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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Levothyroxine Supplementation Following Hemithyroidectomy: Incidence, Risk Factors, and Characteristics

Dongbin Ahn, MD, Gil Joon Lee, MD, and Jin Ho Sohn, MD, PhD

Department of Otolaryngology-Head and Neck Surgery, School of Medicine, Kyungpook National University, Daegu, Korea

ABSTRACT

Background. The goal of the present study was to determine the actual incidence, predictive risk factors, and clinical characteristics of levothyroxine supplementation (LT4S) used for the management of hypothyroidism after hemithyroidectomy.

Methods. From 2008 to 2015, we included 535 patients who underwent hemithyroidectomy. LT4S was initiated based on three major criteria: the development of overt hypothyroidism, subclinical hypothyroidism with thyroid-stimulating hormone (TSH) levels > 10 mIU/L, or subclinical hypothyroidism with TSH levels of 4.5–10 mIU/L with associated signs/symptoms.

Results. During the 69-month follow-up period, 321 patients (60%) developed overall hypothyroidism following hemithyroidectomy, and 141 ultimately required LT4S, with an overall LT4S incidence of 26.4%. The most common cause of LT4S initiation was subclinical hypothyroidism with TSH levels > 10 mIU/L. In 141 patients with LT4S, the mean maintenance dose of levothyroxine was 1.34 μg/kg, and only 6 patients (4.3%) discontinued LT4S during the follow-up. The 1-, 3-, 5-, and 7-year LT4S-free survival rates of 535 patients were 88.6%, 80.2%, 73.8%, and 69.1%, respectively. Preoperative TSH levels > 2.12 mIU/L and coexistence of Hashimoto's thyroiditis were significantly associated with LT4S following hemithyroidectomy. The risk of LT4S increased by 1.401 times, as preoperative TSH levels increased by 1 mIU/L.

Discussion. A quarter of patients required LT4S after hemithyroidectomy for the management of hypothyroidism, with a mean maintenance levothyroxine dose of 1.34 μg/kg. The preoperative TSH level and coexistence of Hashimoto's thyroiditis were significant predictive factors of LT4S following hemithyroidectomy.

Hemithyroidectomy (lobectomy + isthmusectomy) is a valid surgical option for managing unilateral benign thyroid disease and some types of differentiated thyroid carcinomas (DTCs).[1–3] The latest international guidelines for the management of thyroid cancer recommend a more conservative approach to treat 1–4-cm-sized DTCs, unless there are other adverse features, such as extrathyroidal extension and lymph node metastases. Hence, the use of this surgical option is expected to increase.[1,3]

Retaining the functioning contralateral lobe should preserve the endogenous source of thyroid hormones and possibly maintain euthyroidism after surgery, without any requirement for levothyroxine supplementation (LT4S) after surgery. However, hypothyroidism is the most common complication even after conservative thyroidectomies, with the incidence ranging from 6.0 to 64.2%.[4–8] Furthermore, LT4S is required in approximately 10–50% of patients who undergo conservative thyroidectomy, despite efforts to preserve the uninvolved thyroid gland and to maintain normal thyroid function.[5,8–11]

For some patients, receiving LT4S after conservative thyroidectomy would still be disappointing, even though the cancer is completely removed. In addition, long-term LT4S can harm the skeleton and myocardium, and the severity of these adverse effects is dependent on the dose of

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D. Ahn, MD
e-mail: godlikeu@naver.com

exogenous thyroid hormones and duration of therapy.[12–14] Therefore, comprehensive discussions and counseling about possible LT4S are paramount before conservative thyroidectomy in these patients. However, the reported incidence of LT4S following conservative thyroidectomy varies according to the follow-up period, the definition of hypothyroidism used in the study, and the indication for LT4S; thus, the actual incidence of LT4S used for the management of hypothyroidism remains unclear. In addition, few studies have evaluated factors predictive of postoperative LT4S in patients undergoing conservative thyroidectomy, although several studies have evaluated the risk factors of hypothyroidism itself.[5,9–11,15]

Therefore, this study was designed to determine the actual incidence, predictive risk factors, and clinical characteristics of LT4S used for the management of hypothyroidism after hemithyroidectomy to provide better preoperative counseling and postoperative management to patients in whom hemithyroidectomy is indicated.

METHODS

Patients

This study was approved by the Investigation Review Board of our institution. From January 2008 to December 2015, a total of 578 patients underwent hemithyroidectomy for various indications at our institution. Of these patients, we excluded those with preoperative histories of levothyroxine or antithyroid medication usage ($n = 6$), those with unavailable postoperative thyroid function status ($n = 2$), those who were followed for < 12 months ($n = 30$), and those with history of postoperative thyroid-stimulating hormone (TSH) suppression treatment ($n = 5$). Finally, we included 535 patients who underwent hemithyroidectomy and were followed for ≥ 12 months.

Definition of Thyroid Function Status

In accordance with the scientific review and guidelines for subclinical thyroid disorders published in 2004 and standard practice in our institution's laboratory, the reference range of TSH, free $_{L}$-thyroxine (T4), and triiodo-$_{L}$-thyronine (T3) concentration was defined as 0.45–4.5 mIU/L, 0.8–2.0 ng/dL, and 0.6–1.9 ng/mL, respectively.[16,17] Euthyroidism was defined as the presence of normal levels of serum TSH, free T4, and T3. Subclinical hypothyroidism was defined as an elevation in serum TSH levels beyond the upper limit of the reference range, with normal free T4 levels. Overt hypothyroidism was defined as an elevation in serum TSH levels and decrease in free T4 levels.

Follow-Up Strategy and Indication of LT4S

The follow-up protocol for postoperative thyroid function measurements has been described in our previous study and is summarized below.[7] The first postoperative thyroid function measurement was performed within 1–3 months of surgery. If the results were normal, follow-up thyroid function measurements were performed every 6–12 months; no patients with euthyroidism received LT4S for TSH suppression to reduce the risk of DTC recurrence. If subclinical hypothyroidism was identified at any time during the follow-up period, thyroid function measurement was performed 3 months after that point. This was then repeated every 3–6 months without treatment if TSH levels were maintained between 4.5 and 10 mIU/L, without any signs/symptoms. In subclinical hypothyroidism cases, if TSH level increased to > 10 mIU/L, progression to overt hypothyroidism was noted, or if signs/symptoms associated with hypothyroidism were observed, LT4S was initiated. Signs/symptoms of hypothyroidism that were considered to indicate the need for LT4S included unexplained/persistent weight gain of $\geq 5\%$ of the patient's body weight, hair loss, generalized edema, or fatigue that disrupted usual social activities. LT4S was immediately initiated in patients diagnosed with over hypothyroidism during follow-up. In patients receiving LT4S, target TSH levels ranged from 0.45 to 4.5 mIU/L to maintain euthyroidism and to avoid TSH suppression to subnormal levels.

Assessment Parameters and Statistical Analyses

We evaluated clinicopathological characteristics of patients and reviewed all results of 3583 thyroid function measurements collected in the follow-up period. Hypothyroidism development, type of hypothyroidism, the use of LT4S, the reason LT4S was initiated, the interval between surgery and start of LT4S, and the duration and maintenance dose of LT4S were recorded. Overall hypothyroidism included subclinical/overt hypothyroidism and transient/persistent hypothyroidism.

The Chi square test for categorical data and independent Student's t test for continuous data were performed to evaluate the association of clinicopathological characteristics with postoperative LT4S. The cutoff value of the preoperative TSH level for predicting the hypothyroidism development and LT4S was estimated by using receiver-operating characteristic (ROC) curves, if the area under the curve (AUC) was > 0.6. Binary logistic regression was performed to evaluate the impact of each variable, and variables with a p value < 0.05 for the risk of hypothyroidism development and LT4S in the univariate analysis were subsequently included in multivariate analysis. The results of the binary logistic regression are presented as

odds ratios (OR) with 95% confidence intervals (CI) and p values. The Kaplan–Meier method with log-rank test was used to determine and compare the LT4S-free survival rates between the groups during the follow-up period. Statistical significance was defined as a $p < 0.05$, and all statistical tests were two-tailed.

RESULTS

Patients' Baseline Characteristics

The baseline clinicopathological characteristics of the 535 patients are presented in Table 1. The mean follow-up duration was 69.0 (range 12–156) months, and a mean of 6.7 (range 2–23) thyroid function measurements were performed during this follow-up period. Changes in the mean postoperative TSH levels with no LT4S during the follow-up measurements are presented in supplementary material (Supplementary Fig. 1). Serial measurements of postoperative TSH level showed that compensatory elevation of postoperative TSH levels decreased within the reference range by the fourth follow-up TSH measurement (TSH level 4.26 mIU/L) and continued to decrease until the eighth follow-up TSH measurement (TSH level 3.04 mIU/L).

Incidence and Risk of Hypothyroidism After Hemithyroidectomy

Of 535 patients, 321 developed overall hypothyroidism during the follow-up period, including 8 with overt hypothyroidism and 313 with subclinical hypothyroidism, with an overall incidence of 60.0%. The clinicopathological characteristics of patients who developed hypothyroidism following hemithyroidectomy are listed in Table 2. The hypothyroidism group had higher proportions of female patients, patients with preoperative TSH levels > 1.70 mIU/L (preoperative TSH cutoff value for hypothyroidism development obtained from ROC curve), patients positive for antiperoxidase antibodies, and patients with coexisting Hashimoto's thyroiditis. The mean preoperative TSH level was also higher in the hypothyroidism group than in the euthyroidism group.

The results of univariate and multivariate analyses of the risk of hypothyroidism following hemithyroidectomy are summarized in Table 3. In the univariate analysis, female sex (OR 1.980; 95% CI 1.241–3.160; $p = 0.004$), preoperative TSH levels > 1.70 mIU/L (OR 5.719; 95% CI 3.917–8.350; $p < 0.001$), positivity for anti-peroxidase antibodies (OR 1.766; 95% CI 1.077–2.894; $p = 0.024$), and coexistence of Hashimoto's thyroiditis (OR 2.427; 95% CI 1.538–3.828; $p < 0.001$) were each found to be

TABLE 1 Baseline patient characteristics

	Number of patients ($N = 535$)
Age (year)	47.2 (18–79)
Sex	
Male	85 (15.9%)
Female	450 (84.1%)
Follow-up period (month)	69.0 (12–156)
Number of postoperative thyroid function measurements	6.7 (2–23)
Preoperative thyroid function examination	
TSH level (mIU/L)	2.31 (0.1–4.5)
Anti-thyroglobulin antibody positivity (> 60 U/mL)	324/451 (71.8%)
Anti-peroxidase antibody positivity (> 60 U/mL)	89/499 (17.8%)
Final histology	
Malignant	507 (94.8%)
Papillary thyroid carcinoma	503
Follicular thyroid carcinoma	4
Benign	28 (5.2%)
Nodular hyperplasia	10
Follicular adenoma	6
Adenomatous nodule	5
Other benign histology	7
Coexistence of Hashimoto's thyroiditis	121 (22.6%)

Continuous variables are presented as means and ranges

TSH thyroid-stimulating hormone

TABLE 2 Clinicopathological characteristics as a function of overall hypothyroidism development following hemithyroidectomy

	Euthyroidism (n = 214)	Overall hypothyroidism (n = 321)	p value
Age (year)			
Mean (range)	46.9 (18–79)	47.4 (18–77)	0.649
Sex			
Male	46 (21.5%)	39 (12.1%)	0.004
Female	168 (78.5%)	282 (87.9%)	
Preoperative TSH level (mIU/L)			
Mean (range)	1.52 (0.1–4.1)	2.83 (0.1–4.5)	< 0.001
> 1.70	67 (31.3%)	232 (72.3%)	< 0.001
≤ 1.70	147 (68.7%)	89 (27.7%)	
Anti-thyroglobulin antibody			
Positive	127 (59.3%)	197 (61.4%)	0.639
Negative	87 (40.7%)	124 (48.6%)	
Anti-peroxidase antibody			
Positive	26 (12.1%)	63 (19.6%)	0.023
Negative	188 (87.9%)	258 (80.4%)	
Final histology			
Malignant	203 (94.9%)	304 (94.7%)	0.937
Benign	11 (5.1%)	17 (5.3%)	
Coexistence of Hashimoto's thyroiditis			
Present	30 (14.0%)	91 (28.3%)	< 0.001
Absent	184 (86.0%)	230 (71.7%)	

TSH thyroid-stimulating hormone

TABLE 3 Univariate and multivariate analysis for the risk of hypothyroidism after hemithyroidectomy

	Univariate			Multivariate		
	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
Female	1.980	1.241–3.160	0.004	1.429	0.849–2.407	0.179
Preoperative TSH level > 1.70 mIU/L	5.719	3.917–8.350	< 0.001	5.364	3.652–7.878	< 0.001
Positivity for anti-peroxidase antibody	1.766	1.077–2.894	0.024	1.037	0.581–1.850	0.903
Malignant histology	0.969	0.445–2.112	0.937	–	–	–
Coexistence of Hashimoto's thyroiditis	2.427	1.538–3.828	< 0.001	2.007	1.191–3.382	0.009

CI confidence internal, *TSH* thyroid-stimulating hormone

associated with hypothyroidism development following hemithyroidectomy. In the adjusted multivariate analysis, preoperative TSH levels > 1.70 mIU/L (OR 5.364; 95% CI 3.652–7.878; $p < 0.001$) and coexistence of Hashimoto's thyroiditis (OR 2.007; 95% CI 1.191–3.382; $p = 0.009$) each remained significant risk factors for hypothyroidism following hemithyroidectomy.

In addition, preoperative TSH level, as a continuous variable, was significantly associated with overall hypothyroidism following hemithyroidectomy; this demonstrated that the risk of overall hypothyroidism increased by 2.372 times, as preoperative TSH level increased by 1 (OR 2.372; 95% CI 1.943–2.896; $p < 0.001$).

Incidence and Clinical Characteristics of LT4S After Hemithyroidectomy

Of 321 patients who developed postoperative hypothyroidism, 141 ultimately required LT4S; thus, the overall incidence of LT4S following hemithyroidectomy was 26.4% (141/535). The causes of LT4S initiation were the

development of overt hypothyroidism (8 patients), subclinical hypothyroidism with TSH levels > 10 mIU/L (70 patients), subclinical hypothyroidism with TSH levels ≤ 10 mIU/L but with associated signs/symptoms (46 patients), and recurrence of hypothyroidism after recovery from the first episode of hypothyroidism (17 patients). The mean TSH level upon initiation of LT4S was 12.8 (range 4.6–90.4) mIU/L, and the mean interval between surgery and initiation of LT4S was 24.5 (range 1–116) months. The 1-, 3-, 5-, and 7-year LT4S-free survival rates for all 535 patients were 88.6%, 80.2%, 73.8%, and 69.1%, respectively (Fig. 1).

Of 141 patients who required LT4S, only 6 (4.3%) discontinued LT4S and returned to their euthyroid state during the follow-up, whereas the remaining 135 (95.7%) had been receiving LT4S even at the latest follow-up. Their mean maintenance levothyroxine dose was 1.34 (range 0.5–2.8) μg/kg.

The clinicopathological characteristics of patients who received LT4S after hemithyroidectomy are listed in Table 4. The LT4S group had higher proportions of female patients, patients with preoperative TSH levels > 2.12 mIU/L (preoperative TSH cutoff value for LT4S obtained from ROC curve), patients with tumors showing malignant histology, and patients with coexisting Hashimoto's thyroiditis. The mean preoperative TSH levels were higher in the LT4S group than in the LT4S-free group.

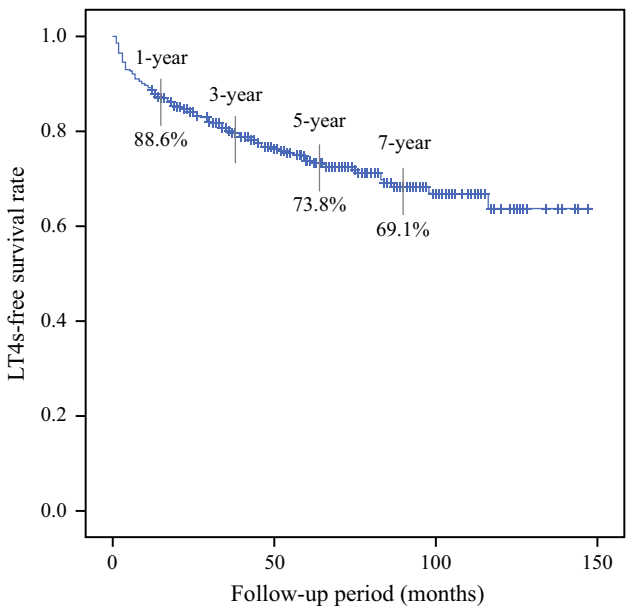

FIG. 1 Kaplan–Meier curve for LT4S-free survival in a total of 535 patients who underwent hemithyroidectomy. *LT4S* levothyroxine supplementation

Univariate and Multivariate Analysis of the Risk of LT4S After Hemithyroidectomy

The results of the univariate and multivariate analyses of LT4S risk following hemithyroidectomy are summarized in Table 5. In the univariate analysis, female sex (OR 1.994; 95% CI 1.085–3.665; $p = 0.026$), preoperative TSH levels > 2.12 mIU/L (OR 3.097; 95% CI 2.076–4.622; $p < 0.001$), malignant histology (OR 4.910; 95% CI 1.150–20.963; $p = 0.032$), and coexistence of Hashimoto's thyroiditis (OR 2.060; 95% CI 1.336–3.174; $p = 0.001$) were each found to be significantly associated with LT4S following hemithyroidectomy. In the adjusted multivariate analysis, preoperative TSH levels > 2.12 mIU/L (OR 2.857; 95% CI 1.895–4.305; $p < 0.001$), malignant histology (OR 5.080; 95% CI 1.160–22.249; $p = 0.031$), and coexistence of Hashimoto's thyroiditis (OR 1.686; 95% CI 1.068–2.661; $p = 0.025$) each remained significant risk factors for LT4S following hemithyroidectomy.

In addition, preoperative TSH level itself, as a continuous variable, was significantly associated with LT4S following hemithyroidectomy; this demonstrated that the risk of LT4S increased by 1.401 times, as preoperative TSH level increased by 1 (OR 1.401; 95% CI 1.241–1.581; $p < 0.001$).

LT4S-Free Survival Rate According to Risk Factors Identified in the Multivariate Analysis

The 1-, 3-, 5-, and 7-year LT4S-free survival rates of patients with preoperative TSH level > 2.12 mIU/L were 82.3%, 70.3%, 61.0%, and 55.0%, respectively, whereas those of patients with preoperative TSH levels ≤ 2.12 mIU/L were 93.4%, 87.8%, 83.8%, and 80.8%, respectively; these differences were statistically significant ($p < 0.001$; Fig. 2a).

Additionally, the 1-, 3-, 5-, and 7-year LT4S-free survival rates of patients with malignant pathologies were 88.1%, 79.3%, 72.9%, and 68.1%, respectively, and those of patients with benign pathologies were 96.4%, 96.4%, 90.4%, and 90.4%, respectively. These differences also were statistically significant ($p < 0.040$; Fig. 2b).

Furthermore, the 1-, 3-, 5-, and 7-year LT4S-free survival rates of patients with Hashimoto's thyroiditis were 81.8%, 70.2%, 63.2%, and 56.1%, respectively, whereas those of patients without Hashimoto's thyroiditis were 90.6%, 83.0%, 76.9%, and 72.8%, respectively. These differences also were statistically significant ($p < 0.001$; Fig. 2c).

TABLE 4 Clinicopathological characteristics as a function of levothyroxine supplementation following hemithyroidectomy

	No LT4S (n = 394)	LT4S (n = 141)	p value
Age (year)			
Mean (range)	46.8 (18–79)	48.4 (18–77)	0.199
Sex			
Male	71 (18.0%)	14 (9.9%)	0.024
Female	323 (82.0%)	127 (90.1%)	
Preoperative TSH level (mIU/L)			
Mean (range)	2.07 (0.09–4.5)	2.97 (0.1–4.5)	< 0.001
> 2.12	143 (36.3%)	90 (63.8%)	< 0.001
≤ 2.12	251 (63.7%)	51 (36.2%)	
Anti-thyroglobulin antibody			
Positive	242 (61.4%)	82 (58.2%)	0.496
Negative	152 (38.6%)	59 (41.8%)	
Anti-peroxidase antibody			
Positive	60 (15.2%)	29 (20.6%)	0.144
Negative	334 (84.8%)	112 (79.4%)	
Final histology			
Malignant	368 (93.4%)	139 (98.6%)	0.018
Benign	26 (6.6%)	2 (1.4%)	
Coexistence of Hashimoto's thyroiditis			
Present	75 (19.0%)	46 (32.6%)	0.001
Absent	319 (81.0%)	95 (67.4%)	

LT4S levothyroxine supplementation, *TSH* thyroid-stimulating hormone

TABLE 5 Univariate and multivariate analysis for the risk of levothyroxine supplementation following hemithyroidectomy

	Univariate			Multivariate		
	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
Female	1.994	1.085–3.665	0.026	1.376	0.726–2.608	0.327
Preoperative TSH level > 2.12 mIU/L	3.097	2.076–4.622	< 0.001	2.857	1.895–4.305	< 0.001
Positivity for anti-peroxidase antibody	1.441	0.881–2.358	0.145	–	–	–
Malignant histology	4.910	1.150–20.963	0.032	5.080	1.160–22.249	0.031
Coexistence of Hashimoto's thyroiditis	2.060	1.336–3.174	0.001	1.686	1.068–2.661	0.025

CI confidence internal, *TSH* thyroid-stimulating hormone

Oncological Outcomes in Patients with DTC

In 507 patients with DTC, recurrence occurred in 25 patients during the 69 months of follow-up, with an overall recurrence rate of 4.9%.

DISCUSSION

Our study showed that the incidence of postoperative overall hypothyroidism reached 60%, and more than a quarter of patients ultimately required LT4S after hemithyroidectomy for the management of hypothyroidism during the 69-month follow-up period. The incidence of LT4S in our study (26.4%) was comparable to that from previous studies, with reported incidences ranging from 10 to 50%.[5,8–10] However, the incidences of LT4S could vary according to the purpose of the LT4S and target postoperative TSH level. In a study of 555 patients with DTC, approximately 73% of patients required LT4S to maintain a TSH level < 2 m IU/L after lobectomy for an oncological purpose, which is compliant with the American Thyroid Association guidelines for patients with low-risk DTC.[15] In contrast, we did not use LT4S for an oncological purpose but used LT4S only for the management of hypothyroidism with target TSH levels between 0.45 and 4.5 mIU/L.

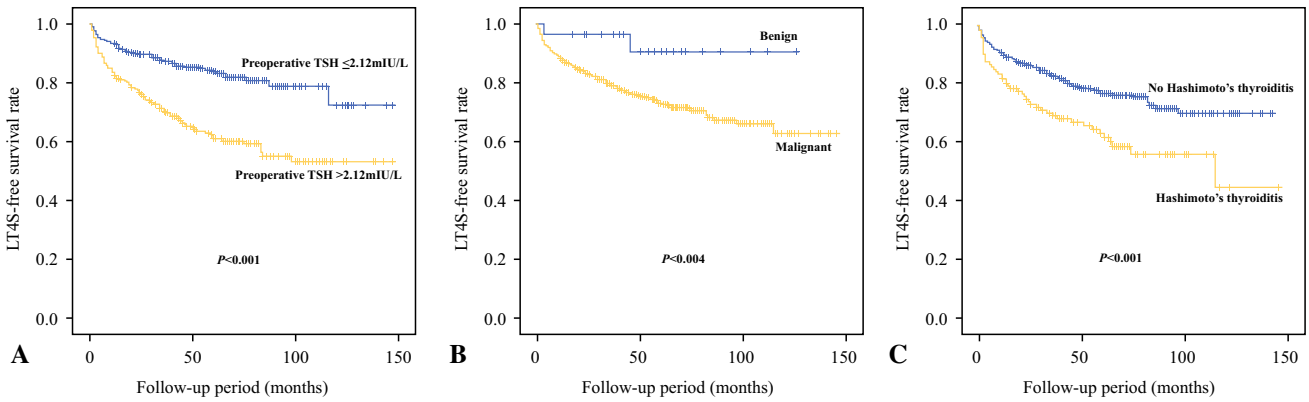

FIG. 2 Kaplan–Meier curves for LT4S-free survival according to preoperative TSH level (**a**), histology (**b**), and Hashimoto's thyroiditis (**c**). *LT4S* levothyroxine supplementation; *TSH* thyroid-stimulating hormone

In the present study, although the mean interval between surgery and the initiation of LT4S was 24.5 months, accumulative incidence of LT4S consistently increased until 100 months of follow-up, as shown in the LT4S-free survival curve (Fig. 2). This steady increase in LT4S incidence was attributed not only to hypothyroidism caused by hemithyroidectomy, but also to the natural increase in the incidence of hypothyroidism with age. Therefore, long-term follow-up of thyroid function is required for timely detection and management of hypothyroidism, along with early detection of tumor recurrence, in patients undergoing hemithyroidectomy.

In 141 patients who required LT4S, the most common cause of LT4S initiation was subclinical hypothyroidism with TSH levels $>$ 10 mIU/L (70/141, 49.6%), followed by subclinical hypothyroidism with TSH levels $\leq$ 10 mIU/L with associated signs/symptoms (46/141, 32.6%). Overt hypothyroidism rarely developed (8/141, 5.7%). These results suggest that checking signs/symptoms of hypothyroidism alone within the follow-up period is not sufficient to provide timely management of hypothyroidism, because the signs/symptoms of hypothyroidism were not present in approximately half of the patients. In addition, the signs and symptoms of hypothyroidism often are too vague to indicate definitive need for LT4S. In the present study, we used unexplained/persistent weight gain of $\geq$ 5% of the patient's body weight, hair loss, generalized edema, or fatigue that disrupts usual social activities as indicators for LT4S initiation. However, besides checking these signs/symptoms, regular evaluation of postoperative thyroid function is necessary even in patients with no signs/symptoms of hypothyroidism, and the need for LT4S should be determined based on the results of postoperative thyroid function assessment, together with associated signs/symptoms of hypothyroidism.

The mean dose of levothyroxine to maintain a euthyroid state was 1.34 μg/kg, and this dose was consistent with that reported in previous studies, which indicated that 1.3 μg/kg is the optimal dose for TSH normalization in patients undergoing hemithyroidectomy.[18] However, during the follow-up period, only six patients (4.3%) discontinued LT4S, and this LT4S discontinuation rate is considerably lower than that reported in previous studies (26.2–49.8%).[10,19] The reason for this may be that the indications for LT4S after hemithyroidectomy in the present study were quite different from those of previous studies; we only started LT4S after hemithyroidectomy based on the three major criteria: development of overt hypothyroidism, subclinical hypothyroidism with TSH levels $>$ 10 mIU/L, or subclinical hypothyroidism with TSH levels 4.5–10 mIU/L associated with signs/symptoms. In previous studies, LT4S was initiated as a routine practice after hemithyroidectomy or only based on clinical symptoms without consideration of the postoperative TSH levels and standardized protocol.[10,19] Therefore, we believe that the results of our study could reflect the actual LT4S discontinuation rate in patients requiring LT4S for the management of hypothyroidism after hemithyroidectomy.

Preoperative TSH levels and coexistence of Hashimoto's thyroiditis were identified as predictive factors for LT4S. Indeed, high preoperative TSH levels or coexistence of Hashimoto's thyroiditis are known risk factors for hypothyroidism and LT4S following hemithyroidectomy.[5,7,10] However, the cutoff value of preoperative TSH levels as a risk factor for LT4S had not been previously identified; thus, the definition of "high" and "low" preoperative TSH levels for risk stratification for postoperative LT4S remained uncertain. To resolve this uncertainty, we calculated the specific cutoff value for the preoperative TSH level that increases the risk of LT4S after hemithyroidectomy using ROC curves. Furthermore, we evaluated specific weight of TSH level increase, which

demonstrated that the risk of LT4S increased by 1.401 times as preoperative TSH levels increased by 1 (OR 1.401; 95% CI 1.241–1.581; $p < 0.001$). The preoperative TSH level has been suggested as a consistent and the most powerful risk factor for LT4S in the present and previous studies.[9,10] Hence, the determination of specific preoperative TSH cutoff level or weight of TSH level increase—rather than the consideration of a "high TSH level"—would be useful in preoperative patient counseling regarding the risks of postoperative LT4S and in selecting patients who require long-term follow-up of postoperative thyroid function. In addition, although hypothyroidism and LT4S following hemithyroidectomy are associated with common risk factors, including preoperative TSH levels and Hashimoto's thyroiditis, we found that the cutoff values for preoperative TSH in hypothyroidism development and LT4S initiation were different (1.70 mIU/L and 2.12 mIU/L, respectively). This result indicates that preoperative risk assessment should be carefully conducted to distinguish patients with hypothyroidism who require LT4S from those who do not require LT4S, because some patients with subclinical hypothyroidism following hemithyroidectomy do not require LT4S. Furthermore, because our study presented the LT4S-free survival rate as a function of each risk factor, this information also can be used to provide a more specific LT4S rate at a certain follow-up point. This could improve patients' understanding about their probability of requiring LT4S during the follow-up period.

Although malignant histology was identified as a significant risk factor for LT4S after hemithyroidectomy in a risk analysis, we could not conclude that malignant histology was a true risk factor for postoperative LT4S. In fact, because malignant histology was not considered a risk factor for hypothyroidism, it should not be considered as an indication for LT4S, which was administered as a treatment for hypothyroidism. We presumed that this was influenced by an internal bias. In the present study, most of the enrolled patients showed malignant histology, and only 28 (5.2%) with benign histology were included. Their follow-up duration was considerably shorter than that of patients with malignant histology, because recurrence is not a concern in cases of benign histology. Therefore, these patients were not followed further unless abnormal thyroid function was identified within 36 months after surgery, whereas patients with malignant histology were usually followed for 60 months for detecting cancer recurrence. Given that the accumulated incidence of hypothyroidism and LT4S increases with time, longer follow-up is associated with a higher incidence of LT4S, whereas a shorter follow-up period is associated with a lower incidence. Therefore, caution should be observed when interpreting results showing the association between malignant histology and LT4S following hemithyroidectomy.

In the present study, we did not use LT4S to suppress TSH, even for patients with DTC. Although many studies have reported that the outcomes of high-risk DTC may be improved by TSH suppression therapy after surgery, no such evidence has been demonstrated for low-risk cases, which were candidates for hemithyroidectomy.[1,13,20,21] In the present study, the overall recurrence rate (4.9%) of patients with DTC was comparable to recurrence rates reported in previous studies (3.1–14.3%).[22–26] We are currently preparing a study to evaluate the impact of postoperative high TSH level and LT4S on prognosis of DTC.

CONCLUSIONS

Approximately a quarter of patients required LT4S after hemithyroidectomy for the management of hypothyroidism, with 1.34 μg/kg as the mean maintenance levothyroxine dose, even though half of these patients did not have evident signs/symptoms of hypothyroidism. Preoperative TSH levels and the coexistence of Hashimoto's thyroiditis were each significant predictive factors for LT4S following hemithyroidectomy. This information could be used to provide comprehensive preoperative counseling in patients who have opted for hemithyroidectomy. In addition, long-term follow-up of postoperative thyroid function should be performed to provide timely and appropriate management of hypothyroidism following hemithyroidectomy.

DISCLOSURE None.

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