Thyroid stimulating hormone suppression and recurrence after thyroid lobectomy for papillary thyroid carcinoma

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Abstract
Background Thyroid lobectomy is recommended as the primary treatment for low-risk thyroid cancer. However, recurrence and hypothyroidism may develop after lobectomy, necessitating thyroid hormone supplementation. The 2015 American Thyroid Association (ATA) guidelines recommended post-lobectomy thyroid-stimulating hormone (TSH) suppression. This study examined the need for TSH suppression and recurrence after lobectomy for unilateral papillary thyroid carcinoma (PTC).
Methods This study involved 369 patients who underwent thyroid lobectomy and ipsilateral central neck dissection for PTC between 2007 and 2015. Thyroid function tests were performed before and regularly after lobectomy. Binary logistic regression analyses were used to find factors predictive of the post-lobectomy need for TSH suppression that was defined by the 2015 ATA guidelines.
Results Serum TSH concentrations gradually increased after lobectomy: proportions with TSH >2 mIU/L at post-lobectomy 1, 3–6, 12, and 24 months were found in 77.0%, 82.3%, 66.7%, and 59.9%, respectively. After lobectomy, 168 (45.5%) patients received levothyroxine (T4) supplementation. Multivariate logistic regression analyses showed that pre-TSH level >2 mIU/L was the sole independent variable predictive of the need for post-lobectomy TSH suppression ($P = 0.003$). During the median follow-up of 72 months, recurrence was found in 4 (1.1%) patients who never received T4 supplementation and had post-lobectomy TSH levels >2 mIU/L.
Conclusions Our data show that thyroid lobectomy for unilateral PTC is associated with a low recurrence rate, but a significant risk of hypothyroidism. Preoperative TSH level can predict the need for post-lobectomy TSH suppression compliant with the 2015 ATA guidelines.

Keywords Papillary thyroid carcinoma · Lobectomy · Hypothyroidism · Recurrence · Risk factor

Introduction
Papillary thyroid carcinoma (PTC) is associated with excellent disease-specific survival of more than 90% [1, 2].

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lobectomy for unilateral PTC. 

Guidelines for thyroid cancer surgery, particularly for low-risk disease [8], possibly with a view to the avoidance of potential complications and cost-effectiveness [9, 10]. Thyroid lobectomy is commonly associated with less surgical morbidity than total thyroidectomy, which might influence patients’ quality of life [11]. Postoperative hypocalcemia, voice and throat dysfunction, and other complication rates are markedly more often observed in patients who have undergone total thyroidectomy [11, 12]. The complication rates after lobectomy are commonly low, but increased thyroid-stimulating hormone (TSH) levels (>2 mIU/L) are observed in most patients who undergo lobectomy [13]. A high rate (55.8%) of post-lobectomy hypothyroidism can occur along with several risk factors, e.g., age and preoperative TSH level [14].

The previous ATA guidelines recommended that TSH level after lobectomy remains biochemically euthyroid (TSH <5 mIU/L) [15]. The 2015 ATA guidelines made the revised recommendation that TSH may be maintained in the range of 0.5–2 mIU/L during post-lobectomy surveillance [6]. TSH suppression therapy reduces the recurrence of patients who underwent thyroidectomy for differentiated thyroid cancer [16]. Levothyroxine (T4) supplementation for TSH suppression may be prescribed in patients with TSH levels >2 mIU/L after thyroid lobectomy [17]. However, it is still unclear whether post-lobectomy TSH suppression reduces recurrence risk for differentiated thyroid cancer [18, 19]. Although there have been several studies on the incidence and risk factors of post-lobectomy hypothyroidism, further studies might be required for the analyses of post-lobectomy TSH changes and the need for T4 supplementation meeting the criteria of the 2015 ATA guidelines [20], in this era of de-escalation paradigms for differentiated thyroid cancer. Therefore, we here examined the need for TSH suppression and recurrence after thyroid lobectomy for unilateral PTC.

Materials and methods

Study patients

We retrospectively analyzed the patients who underwent thyroid lobectomy at our department of tertiary referral center between 2007 and 2015. Inclusion criteria were the euthyroid patients who underwent thyroid lobectomy for previously untreated PTC localized to a single lobe. All the patients received a preoperative diagnosis by high-resolution ultrasonography (US) and fine-needle aspiration biopsy and were scheduled for thyroid lobectomy. Exclusion criteria were patients who underwent total or subtotal thyroidectomy or completion thyroidectomy, had other thyroid malignancies, a prior history of thyroidectomy or previous neck irradiation, preoperative hypo-/hyperthyroidism or T4 or antithyroid medications, and inadequate information without a regular follow-up and surveillance of thyroid function tests for at least 2 years. This study was approved by the Institutional Review Board and the need for obtaining written informed consent from each patient was waived.

Treatments and follow-up

According to our institutional policy, all the study patients underwent thyroid lobectomy plus central compartment neck dissection (CND) involving pretracheal, prelaryngeal, and ipsilateral paratracheal LN [6], even when there was no evidence of clinical LN metastasis [21]. The primary and nodal samples were sent for pathological examination of tumor multifocality, extrathyroidal extension, lymphovascular invasion, and lymphocytic thyroiditis. All the CND samples from each patient were also carefully examined to identify indications of nodal metastasis in the central neck compartment.

All the postoperative complications were reported and reviewed. No patients received radioactive iodine ablation therapy. After surgery, the patients underwent regular follow-up involving clinical examination, neck US, chest radiography, and assessment of serum thyroid function. The patients were scheduled to visit the outpatient clinic at the 1st, 3rd–6th, and 12th months postoperatively, and annually thereafter. Any lesions suspicious of recurrence were confirmed with US-guided fine-needle aspiration biopsy and patients with loco-regional recurrence were scheduled for re-operation.

Definition of thyroid function status

According to the guidelines for diagnosis and management of subclinical thyroid disease and the standard practice of our institutional laboratory, euthyroidism was defined as the presence of normal levels of serum TSH (0.4–5.0 mIU/L) and free L-thyroxine (fT4, 0.8–1.9 ng/dL). Hypothyroidism was defined as the elevation of serum TSH levels beyond the upper limit of the reference range (>5.0 mIU/L) [22]. Subclinical hypothyroidism was defined as normal fT4 levels but elevated TSH levels [22]. Overt hypothyroidism was defined as an increase of serum TSH levels (>5.0 mIU/L) and a decrease in fT4 levels (<0.8 ng/dL) [23]. All study patients underwent regular assessments of serum TSH and T4 levels preoperatively (baseline) and at every postoperative visit at the outpatient clinic. Patients with
subclinical hypothyroidism, with TSH increase to >10 mIU/L, or overt hypothyroidism were assigned T4 replacement [14]. T4 replacement was not prescribed for patients with euthyroidism or subclinical hypothyroidism [14]. Serum TSH and fT4 were calculated for patients who were not on T4 supplementation at the time that thyroid function tests were obtained [20]. To identify factors predictive of the need for T4 supplementation meeting the criteria of the 2015 ATA guidelines [6], the TSH levels were defined at 2.0 mIU/L: a group with TSH ≤2.0 mIU/L without T4 supplementation and another group with TSH >2.0 mIU/L or T4 supplementation at post-lobectomy 1 year [20, 24].

**Statistical analysis**

Median and interquartile range (IQR) are used to summarize continuous variables and number and percentage are used for descriptive data. The end-points of interest were post-lobectomy hypothyroidism and recurrence. Recurrence-free survival (RFS) was defined as the time from surgery to the time of recurrence at any site, or the last follow-up. Binary logistic regression analyses were used to analyze the relationship between the post-lobectomy need for TSH suppression and age, sex, tumor and nodal pathological findings, tumor-node-metastasis (TNM) stage (proposed by the American Joint Committee on Cancer, 8th ed.), MACIS score, and the laboratory findings of preoperative thyroid function. RFS was defined as the time from surgery to the time of recurrence at any site, or the last follow-up. Cox-proportional hazard regression analyses were used to find variables significantly associated with RFS. The estimated odds ratio (OR), hazard ratio (HR), and 95% CI were calculated. Two-sided P values <0.05 were considered statistically significant. Statistical analyses were performed using IBM® SPSS® Statistics version 24.0 for Windows (IBM, Armonk, NY, USA).

**Results**

**Patient characteristics**

This study included a total of 369 lobectomy patients, comprising 89 (24.1%) men and 280 (75.9%) women, with a median age of 49 years (IQR, 40–55). Table 1 summarizes the demographic and clinicopathological data of patients. Most tumors (n = 323, 87.5%) were micropapillary thyroid carcinomas ≤1 cm in size. Extrathyroidal extension and lymphovascular invasion were found in 114 (30.9%) and 70 (19.0%) patients, respectively. Lymphocytic thyroiditis was found in 67 (18.2%) patients. Pathological TNM staging indicated 349 (94.6%) patients as stage I and 20 (5.4%) patients as stage II. Pathological LN metastasis in the central neck compartment was found in 73 (19.8%) patients. The median MACIS score was 4.3 and a score > 6.0 was found in 11 (3.0%) patients. A few patients had post-operative complications: wound seroma, hematoma, and temporary vocal fold paralysis were found in 2 (0.5%), 1 (0.3%), and 1 (0.3%) patients, respectively. The median follow-up period of 72 months (IQR, 56–84 months), only 4 (1.1%) patients had recurrence: 3 (0.8%) patients had a recurrence in the remnant thyroid gland and 1 (0.3%) patient had a recurrence in the lateral neck LNs. One patient died of gallbladder cancer, but the remaining patients survived at the time of the last follow-up. The 5- and 10-year RFS rates were 99.5% and 99.1%, respectively.

### Table 1 Patients characteristics (N = 369)

| Characteristic                               | N    | %    |
|----------------------------------------------|------|------|
| Age, years (IQR)                             | 49 (40–55) | 27.6 |
| ≥55 years                                    | 102  | 27.6 |
| Sex, male/female                             | 89/280 | 24.1/75.9 |
| Size of tumor (mm), median (IQR)             | 7 (5–9) | 9.5 |
| >1 cm                                        | 46   | 12.5 |
| Multifocality                                | 35   | 9.5  |
| Extrathyroidal extension                     |      |      |
| Microscopic/macrosopic                       | 98/16 | 26.6/4.3 |
| Lymphovascular invasion                      | 70   | 19.0 |
| Lymphocytic thyroiditis                      | 67   | 18.2 |
| pTNM staging                                 |      |      |
| T1/T2/T3/T4                                  | 338/15/16/0 | 91.6/4.1/4.3/0 |
| N0/N1a                                       | 296/73 | 80.2/19.8 |
| Overall I/II/III/IV                          | 349/20/0/0 | 94.6/5.4/0/0 |
| No. of total LNs harvested, median (IQR)     | 6 (4–9) |      |
| No. of LNs involved, 0/1/2/3/5               | 296/52/15/5/1 | 80.2/14.1/4.1/1.4/0.3 |
| MACIS score, median (IQR)                    | 4.3  | (3.6–4.8) |
| Follow-up information                        |      |      |
| Median follow-up (IQR), months               | 72   | (56–84) |
| Recurrence                                   | 4    | 1.1  |
| Remnant thyroid gland                        | 3    | 0.8  |
| Lateral neck LNs                             | 1    | 0.3  |
| Last status, NED/DOD/DOC/AD                  | 368/0/1/0 | 99.7/0/0.3/0 |

_ND_ alive with disease, _DOC_ died of other causes, _DOD_ died of disease (index cancer), _IQR_ interquartile range, _LN_ lymph node, _MACIS score_ distant metastasis, patient age, completeness of resection, local invasion and tumor size score, _NED_ no evidence of disease, _ND_ neck dissection, _pTNM_ pathological tumor-node-metastasis stage proposed by the American Joint Committee on Cancer (AJCC, 8th ed.)
Factors predictive of the need for TSH suppression after thyroid lobectomy

Serum TSH concentrations gradually increased up to 3–6 months and then decreased to a level higher than the preoperative level, whereas fT4 concentrations had the opposite trend with TSH in the serial measurements (Fig. 1A). The proportions of patients with TSH >2 mIU/L at post-lobectomy 1, 3–6, 12, and 24 months were found in 77.0%, 82.3%, 66.7%, and 59.9%, respectively (Fig. 1B). The post-lobectomy proportions of TSH >5 mIU/L at the time points were 28.0%, 32.3%, 17.3%, and 16.8%, respectively. Of 369 study patients, 168 (45.5%) received T4 supplementation after lobectomy. At post-lobectomy 1 year, 134 of 201 (66.7%) patients were indicated to receive T4 supplementation according to the 2015 ATA guidelines (Fig. 2). Four patients with post-lobectomy recurrence were not on T4 supplementation and had TSH levels >2 mIU/L. There were no clinicopathological factors significantly associated with RFS after thyroid lobectomy ($P > 0.1$).

Table 2 shows the relationship between clinicopathological factors and the need for TSH suppression: preoperative TSH level >2 mIU/L was the significant factor requiring post-lobectomy T4 supplementation ($P < 0.001$). Multivariate logistic regression analyses showed that preoperative TSH level (OR = 2.182, 95% CI, 1.301–3.659; $P = 0.003$) was the sole independent variable that predicted the post-lobectomy need for TSH suppression (Table 3). There were no clinicopathological factors significantly associated with RFS after thyroid lobectomy ($P > 0.1$) (Supplementary Table S1).

Discussion

The present study showed that post-lobectomy complications developed rarely after thyroid lobectomy, even when
combined with CND. The overall complication rates appeared to be quite low as compared to those after total thyroidectomy [12]. However, post-lobectomy hypothyroidism was a major clinical problem, because a considerable number of patients required thyroid hormone replacement therapy. A previous systematic review reported the pooled risk of post-lobectomy hypothyroidism as 22% (range, 7–49%) [25]. Two studies also showed the incidence of subclinical hypothyroidism (defined as TSH level >4.5 mIU/L) after hemithyroidectomy occurred in as many as 55.8% (226 of 405 patients) and 64.2% (215 of 335 patients) of post-lobectomy cases [14, 26]. In most cases (84.5%), the condition developed in the early postoperative months (1–3 months postoperatively) [14]. Another study showed that hypothyroidism might develop in 43.3% (145 of 335 patients) within 12 months post-lobectomy and in 20.9% (70 of 335 patients) thereafter and that 119 of 215 (55.3%) patients with such hypothyroidism eventually recovered to euthyroid state [26]. A further study also showed that increased TSH levels >2 mIU/L occurred in 59% patients within 12 months after thyroid lobectomy [13]. The present study also showed the elevation of serum TSH levels at 1–6 months after lobectomy and the need for T4 supplementation in most patients undergoing thyroid lobectomy. This study highlights: (1) that the new ATA threshold (TSH ≤2.0 mIU/L) significantly increases the fraction of subjects who are recommended for T4 supplementation; and (2) that while >80% of subjects would have required T4 supplementation at 3–6 months to meet this threshold, that number drops by about 15% with no intervention other than waiting for thyroid physiology to rebalance at 12 months.

The 2015 ATA guidelines recommend maintaining the TSH level of 0.5–2 mIU/L after thyroid lobectomy for low-risk thyroid cancer [6]. In the present study, the proportions of patients with the need for T4 supplementation were found 82.3% at 3–6 months and 66.7% at 1 year after lobectomy. A recent study also showed that a high proportion of 168 study patients met the criteria for T4 supplementation (TSH levels >2 mIU/L) after lobectomy: 67.9% at 6 weeks with a median TSH of 3.73 and 76.2% at 6–12 months with a median TSH of 3.43 [20]. Preoperative TSH level was a sole significant predictor associated with meeting criteria for TSH suppression (OR = 1.70, 95% CI = 1.06–3.40, P = 0.04) [20]. The same result was found in the present and previous multiple studies: high preoperative TSH levels were a significant risk factor for post-lobectomy hypothyroidism [14, 25–29]. A meta-analysis has shown that other factors associated with increased risk for hypothyroidism are antithyroid peroxidase antibody-positivity (48 vs. 19%, P = 0.001) and a high degree of thyroid inflammation (49 vs. 10%, P = 0.006) [25]. These were not significant predictors in the present study, which might result from the different definitions of hypothyroidism and TSH thresholds for the analyses of risk factors. There is still controversy whether TSH suppression therapy increases RFS and overall

### Table 2 Binary logistic regression analysis of factors predictive of the need for TSH suppression

| Characteristic                          | OR    | 95% CI     | P   |
|-----------------------------------------|-------|------------|-----|
| Age, ≥55 years                          | 1.232 | 0.731–2.076| 0.433|
| Sex, female/male                        | 1.623 | 1.975–2.703| 0.063|
| Pathological findings                   |       |            |     |
| Tumor size, >1 cm                       | 1.311 | 0.549–3.128| 0.542|
| Multifocality                           | 1.438 | 0.647–3.194| 0.373|
| Extrathyroidal extension                | 1.444 | 0.892–2.337| 0.135|
| Lymphovascular invasion                 | 1.196 | 0.668–2.142| 0.546|
| Central LN involvement                  | 1.367 | 0.812–2.302| 0.240|
| MACIS, >6.0                             | 2.047 | 0.580–7.223| 0.266|
| Preoperative laboratory findings         |       |            |     |
| Anti-thyroglobulin positivity, >60 IU/mL| 1.773 | 0.961–3.272| 0.067|
| Anti-peroxidase positivity, >60 IU/mL   | 1.803 | 0.811–4.007| 0.148|
| TSH level, >2 mIU/L                     | 2.385 | 1.487–3.823| <0.001*|
| Lymphocytic thyroiditis                 | 1.396 | 0.779–2.501| 0.263|

*CI confidence interval, OR odds ratio, LN lymph node, MACIS score distant metastasis, patient age, completeness of resection, local invasion, and tumor size score, TSH thyroid-stimulating hormone

*According to the 2015 ATA guidelines that recommend the maintenance of TSH in the mid to lower reference range (0.5–2 mIU/L)

### Table 3 Multivariate logistic regression analyses indicating the need for TSH suppression

| Characteristic                          | β     | SE    | Exp (β) | 95% CI          | P   |
|-----------------------------------------|-------|-------|---------|-----------------|-----|
| Sex, female                             | 0.537 | 0.304 | 1.711   | 0.942–3.106     | 0.078|
| Anti-thyroglobulin positivity, >60 IU/mL| 0.480 | 0.357 | 1.616   | 0.803–3.254     | 0.179|
| Anti-peroxidase positivity, >60 IU/mL   | 0.475 | 0.454 | 1.607   | 0.661–3.910     | 0.296|
| Pre-TSH level, >2 mIU/L                 | 0.780 | 0.264 | 2.182   | 1.301–3.659     | 0.003*|
| Constant                                | −0.951| 0.528 |         |                 |     |

*CI confidence interval, Exp (β) odds ratio, SE standard error, Pre-TSH preoperative thyroid-stimulating hormone

*P < 0.05
survival rates in patients undergoing thyroid lobectomy [18, 19]. The present study identified no factors associated with RFS, which might result from a very low rate of recurrence. Therefore, the association between TSH level or T4 suppression therapy and RFS cannot be concluded from this study but be confirmed by further randomized controlled studies [30]. In addition, the T4 supplementation lowering serum TSH level might be balanced with its potential risk of several metabolic complications, e.g., cardiovascular disease and osteoporosis [31, 32]. Further prospective studies are required to elucidate the role of TSH suppression therapy in post-lobectomy patients.

The present study showed a very low rate of recurrence after thyroid lobectomy for PTC. During a median follow-up period of 72 months, post-lobectomy recurrence occurred in only 4 (1.1%) patients, with high RFS rates. Adam et al. [4] found the overall survival of lobectomy cases similar to those with total thyroidectomy in the patients with PTC >1 cm, although more LN, extrathyroidal and multifocal diseases were found in patients with total thyroidectomy. Thyroid lobectomy appeared to result in a survival outcome equal to that achieved by total thyroidectomy in stage I PTC patients <45 years of age [33]. A previous study also showed the overall low recurrence rate and high cause-specific survival rate after thyroid lobectomy in 1088 PTC patients with a median follow-up of 17.6 years [5]. At 25 years after lobectomy, remnant thyroid, regional LN, and distant site recurrence rates were 93.5%, 90.6%, and 93.6%, respectively. They advocated that lobectomy in PTC patients aged <45 years and with a tumor size of ≤4 cm was a valid alternative to total thyroidectomy. Another study also showed excellent outcomes in terms of recurrence: only 23 (3.1%) of 734 PTC patients with thyroid lobectomy developed recurrent diseases [34]. They found a 10-year recurrence rate of 0.8 versus 7.8% in the cases without and with extrathyroidal extension, respectively. The safety for extended applications of lobectomy, e.g., in PTC with extrathyroidal extension, multifocality, and other adverse findings, as well as tumor size 1.1–4 cm, should be further examined. In our cohort, considerable numbers of patients had adverse pathological findings who are not analogous to the population currently recommended by the 2015 ATA guideline [6]. Those met the inclusion criteria of euthyroid state and PTC localized to a single lobe but refused completion thyroidectomy or preferred close surveillance of recurrence. The intermediate- or high-risk patients might have an increased probability for postthyroidectomy recurrence, which appears to be diminished by implementing unilateral CND combined with thyroid lobectomy [21]. However, this should be examined by further studies for the initial optimal extent of surgery in LN dissection as well as thyroidectomy.

Our study had the potential limitations of a retrospective design. A few cases of PTC >1 cm were included in our study because the criteria of tumor size for lobectomy strictly followed the previous version of the ATA guidelines [15]. Routine performance of CND in our study patients is not supported by the previous and current ATA guidelines [6, 15]. However, this approach did allow us to gain accurate pathological nodal information, and other clinical and pathological findings defined considerable numbers of patients with intermediate or high risk in our studies. This information might facilitate further revisions of the current guideline for the extended applications of thyroid lobectomy for differentiated thyroid cancer. Long-term follow-up to obtain accurate information on post-lobectomy recurrence might also be required.

In conclusion, our data show that thyroid lobectomy for PTC localized to a single lobe is associated with a low recurrence rate, but is significantly associated with post-lobectomy hypothyroidism. After thyroid lobectomy, a considerable number of patients had the elevation of serum TSH concentrations >2 mIU/L and the need for TSH suppression to the level of 0.5–2.0 mIU/L. Preoperative TSH level can predict the need for post-lobectomy TSH suppression therapy. This might help identify patients who are likely to require thyroid hormone supplementation.

Author contributions J.L.R. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: M.R.B., S.H.N., and J.L.R. Acquisition, analysis, or interpretation of data: M.R.B., S.H.N., J.L.R., S.H.C., S.H.N., and S.Y.K. Drafting of the paper: M.R.B., J.L.R. Critical revision of the paper for important intellectual content: M.R.B., S.H.N., and J.L.R. Statistical analysis: M.R.B., J.L.R. Administrative technical or material support: J.L.R., S.H.C., S.H.N., and S.Y.K. Supervision: J.L.R., S.H.C., and S.H.N.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethical approval This study was approved by the Institutional Review Board.

Informed consent Informed consent from each patient was waived.

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