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Research

Recovery of the pituitary–thyroid axis after surgical remission of thyroid-stimulating hormone-secreting pituitary adenomas

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Abstract

Purpose: To identify factors associated with postoperative levothyroxine replacement and characterize long-term recovery of endogenous thyroid-stimulating hormone (TSH) responsiveness after surgical remission of TSH-secreting pituitary adenomas (TSHomas).

Methods: We retrospectively analyzed 36 patients with pathologically confirmed TSHoma who achieved early surgical remission after transsphenoidal surgery between 2006 and 2024 and maintained sustained disease control. Clinical, endocrine, tumor, and surgical characteristics were compared according to postoperative levothyroxine use. Serial combined pituitary function tests were used to assess recovery of stimulated TSH responsiveness.

Results: Ten patients (27.8%) required transient levothyroxine replacement, initiated a median of 36 days after surgery and continued for a median of 140 days. Larger tumor diameter was independently associated with replacement (odds ratio 26.5, P = 0.038). A diameter of 1.45 cm was the optimal exploratory cutoff (area under the curve 0.81; sensitivity 100%; specificity 53.8%). Among 31 patients with longitudinal testing, 22 (71.0%) showed recovery of TSH responsiveness when stimulated by thyrotropin-releasing hormone; the estimated median time to recovery was 2.02 years (95% confidence interval 1.64–4.04).

Conclusion: Postoperative impairment of endogenous TSH responsiveness after successful TSHoma surgery is often reversible but may persist for years. Larger tumors are associated with transient levothyroxine requirement, supporting long-term thyroid-axis monitoring and periodic reassessment of replacement therapy.

Keywords: levothyroxine; pituitary adenoma; thyroid-stimulating hormone; thyrotropinoma; transsphenoidal surgery

Abbreviations: ACTH = Adrenocorticotropic Hormone; CPFT = Combined Pituitary Function Test; FSH = Follicle Stimulating Hormone; GH = Growth Hormone; HPT axis = Hypothalamic–Pituitary–Thyroid Axis; IQR = Interquartile Range; IRB = Institutional Review Board; Ki-67 = Ki-67 Proliferation Index; Knosp = Knosp Classification for Cavernous Sinus Invasion; LH = Luteinizing Hormone; MRI = Magnetic Resonance Imaging; T3 = Triiodothyronine; T4 = Thyroxine; TBG = Thyroxine-Binding Globulin; TRH = Thyrotropin-Releasing Hormone; TSH = Thyroid Stimulating Hormone; TSA = Transsphenoidal Approach; TSS = Transsphenoidal Surgery; TSHoma = TSH-Secreting pituitary adenoma.

Introduction

In patients with functioning Pituitary adenomas, successful surgical resection leads to endocrinological remission, characterized by a marked reduction in circulating levels of the hypersecreted pituitary hormone and its corresponding target-organ hormone [1–3]. However, the clinical implications of postoperative hormonal decline differ depending on the type of hormone secreted by the tumor. In acromegaly, for instance, successful transsphenoidal surgery leads to a substantial reduction in circulating growth hormone (GH) levels, yet routine postoperative hormone replacement is generally unnecessary [4]. In contrast, successful resection of an adrenocorticotropic hormone (ACTH)-secreting tumor in patients with Cushing's disease frequently results in transient adrenal insufficiency due to suppression of the hypothalamic–pituitary–adrenal axis. Given the risk of hypotension, hyponatremia, and potentially life-threatening adrenal crisis, postoperative glucocorticoid replacement is often required [5]. These contrasting endocrine outcomes raise an important question regarding the postoperative course of thyroid-stimulating hormone (TSH)-secreting pituitary adenomas (TSHomas). TSHomas are rare functioning pituitary adenomas characterized by autonomous TSH secretion and consequent thyrotoxicosis [6]. Following successful surgical resection, circulating TSH levels decline rapidly [7]. Although transient hypothyroidism requiring levothyroxine replacement may develop postoperatively, the subsequent recovery of the hypothalamic–pituitary–thyroid axis, particularly the restoration of endogenous TSH secretory responsiveness, remains poorly understood.

To address this knowledge gap, we investigated patients with TSHoma who achieved surgical remission and maintained long-term disease control. The primary objectives were to identify clinical and tumor-related factors associated with the need for postoperative levothyroxine replacement and to determine the duration of replacement therapy. Furthermore, we longitudinally assessed the recovery of endogenous TSH secretory responsiveness using serial combined pituitary function tests (CPFTs), aiming to elucidate the temporal dynamics of pituitary–thyroid axis recovery following successful surgical treatment of TSHoma.

Materials and methods

Study population

This retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of our institution. The requirement for written informed consent was waived owing to the retrospective study design. We retrospectively reviewed the medical records of 40 patients who underwent transsphenoidal surgery for endocrinologically and radiologically diagnosed TSHomas between July 2006, and May 2024. All patients had histopathologically confirmed TSHomas and achieved early surgical remission, defined as an undetectable serum TSH level on postoperative day 7 and gross total resection confirmed by immediate postoperative magnetic resonance imaging (MRI).

Of the 40 patients, two who experienced disease recurrence requiring additional treatment and one who had undergone total thyroidectomy before pituitary surgery were excluded. Sustained remission was defined as persistent biochemical disease control without biochemical or radiological evidence of recurrence throughout follow-up. One additional patient who developed Hashimoto thyroiditis during follow-up was excluded because subsequent thyroid function could not be attributed solely to pituitary TSH secretion. Consequently, 36 patients were included in the final analysis of postoperative thyroid-axis outcomes (**Fig. 1**).

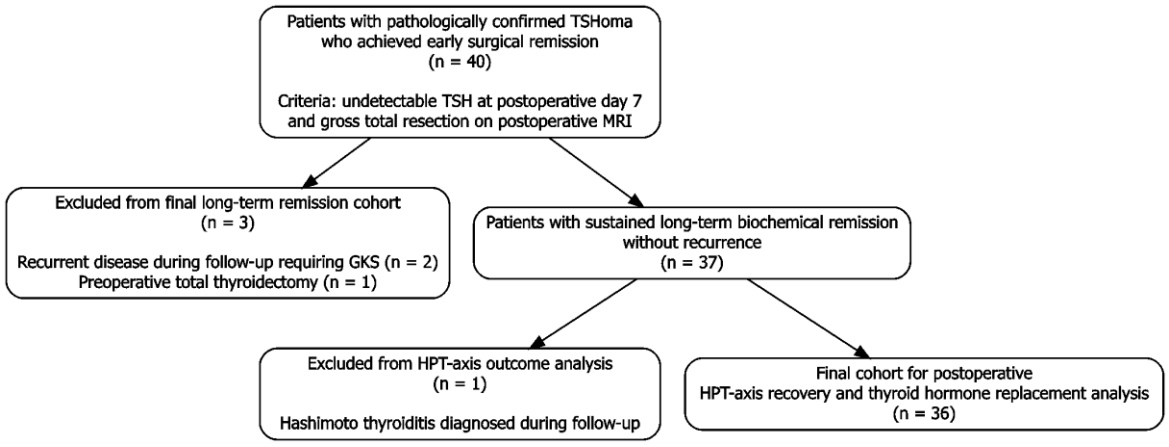


Figure 1. Patient selection flow diagram. Flow diagram showing patient selection for the analysis of postoperative HPT-axis recovery and thyroid hormone replacement.
Abbreviations: GKS, gamma knife surgery; HPT, hypothalamic–pituitary–thyroid; TSHoma, TSH-secreting pituitary adenoma.

For the longitudinal analysis of CPFTs, five patients without evaluable postoperative CPFT data were further excluded, leaving 31 patients for the time-to-recovery analysis of stimulated TSH responsiveness.

Hormonal evaluation

Patients with normal or elevated serum TSH concentrations in the presence of elevated free thyroxine (free T4) levels were considered to have secondary hyperthyroidism. In patients requiring preoperative antithyroid treatment, thyroid function was assessed serially until free T4 levels were sufficiently controlled to permit surgery. Preoperative and postoperative endocrine evaluations included basal measurements of anterior pituitary hormones, including GH, prolactin, TSH, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), together with their corresponding target hormones, including insulin-like growth factor 1 (IGF-1), free T4, T3, testosterone, and estradiol. Postoperative basal thyroid function tests were performed at approximately 1, 3, 6, 12, 18, and 24 months after surgery and subsequently at 6- to 12-month intervals. Postoperative levothyroxine replacement was initiated when serum free T4 decreased below the institutional reference range (0.80–1.23 ng/dL), or when free T4 was near the lower limit of the reference range in the presence of clinical symptoms suggestive of hypothyroidism. The timing of initiation and discontinuation of levothyroxine replacement was determined from longitudinal biochemical and clinical follow-up. Transient levothyroxine replacement was defined as postoperative levothyroxine treatment that was subsequently discontinued after recovery of sufficient endogenous thyroid function.

To assess anterior pituitary function, CPFT was performed using intravenous administration of regular insulin (0.1 IU/kg), thyrotropin-releasing hormone (TRH; 500 μg), and luteinizing hormone-releasing hormone (LHRH; 100 μg) [8]. The CPFT was used to evaluate multiple anterior pituitary axes, including the hypothalamic–pituitary–adrenal (HPA), GH, gonadal, and hypothalamic–pituitary–thyroid (HPT) axes. A peak serum cortisol concentration ≥18 μg/dL (approximately 500 nmol/L) after insulin-induced hypoglycemia was considered an adequate HPA-axis response, whereas a peak GH concentration ≥5 ng/mL was considered an adequate GH-axis response [9]. Gonadotropin responses to LHRH stimulation were assessed as part of routine anterior pituitary evaluation. Because LH and FSH responses vary according to age, sex, and menopausal status, no single uniform cutoff was applied to define an adequate

gonadal-axis response; responses were interpreted according to the relevant clinical context. The gonadal axis was therefore not included as a longitudinal outcome in the present study. Because the primary objective was to evaluate recovery of stimulated pituitary TSH responsiveness, TSH responses to TRH stimulation were analyzed longitudinally as the principal CPFT outcome. An adequate TSH response was defined as an increase in serum TSH of ≥5 mIU/L above the baseline value after TRH stimulation [10]. Recovery of stimulated TSH responsiveness was defined as the first postoperative CPFT demonstrating an adequate TSH response. To characterize overall pituitary hormonal status before and after surgery, HPA-, GH-, and HPT-axis responses were additionally assessed at the preoperative CPFT, first postoperative CPFT, and last available CPFT. At each time point, an axis was classified as intact when the corresponding adequate response criterion was met. The gonadal axis was excluded from this longitudinal comparison because of the absence of a uniform response criterion across age, sex, and menopausal status. Basal serum TSH and free T4 concentrations were used to monitor thyroid status and guide levothyroxine treatment but were not used to define recovery of stimulated TSH responsiveness, because basal hormone concentrations may not fully reflect pituitary TSH secretory reserve [11, 12]. CPFTs were performed preoperatively and during postoperative follow-up, typically at 6 months and 2, 4, 6, and 8 years after surgery.

Radiologic evaluation

All patients underwent preoperative dynamic MRI of the sellar region using either a 1.5-T system (Signa; General Electric) or a 3-T system (Achieva; Philips). Immediate postoperative MRI was performed to assess the extent of tumor resection. Follow-up MRI was subsequently performed at approximately 1, 2, 4, 6, 8, and 10 years after surgery as part of long-term surveillance. Tumors were characterized according to the modified Hardy radiological classification [13]. Maximum tumor diameter and tumor volume were determined from preoperative MRI. Cavernous sinus invasion was assessed on preoperative MRI and classified according to the Knosp classification [14]. The presence of suprasellar extension was also recorded for analysis.

Surgical procedures

Patients with preoperative free T4 concentrations ≥2.0 ng/dL were treated with antithyroid agents, including methimazole or propylthiouracil, until free T4 decreased below 2.0 ng/dL. In patients receiving preoperative antithyroid medication, treatment was discontinued within 2–3 days after surgery following postoperative endocrinological assessment. This perioperative strategy was used to control thyrotoxicosis and reduce the risk of perioperative thyroid storm [15]. From July 2006 to August 2017, tumor removal was performed using conventional microscopic transsphenoidal surgery (TSS), whereas an endoscopic transsphenoidal approach was adopted thereafter. Resection techniques were categorized as en bloc capsulectomy, fragmented capsulectomy, or piecemeal resection, as described previously [16]. En bloc capsulectomy was preferentially attempted when the tumor was completely surrounded by a distinct pseudocapsule. When the pseudocapsule was incomplete or poorly developed, fragmented capsulectomy or piecemeal resection was performed. The choice of surgical technique was based on tumor location, size, consistency, and extension into the cavernous sinus or suprasellar space. Gross total resection was pursued whenever safely feasible. Resected tumor specimens underwent histopathological evaluation, including immunohistochemical staining for anterior pituitary hormones and assessment of the Ki-67 labeling index. Early surgical remission and sustained long-term disease control were assessed using postoperative biochemical and radiological evaluations as defined above.

Statistical analysis

Continuous variables were summarized as medians with interquartile ranges (IQRs), and categorical variables were summarized as numbers and percentages. Continuous variables were compared between patients who did and did not require transient postoperative levothyroxine replacement using the Wilcoxon rank-sum test. Categorical variables were compared using Fisher's exact test because of the small sample size. Logistic regression analyses were performed to identify factors associated with the requirement for transient postoperative levothyroxine replacement. Univariable logistic regression analyses were initially performed for candidate clinical, endocrine, tumor, surgical, and pathological variables. Because maximum tumor diameter and tumor volume represent closely related measures of tumor size, maximum tumor diameter was selected as the representative tumor-size variable for regression analyses. Given

the limited number of patients requiring postoperative levothyroxine replacement, a parsimonious multivariable model was constructed to reduce the risk of overfitting. The multivariable model included maximum tumor diameter and en bloc resection, with en bloc resection selected as a clinically relevant surgical variable. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminative ability of maximum tumor diameter for predicting the requirement for postoperative levothyroxine replacement. The area under the ROC curve (AUC) was calculated, and the optimal cutoff value was determined using the Youden index. Sensitivity and specificity at the optimal cutoff were subsequently calculated.

Time to recovery of stimulated TSH responsiveness was analyzed using the Kaplan–Meier method. Recovery was defined as the first postoperative CPFT demonstrating an increase in serum TSH of ≥5 mIU/L above the baseline value following TRH stimulation. Time to recovery was calculated from the date of surgery to the date of the first CPFT demonstrating recovery. Patients who did not demonstrate recovery during follow-up were censored at the date of their last available CPFT. The median time to recovery and corresponding 95% CI were estimated using the Kaplan–Meier method. To characterize overall pituitary hormonal status before and after surgery, the proportions of patients with intact HPA-, GH-, and HPT-axis responses were descriptively summarized at the preoperative CPFT, first postoperative CPFT, and last available CPFT. Because the number of evaluable patients differed across time points, proportions were calculated using the number of patients with available data for each axis at each time point as the denominator. All statistical tests were two-sided, and a P value <0.05 was considered statistically significant. All statistical analyses were performed using R statistical software (version 4.4.1).

Results

General description of the cohort

Total 36 patients were included to the final analysis. The mean follow-up duration was 6.5 ± 3.8 years, with a maximum follow-up of 15.5 years. Twenty-two of the 36 patients (61.1%) received preoperative antithyroid medication for the control of hyperthyroidism. Ten patients (27.8%) required transient postoperative levothyroxine replacement, whereas none required permanent replacement during long-term follow-up. Levothyroxine replacement was initiated at

a median of 36 days (IQR, 16.2–71.5 days) after surgery and continued for a median duration of 140 days (IQR, 64.8–181 days) (**Fig. 2**).

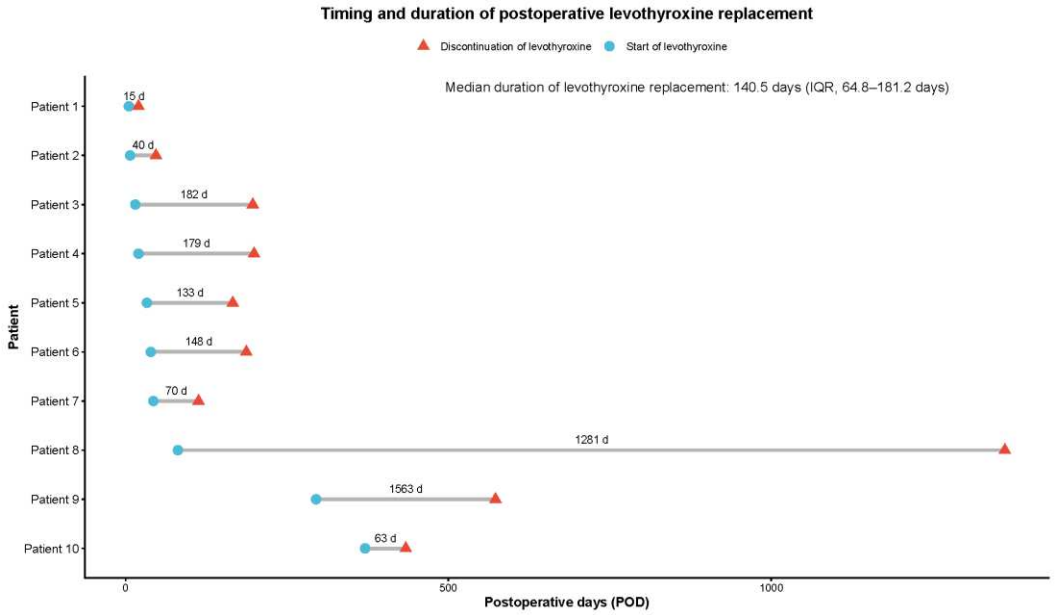


Figure 2. Timing and duration of postoperative levothyroxine replacement. Timing and duration of postoperative levothyroxine replacement in the 10 patients who required transient replacement therapy. Circles indicate initiation and triangles indicate discontinuation of levothyroxine.
Abbreviations: IQR, interquartile range; POD, postoperative day

Comparison according to postoperative levothyroxine replacement

Baseline clinical, endocrine, radiological, surgical, and pathological characteristics stratified by the need for transient postoperative levothyroxine replacement are summarized in **Table 1**. No significant differences were observed between the replacement and non-replacement groups in sex, age, body mass index (BMI), preoperative antithyroid medication use, preoperative T3 or free T4 levels, hormonal phenotype, Knosp classification, suprasellar extension, en bloc resection, or Ki-67 labeling index. Patients requiring postoperative levothyroxine replacement had significantly larger tumors than those who did not. The median maximum tumor diameter was 1.80 cm (IQR, 1.70–2.10) in the replacement group versus 1.40 cm (IQR, 1.10–1.70) in the non-replacement group (P = 0.003). Similarly, the median tumor volume was significantly greater in the replacement group (1.25 cm^3 [IQR, 0.90–4.00] vs. 0.60 cm^3 [IQR, 0.30–1.10]; P = 0.002). Although suprasellar extension (70% vs. 46%; P = 0.274) and en bloc resection (70% vs. 42%; P = 0.264) were more frequent in the replacement group, neither difference reached statistical significance.

Table 1. Baseline characteristics according to postoperative levothyroxine replacement

Characteristics	Overall	Hormone replacement		p-value
		Replacement (-) (n=26)	Replacement (+) (n=10)	
Sex (female)	20 (56%)	14 (54%)	6 (60%)	>0.999
Age, median (Q1,Q3), years	40 (36, 49)	40 (37, 44)	41 (32, 53)	0.735
BMI, median(Q1,Q3), kg/m^2	22.34 (21.15, 24.26)	22.34 (21.07, 24.35)	22.23 (21.39, 24.16)	0.903
Preoperative antithyroid medication	22 (61%)	16 (62%)	6 (60%)	>0.999
Preoperative T3 level(ng/mL)	1.61 (1.43, 1.94)	1.61 (1.44, 1.98)	1.59 (1.39, 1.89)	0.933
Preoperative free T4 level (ng/dL)	1.55 (1.40, 1.84)	1.55 (1.35, 1.90)	1.56 (1.46, 1.67)	>0.999
Hormonal phenotype				0.772
TSH alone	12 (33%)	9 (35%)	3 (30%)	
TSH+GH	15 (42%)	10 (38%)	5 (50%)	
TSH+PRL	3 (8.3%)	3 (12%)	0 (0%)	
TSH+GH+PRL	6 (17%)	4 (15%)	2 (20%)	
Tumor diameter (cm)	1.60 (1.35, 1.90)	1.40 (1.10, 1.70)	1.80 (1.70, 2.10)	0.003*
Tumor volume (cm^3)	0.80 (0.30, 1.15)	0.60 (0.30, 1.10)	1.25 (0.90, 4.00)	0.002*
Knosp classification				0.298
0	17 (47%)	13 (50%)	4 (40%)	
1	11 (31%)	9 (35%)	2 (21%)	
2	7 (19%)	4 (15%)	3 (30%)	
3	1 (2.8%)	0 (0%)	1 (10%)	
Suprasellar extension	19 (53%)	12 (46%)	7 (70%)	0.274
En bloc resection	18 (50%)	11 (42%)	7 (70%)	0.264
Ki-67 labeling index				0.906
0-1%	22 (61%)	16 (62%)	6 (60%)	
1-2%	8 (22%)	6 (23%)	2 (20%)	
2-3%	5 (14%)	3 (12%)	2 (20%)	
3-4%	1 (2.8%)	1 (3.8%)	0 (0%)	

Values are presented as median (Q1, Q3) for continuous variables and n (%) for categorical variables.

*, p-value < 0.05

Abbreviations: BMI, body mass index; GH, growth hormone; PRL, prolactin; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; Q1, first quartile; Q3, third quartile.

In univariable logistic regression analysis, maximum tumor diameter was significantly associated with the need for transient postoperative levothyroxine replacement (OR, 24.7; 95% CI, 2.74–803; P = 0.026). No other evaluated clinical, endocrine, radiological, surgical, or

pathological variables showed a significant association. Given the limited number of outcome events, a parsimonious multivariable model incorporating maximum tumor diameter and en bloc resection was constructed. Maximum tumor diameter remained significantly associated with postoperative levothyroxine replacement after adjustment for en bloc resection (adjusted OR, 26.5; 95% CI, 2.68–1416; P = 0.038), whereas en bloc resection was not significantly associated with replacement (adjusted OR, 3.66; 95% CI, 0.59–33.8; P = 0.191) (Table 2).

Table 2. Logistic regression analyses of factors associated with postoperative levothyroxine replacement

Analysis	Univariate analysis			Multivariate analysis		
Variables	OR	95% CI	P-value	OR	95% CI	P-value
Sex (female)	0.78	0.16, 3.39	0.740			
Age, per year	1.00	0.91, 1.08	0.940			
BMI, per kg/m^2	0.96	0.66, 1.36	0.824			
Preoperative antithyroid medication	0.94	0.21, 4.44	0.932			
Preoperative T3, per ng/mL	1.32	0.19, 8.74	0.768			
Preoperative fT4, per ng/dL	0.54	0.04, 5.43	0.612			
Tumor diameter, per cm	24.7	2.74, 803	0.026*	26.5	2.68, 1,416	0.038*
En bloc resection	3.18	0.71, 17.5	0.146	3.66	0.59, 33.8	0.191
Knosp classification, per 1-grade increase	1.82	0.78, 4.51	0.172			
Suprasellar extension	2.72	0.61, 14.9	0.207			
Ki-67, per 1-category increase [1]	1.03	0.10, 2.43	0.940			

Univariable and multivariable logistic regression analyses of factors associated with postoperative levothyroxine replacement. [1]Ki-67 categories were coded as 0–1%, 1–2%, 2–3%, and 3–4%.
*, p-value < 0.05
Abbreviations: BMI, body mass index; CI, confidence interval; fT4, free thyroxine; OR, odds ratio; T3, triiodothyronine

Tumor diameter cutoff for postoperative levothyroxine replacement

ROC curve analysis demonstrated that maximum tumor diameter had an AUC of 0.81 for discriminating patients who required postoperative levothyroxine replacement from those who did not. The optimal cutoff value, determined using the Youden index, was 1.45 cm, yielding a

sensitivity of 100% and a specificity of 53.8%. Notably, no patient with a maximum tumor diameter below 1.45 cm required postoperative levothyroxine replacement (**Supplementary Fig. S1**).

Recovery of stimulated TSH responsiveness during postoperative follow-up

Of the 36 patients included in the postoperative thyroid-axis outcome cohort, five were excluded from the longitudinal CPFT analysis because of unavailable or unevaluable postoperative CPFT data. Consequently, 31 patients were included in the analysis of stimulated TSH responsiveness. The mean duration of CPFT follow-up was 4.1 ± 2.4 years, with a maximum of 8.9 years. During follow-up, 22 of 31 patients (71.0%) demonstrated recovery of stimulated TSH responsiveness, whereas the remaining nine patients had not achieved recovery by their last available CPFT and were censored. Kaplan–Meier analysis yielded an estimated median time to recovery of 2.02 years (95% CI, 1.64–4.04 years) (**Fig. 3**).

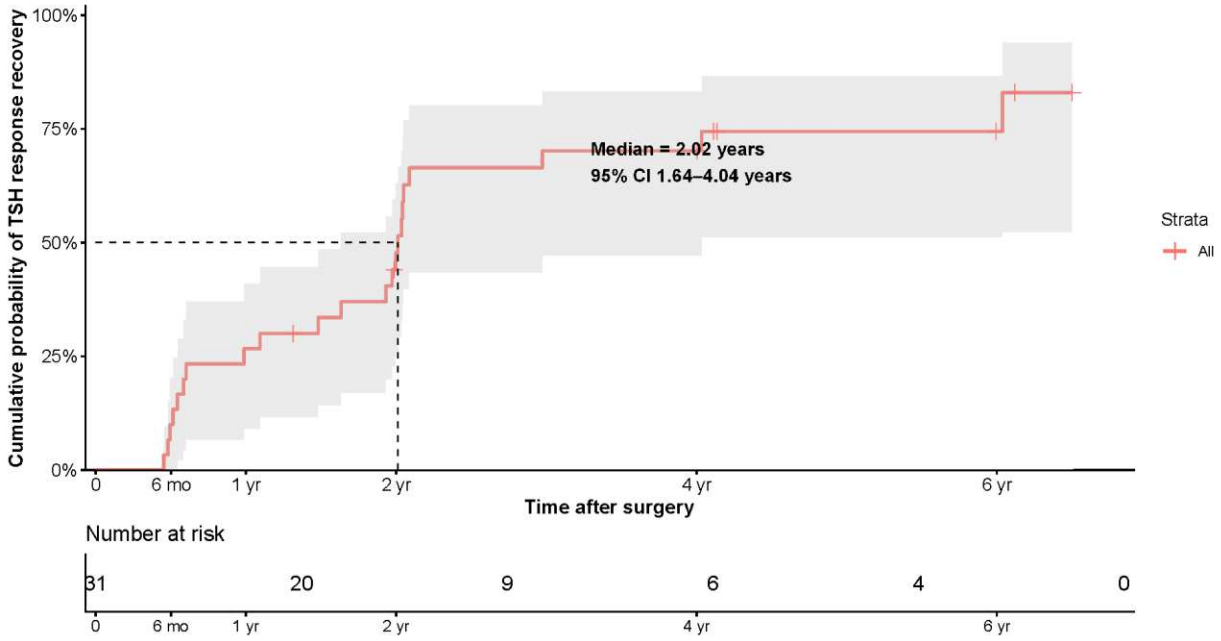


Figure 3. **Postoperative recovery of TSH responsiveness after surgical remission of TSHoma.**
Kaplan–Meier analysis of postoperative TSH response recovery assessed by serial CPFT. Median time to recovery was 2.02 years (95% CI, 1.64–4.04).
Abbreviations: CI, confidence interval; CPFT, combined pituitary function test; TSH, thyroid-stimulating hormone

Pituitary hormonal status before and after surgery

Longitudinal changes in pituitary hormonal status across the hypothalamic–pituitary–adrenal (HPA), growth hormone (GH), and hypothalamic–pituitary–thyroid (HPT) axes are

summarized in **Supplementary Table S1**. The proportions of patients with intact HPA- and GH-axis responses were 74.1% (20/27) and 70.4% (19/27), respectively, before surgery, compared with 64.5% (20/31) for both axes at the first postoperative CPFT. In contrast, the proportion of patients with an intact HPT-axis response increased from 25.9% (7/27) preoperatively to 38.7% (12/31) at the first postoperative CPFT and further to 59.3% (16/27) at the last available CPFT.

Discussion

In this study of patients with TSHoma who achieved surgical remission and maintained long-term disease control, 27.8% required transient postoperative levothyroxine replacement, whereas none required permanent replacement. Larger tumor diameter was significantly associated with the need for postoperative levothyroxine replacement, even after adjustment for surgical technique. Furthermore, stimulated TSH responsiveness recovered in 71.0% of patients undergoing longitudinal CPFT assessment, with an estimated median time to recovery of 2.02 years. These findings suggest that postoperative impairment of endogenous TSH secretory responsiveness following successful TSHoma resection is often reversible, although physiological recovery may extend over several years. Following successful resection of TSHoma, circulating TSH levels decline rapidly, whereas thyroid hormone concentrations may decrease more gradually. This delayed decline may be attributable, at least in part, to intrathyroidal hormone stores and the relatively long circulating half-life of thyroxine (T4) [17, 18]. Consequently, clinically significant thyroid hormone deficiency may not become apparent until several weeks after surgery, despite the abrupt reduction in TSH secretion. In our cohort, levothyroxine replacement was initiated at a median of 36 days (IQR, 16.2–71.5 days) postoperatively. All patients requiring replacement subsequently discontinued treatment, with a median replacement duration of 140 days (IQR, 64.8–181 days). Although 61.1% of patients received preoperative antithyroid medication, which was discontinued within 2–3 days after surgery, its use was not significantly associated with the need for postoperative levothyroxine replacement. These observations highlight the importance of continued thyroid function monitoring during the early postoperative period, even in patients who achieve immediate biochemical remission.

Larger tumor diameter was significantly associated with the need for transient postoperative levothyroxine replacement after adjustment for en bloc resection. Larger tumors

may cause greater compression of the residual normal pituitary gland and make preservation of functional pituitary tissue more challenging during surgery, potentially contributing to transient impairment of endogenous TSH secretion [19]. This interpretation is consistent with previous studies demonstrating an association between larger pituitary tumors and postoperative pituitary dysfunction [20, 21]. Receiver operating characteristic (ROC) analysis identified a maximum tumor diameter of 1.45 cm as an exploratory threshold for predicting postoperative levothyroxine replacement, with an area under the curve of 0.81, sensitivity of 100%, and specificity of 53.8%. Notably, no patient with a tumor diameter below this threshold required replacement. Nevertheless, given the modest specificity, small cohort size, and limited number of replacement events (n = 10), this cutoff should be interpreted cautiously and requires external validation before clinical application.

An important finding of this study was the gradual recovery of stimulated TSH responsiveness during long-term postoperative follow-up. Among 31 patients with evaluable postoperative CPFT data, 22 (71.0%) demonstrated recovery of stimulated TSH responsiveness over a mean follow-up period of 4.1 ± 2.4 years. Kaplan–Meier analysis estimated a median time to recovery of 2.02 years (95% CI, 1.64–4.04 years). These findings suggest that restoration of endogenous pituitary TSH secretory responsiveness may continue for several years following successful TSHoma resection, even after clinical thyroid function has recovered sufficiently to permit discontinuation of levothyroxine replacement. Importantly, recovery of stimulated TSH responsiveness represents a physiological outcome distinct from the restoration of sufficient thyroid hormone production to maintain euthyroidism without replacement therapy.

Previous studies involving nonfunctioning pituitary adenomas have reported relatively limited recovery of central hypothyroidism following surgery. In one prospective multicenter study, thyroid-axis function recovered in only 11.1% of patients with preoperative hypothyroidism at 6 months after surgery [22]. Although direct comparisons are limited by differences in patient populations, underlying pathophysiology, follow-up duration, and definitions of endocrine recovery, the relatively high proportion of patients demonstrating recovery of stimulated TSH responsiveness in our cohort raises the possibility that postoperative HPT-axis dysfunction in TSHoma may involve reversible functional impairment in addition to structural compression or surgical injury. Prolonged autonomous TSH secretion and the resulting thyrotoxicosis may suppress the secretory responsiveness of normal thyrotrophs through negative

feedback mechanisms. Following removal of the tumor and resolution of thyrotoxicosis, these previously suppressed thyrotrophs may gradually regain their responsiveness to TRH stimulation. Although this proposed mechanism provides a plausible explanation for the delayed recovery observed in our cohort, it remains hypothetical and warrants further investigation.

Basal TSH and free T4 measurements are essential for assessing thyroid status and guiding postoperative levothyroxine replacement. However, they may not fully characterize the functional reserve of normal pituitary thyrotrophs. TRH stimulation testing provides complementary information regarding endogenous TSH secretory responsiveness, allowing assessment of physiological recovery beyond normalization of basal thyroid hormone concentrations. Serial CPFT assessment in the present study enabled longitudinal evaluation of this recovery over an extended postoperative period. In addition, the proportion of patients with an intact HPT-axis response increased from 25.9% preoperatively to 38.7% at the first postoperative CPFT and 59.3% at the last available CPFT. In contrast, no comparable increase was observed in the proportions of patients with intact HPA- or GH-axis responses. These findings suggest that restoration of TSH responsiveness may reflect an axis-specific recovery process rather than generalized improvement in anterior pituitary function. However, these comparisons were descriptive, involved different numbers of evaluable patients across time points, and should therefore be interpreted cautiously.

Several limitations should be acknowledged. First, this was a retrospective, single-center study involving a relatively small cohort, reflecting the rarity of TSHoma. The limited number of patients requiring postoperative levothyroxine replacement resulted in wide confidence intervals and restricted the number of covariates that could be included in the multivariable regression model. Second, CPFTs were performed at variable intervals during follow-up, preventing precise determination of the timing of TSH responsiveness recovery. Recovery was assigned to the first CPFT demonstrating an adequate stimulated TSH response, although physiological recovery may have occurred earlier. Accordingly, the estimated time to recovery should be interpreted in the context of intermittent testing. Third, longitudinal comparisons of HPT-, HPA-, and GH-axis function were descriptive and included different numbers of evaluable patients at each time point, limiting direct within-patient comparisons. Fourth, recovery of stimulated TSH responsiveness was defined using a standardized TRH stimulation criterion, which may not fully capture all aspects of physiological thyroid-axis recovery. Finally, the study population was

restricted to patients who achieved surgical remission and maintained sustained disease control. Patients with persistent or recurrent disease were excluded because ongoing autonomous TSH secretion could confound the assessment of endogenous pituitary TSH recovery. Therefore, the findings may not be generalizable to patients with incomplete resection or recurrent TSHoma.

Conclusion

Endogenous TSH secretory responsiveness recovered in most patients following successful surgical treatment of TSHoma, although recovery often occurred over an extended period. Larger tumor diameter was associated with an increased likelihood of transient postoperative levothyroxine replacement, with a diameter of 1.45 cm identified as a potential threshold for identifying patients who may benefit from closer postoperative thyroid function monitoring. However, this exploratory cutoff requires further validation. These findings highlight the reversible nature of postoperative TSH secretory impairment and underscore the importance of long-term assessment of thyroid-axis function following successful TSHoma surgery.

Author contributions

So Young Won: data curation, formal analysis, writing - original draft, formal analysis; Seonah Choi: data curation; Yoon-a Hwang: data curation; Soyoon Jin: data curation; Ju Hyung Moon: data curation; Cheol Ryong Ku: data curation; Eun Jig Lee: writing - review & editing; Sun Ho Kim: writing - review & editing; Eui Hyun Kim: conceptualization, formal Analysis, writing - review & editing, funding acquisition, resources, project administration

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Data availability

Some or all datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Ethics approval This study was approved by the Institutional Review Board of Severance hospital (approval No 4-2025-1729), and the requirement for informed consent was waived. The authors declare no competing interests.

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