Detecting Recurrence Following Lobectomy for Thyroid Cancer: Role of Thyroglobulin and Thyroglobulin Antibodies

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Background: The use of thyroglobulin (Tg) and thyroglobulin antibodies (TgAb) for detecting disease recurrence is well validated following total thyroidectomy and radioiodine ablation. However, limited data are available for patients treated with thyroid lobectomy.

Methods: Patients who had lobectomy for papillary thyroid cancer followed for >1 year, with sufficient data on Tg and TgAb, including subgroup analysis for Hashimoto's thyroiditis and contralateral nodules.

Results: One-hundred sixty-seven patients met the inclusion criteria. Average tumor size was 9.5 ± 6 mm. Following lobectomy, Tg was 12.1 ± 14.8 ng/mL. Of 52 patients with Hashimoto's thyroiditis, 38% had positive TgAb with titers of 438 ± 528 IU/mL, and in patients without TgAb the mean Tg level was 14.7 ± 19.0 ng/mL. In 34 patients with contralateral nodules ≥1 cm, Tg was 15.3 ± 17 ng/mL. During the first 2 years of follow-up, Tg declined ≥1 ng/mL in 42% of patients (by 5.1 ± 3.7 ng/mL), remained stable in 22%, and increased in 36% (by 4.9 ± 5.7 ng/mL). During a mean follow-up of 6.5 years (78 ± 43.5 months), 18 patients had completion thyroidectomy and 12 were diagnosed with contralateral cancer (n = 8) or lymph node metastases (n = 4). In patients with recurrence followed for >2 years, there was a rise in Tg in 3 cases, Tg was stable in 2 cases, and in 1 TgAb decreased from 1534 to 276 IU/mL despite metastatic lymph nodes. Basal Tg and Tg dynamics did not predict disease recurrence.

Conclusions: Serum thyroglobulin used independently is of limited value for predicting or detecting disease recurrence following thyroid lobectomy. Other potential roles of Tg, such as detecting distant metastases following lobectomy, should be further studied. **(*J Clin Endocrinol Metab* 105: e2145–e2151, 2020)**

Freeform/Key Words: papillary thyroid carcinoma, lobectomy, thyroglobulin, thyroglobulin antibodies, recurrence

Dynamic risk stratification has been accepted in recent years as an integral part of differentiated thyroid cancer (DTC) management and follow-up. A response to therapy (RTT) system, first proposed in 2010 by Tuttle et al. (1) and later validated in multiple studies as well as endorsed by the 2015 American Thyroid Association (ATA) guidelines (2-8), is based on data collected within the first 1 to 2 years after initial

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 5 February 2020. Accepted 25 March 2020.
First Published Online 27 March 2020.
Corrected and Typeset 23 April 2020.

Abbreviations: AJCC, American Joint Committee on Cancer; ATA, American Thyroid Association; DTC, differentiated thyroid cancer; ETE, extrathyroidal extension; FNA, fine needle aspiration; HT, Hashimoto's thyroiditis; PTC, papillary thyroid carcinoma; RAI, radioiodine; RTT, response to therapy; Tg, thyroglobulin; TgAb, thyroglobulin antibodies; TSH, thyrotropin; TT, total thyroidectomy; U/S, ultrasound.

therapy with total thyroidectomy (TT) and radioiodine (RAI) ablation. These data include neck ultrasound (U/S) and basal serum thyroglobulin (Tg), Tg antibodies (TgAb), together with recombinant human TSH (rhTSH)-stimulated Tg. The results of the RTT assessment are categorized as excellent, indeterminate, biochemical incomplete, or structural incomplete, and have major implication on patients' follow-up and the need for thyrotropin (TSH) suppression (9).

The clinical utility of this RTT system prompted the development of response to therapy systems for patients treated with TT without RAI ablation, and for patients treated with lobectomy alone (8). With regard to lobectomy, Momesso et al. suggested an RTT system which was validated by 2 additional studies based on neck U/S and basal Tg levels, with a Tg threshold of <30 ng/mL for the definition of excellent response to therapy (10-12). While this system proved effective in predicting long-term risk of recurrence, a recent study questioned the 30 ng/mL threshold, showing that Tg levels and Tg/TSH ratio increased gradually after lobectomy in patients with and without recurrences, without any significant difference (13).

In order to assess the clinical significance of Tg levels following lobectomy for papillary thyroid carcinoma (PTC) in various subgroups (Hashimoto's thyroiditis [HT], contralateral nodules) and in patients with disease recurrence, we performed a study of postsurgical and longitudinal dynamics of Tg and TgAb levels in patients treated with lobectomy.

Methods

Study design, subjects, and data collection

Inclusion criteria for the study were adult patients (≥18 years) who had lobectomy for PTC with a minimum follow-up period of 1 year without completion thyroidectomy, and who had sufficient data on Tg and TgAb levels during follow-up. Decisions on the extent of surgery were at the discretion of the treating physician, with consideration for patient preference. Exclusion criteria included histopathological diagnoses other than PTC, size >4 cm, gross extrathyroidal extension (ETE), cervical lymph node metastases, or distant metastases. HT was determined on the basis of 1 or more of the following: histological report documenting lymphocytic thyroiditis; preoperative diagnosis of hypothyroidism without prior RAI therapy or prior surgery; or positive antithyroid antibodies (thyroid peroxidase autoantibodies or TgAb). In patients with nodules in the nonexcised lobe, nodules were documented if measured ≥3 mm in the longest diameter. Disease stage was determined based on the eighth edition of the American Joint Committee on Cancer (AJCC) staging system (14). The follow-up period was defined as the time between removal of the first lobe and the last documented laboratory tests for TSH, Tg, and TgAb, or the day of completion thyroidectomy surgery.

The electronic records at Rabin Medical Center, a tertiary university-affiliated medical center, were screened for all patients who had thyroid lobectomy for PTC between 2002 and 2017. The following data were collected from the patients' charts: demographics, medical history and physical examination results, thyroid and neck U/S scans, fine needle aspiration (FNA) cytology, serum levels of TSH, Tg, TgAb, thyroid peroxidase autoantibodies, levothyroxine therapy, surgical reports, histopathology, RAI therapy, and outcome. Tg levels, TgAb, and TSH were documented following surgery (at least 3 months after surgery) and then annually for a maximum of 6 years. Levels of TSH, free T4 (FT4), Tg, and TgAb were measured by chemiluminescence assay (DPC 2000 Immulite; Siemens Healthcare Diagnostics, Eschborn, Germany).

The study protocol was approved by the institutional research ethics committee.

Statistical analysis

All statistical analyses were performed with the SPSS v0.23.0 (IBM Corp., Armonk, NY, USA). Associations between 2 categorical variables were examined using the chi-square test and Fisher's exact test. The *t*-test or Mann–Whitney nonparametric U test were used to compare differences between 2 independent groups when the dependent variable was either ordinal or continuous. The 1-way analysis of variance was used to compare differences between means of more than 2 independent groups when the dependent variable was either ordinal or continuous. Associations between 2 continuous variables were examined using the Pearson product–moment correlation test or the Spearman rank-order correlation test. A 2-sided $P < .05$ was considered statistically significant for all analyses.

Results

Patients and disease characteristics

The study cohort consisted of 167 patients who underwent lobectomy for PTC and met inclusion criteria. The median age was 53 years (range, 9-84 years), and the female/male ratio was 7:1 (Table 1). The mean tumor size in the resected lobe was 9.5 ± 6 mm (median, 9 mm; range, 0.5-40 mm), and 49% of patients had tumor ≥1 cm. Histological patterns of PTC included classic (69%), follicular (29%), and other variants (oncocytic and tall cell in 2%). Histopathological examination of the lobectomy specimen revealed multifocal disease in 24 cases (14%), and microscopic (minimal) ETE in 15 cases (9%). All patients had stage I disease according to the AJCC staging system.

Follow-up—entire cohort

Within 1 year following thyroidectomy (range, 3-12 months), the mean Tg level for the whole cohort was 12.1 ± 14.8 ng/mL (median, 8.7 ng/mL; range, 0-103 ng/mL) (Fig. 1), and 18 patients (11%) had TgAb with titers of 438 ± 528 IU/mL. During the first 2 years Tg declined ≥1 ng/mL in 42% of patients

Table 1. Baseline characteristics of patients after lobectomy

Characteristic	All patients (N = 167)
Female gender, n (%)	146 (87)
Median age at study entry, year (range)	53 (18-84)
Mean follow-up, year ± SD	6.5 ± 3.5
Median PTC size, mm (range)	9 (0.5-40)
≥1 cm, n (%)	82 (49)
PTC variant, n (%)	
Classic	115 (69)
Follicular	49 (29)
Other	3 (2)
Multifocality	24 (14)
Minimal ETE	15 (9)
Hashimoto thyroiditis	52 (31)
AJCC 8 stage, n (%)	
Stage I, age < 55 years	90 (54)
Stage I, age ≥ 55 years	77 (46)
ATA initial risk classification, n (%)	
Low	150 (90)
Intermediate[a]	17 (10)
High	0

Abbreviations: AJCC, American Joint Committee on Cancer; ATA, American Thyroid Association; ETE, extrathyroidal extension; PTC, papillary thyroid carcinoma; SD, standard deviation.
[a]Due to minimal extrathyroidal extension or aggressive variant.

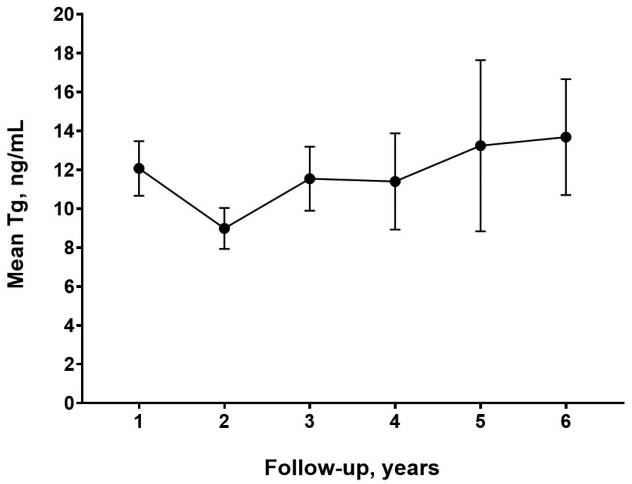

Figure 1. Mean Tg during follow-up, entire cohort.

(by 5.1 ± 3.7 ng/mL), remained stable in 22%, and increased in 36% (by 4.9 ± 5.7 ng/mL). During a 6.5-year follow-up (78 ± 43.5 months) the mean Tg levels increased by 1.6 ng/mL (13.5%); in this time period Tg declined in 45% of patients (by 5.7 ± 4.6 ng/mL), remained stable in 36%, and increased in 18% (by 32.6 ± 36.7 ng/mL). Using higher thresholds for Tg change of ≥3 ng/mL and ≥ 5 ng/mL resulted in change in 64% (40% decrease, 24% increase) and 46% (29% decrease, 17% increase) of patients, respectively. Thirteen patients had extreme Tg change of ≥20 ng/mL during follow-up, with a decrease in 5 patients (range, –22.7 to –62.3 ng/mL), none of whom had HT or recurrence, and increased in 8 patients (range, 27.1-107.4 ng/mL), of whom 2 patients had recurrence, 1 had HT, and 1 had a benign contralateral nodule. Postlobectomy Tg levels did not differ significantly between males and females (P = .77) and did not correlate with primary tumor size (≥1 cm: 12.55 ± 13.5 ng/mL, <1 cm: 11.6 ± 16.3 ng/mL, P = .97) or age (P = .310). No correlation was found between Tg levels and the resected tumor characteristics, including histopathologic variant, multifocality, and minimal ETE.

Mean TSH level 1 year after lobectomy was 2.44 ± 1.63 mIU/L (median, 2.18 mIU/L; range, 0-8.76 mIU/L). Mean TSH level from all measurements during follow-up was 2.3 ± 1.71 mIU/L, with mean maximal TSH level (highest TSH per patient) of 3.5 ± 5.2 mIU/L. To assess the association between Tg and TSH, we divided the mean first year total and maximal TSH levels into 4 categories (TSH < 0.5, TSH = 0.5–2.0, TSH = 2.01–4.00, and TSH > 4). There were no significant difference in Tg levels between groups as determined by 1-way analysis of variance.

Recurrence versus nonrecurrence groups

By the end of the follow-up period, 18 patients (11%) had completion thyroidectomy (Table 2). Twelve of these patients were diagnosed with malignant disease in the contralateral lobe and/or metastases to cervical lymph nodes. The average time to recurrence was 40 ± 30 months (median, 24.5 months; range, 15-86.5 months). Eight patients were diagnosed with contralateral PTC: 5 patients with microscopic PTC (<1 cm) and 3 patients with PTC up to 15 mm confined to the thyroid gland. Of these 8 patients, 2 had FNA before the initial surgery for 30 mm and 22 mm nodules that were benign, and repeated FNA after lobectomy was reported as Bethesda III and V categories, respectfully. The other 6 patients had FNA during follow-up because of growth in 3 patients (size change, 3-22 mm), and at the discretion of the physician in 3 cases. Four other patients were diagnosed with new neck metastases (which were not demonstrated on the preoperative U/S), based on FNA biopsy of sonographically suspicious lymph nodes. All 4 patients were surgically treated with completion thyroidectomy and lateral neck dissection of the involved side. Eleven patients with recurrent PTC received RAI therapy after surgery (range, 30-150 mCi) with no evidence of disease after an additional median follow-up of 7 years (range, 1-14.5 years).

In 11 of the 12 patients with recurrent disease, the average Tg level 1 year after lobectomy for the

Table 2. Serum Tg levels in 18 patients who had completion thyroidectomy during follow-up

						Tg levels during follow-up (ng/mL)				
No.	Age	Sex	Initial tumor sizemm	Reason for completion	Final pathology[a]	1 year	2 years	3 years	4 years	5 years
1	70	F	10	Lateral neck LN	PTC	23.3	15.6	–	37.4	–
2	44	F	10	Nodule—B4	Benign	7.1	9.08	7.99	5.69	S
3	70	F	5	Nodule—B3	Benign	–	–	–	86.7	S
4	39	F	8	Nodule—B3	PTC	18.4	19.7	37.2	S	
5	45	F	13	Nodule—B5	PTC	1.6	1.9	–	1.8	0.2
6	60	F	3	Nodule—B3	Benign	11.9	–	S		
7	25	F	10	Nodule—B4	PTC	–	–	42.7	101	40.7
8	36	F	10	Nodule growth—B2	Benign	14.5	12.6	16.1	16.5	S
9	51	F	12	Multiple nodules	PTC	29.9	11.9	S		
10	35	F	5	Lateral neck LN	PTC	47.6	51	S		
11	63	F	13	Nodule—B5	PTC	106	69.2	S		
12	57	M	4	Lateral neck LN	PTC	19.5	14.3	S		
13	66	M	4	Nodule—B3	PTC	8.9	6.71	S		
14	24	F	6	Multiple nodules	Benign	12.7	8.9	6.7	S	
15	67	F	12	Nodule—B5	PTC	10.1	2.61	S		
16	47	F	20	Physician decision	Benign	4.56	S			
17	65	M	15	Nodule—B5	PTC	9.4	12.5	17.5	20.5	S
18	37	F	5	Lateral neck LN	PTC	Ab-1534	Ab-738	Ab-276	S	

Abbreviations: F, female; M, male; PTC, papillary thyroid cancer; LN, lymph nodes; S, surgery.
[a]Of the completion thyroidectomy side.

primary tumor was 22.5 ± 22.3 ng/mL (median, 14.3 ng/mL; range, 2.6-69.2 ng/mL). One patient had a postoperative TgAb level of 1534 IU/mL. One-year Tg levels did not differ significantly between recurrence and nonrecurrence groups (22.5 ± 22.3 vs 11.3 ± 13.8 ng/mL; $P = .164$). In 6 patients with recurrent disease who were followed for >2 years there was a steady rise in Tg in 3 cases, Tg was stable in 2 cases, and in 1 case TgAb decreased from 1534 to 276 IU/mL in the presence of a new neck metastasis. In subgroup analysis for patients with primary tumor larger than 1 cm, 7 patients had recurrence with a mean postoperative Tg of 22.9 ± 32.4 ng/mL (elevated mostly due to patient no. 11 in Table 2 with Tg of 106 ng/mL), compared with 11.7 ± 11.6 ng/mL in patients without recurrence ($P = .3$). Analyzing the whole cohort, basal Tg and Tg change did not predict disease recurrence.

Further analysis of Tg levels was performed for patients with nonrecurrent disease (n = 155). Within 1 year following lobectomy, the mean Tg level was 11.3 ± 13.8 ng/mL (median, 8.2 ng/mL; range, 0-103 ng/mL). This correlates with a normal range (defined as mean ± 2 standard deviation) of 0 to 38.9 ng/mL. During the first 2 years Tg declined ≥1 ng/mL in 43% of patients (by 5.1 ± 3.7 ng/mL), remained stable in 23%, and increased in 34% (by 4.5 ± 5.3 ng/mL). During an average follow-up of 81 ± 43 months, the mean Tg levels in patients with nonrecurrent disease increased by 0.6 ng/mL (5%). In this time period Tg declined in 47% of patients (by 5.7 ± 4.7 ng/mL), remained stable in 37%, and increased in 16% (by 17.6 ± 18.5 ng/mL). None of the patients had completion thyroidectomy based on Tg levels or Tg dynamics during follow-up.

Hashimoto's thyroiditis

Fifty-two patients (31%) had a prior history of HT. One year following thyroidectomy, 38% had positive TgAb with titers of 438 ± 528 IU/mL, and in patients without TgAb the mean Tg was 14.7 ± 19.0 ng/mL (median, 4.19 ng/mL; range, 0-69.20 ng/mL). During the follow-up period Tg in HT subgroup did not change significantly (Δmean-Tg < 1 ng/mL). Tg levels in HT patients (without TgAb) did not differ significantly from Tg levels in the general study population.

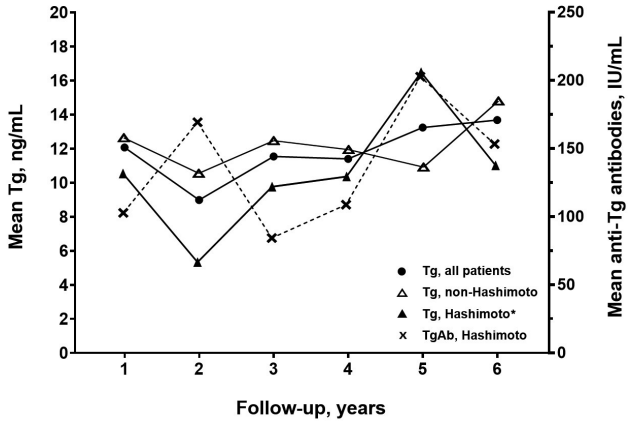

Figure 2. Mean Tg during follow-up, stratified according to Hashimoto's thyroiditis. *In patients with negative TgAb.

Contralateral thyroid nodules

A total of 104 patients (62%) had sonographically benign-appearing contralateral thyroid nodules at the time of surgery for PTC. The average size of contralateral nodules was 8.8 ± 6.2 mm (median, 6 mm; range, 2-30 mm). Thirty-four patients (20%) had contralateral nodules ≥ 1 cm. More than 1 detectable nodule was seen on U/S in 37% of patients before surgery. Of the 34 nodules ≥ 1 cm, 35% were biopsied and found to be benign (Bethesda category II) before initial surgery. One year following thyroidectomy the Tg levels in patients with contralateral nodules were 13.1 ± 16.7 ng/mL (median, 8.9 ng/mL; range 0-103 ng/mL), and in patients with contralateral nodules ≥1 cm, Tg was 15.3 ± 17 ng/mL. During the first 2 years Tg declined ≥1 ng/mL in 47% of patients (by 5.6 ± 6.8 ng/mL), remained stable in 16%, and increased in 37% (by 5 ± 4.8 ng/mL). Thyroglobulin and ΔTg levels in this subgroup of patients did not differ significantly from the general study population (Fig. 2).

Discussion

The prognostic value of Tg following lobectomy for DTC has gained interest in recent years as part of a paradigm shift aimed at risk-adapted, individualized therapy and follow-up. While Tg is a well-established component of the 2015 ATA RTT system following TT and RAI ablation, its interpretation following lobectomy is challenging. This is due to Tg produced by the remaining lobe, which shows considerable interpatient variability due to lobe size, TSH levels, lymphocytic thyroiditis, thyroid nodules, and other factors. If a lobe produces about half the Tg produced by the intact thyroid gland (range 20-60 ng/mL), then small amounts of Tg produced by persistent/recurrent cancer tissue might go unnoticed within the total amount measured.

Despite this challenge, Momesso et al. suggested an RTT system which was validated by 2 additional studies based on neck US and basal Tg levels, with a Tg threshold of <30 ng/mL for the definition of excellent response to therapy (10-12). To evaluate whether 30 ng/mL is a valid threshold, and whether Tg dynamics during follow-up can predict recurrence, we performed a study of Tg levels in patients who had lobectomy for PTC, followed for 6.5 ± 3.5 years. Our results demonstrate an overlap between Tg levels in patients with or without disease recurrence (22.5 ± 22.3 ng/mL vs 11.3 ± 13.8 ng/mL, non-significant [NS]), with no threshold that could distinguish between the 2 groups. Though in half the cases with recurrence there was a steady rise in Tg levels during follow-up, this was also observed in 34% of the nonrecurrent group. Therefore, both basal Tg levels and increasing Tg levels during follow-up were not indicators of disease recurrence.

Previously published studies evaluating RTT for patients not treated with RAI (either TT without RAI ablation or lobectomy) found it an effective tool to modify initial risk estimates of recurrent/persistent structural disease (10-12). In a study by Momesso et al. (10), biochemical incomplete response (Tg > 30 ng/mL or rising Tg) were observed in 12/187 patients (6.4%), of whom 6 patients (50%) had structural recurrence. However, the actual Tg levels were not provided for these patients in this study and also in the study by Park et al. (13) to assess how high was Tg above the 30 ng/mL threshold, and how significant was the observed increase during follow-up. A third study by Cho et al. (12) did report the Tg levels for 19 patients with structural recurrence: levels at the time of RTT restratification were 4.12 ± 4.3 ng/mL (range 0.1-12.8 ng/mL) and at the time of recurrence 5.3 ± 6.3 ng/mL (range 0.3-22.9 ng/mL). All these levels are well below 30 ng/mL, and are also lower than the average Tg levels observed in our study. This may be due to the known limitations of Tg measurement: multiple Tg immunoassays used in different centers, the complex relationship between Tg and TSH levels, the volume of residual thyroid tissue, iodine supply, and many other individual factors (15). Specifically, while TSH levels are known to affect Tg levels, the previously suggested threshold of 30 ng/mL did not suggest a target TSH or formula to correct for high or low levels. To overcome this challenge, Park et al. (13) evaluated the ratio of serum Tg divided by serum TSH levels (Tg/TSH ratio). However, the validity of this formula was not established, and is not used routinely in clinical practice. Therefore, we assessed the association between Tg and TSH by dividing the mean first year, total, and maximal TSH levels into 4 categories (TSH < 0.5, TSH = 0.5-2.0,

TSH = 2.01-4.00, and TSH > 4), with no significant difference in TG levels between groups. Overall, due to the wide variability of the observed Tg levels, we did not find significant differences between patients with an apparently normal lobe and patients with HT (without TgAb) or thyroid nodules. Therefore, a universally applicable threshold of "normal" Tg levels after lobectomy may be impossible to define.

Another potential use of Tg assessment following lobectomy is detection of rare cases with distant metastases despite apparently low-risk tumor at initial surgery. Harvey et al. (16) reported in 1990 of 84 patients treated with lobectomy for DTC, of whom 2 patients were found to have distant metastases with Tg levels >100 ng/mL. Another study by Slutzky-Shraga et al. (17), which provides indirect support for this concept, describes 7 patients diagnosed with metastatic DTC who had been initially misdiagnosed with benign follicular lesion and treated with lobectomy. Distant metastases were diagnosed 5.3 years (range, 2-13 years) after surgery. In all 6 patients with available data, Tg levels were highly elevated at detection of distant metastases (range 369-3363 ng/mL). For comparison, in our series the highest Tg level measured was 106 ng/mL (in a patient diagnosed with contralateral PTC). Although Tg was not predictive of recurrence, our data indicate that follow-up with U/S in patients with even mildly elevated Tg after lobectomy is safe, and when needed, delayed surgery is effective with excellent clinical outcomes. Conversely, in patients with highly elevated Tg (hundreds to thousands) it is reasonable to consider completion thyroidectomy to rule out metastatic disease.

The major limitation of our work is its retrospective design, which is similar to previous studies on the topic given the long follow-up required to assess for prognostic factors such as Tg. Also, while our study included 167 patients followed for 6.5 ± 3.5 years, it is possible that a larger cohort followed for many years would result in better understanding of Tg dynamics. In order to assess a homogeneous group of patients, we included only patients with PTC, and decided not to include patients with follicular carcinoma or Hurthle cell carcinoma, as these tumors tend to spread hematogenously, which may give rise to distant metastases without any locoregional disease apparent on neck U/S. As Tg may have a more crucial role in detecting disease in these cancer types, we believe this group requires separate assessment. Another potential limiting factor is the small size of primary tumors included in our study, with a median of 9 mm (range, 0.5-40 mm). As current guideline recommend performing FNA only for nodules ≥1 cm, the subgroup of microscopic PTC may not reflect patients in current practice. We therefore evaluated how the size of the primary tumor affects postoperative Tg, and found no association (with a *P*-value close to 1). Next, we performed a subgroup analysis for patients with PTC ≥1 cm, and found similar results as in the whole cohort, with a slightly higher Tg levels in the recurrence group (with high variability) and no threshold that can differentiate between recurrent and nonrecurrent disease.

In conclusion, Tg levels following lobectomy are of limited value in predicting or detecting locoregional recurrence of PTC. Potentially, Tg could be used to guide the need for completion thyroidectomy in cases of very high levels or significant increase over time, but evidence to support such an approach is of low quality. Currently, neck U/S remains the mainstay modality for follow-up after thyroid lobectomy.

Acknowledgments

***Financial Support*:** No funding was secured for this study.

Additional Information

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***Disclosure Summary*:** The authors have no financial relationships relevant to this article to disclose.

***Data availability*:** The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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