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_4) 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_4 therapy postoperatively for TSH suppression (group A) or to have no L-T_4 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_4 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 very 4 weeks, during which L-T_4 doses were adjusted to keep the TSH levels to <0.1 μU/ml. Serum free thyroxine (FT_4) and free triiodothyronine (FT_3) 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_3, and FT_4 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 ^{131}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 ^{131}I whole-body scans were not used. L-T_4 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 (±SD) duration of follow-up was 6.9±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_4 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.

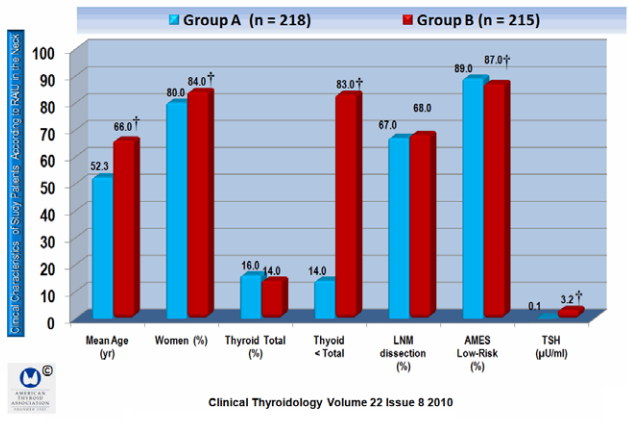

Figure 1. This figure shows the clinical characteristics of each trial group †P<0.0001. The values shown are the mean values for the study period. LNM = lymph-node metastases; RAIU = radioactive iodine uptake.

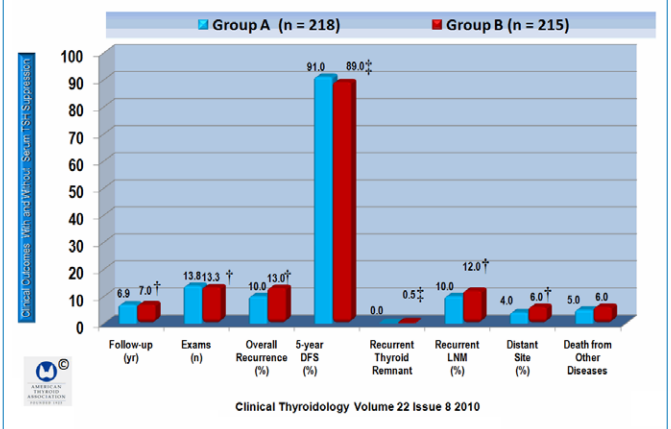

Figure 2. This figure shows the outcomes for patients with and without TSH suppression therapy †P = from 0.82 to 0.5; ‡P = 0.3 to 0.31. DFS = disease-free survival.

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_4 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).

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