which they were enrolled in the observation group; however, after an average of 51 months of observation, (range 18 to 175), 109 (32%) of this group required surgery. Of the 109 patients, 102 were women (94%) and 7 were men (6%).

#### Surgery in 109 patients in the observation group (Figures 1 and 2)

109 patients in the observation group (32%) who required surgery had it for the following reasons: five had developed new lymph-node metastases (5%), 1 had surgery because of young age (1%), 7 for suspicion of tumor multicentricity (6%), 17 for tumor near the dorsal surface (11%), 10 for coexistent thyroid



disease (9%) and 25 for unknown reasons (23%) (Figure 1). The extent of thyroid and lymph-node surgery was considerably different among the 109 patients; all but 2 had thyroid surgery ranging from total thyroidectomy to isthmusectomy alone, and lymph node compartment dissection was performed in all but one patient, using complete radical neck dissection (CND) in 79 (72.5%) patients, unilateral modified radical neck dissection (MND) in 26 patients (3%) and bilateral MND in 2 patients (1.8%).(Figure 2) None of the 109 patients in the observation group who had surgery developed tumor recurrence.

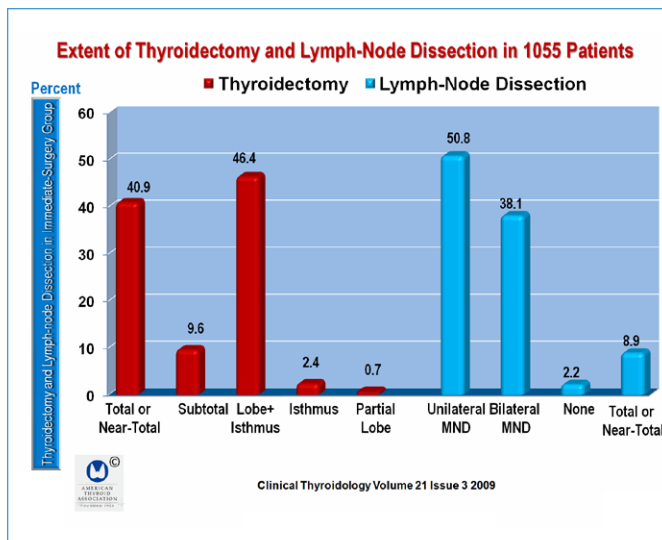
**Surgery in 1,055 patients in the immediate surgery group (Figure 3)**

In the immediate surgery group, thyroid surgery was total or near total thyroidectomy in 432 patients (40.9%), subtotal

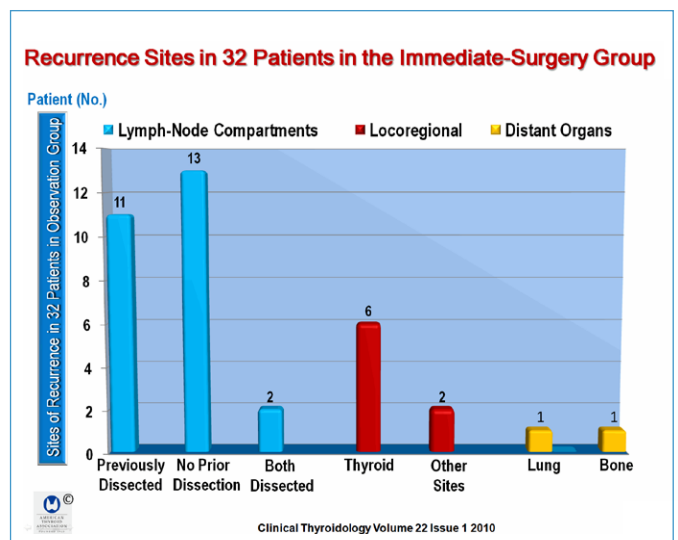
thyroidectomy in 101 (6%), lobectomy with isthmusectomy in 490 (46.4%), isthmusectomy in 25 (2.4%) and partial lobectomy in 7 (0.7%) (Figure 3) In this group, 32 patients had a recurrence. Clinically apparent lateral node metastasis (N1b) and male gender were recognized as independent prognostic factors of disease-free survival.

**Sites of tumor recurrence in 1,005 patients in the immediate surgery group (Figure 4)**

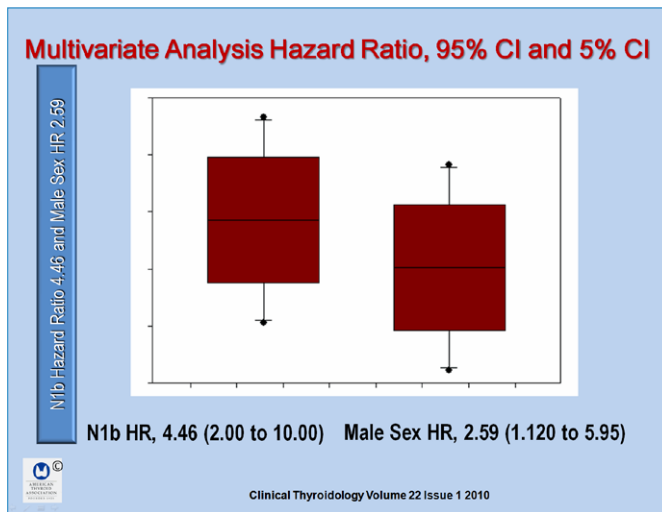
Tumor recurrence was found in 32 patients (3.0%). The organs involved with tumor recurrence were lymph nodes in 26 patients (2.5%). Among those who had lymph node tumor recurrences, 11 had previously dissected compartments, 13 had neck compartments that had not been dissected, and 2 had both lymph node compartments dissected. Locoregional



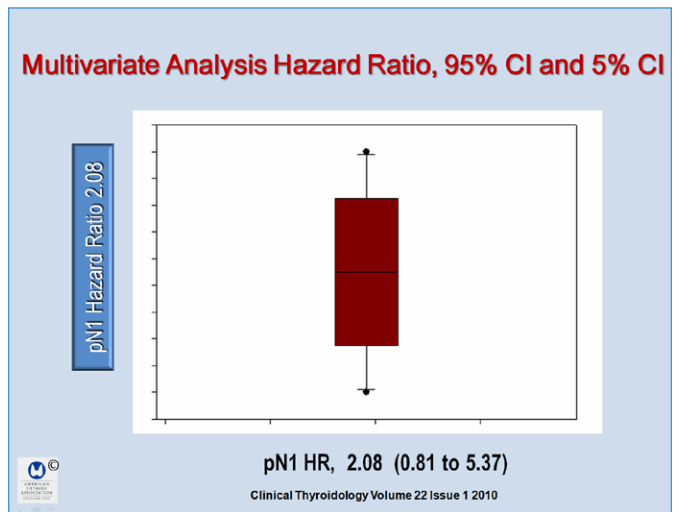
**Figure 3.** This figure shows the extent of thyroidectomy and lymph-node dissection in 1055 patients in the immediate surgical treatment group. The data for this figure are derived from Table 3 of Ito et al.



**Figure 4.** This figure shows the recurrence sites in 32 patients (0.3%). The data for this figure are derived from Table 4 of Ito et al.



**Figure 5 (A).** This figure shows the results of Cox multivariate analysis regarding disease-free survival. The data for this figure are derived from Table 5 of Ito et al. HR = hazard ratio, N1b = metastases in bilateral, midline or contralateral cervical or mediastinal lymph nodes.



**Figure 5 (B).** pN1 = metastases in ipsilateral cervical lymph nodes. The independent variables influencing disease-free survival were N1b tumors, male sex, and pN1, although patients with NO did not differ from that of patients with N1a. Male sex, P ≤0.0001.

organs involved the thyroid in 6 patients, (0.6%), and other sites in 2; distant metastases involved the lung in 1 patient and bone in another patient. (Figure 4) In patients who underwent immediate surgical treatment, clinically apparent lateral node metastasis (N1b) and male gender were recognized as independent prognostic factors of disease-free survival (Figure 5)

Analysis of this group found that sex, age, tumor size, multicentricity, TSH suppression, serum thyroglobulin levels or the presence of antithyroid antibodies had no significant bearing on tumor growth. Although patients aged  $\leq 45$  yr tended to have more tumor enlargement than those older than 45 yr, the difference was not statistically significant ( $P = 0.0624$ ).

#### Cox multivariate Analysis independent variables predicting disease-free survival (Figure 5)

Cox multivariate analysis found disease-free survival was worsened by N1b lymph-node metastases; Hazard Ratio (HR) with 95% confidence intervals (95% CI) were HR 4.46 95% CI 2.0 to 10.00,  $P = 0.0003$ ); male gender HR 2.59 95% CI 1.12 to 5.95;  $P = 0.255$ ) and clinically apparent pN1 metastases HR 2.08 95% CI 0.81 to 5.38. (Figure 5).

#### CONCLUSION

Papillary microcarcinomas without unfavorable features may be candidates for observation alone

#### COMMENTARY

In 1993, Ito et al. (1) began performing ultrasound screening with fine-needle aspiration biopsy, which by 2001 identified 732 patients with PTMC. As a consequence of the uncertainty surrounding the treatment of patients with such small tumors, the authors initiated a study in which patients were offered the option of observation alone without surgical therapy. In response, 162 of the 732 patients chose observation (22%) and 570 opted for immediate surgery (78%). During follow-up, more than 70% of tumors in the observation group either did not change or decreased in size as compared with tumor size at the time of diagnosis and, 10.2% of the other tumors enlarged by more than 10 mm. During this time, 56 patients in the observation group (35%) had surgery and were subsequently classified as the surgical treatment group. Of these 626 patients, lymph node dissection was performed in 594, and metastases were histologically confirmed in 50.5%. Also, multiple tumors were found in almost 43% of the patients. The tumor recurrence rate 2.7% at 5 years and 5.0% at 8 years after surgery, but none of the 109 patients in the observation group had recurrences after surgery. The authors opined that the preliminary data suggest that PTMC tumors do not frequently become clinically apparent, and that patients can choose observation while their tumors are not progressing, with the caveats that these tumors often are multifocal and further observation is necessary.

In 2007, Ito et al. published a review of this problem (2), noting that in their studies only 6.7% of PTMCs had enlarged by 3.0 mm or more in diameter during 5 years of follow-up, and that nodal metastases had become detectable in 1.7% of the patients in this study. They concluded that observation without surgery could be an attractive alternative for patients with low-risk PMCT, with the caveat that occult PMCT with lymph-node metastases may serve as the origin of distant metastasis, which has a more serious prognosis.

The main conclusion of the current study by Ito et al is that patients with PTMC can be candidates for observation, providing the tumor is not associated with unfavorable features, and regardless of patient demographic and clinical features, it would

not be too late for thyroid surgery, and should include modified neck dissection for N1b tumors.

There are several important features of the Ito study that warrant comment. First, none of the patient features were linked to tumor enlargement or lymph-node metastases, including male gender, tumor multicentricity, and advanced age and tumor size. Two patients in this study had distant metastases, 1 in lung and the other in bone.

A study by Noguchi et al (3) of 2070 patients with PTMC—which is the largest report of PTMC and the greatest long-term follow-up study of PTMC in the literature (median 15.1, mean 16.5 years)—found that that prognosis is better with smaller tumors (<6 mm) than larger tumors (6 to 10 mm). Recurrence rates after a 35 year follow-up were 14% in patients with larger tumors and 3% in those with smaller tumors. Moreover, 40% of patients older than 55 yr were found to have 30-year recurrence rates of 40%, which is worse than that in younger patients who had a tumor recurrence rate of less than 10%. Noguchi et al. found that extracapsular invasion of the primary PTMC has a high recurrence than that of tumors without this feature. Although the majority of recurrences in this study were in the neck, 73 patients had recurrences, 12 of which were distant metastases (1 lung, 4 bone 1 mediastinum and 1 multiple sites) after a median follow-up of 10.29 years. The authors concluded that PTMC is similar to larger papillary carcinomas with tumor characteristics and age-based recurrence rates that extend over many years. However, the independent risk factors on Cox proportional hazard model found the following were independent variables for outcome: autoimmunity  $p < 0.0001$ , gross nodal metastases  $p < 0.004$ , maximum primary tumor diameter  $P < 0.004$  and adhesion to the esophagus  $P < 0.03$ , and sex  $p < 0.14$ ; however, age at surgery was not an independent factor predicting outcome.

A study by Bilimoria et al (4) found the extent of surgery (total thyroidectomy) did not impact recurrence or survival for PTMC, whereas patients with tumor  $\geq 1$  cm treated with total thyroidectomy resulted in a significantly lower risk of recurrence ( $P = 0.04$ ) and death ( $P = 0.04$ ). This large study found the 10-year recurrence rate was 5% and the 10-year cancer-specific



mortality rate was 2% at 10 years. Both are somewhat higher than those reported by Ito and Noguchi.

The current study by Ito et al. has several features that warrant further comment. The observation cohort had patients with aggressive disease that required surgery, after which the patients were assigned to the surgical group. This likely alters the statistics concerning both the observation and surgery groups, and appears to change the conclusion of this study. The second is that most of the patients in these studies have had total thyroidectomy often with lymph-node compartment dissection, neither of which is recommended as primary therapy for PTMC by the ATA guidelines(5) and the European consensus for the management of differentiated thyroid cancer(6).

Although lobectomy is the optimal therapy for patients with PTMC, multiple lymph-node metastases are often found after total thyroidectomy and extensive lymph-node compartment dissection, which may require further therapy with radioiodine. (7;8) Still, it is not certain whether this impacts long-term outcome.

By all measures, the decision for treatment of small papillary thyroid cancers rests in the hands of the final arbitrator: The Patient.

— Ernest L. Mazzaferri, MD, MACP

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# A single thyroid lobe is usually sufficient to maintain euthyroidism albeit with significantly higher than usual TSH and FT<sub>3</sub> levels

Ruchala M, Szczepanek E, Szafarski W, Moczko J, Czarnywojtek A, Pietz L, Nowicki M, Niedziela M, Zabel M, Kohrle J, Sowinski J. Increased risk of thyroid pathology in patients with thyroid hemiagenesis: results of a large cohort case-control study. *Eur J Endocrinol* 2010;162:153-60.

## SUMMARY

### BACKGROUND

Thyroid hemiagenesis (THA) is a rare congenital abnormality in which one thyroid lobe fails to develop. Its incidence is uncertain because the absence of one thyroid lobe does not usually cause clinical symptoms and thus often goes unrecognized. THA is usually detected incidentally during an evaluation of other thyroid disorders, and its management remains a matter of debate. It is more frequently found in women than in men, and it is more common in the left thyroid lobe. This is a study of 40 patients with THA that provides the first extensive hormonal and ultrasound analysis of the disorder.

### SUBJECTS AND METHODS

This study was designed to prospectively study all patients with THA seen from January 2002 through December 2008 in the Ultrasound Unit of the Department of Endocrinology, Metabolism and Internal Medicine at the University of Medical Sciences, Poznan, Poland. The 40 study patients were referred for thyroid ultrasonography, during which THA was discovered by serendipity during screening ultrasonography in 17 patients and for nonthyroidal disorders, thyroid-related symptoms, or thyroid asymmetry in the others. It was found by self-examination in 1 patient, on physical examination in 22, and as a consequence of mild symptoms of hypothyroidism or hyperthyroidism in 1 patient.

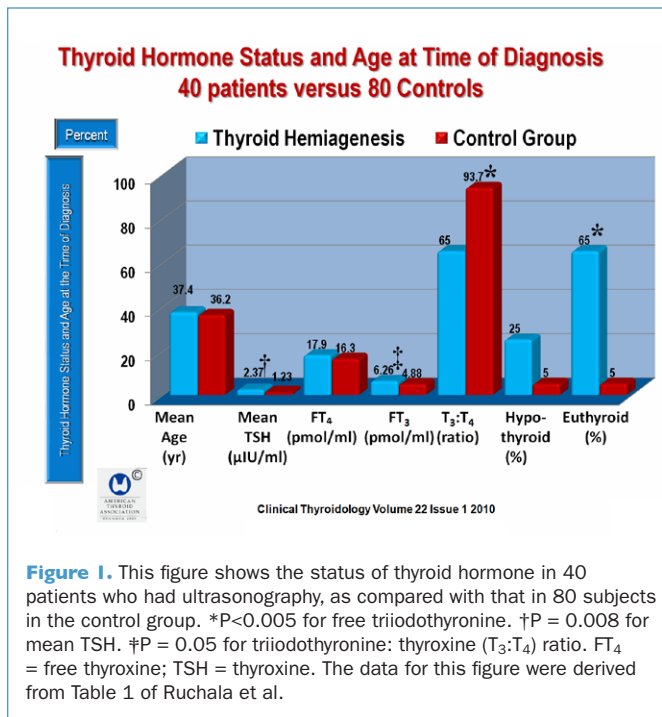
A control group of 80 persons was matched for age and sex to the study patients by randomly selecting participants from 2159 people in a cross-sectional population-based thyroid screening program that was also performed by the authors. After ultrasonography, THA was confirmed by thyroid scintigraphy. All the subjects live in the same region of Poland, which is classified by the World Health Organization as a mildly iodine-deficient area.

### RESULTS

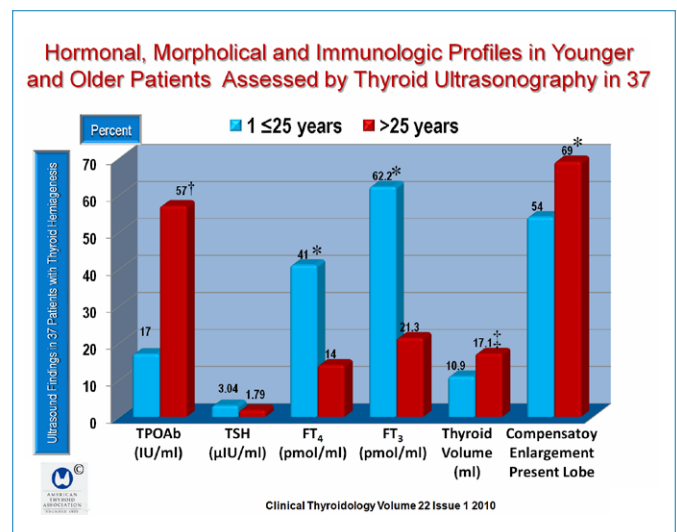
The 40 study patients ranged in age from 12 through 79 years, and the prevalence of women was 7:1. Of the 40 patients, 35 (88%) had THA in the left thyroid lobe; 2 patients had a large pyramidal lobe, and the isthmus was absent in all 5 patients with right-sided THA. The most common finding was isolated agenesis of the left thyroid lobe in 28 patients (70%), and the remaining patients had agenesis of the left thyroid lobe and isthmus. THA was often associated with several thyroid disorders, including Graves' disease, nodular variant Graves' disease, nonautoimmune hypothyroidism, nontoxic nodular goiter, simple goiter, or toxic nodular goiter.

### Thyroid Hormone Status and Ultrasound Findings in Patients versus Controls (Figure 1)

The most frequent thyroid disorders were thyroid nodules and autoimmune thyroid disease. Most patients (26) were euthyroid (65%), 10 had hypothyroidism (25%), and the remaining 4 had



**Figure 1.** This figure shows the status of thyroid hormone in 40 patients who had ultrasonography, as compared with that in 80 subjects in the control group. \*P<0.005 for free triiodothyronine. †P = 0.008 for mean TSH. ‡P = 0.05 for triiodothyronine: thyroxine (T<sub>3</sub>:T<sub>4</sub>) ratio. FT<sub>4</sub> = free thyroxine; TSH = thyroxine. The data for this figure were derived from Table 1 of Ruchala et al.



**Figure 2.** This figure shows the morphologic and immunologic profiles in younger vs older patients with ultrasound findings in 37 patients with thyroid hemiagenesis as compared to that in a control group of 80 subjects with a bilobate thyroid gland. \*P<0.005 for compensatory enlargement of a thyroid lobe in patients vs. 80 controls. †P <0.008 for thyroid volume comparing the two study groups. ‡P = 0.02 for thyroid volume. FT<sub>4</sub> = free thyroxine; FT<sub>3</sub> = free triiodothyronine; TPOAb = antithyroid peroxidase antibodies; TRAb = thyrotropin-receptor antibodies; TSH = thyrotropin. The data for this figure were derived from Table 2 of Ruchala et al.

hyperthyroidism (10%). The thyroid lobe was within the normal range in only 9 of the 40 subjects (23%). In the remaining 31 patients (78%) it was enlarged, as compared with half the normal thyroid volume, and 12 (30%) fulfilled the criteria for goiter in a bilobate thyroid gland. The general information and hormonal status of the subjects with THA are shown in Figure 1.

**Comparison of Hormonal, Morphologic, and Immunologic Profiles in Two Age Groups (Figure 2)**

The Patients were divided into two age groups, one ( $\leq 25$  yr) and the other ( $>25$  yr) (Figure 2). There were significant differences in thyroid volume, presence of heterogeneous decreased echogenicity on ultrasonography, and the incidence of antithyroid antibodies (TPOAb) were increased. There also was a significant positive correlation between thyroid volume and age at diagnosis ( $P = 0.009$ ). Of the 40 patients with THA with absent TPOAb, 18 were selected for hormone analysis to exclude the influence of autoimmune disturbances on these tests; there was no significant correlation between thyroid volume and age. There also were no significant differences in thyrotropin (TSH), free thyroxine ( $FT_4$ ), and free triiodothyronine ( $FT_3$ ) or incidence of focal lesions (Figure 2).

**Thyroid Fine-Needle Aspiration Biopsy Results in Patients with THA (Figure 3)**

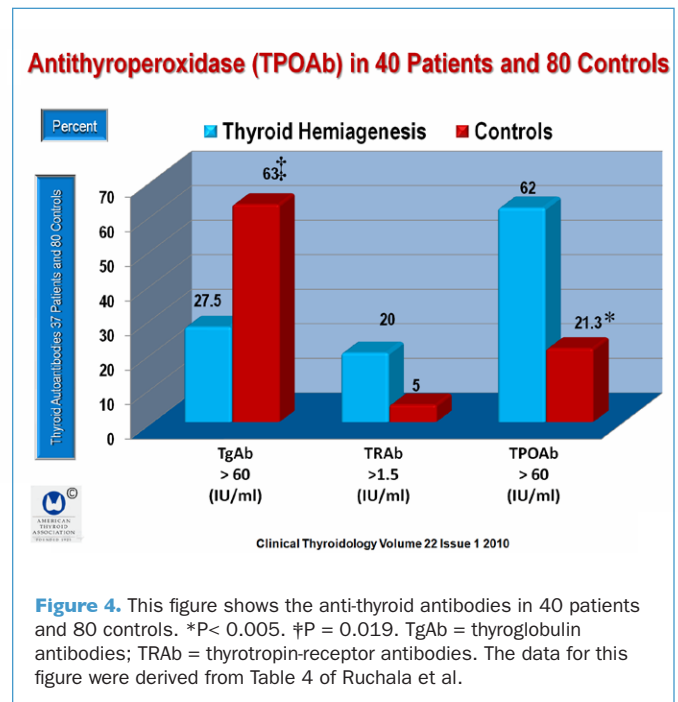
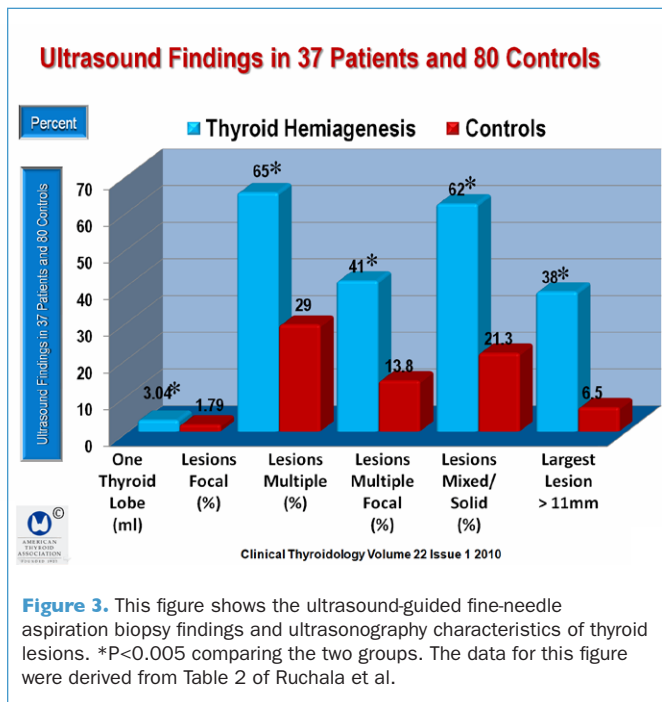
THA was very often associated with several thyroid pathologies (Figure 3). The most frequent associated thyroid disorders were thyroid nodules and autoimmune thyroid diseases. Simple goiter and nonautoimmune subclinical hypothyroidism were less often observed. Patients were usually euthyroid (26 persons); however, hypothyroidism was observed in 10 subjects, and hyperthyroidism in the remaining 4 (Figure 3).

**Antithyroid Peroxidase Antibodies in 40 Patients and 80 Controls (Figure 4)**

Immunologic assessment revealed a significantly increased prevalence of elevated thyroid autoantibodies (TRAb, TPOAb, and TgAb) in comparison with the control group (Figure 4).

**CONCLUSION**

A single thyroid lobe was usually sufficient to maintain euthyroidism, with significantly higher than usual TSH and  $FT_3$  levels among the study subjects.



**COMMENTARY**

Thyroid hemiagenesis is a perplexing problem. What we know with reasonable certainty is that THA is a rare congenital abnormality in which one thyroid lobe—usually the left—fails to develop. Almost everything else is controversial. Although its prevalence is uncertain, 5 ultrasound screening studies, 3 of which involved children, which comprised a total of 41,895 patients, found an average prevalence of 0.06%, with a range of 0.16 to 0.05 (1-5). The prevalence range is wide because the absence of one thyroid lobe usually does not cause clinical symptoms, and most of the studies are case studies or small

reports that find myriad thyroid abnormalities ranging from thyroid cancer to autoimmune thyroid disease, and most report thyroid dysfunction (6-11). Still, such small studies are always subject to selection bias, which is particularly true in a literature based on case studies.

The study by Ruchala et al. is unique in that it is the largest study of patients with this disorder, and it has a control group that was randomly selected from large cohort that had previous screening ultrasonography, 80 of which were matched for age and sex with the study population. Patients with THA, while usually clinically euthyroid, were found to have significantly

higher serum TSH, FT<sub>3</sub>, and FT<sub>4</sub> concentrations as compared with those in controls. Furthermore, there was a higher incidence of functional, morphologic, and autoimmune thyroid disorders in the patients with THA as compared with that in normal subjects with a bilobate thyroid (P<0.05).

The authors conclude that patients with THA should have ongoing follow-up because thyroid pathologies are likely to develop, presumably due to long-lasting TSH overstimulation, and patients with elevated TSH levels should be treated with levothyroxine. In effect, they are suggesting levothyroxine therapy for subclinical hypothyroidism on the basis of the 40 study patients who remained clinically euthyroid during the period under study.

It is a matter of debate whether THA should be considered clinically insignificant, or whether the absence of one lobe regularly predisposes a patient to the development of clinically important thyroid disease that requires therapy. This dilemma is nearly impossible to resolve, considering the long-term clinical outcome of this anomaly has not been fully studied. It is a fact that the diagnosis of THA is usually made by serendipity when some other thyroid disease is being evaluated or is identified during screening ultrasonography, which, along with the paucity of clinically overt cases of thyroid disease, makes it difficult to provide strong recommendations concerning treatment. The detection of THA is almost always discovered incidentally in the course of evaluating patients for other thyroid disorders. It is more frequently found in women than in men (3:1 ratio) and in the left lobe as compared with the right.

We have no clear information concerning the inherent pathogenesis of this condition, or why one lobe or the other is involved. A literature search by Ruchala et al. found that nearly 300 patients with THA have been described in the literature; most of these reports are case studies. Although there were no malignant thyroid lesions in Ruchala et al.'s patients, therapy was instituted on the basis of cytologic examination and ultrasonography. Surgical treatment was recommended to six patients because of a "suspicious sonographic appearance,"

nondiagnostic fine-needle aspiration biopsy findings, toxic nodular goiter, and a large goiter volume. In the final analysis, the real question is, does this provide compelling evidence that therapy should be instituted in this group of patients?

A recent study by Gursoy et al. (2) found 12 cases of THA among 4883 patients with various thyroid disorders, along with ultrasonography data from a large community screening survey of 4722 children and of 2935 adults with thyroid disorders. The underlying thyroid diseases that were discovered were Hashimoto's thyroiditis (n = 4), euthyroid multinodular goiter (n = 4), and toxic adenoma (n = 1). None of the patients had thyroid dysfunction.

In another study by Maiorana et al. (4), thyroid hemiagenesis was studied by neck ultrasonography in almost 25,000 unselected 11 to 14-year-old schoolchildren from southeastern Sicily. Twelve cases of thyroid hemiagenesis were identified, giving a prevalence of 0.05%, which in all 12 cases involved the left thyroid lobe. Yet thyroid volume was within the normal range of total thyroid volume normalized to age, was enlarged in 3, and was significantly reduced in 5. Thyroid-function studies were always within the normal range; however, children with THA had an average serum TSH significantly higher than that of 18 matched controls (2.8±0.6 vs. 1.9±0.5 mU/L, P<0.001). The authors concluded that their study confirms that thyroid hemiagenesis is nearly always due to left-lobe defect and that compensatory hypertrophy of the residual thyroid lobe occurs in most, but not all, cases and is due to thyroid-tissue overstimulation by TSH. They also suggest systematic follow-up of all identified cases of THA.

In conclusion, there is a reasonable consensus that patients with THA should have long-term follow-up with thyroid-function tests, but treatment of subclinical hypothyroidism in this group appears to be no different from that for patients with routine subclinical hypothyroidism that only mandatorily demands therapy when the overt hypothyroidism develops.

— Ernest L. Mazzaferri, MD, MACP

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# There is a high prevalence of papillary thyroid cancer in patients with systemic lupus erythematosus

Antonelli A, Mosca M, Fallahi P, Neri R, Ferrari SM, D'Ascanio A, Ghiri E, Carli L, Miccoli P, Bombardieri S. Thyroid cancer in systemic lupus erythematosus: a case-control study. *J Clin Endocrinol Metab* 2010;95:314-8. doi:10.1210/jc.2009-0677 [pii];10.1210/jc.2009-0677 [doi]

## SUMMARY

### BACKGROUND

A previous large retrospective cohort study of patients with systemic lupus erythematosus (SLE) found a high incidence of several cancers, including thyroid cancer. This is a prospective study aimed at further investigating the prevalence and features of thyroid cancer in a large series of unselected patients with SLE.

### METHODS

The study subjects were 153 consecutive patients with SLE who were seen in the Department of Internal Medicine at the University of Pisa from January 1995 through December 2007. The diagnosis of SLE was established according to the 1997 revised classification of SLE by the American College of Rheumatology. The duration of SLE, which was  $12 \pm 8.1$  yr (range 1 to 29, median 9), was established according to the European Consensus Lupus Activity Measurement (ECLAM) scale score of five. Although iodine intake differs between areas of Tuscany, reliable data on local levels of intake were available from urinary iodine excretion data. Patients who had resided in an iodine-deficient area for at least 20 yr were included in the iodine-iodine-deficient group.

### CONTROLS

The study population was classified into two groups: iodine-deficient and iodine sufficient.

### Iodine-deficient controls:

Three controls matched for gender and similar age ( $\pm 5$  yr) were randomly selected from 2011 subjects from the general registry of North-West Tuscany who had been systematically screened from 1994 through 2004 for thyroid disorders. The majority (84%) of this control group had resided in an iodine deficient area for 20 years or more, which was considered the minimum criterion for historical iodine deficiency.

### Iodine-sufficient controls:

The iodine-sufficient control group was obtained by selecting three individuals of the same gender and similar age ( $\pm 5$  yr) for each SLE patient from the population of an iodine-sufficient area (central Tuscany) that had been previously screened for thyroid disorders. Only 19% of this group of controls had resided in an iodine-deficient area for 20 yr or more (Figure 1).

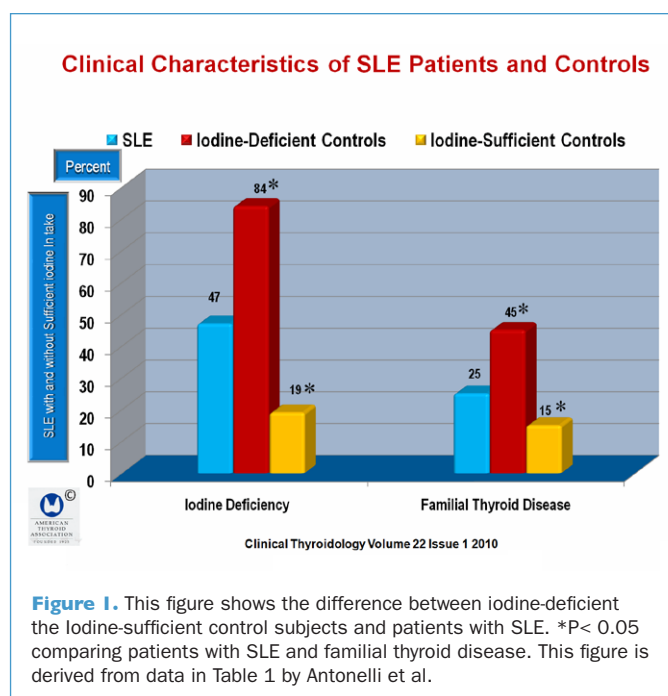
Thyroid function was evaluated in all SLE patients and controls by clinical examination including measurement of serum TSH, free  $T_3$ , free  $T_4$  ( $FT_4$ ) anti-thyroglobulin antibodies (AbTg) and anti-thyroperoxidase antibodies (TPOAb).

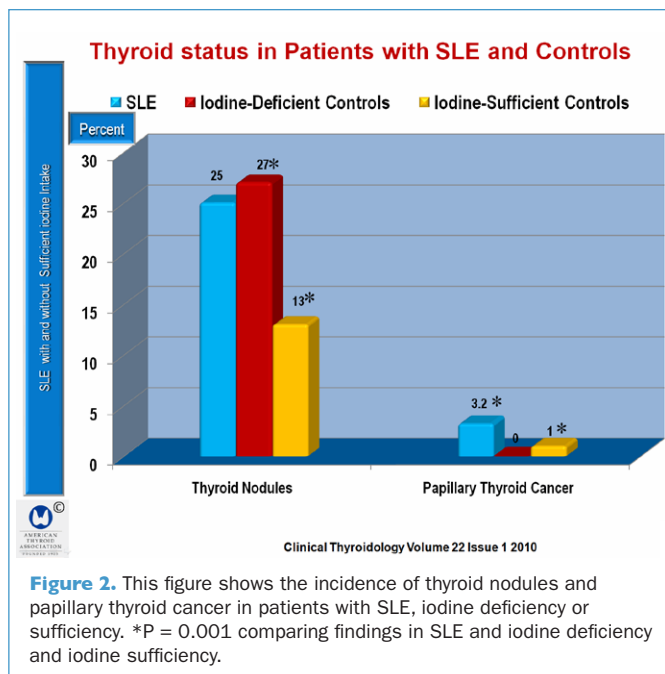
### RESULTS (Figure 1)

The SLE group comprised 153 patients with a mean age of  $38 \pm 13$  years, and 9 men (6%) and 144 women (94%). Of this group, 47% were in the iodine-deficiency group and 25% had familial thyroid disease. (Figure 1)

A family history of thyroid disease was significantly more frequent in the iodine-deficient controls. The serum TSH, TgAb, and TPOAb levels were significantly higher in SLE patients, but  $FT_3$  and  $FT_4$  levels were significantly lower than those in the two control groups. Hypothyroidism ( $TSH > 4 \mu\text{g/ml}$ ) was significantly more common in the patients with SLE as compared with the two control groups. Subclinical and clinical hyperthyroidism ( $TSH < 0.3 \mu\text{IU/ml}$ , with or without high serum  $FT_3$  or  $FT_4$  levels) was significantly higher in patients with SLE as compared with those in the two control groups. Nonthyroidal illness syndrome (low serum  $T_3$ , normal  $FT_4$ , high reverse ( $rT_3$ ) and normal TSH) was found in 4% of patients with SLE.

Thyroid nodules were significantly more common in patients with SLE (25%) and in control subjects in iodine-deficient areas (27%);  $P < 0.001$ , comparing both control groups. (Figure 1) Fine-needle aspiration biopsy (FNAB) was performed in 24 patients with SLE (16%), and on 31 nodules (mean 1.2, nodules per patient, range 1 to 2). The median nodule size was 19 mm. The cytologic samples were classified as follows: class 1, (macrophages and colloid with no or rare follicular cells); class 2, (benign nodule); class 3, (indeterminate follicular lesion), and class 4, (suspect of or frankly malignant). The cytology was class 1 in 8%, class 6 in 6%, class 4 in 13%, class 9 in 12%.





There were no significant differences in the distribution of class 1,2, and 3 among the three study groups (P = 0.9). A total of five papillary thyroid cancers were detected in the SLE group, and none were identified in the controls (P< 0.001) comparing the SLE group with the control groups.

The SLE patients with papillary thyroid cancer did not differ significantly from the other SLE patients in terms of sex (9 men and 5 women), mean age (38± 12 vs. 37±13 yr), serum TSH FT<sub>3</sub> FT<sub>4</sub> and TPOAb levels and serum TgAb. Four patients with SLE who had papillary thyroid cancer had circulating TgAb and TPOAb. Of the patients with SLE and papillary thyroid cancer, 80% had evidence of thyroid autoimmunity, as compared with thyroid autoimmunity in 31% of SLE patients without thyroid cancer. (P = 0.02)

**CONCLUSION**

This study suggests that the prevalence of papillary thyroid cancer in patients with SLE is higher than that in age-matched controls, particularly in patients with thyroid autoimmunity. As a result, careful thyroid surveillance is recommended during the follow-up of patients with SLE.

**COMMENTARY**

The impetus for the study by Antonelli et al came from a retrospective cohort study of patients in California by Parikh-Patel(1) et al. that examined the risk for cancer in a large cohort of patients with SLE (1). In that study, statewide patient discharge data were provided from 1991 through 2002, and patients with SLE had follow-up using a cancer registry to examine the patterns of cancer development. The study cohort comprised 30,478 patients with SLE that was observed for 157,969 person-years during which a total of 1,273 cancers occurred. The standard incidence ratios (SIRs) were significantly elevated (SIR = 1.14, 95% CI = 1.07-1.20), showing that SLE patients had higher risks of vagina/vulva (SIR = 3.27, 95% CI = 2.41-4.31) and liver cancers (SIR = 2.70, 95% CI = 1.54-4.24). In addition, there were elevated risks of lung, kidney, and thyroid cancers and several hematopoietic malignancies. These data thus suggested that risks of several cancer types are elevated among patients with SLE. The authors concluded that detailed studies of endogenous and exogenous factors that drive these associations are needed.

Antonelli et al found that 5 of 153 patients with SLE (3.2%) had papillary thyroid cancer, only one of which was observed in the iodine-sufficient control group. To eliminate bias, the observed prevalence of thyroid cancer due to differences in iodine uptake, control groups from both high and low iodine intake regions were

used. Still, the results illustrate a significantly higher prevalence of papillary thyroid cancer in patients with SLE as compared with the incidence of papillary thyroid cancer (0%) in both control groups. These results corroborate the studies by Parikh-Patel, et al. and extend their observations. Antonelli et al. suggest that their study has a number of advantages over that in the California study. First, the Antonelli study used a prospective follow-up design over a 12-year period as compared with a retrospective follow-up in the California study. Secondly, the Pisa investigators were able to establish a definitive diagnosis of SLE, whereas the California group was unable to verify the diagnosis of SLE from the hospital discharge data. Thirdly, the results of the Pisa study were able to confirm the high incidence of thyroid cancer, 3.2%, which is in the range of papillary thyroid cancers found in patients undergoing FNAB for thyroid nodules.

Why patients with SLE might develop thyroid cancer is uncertain, but Antonelli et al. suggest that the increased risk for thyroid cancer in patients with SLE might be caused by autoimmunity, the presence of which was verified by the Pisa investigators.

Antonelli et al. advise neck ultrasonography on the basis of the current findings, which seems reasonable, considering the increased incidence of thyroid cancer in this group.

— Ernest L. Mazzaferri, MD, MACP

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# Repeat fine-needle aspiration biopsy (FNAB) should be considered for thyroid nodules with suspicious features on ultrasound, even when the initial FNAB results are benign.

Kwak JY, Koo H, Youk JH, Kim MJ, Moon HJ, Son EJ, Kim EK. Value of US correlation of a thyroid nodule with initially benign cytologic results. *Radiology* 2010;254:292-300.

## SUMMARY

### BACKGROUND

Fine-needle aspiration biopsy plays a key role in selecting patients for surgery; however, it has some limitations, such as false negative or false positive results or inadequate cytologic specimens. This study was aimed at assessing the value of ultrasound (US) features in thyroid nodules that initially yield benign cytologic results.

### METHODS

From October 2003 through February 2006, a total of 6025 consecutive patients who were seen in Severance Hospital in Seoul, Korea, had US-guided FNAB of 6118 nodules, 3540 of which were  $\geq 1$  cm with benign cytologic results (58%). Benign cytology comprised colloid nodules, adenomatous hyperplasia, lymphocytic thyroiditis, Graves' disease, and postpartum thyroiditis

#### The Winnowing of Thyroid Nodules for Study (Figure 1)

A total of 2136 nodules were excluded (60%) because no further evaluation results were available, and 60 of the remaining 1404 nodules were excluded because they increased in size on follow-up US without further cytologic or pathologic evaluation, and 1 nodule was excluded because it revealed follicular neoplasm, leaving a total of 1343 nodules for ultrasound analysis in 1324 patients (Figure 1).

Focal thyroid nodules were interpreted by using the following US features: internal nodule echogenicity, the tumor margin,

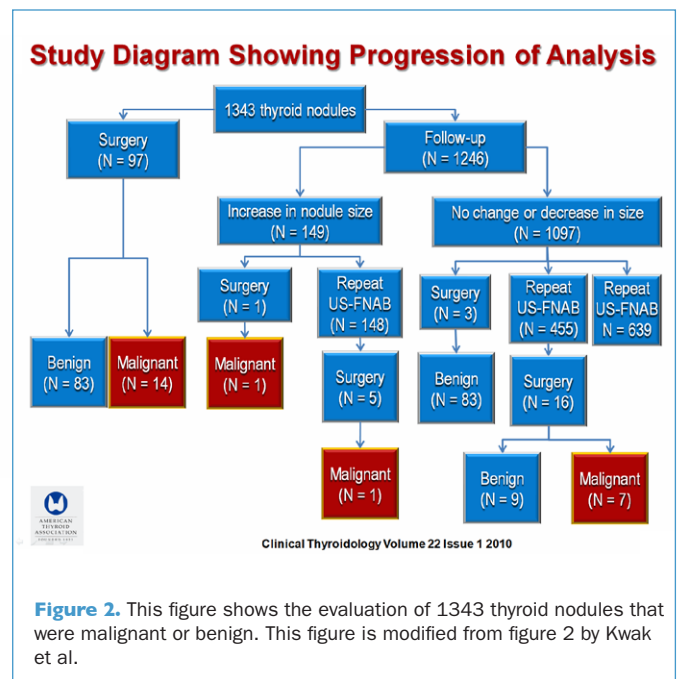
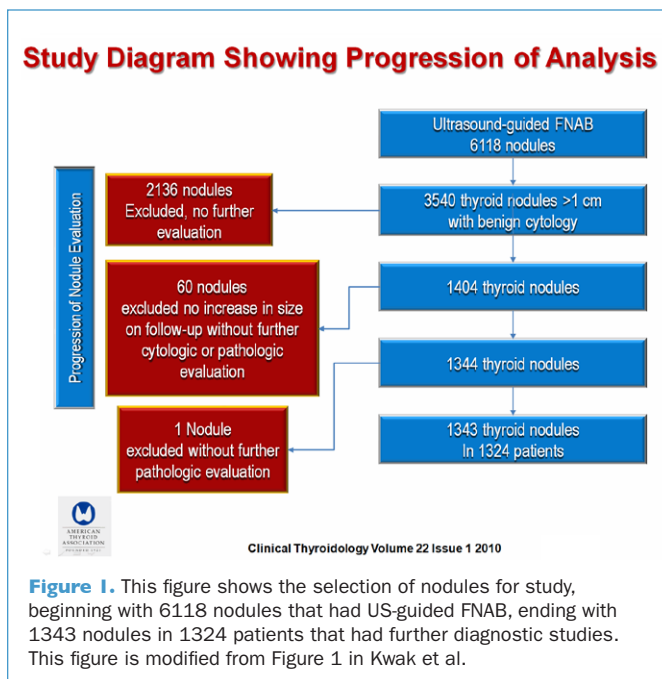
calcifications, and shape. Internal components of the nodule were defined as solid, mixed, or cystic, and a nodule with mixed components was interpreted as a mixed solid-cystic lesion. Nodules with mixed components were evaluated on the basis of the internal solid components. Based on these authors previously published criteria, a nodule was considered suspicious for malignancy if any of the following were found on neck US: marked hypoechoogenicity, microlobulated or irregular margin, microcalcifications, or a greater anteroposterior than transverse configuration.

A calculation of the likelihood of having a benign nodule was subdivided into various subgroups, including the number of aspirations, US features, and follow-up data. After this estimation, the likelihood of benign thyroid nodules in the group with benign cytologic results was compared with those of the remaining subgroups. The likelihood of thyroid nodules with benign cytologic results on at least two FNAB aspirations was compared with benign nodules from the remaining subgroups. Finally, a comparison was made of the likelihood of negative US results in nodules with initially benign cytologic results, and during follow-up US with nodules that had initially showed benign cytologic results, negative US results, and increased size at follow-up US.

## RESULTS

### Patient Nodule Demographics (Figures 2 and 3)

The mean age of all study patients was 48.9 years (range, 14 to 81); the mean age for men was 49.3 (range, 16 to 76), and for women 48.8 (range, 14 to 81). The mean thyroid nodule



size was 22.2 mm (range, 10 to 60). Malignant nodules were confirmed by surgery or repeat FNAB, and nodules were confirmed as benign by surgery or repeat FNAB or no change or a decrease in nodule size during US follow-up.

Of the 1343 nodules, 97 (7.2%) were surgically excised without follow-up US or FNAB, and the histologic results of this group were benign in 83 of the 1343 nodules (86%) and malignant in 14 (14%). Of the 1246 nodules that had follow-up, 149 (12%) increased in size and 1097 (88%) had no change or decreased in size. Of the 149 nodules that increased in size, 1 had surgery (0.7%) and 148 (99%) had repeat aspiration or surgery; 5 of the 149 patients were found to have malignant tumors (3%). Thus, of the total of 1343 nodules that were initially considered benign on FNAB, 23 (1.7%) had malignant tumors (Figure 2).

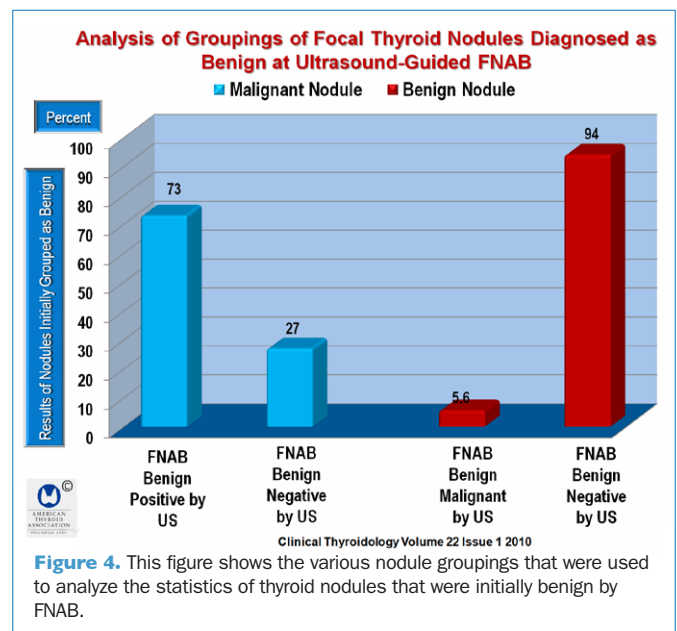
The diagnosis of 1343 nodules was confirmed by surgery in 122, by repeat FNAB in 543, and by follow-up US in 678 (Figure 2). Of 122 patients who had surgery, there were 122 nodules, 23 of which were malignant and 99 benign. Of the malignancies, 83% were papillary thyroid cancer, 13% were follicular variant papillary thyroid cancer, and 4% were minimally invasive follicular thyroid cancer. Of the 99 benign nodules, 87 (88%) were caused by benign adenomatous hyperplasia, 8 were follicular adenoma (8%), and 4 (4%) were thyroiditis (Figure 3).

**Outcome on the Basis of Ultrasonography (Figure 4)**

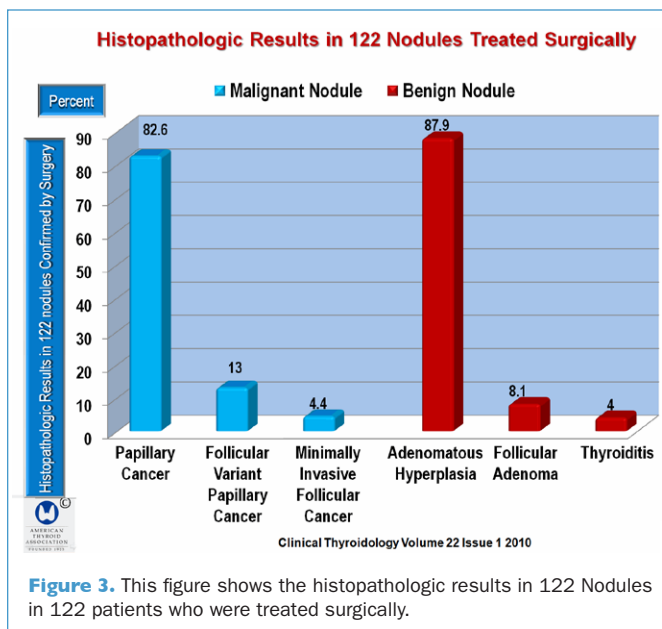
Based on the US findings, there were 93 nodules with positive features and 1250 with negative features, and the final rate of malignancy was 1.9%. The histopathologic results in 122 patients were confirmed by surgery, 543 by repeat FNAB, and 678 by follow-up US. The mean interval between the initial and follow-up FNAB was 15.6 months (range, 3 to 51) in 543 nodules. The time between the first and repeated FNABs was >90 days for all patients, and 94 of 753 (12%) had more than two follow-up FNABs. The mean time between initial and follow-up US was 26.7 months (range, 3 to 60) in 678 nodules. Of the 122 nodules treated surgically, 23 (19%) were histopathologically malignant, and 99 (81%) were histologically benign (Figure 4).

**Comparison of US Findings and the Risk for Malignancy in a Thyroid Nodule (Figure 5)**

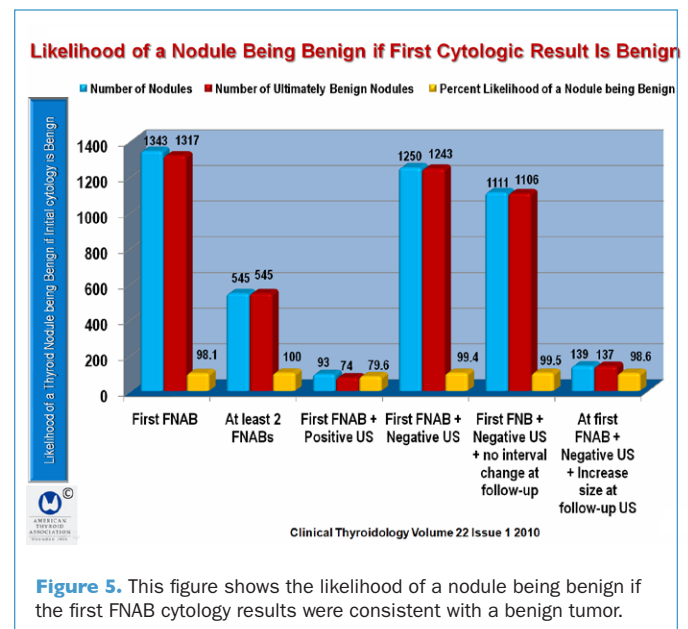
Results of the analysis of benign and malignant thyroid nodules determined that the mean (±SD) diameter of benign nodules was 22.3 ±10.8 mm, which was significantly larger than the size of malignant nodules (18.2±8.7 mm) (P<0.001). There was no significant relationship between the risk of malignancy and patient sex or age. In the final analysis, 26 (1.9%) malignant and 1317 (98.1%) benign nodules were found according to reference standards established by the investigators. If the initial cytologic results showed benign thyroid nodules, the likelihood of the nodule actually being benign was 98.1%, and when a thyroid nodule had benign results at both initial and repeat FNAB, the likelihood increased to 100%. The likelihood of having a benign thyroid nodule with suspicious US features was lower



**Figure 4.** This figure shows the various nodule groupings that were used to analyze the statistics of thyroid nodules that were initially benign by FNAB.



**Figure 3.** This figure shows the histopathologic results in 122 Nodules in 122 patients who were treated surgically.



**Figure 5.** This figure shows the likelihood of a nodule being benign if the first FNAB cytologic results were consistent with a benign tumor.



(80%) than having a benign thyroid nodule with negative US features (99.4%) ( $P < 0.001$ ). The risk for malignancy was slightly higher (1.4%) in a thyroid nodule with benign features on the initial US study and an increase in size during follow-up, and it was slightly higher than that of a thyroid nodule with no change during follow-up, (5%) but the difference was not significant  $P = 0.4$  (Figure 5).

Logistic-regression analysis demonstrated that for tumor size, the odds ratios and 95% confidence intervals (CIs) were 0.956 (95% CI, 0.912 to 1.002;  $P = 0.06$ ); for age were 1.021 (95%

CI, 0.987 to 1.057;  $P = 0.23$ ); for sex, were 0.592 (95% CI, 0.201 to 1.745;  $P = 0.34$ ); and for US groupings were 45.588 (95% CI, 18.577 to 111.874;  $P < 0.001$ )

**CONCLUSION**

The risk for malignancy is extremely low if the initial FNAB is negative and the US features are not suspicious; however, if there are suspicious US features, the false negative rate of cytology may be as high as 20%. As a consequence, it seems that repeat FNAB should be considered.

**COMMENTARY**

Fine-needle aspiration biopsy is currently the best diagnostic means of identifying malignant thyroid tumors. Yet the false negative rate can range from 1 to 11% (1). Limitations of FNAB are related to the skill of the operator, the expertise of the cytologist, and the difficulty in distinguishing some benign cellular adenomas from their malignant counterparts. Nonetheless, experts in the field and current American Thyroid Association guidelines recommend that a nodule of any size with sonographically suspicious features can be considered for FNAB (2;3). This includes microcalcifications, hypoechoic solid nodules, irregular or lobulated margins, intranodular vascularity, and nodal metastases (or signs of extracapsular spread). However, this recommendation is controversial because it includes patients with microcarcinomas in whom a survival benefit after an FNAB diagnosis has been challenged. The recent National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science conference indicated that lesions with a maximum diameter greater than 1.0 to 1.5 cm should be considered for biopsy unless they are simple cysts or septated cysts with no

solid elements. FNAB also may be replaced by periodic follow-up of small nodules ranging from 8 mm to 1 cm in diameter if they have sonographic features that are strongly associated with benign cytology. This underscores the clinical importance of US in the management of thyroid nodules. For example, one study concludes that US evaluation changes the management of 63% of patients with palpable thyroid nodules (4;5). Still, the skill of the US operator plays a key role in the decision to rebiopsy nodules based on a US evaluation.

Kwak et al. point out a few limitations of this study, including some variability among the findings of the five cytopathologists, making the precise rate of malignant nodules uncertain.

Nonetheless, the authors provide strong evidence that benign cytologic FNAB results should be repeated if neck ultrasonography is suspicious for malignancy. The 20% rate of false-negative FNAB cytology under these circumstances is a compelling endorsement of their recommendation.

— Ernest L. Mazzaferri, MD, MACP

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## Disclosure

Dr. Mazzaferri is a consultant to Genzyme.

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

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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	EARLY RISER SYMPOSIUM
8:00 AM - 8:15 AM		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	ADVANCED ULTRASOUND WORKSHOP (9:30 AM-1:30 PM)	COFFEE BREAK (9:15-9:45)	COFFEE BREAK (9:15-9:45)	SYMPOSIUM (9:30-11:00)
9:45 AM - 11:15 AM		SYMPOSIUM (9:45-11:15)	SYMPOSIUM (9:45-11:15)	<i>Program subject to change</i>
11:15 AM - 12:45 PM		SYMPOSIUM (11:15-12:45)	SYMPOSIUM (11:15-12:45)	
12:45 PM - 1:30 PM	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	WOMEN IN THYROIDOLOGY MEETING (4:30-6:00)	SYMPOSIUM (2:30-4:00)	SYMPOSIUM (2:30-4:00)	 AMERICAN THYROID ASSOCIATION FOUNDED 1923  <a href="http://www.thyroid.org">www.thyroid.org</a>
4:30 PM - 6:00 PM		COFFEE BREAK (4:00-4:30)	COFFEE BREAK (4:00-4:30)	
6:00 PM - 7:30 PM	WELCOME RECEPTION (6:00-7:30)	SYMPOSIUM (4:30-6:00)	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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