

# CLINICAL THYROIDOLOGY

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**Editor-in Chief**

**Ernest L. Mazzaferri, MD,  
MACP**

University of Florida  
1600 SW Archer Road  
PO Box 100226  
Gainesville FL 32610-0226  
Telephone: 352-392-2612  
Fax: 352-846-2231  
Email: [thyroid@thyroid.org](mailto:thyroid@thyroid.org)

**Associate Editor**

**Jennifer A. Sipos, MD**

The Ohio State University  
4th Floor McCampbell Hall  
1581 Dodd Drive  
Columbus, OH 43210  
Telephone: (614) 292-3800  
Email: [thyroid@thyroid.org](mailto:thyroid@thyroid.org)

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American Thyroid Association  
6066 Leesburg Pike, Suite 550  
Falls Church, VA 22041  
Telephone: 703-998-8890  
Fax: 703-998-8893  
Email: [thyroid@thyroid.org](mailto:thyroid@thyroid.org)

**Designed By**

Karen Durland  
Email: [kdurland@gmail.com](mailto:kdurland@gmail.com)

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# CLINICAL THYROIDOLOGY

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## EDITORS' COMMENTS

This is the eighth 2010 issue of *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 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.

**WHAT'S 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.

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

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# Patients with very low-risk papillary thyroid microcarcinoma treated with total or near-total thyroidectomy rarely have persistent or recurrent disease and likely do not require adjuvant radioiodine therapy

Durante C, Attard M, Torlontano M, Ronga G, Monzani F, Costante G, Ferdeghini M, Tumino S, Meringolo D, Bruno R, De Toma G, Crocetti U, Montesano T, Dardano A, Lamartina L, Maniglia A, Giacomelli L, Filetti S. Identification and optimal postsurgical follow-up of patients with very low-risk papillary thyroid microcarcinomas. *J Clin Endocrinol Metab* 2010.doi:10.1210/jc.2010-0762

## SUMMARY

### BACKGROUND

For the past three decades, the incidence of thyroid cancer has been steadily rising worldwide and the vast majority of it (80%) is papillary thyroid cancer. Approximately half of these tumors are 10 mm or less and are designated as papillary thyroid microcarcinoma (PTMC). Despite the small size of these tumors ( $\leq 1$  cm), there has been considerable controversy concerning their management. This is a retrospective study that tests the hypothesis that clinical criteria could be used to identify patients with the lowest risk for PTMC mortality and recurrence. This retrospective study is based on explicit criteria aimed at tailoring a postoperative management protocol for patients with very-low-risk PTMC that would diminish the odds of developing recurrent or progressive disease.

### SUBJECTS AND METHODS

Data for this study were collected from nine hospital-based referral centers for thyroid disease in Italy, including seven thyroid clinics and two nuclear medicine units that identified a total of 946 patients with PTMC treated over the past two decades. Study coordinators in each center identified 710 consecutive patients (75%) with sufficient data to satisfy the criteria for very-low-risk PTMC, which included all of the following: no family history of thyroid cancer, no history of head and neck irradiation, tumor stage pT1, tumor size  $\leq 1$  cm, pNO and pMO, with no extension beyond the thyroid capsule, unifocal tumors, and tumors without histologically aggressive subtypes, such as tall-cell PTMC.

The study subjects comprised 312 patients with complete follow-up from the time of surgical diagnosis through at least 5 years of follow-up or until the date of death. An electronic form was completed that provided all the information required to fulfill the study criteria for very-low-risk PTMC, surgical treatment and radioiodine ablation, levothyroxine therapy and follow-up findings including the cervical ultrasound findings, and laboratory results at the last follow-up visit.

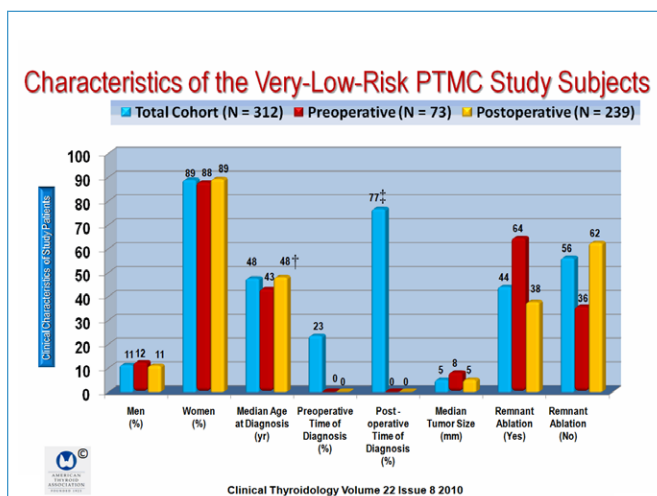
All patients had total or near-total thyroidectomy, and the histologic surgical specimens were cut into fine microscopic specimens for examination to exclude other tumor foci. Radioiodine ablation was performed at the discretion of the team treating the patient, which reflected the institutional guidelines at the time the patient had surgery. Levothyroxine was administered to maintain serum thyrotropin (TSH) levels at normal or suppressed levels. All patients had follow-up according to the same protocol. They had initial postoperative follow-up within 12 months after surgery and yearly visits thereafter, at which time a physical

examination was performed and serum TSH, thyroglobulin (Tg), and Tg autoantibody (TgAb) levels were measured. However the mainstay of follow-up was neck ultrasonography with Doppler scanners, which was the most sensitive technique for detecting locally recurrent tumor. The standard ultrasound criteria were used to identify cervical-lymph-node metastases, and fine-needle aspiration biopsy was performed for suspicious lymph nodes, and Tg levels were measured in the needle washout fluid. After 1997, aspirates were also assayed for Tg, TSH, and mRNA. At each follow-up visit, the outcome was classified as positive or negative for persistent or recurrent disease on the basis of ultrasound findings and unstimulated serum Tg levels. In the presence of negative ultrasound findings in a patient who had  $^{131}\text{I}$  remnant ablation, serum Tg levels were considered suspicious if they were within the detectable range of the assay used. If  $^{131}\text{I}$  ablation had not been performed, serum Tg was considered suspicious if the Tg levels increased over time.

## RESULTS

### Characteristics of the Study Population (Figure 1)

The characteristics of the study population are summarized in Figure 1. In all, 239 of 312 (77%) of the PTMCs had been diagnosed after surgery for multinodular goiter. The other 73 had PTMC diagnosed preoperatively with fine-needle aspiration



**Figure 1.** This figure shows the characteristics of the total study cohort and the number of patients that had a diagnosis of PTMC made preoperatively or postoperatively. Patients at the time of diagnosis were significantly older than the patients whose diagnosis of PTC was made after surgery for multinodular goiter. †P = 0.003 comparing preoperative or postoperative age of diagnosis. ‡P < 0.001 for tumor size and comparing those with and without remnant ablation. The data in Figure 1 are derived from Table 2 in the study by Durante et al.

biopsy, which tended to be performed in younger patients with larger tumors than those diagnosed postoperatively. Also, the younger patients were more likely to have <sup>131</sup>I remnant ablation, which was performed in 137 patients (44%) of the total cohort. A median of 73 mCi of <sup>131</sup>I was administered. In all patients, the whole-body posttherapy <sup>131</sup>I scan revealed <sup>131</sup>I uptake exclusively in the thyroid bed.

**Follow-up and Clinical Outcome in the Study Population (Figure 2)**

Figure 2 summarizes the findings at the end of the study for the total cohort, and subgroups are defined on the basis of time of diagnosis and treatment with <sup>131</sup>I. There were no significant differences in the time of diagnosis, although follow-ups were significantly longer in the group that had received <sup>131</sup>I remnant ablation.

None of the patients died of thyroid cancer or had to have more surgery. The first follow-up cervical ultrasound after surgery at 6 to 12 months after surgery found no evidence of lymph-node metastases in any of the 312 patients and was consistently confirmed in all patients by the results of subsequent annual follow-up and final ultrasound examinations. The negative predictive value of the initial ultrasound study was thus 100%.

**Thyroglobulin Levels at the End of the Follow-up Period (Figure 3)**

Serum Tg levels were not correlated with serum TSH levels in both the <sup>131</sup>I and non-<sup>131</sup>I subgroups. All 137 patients treated with <sup>131</sup>I remnant ablation had undetectable serum Tg levels, which confirmed the disease-free status of the patients indicated by the ultrasound findings. The final Tg levels were also <1 ng/ml in most of the patients (163 of 157; 93%) who had not had <sup>131</sup>I remnant ablation. The characteristics of the other 12 patients in this group are shown in Figure 3. Their final serum Tg levels ranged from 1.3 to 6.0 ng/ml. In all 12 patients, the Tg levels had remained stable or decreased progressively

during follow-up. Although thyroid remnants were documented by cervical ultrasonography, none of the final scans showed any sign of lymph-node metastases. Patient 12, whose final Tg was especially high at 6.0 ng/ml, was extensively investigated to rule out persistent or recurrent disease; after the administration of recombinant human TSH (rhTSH), his Tg increased to 10 ng/ml and the whole-body scan revealed uptake only in the thyroid bed, which the authors concluded were very unlikely to be expressions of persistent disease.

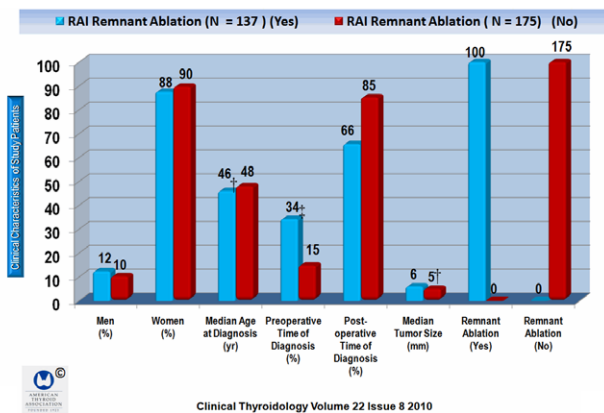
**Patients with Detectable Tg Levels at the Last Follow-up Visit**

Twelve patients had detectable serum Tg levels at the last follow-up visit. All were women, and the time of diagnosis was postsurgical in 10 patients and presurgical in 2; median age at the time of diagnosis was 50±9.4 years (range, 34 to 64). The mean final Tg was 2.8±1.3 ng/ml (range, 1.3 to 3.97). The mean final TSH was 1.06±1.45 mIU/L (range, 0.03 to 5.1) and the mean follow-up 10.2±5.5 years (range, 5.9 to 20.4). (These data are calculated from Table 4). None of these patients had evidence of persistent or recurrent disease

**CONCLUSION**

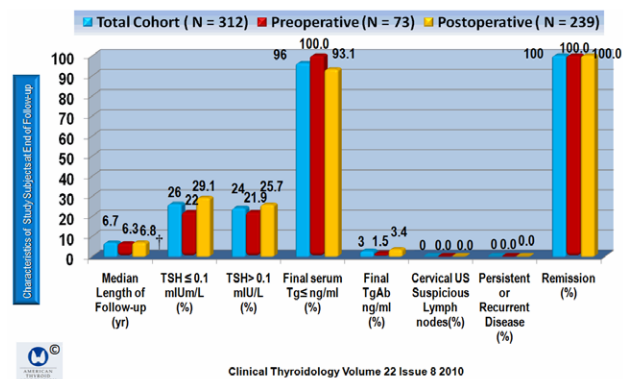
Very-low-risk patients with PTMC had persistently negative neck ultrasound examinations, even in the 66 patients (24.3%) that had follow-up for more than 10 years, which thus indicates that in the vast majority of patients (~75%), effective postoperative surveillance can be based exclusively on neck ultrasonography. The initial postoperative studies found a negative predictive value of 100% for persistent or recurrent disease after surgery for up to 23 years, suggesting that yearly neck ultrasound examinations are unnecessary, at least after 5 years of follow-up, when the most recurrences are found. Also, the use of adjuvant <sup>131</sup>I remnant ablation in this group of patients, especially to monitor serum Tg levels is not likely to provide additional benefit to the patient, as shown in the group that did not have <sup>131</sup>I remnant ablation.

**Characteristics of the Very-Low-Risk PTMC Study Subjects**



**Figure 2.** This figure shows the characteristics of patients who had remnant <sup>131</sup>I ablation and those who did not have remnant ablation. Those who had remnant ablation were significantly younger (46 years) as compared with those who did not have <sup>131</sup>I ablation (48 years) †P = 0.041, and the time of diagnosis was significantly different (43 vs. 47.5 hrs †P< 0.0001. The rest of the differences in this figure are not statistically significant. RAI = radioactive iodine. The data in Figure 2 are derived from Tables 2 and 3 in the study by Durante et al.

**Very-Low-Risk PTMC Study Subjects at the End of Follow-up**



**Figure 3.** This figure shows the characteristics of the very-low-risk PTMC study population at the end of the follow-up period. The length of follow-up was greater in patients who had remnant ablation than in those who did not (median years of 6.3 vs 6.8). †P = 0.028. The rest of the differences were not statistically significant, except for the final serum Tg level, which was 72 ng/ml in the preoperative group and 229 in the postoperative group; †P< 0.001). US = ultrasound; TgAb = antithyroglobulin antibodies

**COMMENTARY**

The increasing incidence of thyroid cancer in the United States and other countries is thought by some to be predominantly due to the increased detection of small papillary cancers that require little or no therapy (1). This alone is a controversial opinion based upon data in the Surveillance, Epidemiology, and End Results (SEER) database (2).

Thyroid microcarcinoma, defined as a tumor  $\leq 1$  cm, is thus generally regarded as a low-risk tumor that requires minimal or no therapy. The ATA guidelines (3) recommend that thyroid lobectomy alone may be sufficient treatment for small ( $< 1$  cm), low-risk, unifocal, intrathyroidal papillary carcinomas in the absence of prior head and neck irradiation or radiologically or clinically involved cervical-lymph-node metastases. (Recommendation rating: A)

Still, there is considerable controversy concerning the management of these small tumors (4). Part of the disagreement is that large studies have found that there is a risk for tumor recurrence and cancer-specific mortality for tumors  $< 1$  cm. A study of 52,173 patients by Bilimoria et al. (5) found that the 10-year tumor recurrence rate of papillary cancers  $< 1$  cm was 4.6% and the 10-year cancer-specific mortality 2%.

A study of by Noguchi et al. (6) of 2070 patients with PTMC found that over a 35-year follow-up, there were 73 cases of recurrence from the time of initial surgery to the first recurrence, among which there were distant metastases outside the neck, 1 in the lung, 4 in the bone, and 1 with multiple distant metastases. In the interval between the primary surgery and the second recurrence there were 12 cases of recurrence, including 4 in lung, 1 in bone and 1 in the mediastinum. The Bilimoria and Noguchi studies thus show a spectrum of clinical behavior of PTMC (7;8).

The very important study by Durante et al. directly addresses the conflicting views concerning the initial management of

PTMC by carefully defining a very-low-risk group of tumors. This large multicenter study of 710 patients defined very-low-risk PTMC on the basis of clinical features that affected outcome, including all of the following: unifocal tumor, total or near-total thyroidectomy, no family history of thyroid cancer, no history of head and neck irradiation, tumor stage pT1,  $\leq 1$  cm, pN0 and pM0 and no extension of tumor beyond the thyroid capsule. The authors documented that this subset of tumors is indeed very-low-risk and that they require little therapy other than total or near-total thyroidectomy. After a mean follow-up of  $10.2 \pm 5.5$  years (range, 5.9 to 20.4), none of these patients had evidence of persistent or recurrent disease over an extended follow-up. This is the main feature of the study.

I think this is a major contribution that carefully identifies a group of patients with very-low-risk PTMC that require only total or near-total thyroidectomy without remnant ablation and TSH suppression.

The Durante study has a second feature: it will focus the debate on the remaining group of patients with PTMC who do not have the defining characteristics for very-low-risk tumors identified by Durante et al.

For example, an important study by Bonnet et al. (9), in which total or near-total thyroidectomy with prophylactic, multi-compartment neck dissection was performed shows that patients with tumors  $< 1$  cm to 2 cm still are at risk for recurrence unless the residual lymph-node metastases, invasive tumors, or tumors with aggressive histology are treated with remnant ablation.

Taken together, these two studies shine a bright light on the ongoing debate concerning the management of PTMC that offers several therapeutic options to patients with different PTMC tumor characteristics.

— Ernest L. Mazzaferri, MD, MACP

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# BRAF mutations in pT1 tumors invading the thyroid capsule should be considered a marker of worse prognosis

Basolo F, Torregrossa L, Giannini R, Miccoli M, Lupi C, Sensi E, Berti P, Elisei R, Vitti P, Baggiani A, Miccoli P. Correlation between the *BRAF* V600E mutation and tumor invasiveness in papillary thyroid carcinomas smaller than 20 millimeters: analysis of 1060 cases. *J Clin Endocrinol Metab* 2010 doi:10.1210/jc.2010/jc.2010-0337.

## SUMMARY

### BACKGROUND

The incidence of thyroid cancer has been increasing worldwide for the past several decades. Papillary thyroid cancer (PTC) comprises nearly 90% of all thyroid cancers, about half of which are tumors  $\leq 10$  mm, and approximately 87% are papillary thyroid cancers  $\leq 20$  mm. Although small PTCs usually have a good outcome, there is disagreement concerning the management of tumors measuring 10 to 20 mm. Previously classified as pT2, these tumors are now are classified as pT1 according to the sixth edition of the tumor–node–metastases (TNM) staging system. PTCs  $< 2$  cm that are limited to the thyroid gland and have no lymph-node metastases are generally considered to be low-risk tumors that can be treated with thyroidectomy. Still, tumors with extrathyroidal extensions require more aggressive management, as an unfavorable outcome is more likely. *BRAF* V600E activating mutation, with a prevalence of approximately 45%, has become a promising prognostic factor in the risk stratification of PTC. The aim of this retrospective study was to correlate *BRAF* V600E mutations with the clinical and pathological features in a large and homogeneous series of patients with PTC tumors  $< 2$  cm.

### PATIENTS AND METHODS

#### The Pathology Descriptions

Thyroid specimens were retrieved from archival formalin-fixed and paraffin-embedded thyroid specimens maintained in the Department of Surgical Pathology, University of Pisa, from 1060 consecutive patients, 254 of whom were men (24%) and 806 women (76%), with PTCs  $\leq 20$  mm that were diagnosed from January 2006 through April 2009. All of the patients were treated and observed at the Institute of Endocrinology at the University of Pisa and had total or near-total thyroidectomy and excision of suspicious cervical lymph nodes by surgeons in the Department of Surgery of the same university.

Two pathologists reviewed the diagnosis to ensure that the specimens were in accord with the World Health Organization classification of thyroid malignancy. Tumors were staged according to the sixth edition of the TNM staging system as pT1 for tumors  $\leq 20$  mm and pT3 for tumors with minimal extrathyroidal extension of the tumor.

Tumors were divided into four groups: (1) totally encapsulated—tumors completely surrounded by a well-defined fibrous capsule that separated the tumor from the surrounding nonneoplastic thyroid tissue, (2) not encapsulated without thyroid capsular invasion—tumors without a complete capsule around the tumor, extension into the collateral thyroid parenchyma, and absences of contact with the adjacent thyroid capsule, (3)

thyroid capsular invasion—tumors with clear tumor infiltration of the thyroid capsule with no extension into the perithyroidal soft tissues, and (4) extrathyroidal extension—tumors that showed signs of infiltration, including even minimal infiltration beyond the confines of the thyroid capsule into the adjacent soft tissues. When there was thyroid capsule invasion, at least 10 consecutive serial tissue sections were evaluated per sample to exclude tumor extension into the perithyroidal soft tissues.

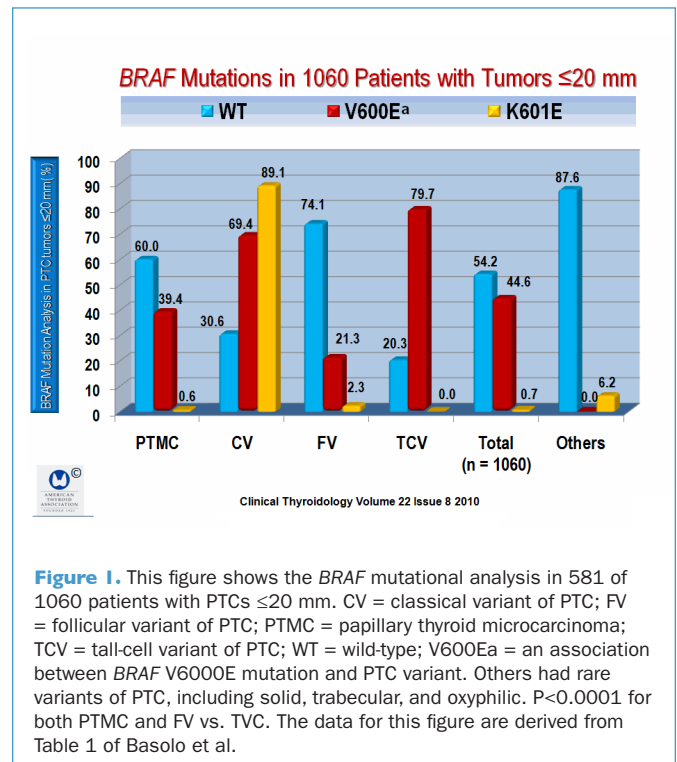
### BRAF Mutation Analysis

*BRAF* detection was performed by polymerase-chain-reaction single-strand conformation polymorphism, and direct DNA sequencing was performed according to standard procedures.

### RESULTS

#### TNM Tumor Sizes and Stages (Figure 1)

A total of 581 of 1060 patients (54%) had histologically diagnosed papillary thyroid microcarcinoma (PTMC), defined as a tumor  $\leq 10$  mm. Among this group, 225 (21.3%) had classic PTC, 174 (16.4%) had follicular variant PTC, 64 (6%) had tall-cell variant, and 16 (1.5%) were categorized as “others,” including solid, trabecular, and oxyphilic variants (Figure 1).



**Figure 1.** This figure shows the *BRAF* mutational analysis in 581 of 1060 patients with PTCs  $\leq 20$  mm. CV = classical variant of PTC; FV = follicular variant of PTC; PTMC = papillary thyroid microcarcinoma; TCV = tall-cell variant of PTC; WT = wild-type; V600E<sup>a</sup> = an association between *BRAF* V6000E mutation and PTC variant. Others had rare variants of PTC, including solid, trabecular, and oxyphilic.  $P < 0.0001$  for both PTMC and FV vs. TVC. The data for this figure are derived from Table 1 of Basolo et al.

The mean ( $\pm$ SD) tumor size was 10.3 $\pm$ 5.3 mm (median, 10.0). Tumor multifocality was found in 404 cases (38.1%). Minimal extrathyroidal neoplasm extension (pT3) was found in 311 PTCs (29.3%), and lymph-node metastases were found in 186 (17.5%). According to the TNM staging system, 917 patients (87%) had stage I tumors, 108 (10.3%) had stage III tumors, and 29 (2.7%) had stage IV tumors (Figure 2).

**BRAF Mutations**

BRAF alterations were found in 486 of 1060 patients (45.8%). BRAF V600E was identified in 473 patients (44.6%). BRAF K601E was found in 8 patients (0.7%), and BRAF VK600-1E in 2 (0.2%). In addition, a complex BRAF exon 15 deletion–insertion mutation (1798–1811) was found in 3 patients, with a concomitant 2-bp insertion (1798–1799), and 1 patient had a 2-bp insertion (1796–1797) with a concomitant 8-bp insertion (1798–1805).

**Correlation between BRAF V600E and Clinical Pathological Features (Figure 3A)**

Concerning patients with PTC variants, BRAF V600E was found in 229 of 581 patients with PTMC (39.4%), in 156 of 225 with classic PTC (69.4%), in 37 of 174 with follicular PTC variants (21.3%), and in 51 of 64 with tall-cell variants (79.7%). BRAF K601E was found in 3 patients with PTMCs with follicular patterned-type architecture, in 4 patients with the follicular variant of PTC, and in 1 with the prevalent trabecular pattern–type of architecture designated as “others”; BRAF VK600-1E was found in only 2 patients, 1 with follicular variant PTC and 1 with trabecular variant PTC (Figure 3).

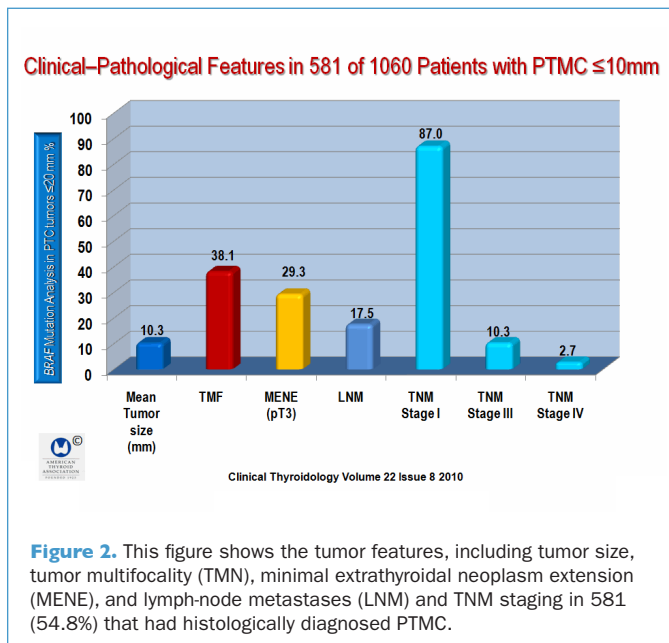
A total of 13 patients with BRAF K601E, BRAF VK600-1E, and BRAF deletion mutations were excluded.

**Univariate Analysis Odds Ratio (Figure 3B)**

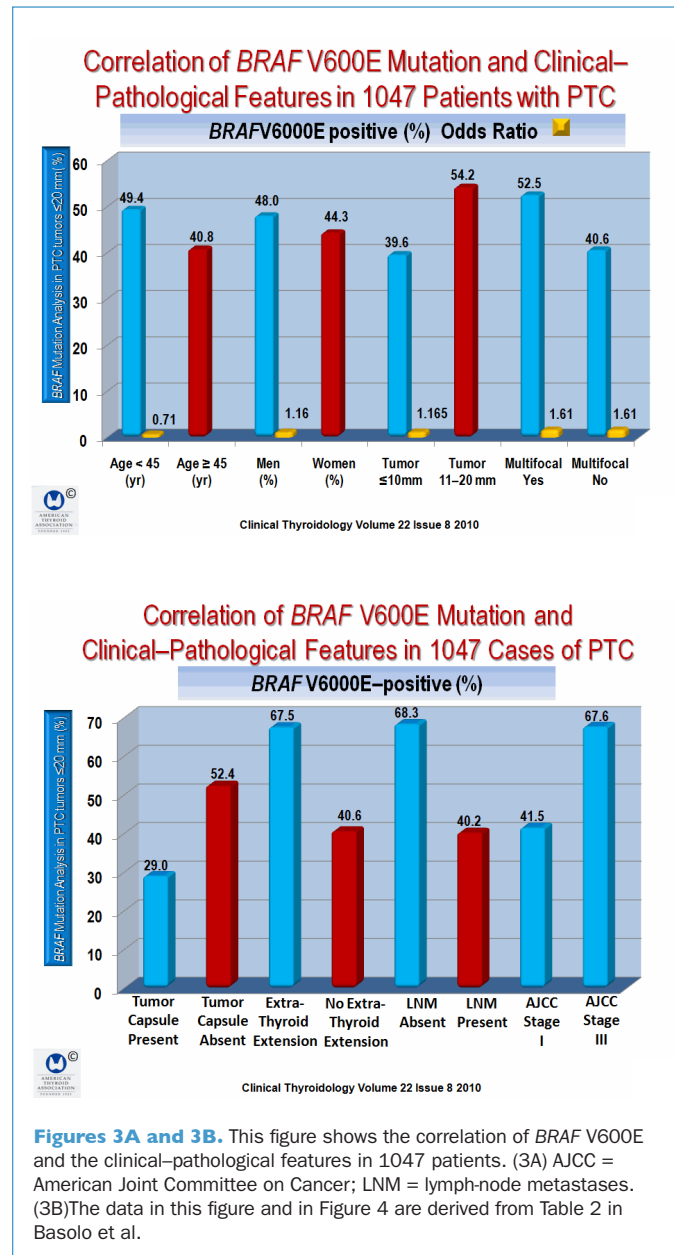
In univariate analysis that considered the clinical risk factors of patient age and sex, only age at diagnosis was significantly

associated with the presence of a BRAF mutation. The percentage of BRAF among patients younger than 45 years of age was 49.4%, while the percentage of BRAF positivity was 40.8% in patients 45 years of age or older (P = 0.006). BRAF mutations were significantly associated with tumor size (P = 0.0001), multifocality (P<0.0001), absence of tumor capsule (P<0.0001), extrathyroidal extension (P<0.0001), and presence of lymph-node metastases (P<0.001). Also, patients with BRAF mutations more frequently had stage III or IV as compared with stage I tumors (67.6 vs. 4.5%, P<0.0001) (Figure 3B).

The association of BRAF mutation and the clinical–pathological features expressed as an odds ratio (OR) ranged from 0.71 for age at diagnosis to 3.74 for the presence of extrathyroidal extension. Similar results were obtained only for tumors <1 cm, with the exception of tumor multifocality (Figure 3B).



**Figure 2.** This figure shows the tumor features, including tumor size, tumor multifocality (TMN), minimal extrathyroidal neoplasm extension (MENE), and lymph-node metastases (LNM) and TNM staging in 581 (54.8%) that had histologically diagnosed PTMC.



**Figures 3A and 3B.** This figure shows the correlation of BRAF V600E and the clinical–pathological features in 1047 patients. (3A) AJCC = American Joint Committee on Cancer; LNM = lymph-node metastases. (3B) The data in this figure and in Figure 4 are derived from Table 2 in Basolo et al.

**Multivariate Analysis (Figures 4 and 5)**

Multivariate analysis identified the following independent variables: age at the time of diagnosis, tumor size, and tumor multifocality. Absence of tumor capsule, extrathyroidal extension, lymph-node metastases, and AJCC stage were all significantly associated with a high frequency of *BRAF* mutations. When only the 723 patients with nonencapsulated tumors were considered, all clinical–pathological features increased their statistical association with *BRAF* mutations ( $P < 0.001$ ) in both the univariate and multivariate analyses.

**Association between *BRAF* V600E and Tumor Invasion (Figures 4 and 5)**

PTCs were subdivided into four associations: group A comprised 324 totally encapsulate tumors; group B had 305 nonencapsulated tumors without thyroid capsule invasion; group C had 107 tumors with thyroid capsular invasion; and group D had 311 tumors with extrathyroidal invasion.

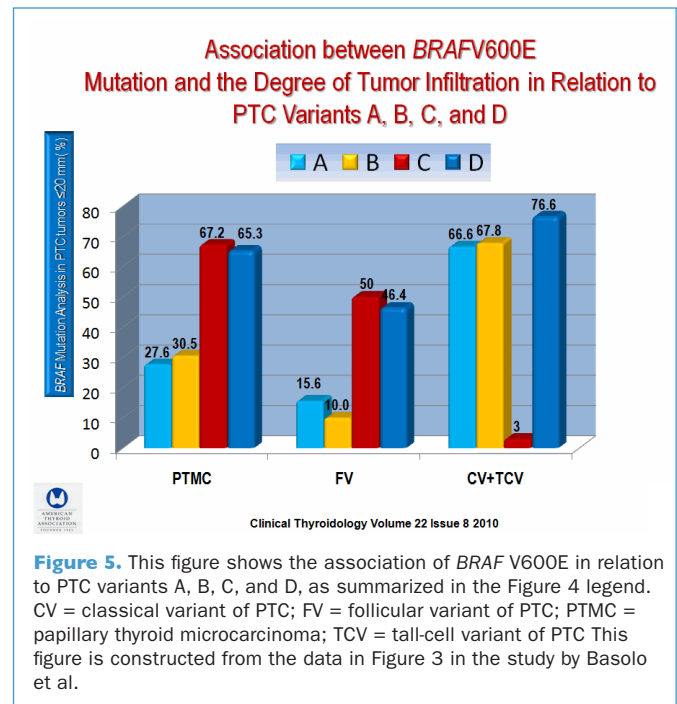
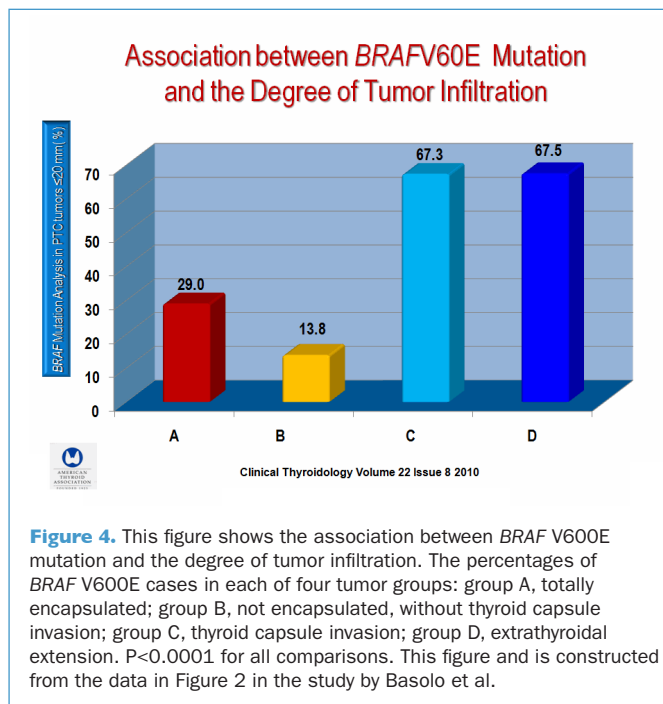
The percentages of *BRAF* V600E were as follows: group A, 94 Of 324 tumors (29%); group B, 97 of 305 (31.8%) tumors; group C, 72 of 107 (67.3%); and group D, 210 of 311 tumors (67.5%). The percentage of *BRAF* V600E cases for the group of totally encapsulated tumors and the value of group B did not differ significantly (29 vs. 31.8%,  $P > 0.005$ ). However, the

percentage of *BRAF* V600E cases was significantly higher for group C than for group B (67.3 vs. 31.8%,  $P < 0.0001$ ). Also, a statistically significant difference was found between group B and group D (31.8 vs. 67.5%,  $P < 0.0001$ , but there was no significant difference between PTCs invading the thyroid capsule (group C) and the tumors with extrathyroidal extension (group D; 67.3 vs. 67.5%;  $P > 0.05$ ) The correlation between *BRAF* V600E and the degree of tumor infiltration was present in different histologic variants. There was no significant difference between encapsulated tumors (Figures 4 and 5).

Verification of the correlation of *BRAF* V600E and the degree of tumor infiltration was found in different histological variants of PTC, including *BRAF* mutated PTMC, follicular and classical as well as tall cell PTC variants, taking into account the degree of tumor infiltration

**CONCLUSION**

There were no significant differences between totally encapsulated tumors and tumors invading only the surrounding parenchymal tissue, and *BRAF* was significantly more common in PTCs invading the thyroid capsule than in tumors that were not invading the thyroid capsule ( $P < 0.0001$ ), and there was no statistically significant difference in *BRAF* alterations between pT1 tumors with thyroid capsule invasion and pT3 tumors.



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**COMMENTARY**

Although the large majority of small papillary thyroid cancers generally have a favorable prognosis, the prognostic features of these small tumors have until now not been fully defined. A PTC  $\leq 20$  mm can be staged as pT1 or pT3, but the designation of pT3 means that the tumor is infiltrating beyond the thyroid capsule and perithyroidal soft tissues. Still, a PTC  $\leq 20$  mm is considered to be low-risk when the tumor is confined to the thyroid gland (pT1), although PTCs of the same size but with extrathyroidal extension (pT3) have a high potential for tumor persistence or recurrence, thus requiring more aggressive therapy (1;2). The authors of this study make the point that evaluating the degree of tumor infiltration beyond the thyroid capsule by histologic examination is a unique way to label a PTC  $\leq 20$  mm as pT1 or pT3, thus making a dividing line between low- and high-risk PTCs.

The authors examined *BRAF* mutation as a means of facilitating the differentiation between pT1 and pT3 tumors. *BRAF* mutation has been investigated by many studies that showed that this mutation is related to poor clinical–pathological parameters (3). However the correlation of patient age and the presence of *BRAF* mutations has been the subject of controversy (4). However, Basolo et al. found a correlation between age at the time of diagnosis and the presence of *BRAF* mutations in almost half the patients (49.4%), with only 41% of patients 45 years of age or younger ( $P = 0.006$ ), which is in accord with the study by Lee et al. (3).

In the study by Basolo et al., multivariate analysis confirmed the association of age at diagnosis, tumor size, and multifocality, absence of tumor capsule, extrathyroidal extension, lymph-node metastases, and AJCC stage. As a result, the authors focused their study on the association of *BRAF* mutations with the degree of tumor infiltration. The study found that tumors classified as pT1 were significantly less likely to have *BRAF* mutations (40.6%), as compared with tumors classified as pT3, which had a 67.5% rate of *BRAF* mutations.

The tumors in this study were subdivided into four groups (Figure 4) to take into account the degree of tumor infiltration in each of the groups, which yielded the following results. There was no significant difference between totally encapsulated tumors and tumors invading only the surrounding parenchymal tissue (Figure 4). Also, *BRAF* mutations were significantly more common (67.3%) in PTCs invading the thyroid capsule than in tumors that were not invading the thyroid capsule (Figure 5) ( $P < 0.1000$ ). And there was no statistically significant difference in *BRAF* mutations between pT1 tumors with thyroid capsular invasion (67.3%) and pT3 tumors (67.5%).

Basolo et al made several important conclusions. The presence of *BRAF* mutations in pT1 tumors invading the thyroid capsule should be considered a marker of an unfavorable prognosis, and that *BRAF* V600E status of a tumor could be useful, even for pT1 tumors, to improve the risk stratification and management of PTCs, especially for PTMC tumors and small tumors with follicular variants of PTC.

This study and the study by Durante et al. provide a new look on the clinical assessment and treatment of papillary thyroid microcarcinomas that is likely to change the management of these common tumors. Both studies are likely to challenge the current ATA guideline (5) that recommends that thyroid lobectomy alone may be sufficient treatment for small ( $< 1$  cm), low-risk, unifocal, intrathyroidal papillary carcinomas in the absence of prior head and neck irradiation or radiologically or clinically involved cervical lymph-node metastases. (Recommendation rating: A)

Both this and the Durante study should be read in their entirety to fully understand the scope of these studies that are likely to set the pace for the management of papillary thyroid microcarcinomas.

— Ernest L. Mazzaferri, MD, MACP

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# Lemon juice stimulation of salivary-gland flow increases the absorbed doses of $^{131}\text{I}$ to the salivary glands after the administration of $^{131}\text{I}$

Jentzen W, Balschuweit D, Schmitz J, Freudenberg L, Eising E, Hilbel T, Bockisch A, Stahl A. The influence of saliva flow stimulation on the absorbed radiation dose to the salivary glands during radioiodine therapy of thyroid cancer using ( $^{124}\text{I}$ ) PET/(CT) imaging. *Eur J Nucl Med Mol Imaging* 2010. July 13 [Epub ahead of print.] 10.1007/s00259-010-1532-z [doi]

## SUMMARY

### BACKGROUND

Radioiodine therapy with  $^{131}\text{I}$  is taken up by target tissues, including tumors and thyroid remnants, but is also taken up by the submandibular and parotid salivary glands. As a result, high levels of  $^{131}\text{I}$  therapy may be associated with salivary-gland damage, leading to long-term side effects, including sialadenitis, which occurs in about 30% of patients, and xerostomia, which has an incidence of about 10 to 20%. Several radioprotective procedures have been proposed for this problem, but perhaps the most common approach for this problem is the use of sialogogic agents such as lemon juice to increase saliva flow by stimulating salivary glands. Although several studies suggest that sucking or chewing on lemon slices during  $^{131}\text{I}$  therapy decreases the effect of radiation on the salivary glands, a recent prospective study sparked controversy about this practice by finding that sucking lemon candies induced a significant increase in the frequency of sialadenitis and xerostomia, as compared with a 24-hour delayed stimulation. Moreover, the current ATA guidelines recommend that there is no objective proof that stimulation with lemon juice prevents radiation damage to the salivary glands, whereas the European Association of Nuclear Medicine recommended this practice in their recent guidelines. The aim of the present study was to assess the effect of chewing lemon slices on the absorbed radiation doses to the salivary glands.

### METHODS AND STUDY SUBJECTS

#### Study Subjects

The study subjects were 10 patients referred to the author's clinic to receive an  $^{124}\text{I}$  positron-emission tomographic/computed tomographic (PET/CT) scan after having been treated with thyroidectomy for differentiated thyroid cancer. Excluded from the study were patients with a history of salivary gland disease or treatment with external-beam radiotherapy to the neck or head or who were taking medication that would affect salivary flow such as anticholinergic, beta-blockers, or antidepressants. Prior to their first  $^{131}\text{I}$  treatment, the serum thyrotropin (TSH) levels were stimulated by thyroid hormone withdrawal or by recombinant human TSH (rhTSH) injections. Before imaging, TSH levels were  $\geq 25$   $\mu\text{l/ml}$  and the mean ( $\pm$ SD)  $^{124}\text{I}$  activity was  $26.5 \pm 3.3$  MBq (range, 22.6 to 30.5).

#### Patient Study Protocols

The study comprised a stimulation and a nonstimulation protocol. Ten patients in the stimulation group chewed lemon slices for approximately 20 minutes after ingesting a capsule containing  $^{124}\text{I}$ . This group continued chewing lemon slices over the first day. Approximately 10 minutes elapsed between stimulation and emission scans. The patients ate lunch after 2 to 4 hours, a

snack after 6 to 7 hours, and dinner 9 to 10 hours after  $^{124}\text{I}$  administration. The patients in the nonstimulation group did not chew lemon slices during the  $^{124}\text{I}$  pretherapy procedure and were not permitted to have food or drink until after completion of the last PET scan on the first day, approximately 4 hours after  $^{124}\text{I}$  administration. Thereafter, the patients ate a snack and had dinner at about the same time as the stimulation group, and the food composition was almost identical in the two study groups.

#### Salivary-Gland Dosimetry Protocol

Patients had a series of six stand-alone scans (Exact HR+ PET) and one PET/CT scan. Stand-alone PET imaging was performed at approximately 0.5, 1, 2, 4, 48, and  $\geq 96$  hours after oral intake of a capsule containing  $^{124}\text{I}$ NaI. Imaging at approximately 24 hours was performed using the PET/CT system. On the stand-alone PET system, emission and transmission times per bed position were 300 seconds and 120 seconds, respectively. The PET/CT scans also lasted 300 seconds, and the CT acquisitions were as follows: 130 m as effective tube current, 130 kVp tube voltage, 5 mm slice width, 0.08 second rotation time, and a prerotation table speed of 8 mm.

#### Blood-Count Protocol

The radioiodine kinetics in blood were determined by measuring the activity concentration for each patient's blood samples taken at different time points following  $^{124}\text{I}$  administration. A 2-ml blood sample was collected at approximately 2, 4, 24, 48, and  $\geq 96$  hours. After the last blood sample, the total blood mass of each sample was measured and the sample activity was counted in a calibrated gamma counter.

#### Imaging Reconstruction

The protocol for imaging reconstruction is carefully summarized in the article and is available to physicians who require these details.

#### Imaging Coregistration, Salivary-Gland Volume, and Isovolume $^{124}\text{I}$ Recovery

Images were coregistered across time by matching the transmission images at each time point with the CT portion of the PET/CT image. The resulting transformation parameters were applied to the emission image for each time point. Salivary-gland volumes were determined from the CT images. The volumes of interest were projected onto the coregistered emission image for each patient and used to determine the ratios of total activity within the gland to the gland volume, and these ratios are referred to as the image isovolume activity concentrations, which were then corrected for the most dominant partial-volume effect and the less-dominant prompt gamma coincidence effect using the  $^{124}\text{I}$  recovery coefficients.

**RESULTS**

**Organ Absorbed Doses per <sup>131</sup>I Activity (ODpAs) (Figure 1)**

The characteristics of the patients in the nonstimulation and stimulation groups are shown in Figure 1. Within-group statistical analysis revealed no significant differences between the mean ODpAs of the submandibular and parotid glands ( $P > 0.32$ ). More importantly, the intergroup comparisons revealed that the ODpAs average over both gland types was reduced by 28% in the nonstimulation group (0.23 Gy/GBq) as compared with the stimulation group (0.32 Gy/GBq), which was statistically significant ( $P = 0.01$ ). An even lower P value of 0.001 was obtained in an intergroup comparison of ODpA in only patients stimulated by thyroid-hormone withdrawal (eight hypothyroid patients in the stimulation group and nine in the nonstimulation group).

Lastly, separate intergroup comparisons for the parotid or submandibular glands exhibited a significant difference in ODpA between the groups for the parotid gland ( $P = 0.23$ ) but not for the submandibular gland ( $P = 0.23$ ) (Figure 1).

The salivary-gland absorbed dose was split into two parts:  $ODpA = ODpA_{\leq 24h} + ODpA_{>24h}$ . The first part gives the absorbed dose up to 24 hours after <sup>131</sup>I administration, and the second part is the dose absorbed between 24 and 96 hours. From the average gland <sup>124</sup>I uptake, the ratio of the  $ODpA_{\leq 24h}$  was approximately 70%.

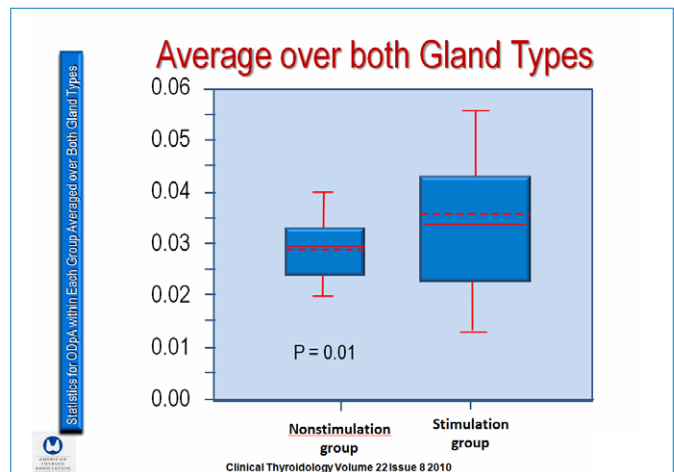
The TSH level in the nonstimulation group was lower than the TSH level in the stimulation group (Figure 1), but this did not reach statistical significance. The relationship between ODpAs averaged over the right and left glands as a function of the TSH levels in each patient in the stimulation and nonstimulation groups were not significant.

**Residence Time and Salivary-Gland Volume (Figures 2 to 4)**

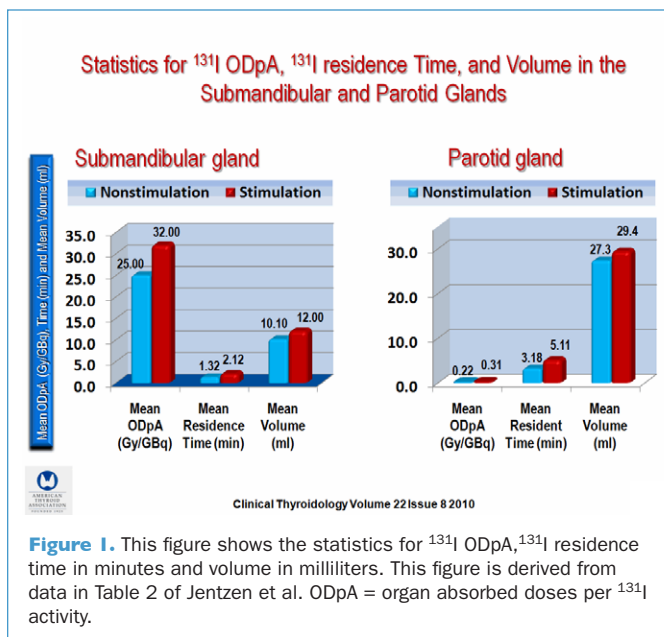
Figure 2 also provides the residence time and the salivary-gland-volume statistics. Within-group comparisons showed that the mean residence time was significantly different between

the submandibular and the parotid glands ( $P < 0.001$ ), which was attributed to the difference in gland volume of the two gland types. An intergroup comparison showed that the mean residence times were about 38% lower in the nonstimulation group than in the stimulation group; the differences were not significant ( $P \geq 0.07$ ). Moreover, no significant differences were found between salivary-gland volumes in the stimulation group and those in the nonstimulation group ( $P \geq 0.31$ ).

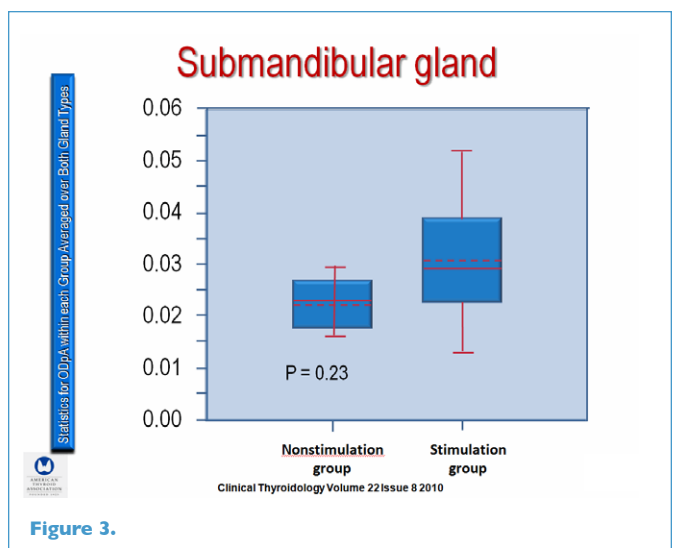
The lemon-juice-induced stimulation shortly after radioiodine administration led to an overall increase in the initial uptake by the salivary glands; however, stimulation may not have accelerated the radioiodine clearance, which was almost identical to the value in the nonstimulation group. The average blood <sup>124</sup>I uptake was clearly similar in the stimulation and the nonstimulation groups. The curve-fitting parameters show that the difference in ODpA between the stimulation and nonstimulation groups was correlated with a higher extrapolated uptake value; thus, the lemon-juice-



**Figures 2 to 4.** These figures show the ODpA distributions within each group averaged for both gland types and separately for the submandibular glands and the parotid glands. The boxes represent the boundary of the 25th and 75th percentiles, and the solid lines and dashed lines indicated the median and mean values, respectively. The figures are modified from Figure 1 and 2 of Jentzen et al.



**Figure 1.** This figure shows the statistics for <sup>131</sup>I ODpA, <sup>131</sup>I residence time in minutes and volume in milliliters. This figure is derived from data in Table 2 of Jentzen et al. ODpA = organ absorbed doses per <sup>131</sup>I activity.



**Figure 3.**

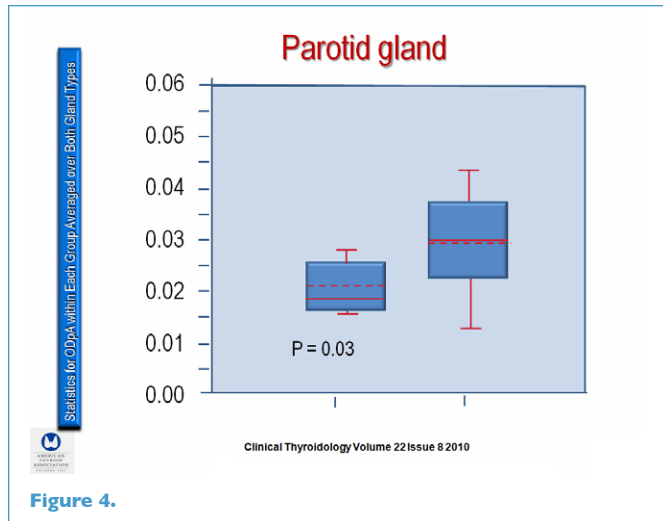


Figure 4.

induced stimulation shortly after radioiodine administration led to an overall increase in the initial uptake by the salivary glands; however, stimulation may not have accelerated the radioiodine clearance (Figures 2 to 4).

**CONCLUSION**

This is the first prospective study to examine the influence of saliva flow stimulation on the absorbed dose to the major salivary glands in radioiodine therapy of differentiated thyroid cancer. The use of <sup>124</sup>I PET/CT permitted an estimate of the absorbed dose in the salivary glands of patients who either chewed lemon slices (n = 10) or did not (n = 10). <sup>124</sup>I PET/CT salivary-gland dosimetry indicated that saliva flow stimulation after <sup>131</sup>I administration may increase the ODpA to salivary glands.

**COMMENTARY**

This is a novel study that is the first prospective study to examine the influence of stimulation of saliva flow on the absorbed radiation dose to the major salivary glands in the course of <sup>131</sup>I therapy. <sup>124</sup>I PET/CT was used to estimate the absorbed dose in the salivary glands of patients who either did or did not chew lemon slices. There were 10 patients in each group. Contrary to the usual <sup>131</sup>I therapy protocol, the patients were not stimulated with lemon juice during the pretherapy procedure and neither ate nor drank until after completion of the last PET scan on the first day. The study showed that the mean organ absorbed doses per <sup>131</sup>I activity (ODpA) for the submandibular glands was not significantly different from that for the parotid glands. The study found that the nonstimulation group averaged over the mean ODpA in the nonstimulation group averaged over both the parotid and submandibular glands was reduced by 28% as compared with the mean ODpA in the stimulation group (P = 0.01). The mean ODpA reductions in the nonstimulation group were statistically significant for the parotid but not the submandibular glands (P = 0.23), instead showing that the <sup>131</sup>I therapy increased the absorbed doses to the salivary glands.

The authors make the point that if lemon-juice-induced stimulation during the course of <sup>131</sup>I therapy is associated with a higher ODpA, then salivary-gland dysfunction would be expected to be higher in patients in the stimulation group than those in the nonstimulation group.

In a study by Nakada et al. (1), 116 consecutive patients were asked to suck one or two lemon candies every 2 to 3 hours in the daytime of the first 5 days after <sup>131</sup>I therapy (group A). Lemon candy sucking was started within 1 hour after <sup>131</sup>I ingestion. In addition, 139 consecutive patients (group B) were asked to suck lemon

candies in a manner similar to that of group A. In the group B, lemon candies were withheld until 24 hours after the ingestion of radioiodine. The onset of salivary-gland side effects was monitored during hospital admission and regular follow-up on the basis of interviews with patients, a visual analog scale, and salivary gland scintigraphy using (99m) Tc-pertechnetate. When a patient showed a persistent (>4 months) dry mouth associated with a nonfunctioning pattern on salivary-gland scintigraphy, a diagnosis of xerostomia was established. The incidence of sialadenitis, hypogeusia or taste loss, and dry mouth with or without repeated sialadenitis in group A versus group B were 63.8% versus 36.8% (P<0.001), 39.0% versus 25.6% (P<0.01), and 23.8% versus 11.2% (P<0.005), respectively. Permanent xerostomia occurred in 15 patients in group A (14.3%) and 7 patients in group B (5.6%) (P<0.05). In both groups, bilateral involvement of the parotid gland was the most frequently seen and was followed by bilateral involvement of the submandibular gland. The authors thus concluded that an early start of sucking lemon candy may induce a significant increase in salivary-gland damage.

Jentzen et al. point out that, on the one hand, sucking lemon candies increases blood flow to the salivary glands, which may lead to higher <sup>131</sup>I uptake; whereas, the increased uptake could be compensated only to some extent by increased salivary flow. This phenomenon was referred to as a rebound effect by Van Nostrand et al. (2).

Although the studies by Nakada et al. and Jentzen et al are quite different, together they reach the firm conclusion that sucking lemon sialagogues should not be done during <sup>131</sup>I therapy. Jentzen et al. suggest that further studies should focus on alternative strategies to prevent <sup>131</sup>I-induced salivary-gland damage.

— Ernest L. Mazzaferri, MD, MACP

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## Neck ultrasound and Tg levels but not a diagnostic $^{131}\text{I}$ scans are useful tools during follow-up of patients with persistent $^{131}\text{I}$ neck uptake on diagnostic whole-body $^{131}\text{I}$ scans

Kim EY, Kim WG, Kim WB, Kim TY, Ryu JS, Gong G, Yoon JH, Hong SJ, Lee JH, Baek JH, Shong YK. Clinical outcomes of persistent radioiodine uptake in the neck shown by diagnostic whole body scan in patients with differentiated thyroid carcinoma after initial surgery and remnant ablation. *Clin Endocrinol (Oxf)* 2010;73:257-63.

### SUMMARY

#### BACKGROUND

Patients with differentiated thyroid cancer (DTC) usually are initially treated with total or near-total thyroidectomy and radioactive iodine ( $^{131}\text{I}$ ) for thyroid remnant ablation. This is a retrospective study that is focused on the subset of patients who have residual uptake of  $^{131}\text{I}$  following their preliminary treatment. The aim of the study is to assess the efficacy of a second remnant ablation in this situation.

#### PATIENTS AND METHODS

##### Patients

The study subjects were 874 consecutive patients with DTC who were treated from January 2000 through January 2004 with total thyroidectomy followed by immediate  $^{131}\text{I}$  remnant ablation, according to the protocol established by the Endocrinology Department of the Asan Medical Center in Seoul, Korea. Excluded from the study were patients with distant metastases or with  $^{131}\text{I}$  uptake (RAIU) outside the thyroid bed on the initial posttherapy whole-body scan (RxWBS), and patients with serum thyroglobulin (Tg) antibody (TgAb) concentrations  $>100$  U/ml. One year after remnant ablation, a diagnostic whole-body  $^{131}\text{I}$  scan (RxWBS) was performed in 782 of the 874 (90%) patients who had serum TSH concentrations  $>30$  mIU/L after thyroid hormone withdrawal (THW). Ablation activities were 30, 80, and 150 mCi (1.11, 2.96, and 5.55 GBq, respectively), depending on the tumor size and the presence of extrathyroidal tumor extension and lymph-node metastases. The 572 patients who received high  $^{131}\text{I}$  activities (150 mCi) were included in the retrospective study. Excluded were patients who received 30 or 80 mCi.

##### Initial Treatment and Follow-up with Diagnostic Whole-Body Scan

Patients had THW during the 5 to 6 weeks after initial surgery; all received 150 mCi of  $^{131}\text{I}$ , followed by RxWBS 2 to 7 days after the administration of  $^{131}\text{I}$ . Suppressive treatment with thyroid hormone was started 2 days after the administration of  $^{131}\text{I}$  to decrease serum thyrotropin (TSH) levels in patients without clinical thyrotoxicosis. After 4 weeks of THW with a TSH of  $>30$  mIU/L, a diagnostic whole-body scan (DxWBS) was performed with 4 mCi of  $^{131}\text{I}$ ; this was usually 12 months after remnant ablation and when serum Tg and TgAb levels were measured. A successful remnant ablation was defined as the absence of abnormal  $^{131}\text{I}$  uptake in the DxWBS.

##### Definitions of Recurrence and Persistent Disease

Tumor recurrence was defined as the reappearance of tumor after complete remnant ablation, which was confirmed by cytologic or histopathological examination or persistent extracervical uptake on RxWBS after the administration of 150 mCi of  $^{131}\text{I}$ .

##### Measurements of Tg, TgAb, and TSH

These laboratory studies were performed at the time of DxWBS or during THW for the administration of  $^{131}\text{I}$  for remnant ablation. The stimulated Tg (sTg) at the initial DxWBS measured 1 year after initial treatment was sTg1; sTg2 was the sTg measured 2 years after the initial therapy.

##### Whole-Body Scanning and Other Imaging Studies

Patients with distant metastases or persistent uptake in the neck found 1 year after remnant ablation on a THW-stimulated 4 mCi  $^{131}\text{I}$  DxWBS had DxWBS every year thereafter.

Patients with high-risk tumors had periodic DxWBS with Tg measurement after THW. RxWBS was performed 2 to 7 days after the administration of 150 mCi of  $^{131}\text{I}$ . All patients were advised to restrict dietary iodine intake for at least 15 days before  $^{131}\text{I}$  therapy. Patients with low-risk tumors had yearly neck ultrasonography and Tg measurements during THW.

##### Neck Ultrasonography

Ultrasound examinations of the neck were performed by two experienced radiologists. Using high-resolution phase-array linear transducers, the thyroid bed was scanned for the presence of hypoechoic abnormalities with marginal spiculation, microcalcification, or nodules whose appearance was taller than it was wide, suggesting locoregional recurrence. The lateral neck was evaluated for lymph-node metastases, which were determined by calcification, cystic changes, and cortical hyperechogenicity, with or without a round configuration; these were further studied by ultrasound-guided fine-needle aspiration biopsy.

##### Subsequent Management and Follow-up of Patients with Persistent RAIU on the First DxWBS

Patients with undetectable sTg and negative neck ultrasonography were observed without further therapy. Patients with limited intrathyroidal disease without regional lymph-node metastases at surgery (very-low-risk group) did not undergo a second ablation, if neck ultrasonography was negative, even if their serum sTg concentrations were mildly elevated (to 2.2  $\mu\text{g}/\text{L}$  in one patient and 8.5  $\mu\text{g}/\text{L}$  in another).

**RESULTS**

**Patient Characteristics (Figure 1)**

The study subjects comprise 572 patients, 70 men (12%) and 502 women (88%), mean (±SD) age 46.7±12.4 (range, 9.7 to 79.4). Of this group, 550 (96%) patients had conventional papillary thyroid cancer (PTC), 14 (2%) had follicular variant PTC, and 8 (1.4%), and 14 (2.4%) had Hürthle-cell carcinomas. The mean tumor size was 2.1±1.3 cm, and the tumors that were multifocal (54.5%), had extrathyroidal extensions (79.4%), and lymph-node metastases (64.9%), although none had evidence of distant metastases at the time of entry into the study. Of these 572 patients, 258 (45%) had tumor–node–metastasis (TNM) stage I, 8 (1.4%) had stage II, 262 had stage III, and 44 had stage IV-A.

**Clinicopathological Factors Related to Persistent Uptake in the Neck at DxWBS**

A total of 25 of the 572 patients (4.4%) had persistent RAIU in the neck on DxWBS. Among this group of 25, there were no differences in age (P = 0.19), sex (P = 0.53), tumor size (P = 0.84), multifocality (P = 0.31), extrathyroidal extension (P = 0.32), cervical-lymph-node metastases (P = 0.1) comparing the positive and negative remnant-uptake groups.

**Association of Persistent Disease with Persistent DxWBS Uptake in the Neck (Figure 2)**

Of the 25 patients in the remnant-positive group, 5 (20%) had recurrent or persistent disease after a median follow-up of 65.7 months (range, 7.5 to 118.5), as compared with 67 of the 547 patients (12%) in the remnant-negative group. There was no significance in disease-free survival in the two groups (P = 0.169).

Univariate analysis found that the clinicopathological factors associated with recurrent or persistent disease were sex (hazard ratio [HR], 2.60; P = 0.002), tumor multifocality (HR, 2.12; P = 0.002), and cervical lymph-node metastases (N1a; HR, 2.44; P < 0.001; and N1b; HR, 4.31; P < 0.001), without persistent RAIU in the neck on DxWBS (HR, 1.87; P = 0.216) (Figure 2).

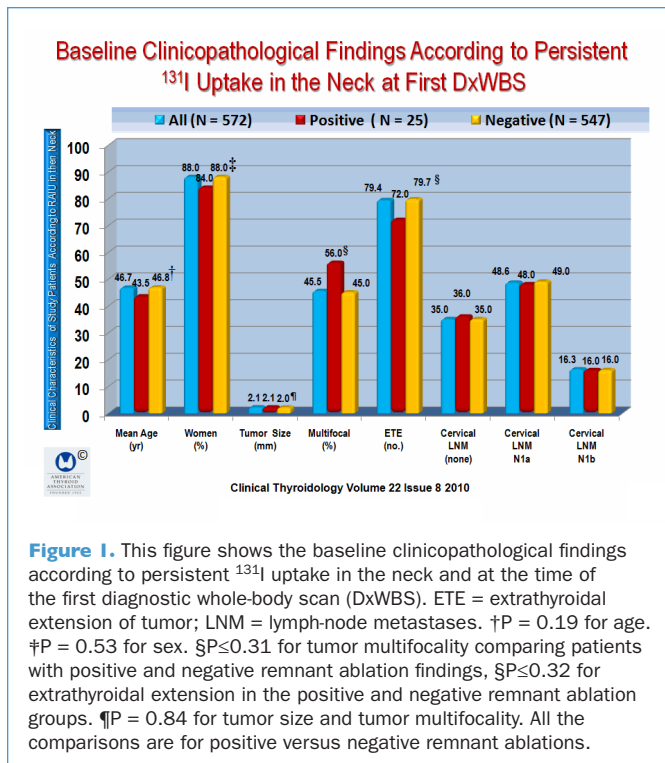
Multivariate analysis found that sex (HR, 2.63), tumor multifocality (HR, 2.01; P = 0.004), and cervical-lymph-node metastases N1a (HR, 2.29; P < 0.001) and N1b (HR, 3.84; P < 0.001) each had an independent association with persistent disease.

At the time of the first DxWBS, all of the patients who had reoperation had cervical-lymph-node metastases on neck ultrasonography, and sTg concentrations >2 µg/L; whereas 6 patients in the second ablation group had detectable serum sTg, and all of the patients in the observational group had negative ultrasonography and only 2 had undetectable serum sTg levels.

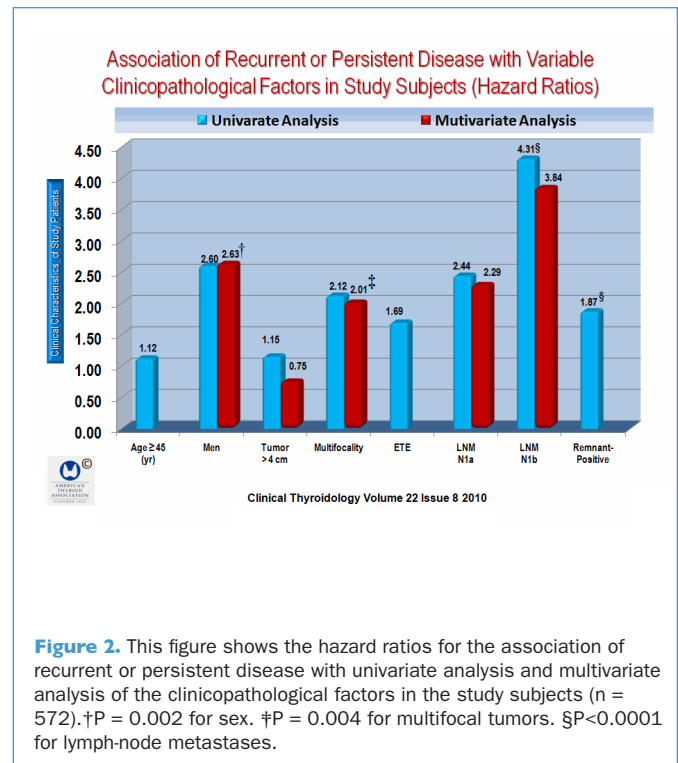
At the time of Tg measurements, TgAb was not detected in any patients, and TSH levels were >30 mIU/L. In the second ablation group, sTg levels decreased and became undetectable during the follow-up in all but one patient, whereas the observation group had sTg concentrations that spontaneously decreased during follow-up and the TSH had undetectable sTg at the time of the final evaluation.

**CONCLUSION**

Neck ultrasound and Tg levels but not diagnostic <sup>131</sup>I scans are useful tools during the follow-up of patients with persistent <sup>131</sup>I neck uptake on diagnostic whole-body <sup>131</sup>I scans.



**Figure 1.** This figure shows the baseline clinicopathological findings according to persistent <sup>131</sup>I uptake in the neck and at the time of the first diagnostic whole-body scan (DxWBS). ETE = extrathyroidal extension of tumor; LNM = lymph-node metastases. †P = 0.19 for age. ‡P = 0.53 for sex. §P ≤ 0.31 for tumor multifocality comparing patients with positive and negative remnant ablation findings, ¶P ≤ 0.32 for extrathyroidal extension in the positive and negative remnant ablation groups. ¶P = 0.84 for tumor size and tumor multifocality. All the comparisons are for positive versus negative remnant ablations.



**Figure 2.** This figure shows the hazard ratios for the association of recurrent or persistent disease with univariate analysis and multivariate analysis of the clinicopathological factors in the study subjects (n = 572). †P = 0.002 for sex. ‡P = 0.004 for multifocal tumors. §P < 0.0001 for lymph-node metastases.

**COMMENTARY**

Although the 25 patients with persistent <sup>131</sup>I uptake in the neck were evaluated for persistent disease, neck ultrasonography and other imaging methods showed that only five patients had tumor in cervical-lymph-node compartments, all of which appeared to be cured by surgery, confirmed by negative serum sTg levels and negative neck ultrasonography during follow-up after the second surgery. Seven patients had a second <sup>131</sup>I ablation and all have remained free of disease, with absence of neck RAIU 1 year after the second ablation; 2 other patients with persistent neck uptake even after a second ablation had negative ultrasound findings. All 13 patients in the observation group were disease-free during the observation period, during which 10 had second DxWBS 12 months later. In 5 of these patients, neck uptake vanished spontaneously, although a third DxWBS was not performed.

Perhaps one of the more important observations was a 50% spontaneous remission in patients with no ultrasound abnormalities and undetectable sTg or who were at very low risk. The authors suggest that as no patient in the observation group had recurrence disease, a second <sup>131</sup>I ablation may not be necessary in low-risk patients with persistent neck uptake, negative neck ultrasonography, despite the presence of mildly elevated serum Tg levels.

The authors concluded that success of remnant ablation was not an independent risk factor predicting recurrence in low-risk patients with DTC.

This study is not dissimilar to a study by Al-Saif et al. (1) of 95 consecutive patients with recurrent or persistent PTC in the neck, all of whom had previous thyroidectomy with or without cervical-lymph-node dissection and <sup>131</sup>I therapy. A total of 25 patients with TgAb were excluded from the study. The main outcome was complete remission, defined as undetectable TSH-

stimulated serum Tg with no imaging evidence of disease. A total of 107 lymphadenectomies were performed in 70 patients and remission was initially achieved in 12 (17%). Of the 58 patients with detectable postoperative Tg, 28 had a second reoperation, and remission was achieved in 5 (18%), 7 had a third reoperation, and none achieved remission. No patient achieving a remission had a recurrence after a mean follow-up of 60 months. In addition, two more patients achieved remission during a long-term follow-up without further intervention.

In total, 19 patients (27%) achieved remission and 32 (46%) achieved a TSH-stimulated Tg <2.0 ng/ml. Patients who did not achieve a remission had a significant reduction in Tg after the first (P<0.001) and second (P = 0.008) operations. No patient had detectable distant metastases or died from PTC. The main finding was that surgical resection of persistent PTC in cervical lymph nodes achieves remission, which was 27% when stringently defined, sometimes requiring several surgeries, and no clinical recurrences occurred during follow-up. In patients who do not achieve remission, Tg levels were significantly reduced. The authors offered the caveat that long-term durability and impact of this intervention will require further investigation.

The ATA guidelines recommend that <sup>131</sup>I when RxWBS is positive for uptake only in the thyroid bed, follow-up should be 6 to 12 months. The algorithm suggests that a positive DxWBS should be considered for <sup>131</sup>I therapy (2).

There is a general consensus that diagnostic whole-body <sup>131</sup>I scans are not routinely recommended for follow-up and TSH-stimulated serum Tg and neck ultrasonography are more likely to identify persistent or recurrent disease. Also, a serum Tg measurement that is rising is much more likely to identify persistent disease, and conversely, a declining serum Tg is a harbinger of successful therapy (3-5).

— Ernest L. Mazzaferri, MD, MACP

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## Thyroid-conserving surgery without TSH suppression may be considered for patients with low-risk PTC to avoid potential adverse effects of TSH suppression

Sugitani I, Fujimoto Y. Does postoperative thyrotropin suppression therapy truly decrease recurrence in papillary thyroid carcinoma? A randomized controlled trial. *J Clin Endocrinol Metab* 2010. jc.2010-0161 [pii];10.1210/jc.2010-0161 [doi]

### SUMMARY

#### BACKGROUND

Differentiated thyroid cancer expresses the thyrotropin (TSH) receptor on the cell membrane and responds to TSH stimulation by increasing the expression of several proteins, including thyroglobulin (Tg) and the sodium-iodide symporter, and also increases the rates of cell growth. It is thus common practice to use supraphysiologic doses of levothyroxine (L-T<sub>4</sub>) to treat patients with differentiated thyroid cancer in an effort to diminish the risk for tumor recurrence. Recommendation 40 of the ATA guidelines suggests initial suppression of TSH to <0.1 mIU/L for high-risk and intermediate-risk patients with differentiated thyroid cancer, which is a B rating.

The study by Sugitani et al. is a single-center, open-label, randomized, controlled trial that tested the hypothesis that disease-free survival (DFS) for patients with papillary thyroid carcinoma (PTC) without TSH suppression is similar to DFS in patients with TSH suppression.

#### SUBJECTS AND METHODS

##### Criteria for Patient Eligibility

All patients who had initial surgery at the Cancer Institute Hospital, a tertiary oncology referral center in Japan, were considered for inclusion in the study. Excluded were any of the following: patients with maximum tumor diameter ≤1 cm (microcarcinoma), patients 80 years of age or older; those with distant metastases, Graves' disease, ischemic heart disease or arrhythmia, or severe osteoporosis; and patients with tumors other than PTC.

##### Methods for Randomization and Intervention

Patients were randomly assigned to receive either L-T<sub>4</sub> therapy postoperatively for TSH suppression (group A) or to have no L-T<sub>4</sub> suppressive therapy (group B). To minimize any imbalance between the two groups, the study subjects were categorized as low- or high-risk PTC according to AMES risk-group classification, comprising age, metastases, tumor extension, and tumor size.

Patients in group A were treated from 1 day after surgery with an initial dose of 100 µg/day of L-T<sub>4</sub> for patients weighing 50 kg, 150 µg/day for those weighing 50 to 70 kg, and 200 µg/day for those weighing ≥70 kg. Blood tests were conducted every 4 weeks, during which L-T<sub>4</sub> doses were adjusted to keep the TSH levels to <0.1 µU/ml. Serum free thyroxine (FT<sub>4</sub>) and free triiodothyronine (FT<sub>3</sub>) were maintained within the normal range (0.5 to 5.0 µU/ml) for patients assigned to group B. Thereafter,

blood tests for TSH, FT<sub>3</sub>, and FT<sub>4</sub> were repeated every 6 months to confirm that the hormone balances were as intended.

During the study period, 61% of all thyroid surgeries were performed by one surgeon or were assisted by the same surgeon. The basic standard for primary surgery was complete resection of the tumor in accordance with the ultrasound findings. When tumor was limited to a single thyroid lobe without clinically evident lymph-node metastases, ipsilateral lobectomy was performed with prophylactic central-compartment lymph-node dissection. Patients with clinically evident lateral lymph-node metastases were treated with modified radical lateral neck dissection. When the primary tumor was invading surrounding organs such as the trachea or esophagus, resection and reconstruction of the involved organs were performed. Patients had total or near-total thyroidectomy only when the cancer extended into the contralateral lobe or when lymph-node metastases were evident bilaterally in the neck. Patients were not treated with <sup>131</sup>I remnant ablation.

##### Outcome Measures and Follow-up

The primary end point of the study was DFS. Every 6 months, patients were evaluated for lymph-node metastases and recurrence in the thyroid bed, which was determined by chest x-ray examination or lung computed tomography (CT) and neck ultrasonography. For the latter, the criteria used to identify lymph-node metastases were a tumor diameter ≥1 cm, clear hypoechoic or inhomogeneous ultrasound pattern, irregular cystic appearance, internal microcalcification, and rounded tumor shape with increased anterior to posterior diameter. Recurrences were confirmed by cytologic or pathological evaluation for cervical lesions but not for distant metastases. TSH-stimulated serum thyroglobulin measurement and <sup>131</sup>I whole-body scans were not used. L-T<sub>4</sub> therapy was discontinued in patients who had symptoms of thyrotoxicosis, cardiovascular disease, including angina or atrial fibrillation, or progressive osteoporosis, defined as a T-score >3.0 standard deviations below the mean for controls.

#### RESULTS

Eligible patients were recruited into the study from January 1996 through February 2005. A total of 441 patients with PTC diagnosed on the basis of preoperative fine-needle aspiration biopsy were randomly assigned to group A (n = 221) or group B (n = 220). Postoperative histologic analysis found that 8 patients did not have PTC and thus were ineligible for the study, leaving 433 study patients for the final analysis; 218 of these patients were assigned to group A for TSH-suppression therapy and 215 to group B for follow-up without TSH suppression.



**Clinical Characteristics of the Patients and Duration of Follow-up**

As of February 2009, the mean ( $\pm$ SD) duration of follow-up was 6.9 $\pm$ 2.9 years (range, 0.5 to 12). Five-year follow-up was completed in 325 patients (75%), and 33 patients (8%) were lost to follow-up but were included in the analysis by censoring these patients at the point of the last follow-up. Another 33 (8%) discontinued the assigned intervention. In group A, TSH suppression was suspended in 12 patients with thyrotoxicosis, 5 with angina or atrial fibrillation, and 6 with osteoporosis.

The clinical characteristics of the patients in each group are summarized in Figure 1. The baseline demographic characteristics were age, sex, extent of thyroidectomy, lymph-node dissection, risk-group distribution, and status of lymph-node metastases, none of which were significantly different between the two study groups.

**The Outcome of Analysis**

The primary analysis was intention to treat, involving all 433 patients. Of this group, 49 (11%) had a recurrence, and 9 (2%) died of PTC. Disease-free 5-year survival, disease-specific 5-year

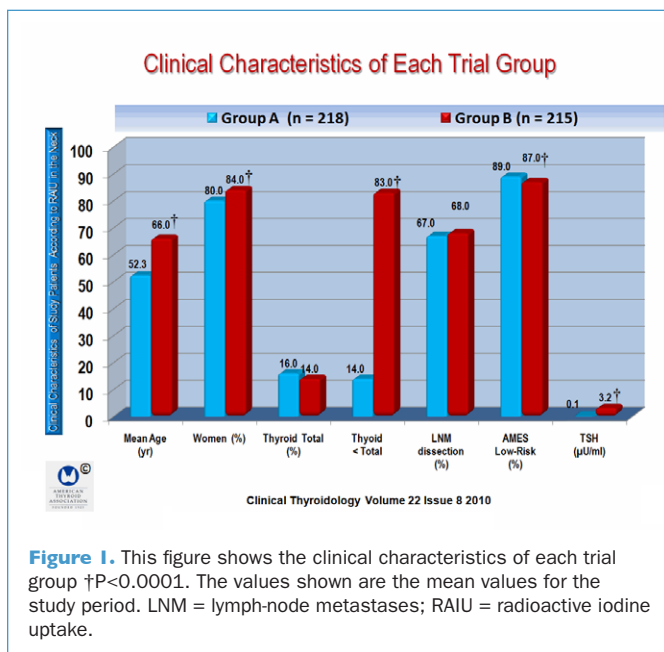
survival, and sites of recurrence were not significantly different in groups A and B (Figure 1). DFS curves for patients with TSH suppression did not differ significantly from those without TSH suppression (Figure 2).

Cox proportional-hazards analysis found that a hazard ratio of 1.27 (95% confidence interval, 0.85 to 1.27), with a margin of 2.12, was required to declare a 10% criterion for noninferiority for DFS in patients without TSH suppression as compared with patients on L-T<sub>4</sub> therapy, and was even less than 1.54, for a 5% criterion for inferiority.

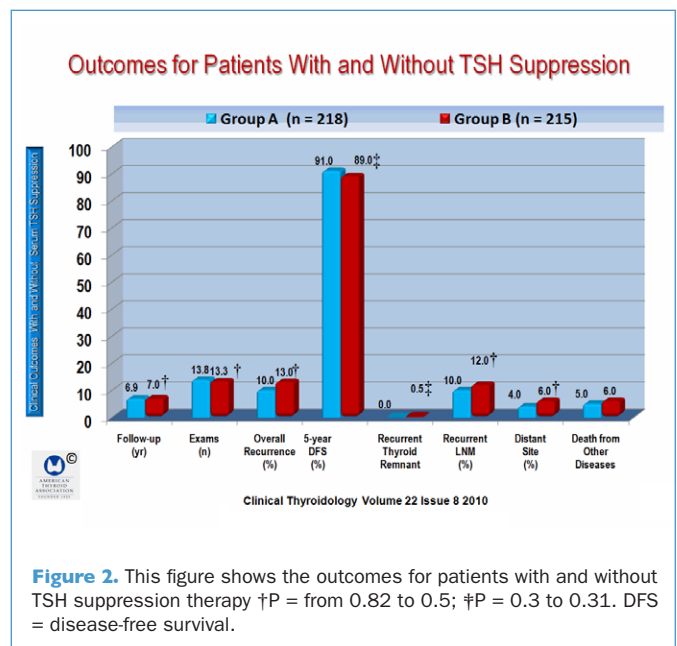
DFS was similar for the two groups in a subset analysis that divided patients into low-risk and high-risk groups according to the AMES risk-group classification.

**CONCLUSION**

The authors of this study concluded that thyroid-conserving surgery without TSH suppression should be considered for patients with low-risk PTC to avoid potential adverse effects of TSH suppression.



**Figure 1.** This figure shows the clinical characteristics of each trial group †P<0.0001. The values shown are the mean values for the study period. LNM = lymph-node metastases; RAIU = radioactive iodine uptake.



**Figure 2.** This figure shows the outcomes for patients with and without TSH suppression therapy †P = from 0.82 to 0.5; †P = 0.3 to 0.31. DFS = disease-free survival.

**COMMENTARY**

This is an interesting study from Japan that reaches conclusions that differ widely from analyses in the United States and Europe. For example, Recommendation 40 of the 2009 ATA guidelines recommend TSH suppression to <0.1 mIU/L for patients with high-risk and intermediate-risk thyroid cancer, while maintenance of the TSH at or slightly below the lower limit of normal (0.1 to 0.5 mIU/L) is appropriate for low-risk patients. Similar recommendations apply to low-risk patients who have not undergone remnant ablation (i.e., serum TSH 0.1 to 0.5 mIU/L. Recommendation rating: B

The ATA recommendations for a graded TSH suppression reflects the strength of the data that underpin this therapeutic maneuver and take into account the risks for thyroid hormone suppression of TSH, particularly to avoid serious side effects such as thyrotoxicosis, cardiac arrhythmias, or osteoporosis (1).

A meta-analysis by McGriff et al. (2) found that a group of patients who received thyroid hormone suppression had a decreased risk of major adverse clinical outcome events (relative risk, 0.73; 95% confidence interval, 0.60 to 0.88); P<0.05). Furthermore, by applying a Likert scale, 15 of 17 interpretable studies showed either a likely or questionable beneficial effect of L-T<sub>4</sub> suppression of TSH. The authors concluded that thyroid hormone suppression therapy appears justified in patients with thyroid cancer following initial therapy.

Other studies (3) confirm that higher TSH concentrations, even within the normal range, are associated with a subsequent diagnosis of thyroid cancer in individuals with thyroid abnormalities, which further supports the hypothesis that TSH stimulates the growth or development of thyroid malignancy during its preclinical or early clinical phase.

It is difficult to compare the Sugitani study in terms of those published in the United States and Europe. There are several substantial differences. Most of the Sugitani patients were not treated with total thyroidectomy; most had lobectomy and central compartment lymph-node metastases. Large studies now confirm that total thyroidectomy is the treatment of choice for PTC except for those with microcarcinomas (4).

Also, the AMES staging system that was used in the Sugitani study presents several problems. This system has only two options: low-risk and high-risk. This prognostic index, which categorizes patients on the basis of age, distant metastases, and extent and size of primary tumor is much different from the tumor–node–metastasis (TNM) staging system. The ATA and most other guidelines suggest that the TNM staging system be used for reporting data, mainly because TNM staging provides a standardized spectrum of tumors, nodes, and metastases to identify risk, resulting in a spectrum of tumor designations that is endorsed by the International Union Against Cancer (UICC) and the American Joint Commission on Cancer (AJCC), providing a worldwide means of communicating well-defined data among different studies.

Another important difference in the Sugitani study is that serum Tg levels were not used in validating that a patient is free of disease. The ATA guidelines and European Thyroid Association (ETA) consensus agree that a patient can best be identified as being free of disease if all of the following criteria are satisfied:

- 1) No clinical evidence of tumor,
- 2) No imaging evidence of tumor (no uptake outside the thyroid bed on the initial posttreatment whole-body scan, or, if uptake outside the thyroid bed had been present, no imaging evidence of tumor on a recent diagnostic scan and neck ultrasound), and
- 3) Undetectable serum Tg levels during TSH suppression and stimulation in the absence of interfering Tg antibodies.

Sugitani recommends TSH suppression therapy only for patients who will inevitably receive levothyroxine supplementation for postoperative hypothyroidism or who desire to receive TSH suppression, paying special attention to the risk for cardiovascular disease and osteoporosis. This recommendation is sensible, but is far from the current practice and recommendations for TSH suppression in the United States and Europe (5-7).

— Ernest L. Mazzaferri, MD, MACP

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## REVIEWS, GUIDELINES AND META-ANALYSES

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2. Youens KE, Bean SM, Dodd LG et al. Thyroid carcinoma showing thymus-like differentiation (CASTLE): Case report with cytomorphology and review of the literature. *Diagn Cytopathol* 2010.

## DISCLOSURE

Dr. Mazzaferri is a consultant to Genzyme.

Dr. Sipos Lectures for Abbott Pharmaceutical and Genzyme.



## Call for Applications

### Editor-in-Chief of *Clinical Thyroidology*

The Publications Committee of the American Thyroid Association (ATA) is soliciting applications for the position of Editor-in-Chief of *Clinical Thyroidology*. The new Editor-in-Chief (EIC) will officially assume responsibility for the journal on January 1, 2011 but should be willing to assume some responsibilities by November/December 2010. The Committee seeks an individual who will continue the growth, quality, reputation, and scholarship of this important ATA publication. The applicant should be a respected thyroid clinician or investigator who is well organized, innovative, energetic and dedicated to making *Clinical Thyroidology* indispensable to clinicians and scientists interested in thyroid diseases. She/he should have experience as a writer and as an editor, associate editor, or editorial board member of a peer-reviewed journal. The initial appointment will be for a three-year term renewable by mutual agreement between the EIC and the ATA.

Applicants should submit a cover letter, their curriculum vitae, and a general statement outlining their vision and aims for *Clinical Thyroidology* to Dr. James Fagin, Chair of the ATA Publications Committee, by email to Ms. Bobbi Smith, CAE, ATA Executive Director ([bsmith@thyroid.org](mailto:bsmith@thyroid.org)).

The applications will be reviewed during August/September, and candidates should be available to be interviewed in person at the 14<sup>th</sup> International Thyroid Congress (ITC) in Paris, France. Questions regarding this position may be directed to Dr. James Fagin, Search Committee Chair [Phone 646-888-2136 Email [faginj@mskcc.org](mailto:faginj@mskcc.org)].

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