

Natural History of Contralateral Nodules After Lobectomy in Patients With Papillary Thyroid Carcinoma

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Background: Bilateral thyroid nodularity is considered an indication for total thyroidectomy in papillary thyroid carcinoma (PTC). However, the natural history and outcome of contralateral nodules have never been studied.

Objective: To investigate the natural history of nonsuspicious contralateral nodules after lobectomy for PTC.

Methods: We included patients who had one or more solid nodules (≥ 3 mm) in the contralateral lobe with benign cytology before surgery or small nonsuspicious nodules per ultrasonography.

Results: One hundred and twelve patients were included. Median age was 57 years, and median size of the PTC (initial lobectomy) was 8 mm (range, 0.5 to 28 mm). On the contralateral side, the median size of nodules was 7 mm (range, 3 to 30 mm). Thirty-three nodules (29%) had fine-needle aspiration (FNA) before surgery, and all were benign. After a median follow-up of 6 years, median growth was zero (range, -20 to 19 mm). Twenty-six nodules (23%) increased ≥ 3 mm in size (median, 6 mm; range, 4 to 19 mm). Twenty patients (18%) developed new nodules. Twelve patients (11%) underwent completion thyroidectomy for growth (three), suspicious FNA (seven; Bethesda III to V), malignancy (one), or unknown reason (one). Overall, according to the completion thyroidectomy specimen, six patients (5%) were diagnosed with contralateral PTC (five micro-PTCs, one 20 mm), and all were without evidence of disease at the end of follow-up. There were no surgical difficulties or local complications during completion surgery.

Conclusions: Lobectomy for low-risk patients with a small PTC and nonsuspicious contralateral thyroid nodule(s) is a reliable and safe initial treatment option. In the few patients who required completion thyroidectomy, treatment with surgery and radioiodine was effective. (*J Clin Endocrinol Metab* 103: 407–414, 2018)

Thyroid nodularity is very common. Nodules are clinically apparent in more than 6% of women and 1.5% of men (1, 2) and by ultrasonography (US) examination in up to 75% of women (3, 4). Thyroid cancer

occurs in 5% to 15% of patients with thyroid nodules, depending on factors such as sex, age, family history, and radiation exposure (5, 6). In the last 3 decades, there has been a rapid rise in the incidence of thyroid cancer (7, 8),

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Abbreviations: ATA, American Thyroid Association; ETE, extrathyroidal extension; FNA, fine-needle aspiration; PTC, papillary thyroid carcinoma; RAI, radioiodine; Tg, thyroglobulin; TgAb, thyroglobulin autoantibody; TSH, thyroid-stimulating hormone; US, ultrasonography.

which is attributed mainly to increased use of neck US and detection of clinically occult tumors (9, 10). Given the increasing incidence of thyroid cancer and the high prevalence of thyroid nodules, detection of contralateral nodules by US is common in patients with cytologically proven thyroid cancer scheduled for surgery.

According to the 2015 American Thyroid Association (ATA) guidelines, contralateral thyroid nodules may be a criterion for a bilateral procedure because of plans for radioiodine (RAI) therapy or to facilitate follow-up strategies or address suspicions of bilateral disease (Recommendation 35) (11). Several studies have shown the risk for contralateral papillary thyroid carcinoma (PTC) is high, with reporting rates up to 44% (12–19). However, these numbers do not take into consideration the sonographic features of the contralateral lobe by which these lesions can be detected and evaluated (17).

Recent trends in the management of thyroid cancer call into question the need for routine total thyroidectomy in patients with low-risk PTC who have a nonsuspicious or cytologically benign contralateral nodule. The decrease in use of RAI ablation in patients with low-risk PTC enables lobectomy in a larger number of patients (20, 21). Also, with better understanding of the epidemiology of thyroid cancer, we now know that many small thyroid cancers are “subclinical” and of little clinical significance, leading to the ATA recommendation not to perform fine-needle aspiration (FNA) for nodules smaller than 1 cm even with high-risk sonographic features and the option for active surveillance in patients with microscopic PTC (11, 22). The goal of this less-aggressive approach is to decrease surgical risks (for hypoparathyroidism and vocal cord palsy), reduce the need for lifelong thyroid hormone replacement, and reduce the psychological and financial burdens of the disease.

To guide treatment decisions in patients with low-risk PTC and bilateral nodularity, we studied the natural history of nonsuspicious contralateral nodules in patients treated with lobectomy alone. This cohort is based on a long-time approach in our institution to offer lobectomy for patients with low-risk PTC and either contralateral nodules proven benign by FNA or microscopic nodules with nonsuspicious features at US.

Materials and Methods

Study design, subjects, and data collection

Inclusion criteria for the study were one or more nonsuspicious solid nodules (size ≥ 3 mm) in the contralateral lobe before surgery in patients with PTC, with a minimum follow-up period of 2 years after lobectomy. Nonsuspicious nodules were defined as either benign by FNA before surgery or small nodules with benign features at US. 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, thyroid cancer >4 cm, gross extra-thyroidal extension (ETE), cervical lymph node metastases, or distant metastases.

Electronic records at Rabin Medical Center, a tertiary university-affiliated medical center, were reviewed for all adult patients (≥ 18 years) who underwent thyroid lobectomy for PTC between 2002 and 2013. We reviewed a total of 1737 medical records of patients after thyroid lobectomy, 510 of whom had nonmetastatic PTC. One-hundred seventeen patients met the inclusion criteria, of whom five patients were excluded because of a tall cell variant of PTC (apparent indication for completion surgery, one patient), contralateral nodule with Bethesda III cytology before lobectomy (one patient), no completion because of vocal cord palsy (two patients), and no completion because of high surgical risk (one patient) (Fig. 1). Therefore, 112 patients were included in the study.

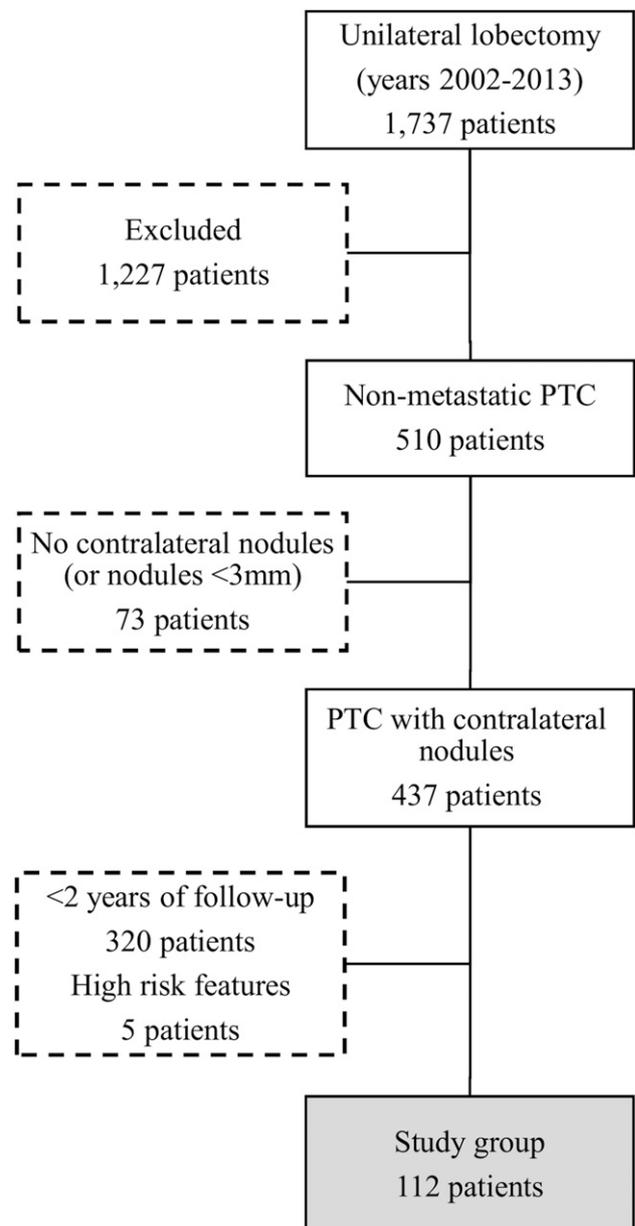


Figure 1. Case selection process.

The following data were collected from the patient files: demographics, medical history and physical examination results, thyroid and neck US scans, FNA cytology, serum levels of thyroid-stimulating hormone (TSH), thyroglobulin (Tg), Tg autoantibody (TgAb), thyroid peroxidase autoantibodies, levothyroxine therapy, surgical reports, histopathology, RAI therapy, and outcome. Data on vascular invasion were not available for most patients with microscopic PTC. Levels of TSH, free thyroxine, Tg, and anti-Tg antibodies were measured by chemiluminescence assay (DPC 2000 Immulite; Siemens Healthcare Diagnostics, Eschborn, Germany). Hashimoto thyroiditis was determined on the basis of the histological report, diagnosis of hypothyroidism, or presence of thyroid antibodies (thyroid peroxidase autoantibodies or TgAbs). Nodule growth was defined as a change of ≤ 3 mm. In cases of multinodular disease, the change in size was documented for the dominant nodule only.

The follow-up period was defined as the time between removal of the first lobe and the last documented visit or the day of completion thyroidectomy surgery. A second follow-up period for patients who underwent completion surgery was defined as the time between completion thyroidectomy and the last documented visit.

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

Statistical analysis

All statistical analyses were performed with SPSS v.17.0 (IBM Corp., Armonk, NY). Associations between two categorical variables were examined using the χ^2 test and Fisher's exact test; associations between continuous and quantitative variables were examined using the Mann-Whitney non-parametric *U* test. A two-sided *P* value of < 0.05 was considered statistically significant for all analyses.

Results

The study cohort consisted of 112 patients who underwent lobectomy for PTC. The median age was 57 years (range, 25 to 84 years), and the female/male ratio was 10.2:1 (Table 1). The median tumor size in the resected lobe was 8 mm (range, 0.5 to 28 mm), and 40% of patients had a tumor ≥ 1 cm. Histopathological examination of the lobectomy specimen revealed multifocal disease in 13 cases (12%), and microscopic (minimal) ETE in eight cases (7%). Histological patterns of PTC included classic (70%) and follicular (30%) variants. None of the included patients had a family history of PTC or radiation exposure. Ninety-three percent of patients had stage I disease, 2% had stage II, and 5% had stage III (> 45 years with minimal ETE) according to the seventh edition of the American Joint Committee on Cancer staging system (23). Twenty-seven patients (24%) had a background of Hashimoto thyroiditis.

Contralateral lobe characteristics

The median size of contralateral nodules was 7 mm (range, 3 to 30 mm), and 40% were ≥ 1 cm. More than one detectable nodule was seen at US in 56% of patients

Table 1. Baseline Characteristics

Characteristic	N
No. of patients	112
Median age at study entry, y (range)	57 (25–84)
Median follow-up, y (range)	6 (2–17.5)
Female sex, n (%)	102 (91)
Initial Lobectomy	
Right lobe, n (%)	55 (49)
Median PTC size, mm (range)	8 (0.5–28)
≥ 1 cm, n (%)	45 (40)
PTC variant (lobectomy), n (%)	
Classic	78 (70)
Follicular variant	34 (30)
Multifocality	13 (12)
Hashimoto thyroiditis	27 (24)
AJCC 7 stage, n (%)	
I, age < 45 y	26 (23)
I, age ≥ 45 y	78 (70)
II, age ≥ 45 y	2 (2)
III, age ≥ 45 y ^a	6 (5)
ATA initial risk classification	
Low, n (%)	104 (93)
Intermediate, ^a n (%)	8 (7)
High, n (%)	0
Tg at study entry, ng/mL \pm SD	12.5 \pm 21.2
TgAb positive at study entry, n (%)	12 (11)
Contralateral Lobe	
Median nodule size, mm (range)	7 (3–30)
≥ 1 cm, n (%)	45 (40)
> 1 nodule, n (%)	63 (56)
FNA before surgery (n = 33)	
Bethesda II, n (% of FNAs)	33 (100)

Abbreviations: AJCC, American Joint Committee on Cancer; SD, standard deviation.

^aDue to minimal extrathyroidal extension.

before surgery. Notable sonographic patterns included hypoechogenicity (45% of nodules), cystic components (17%), and coarse calcifications (21%). Of the nodules with macrocalcifications, 44% were biopsied and found to be benign before initial surgery, and the median size of the nonbiopsied nodules was 7 mm. None of the included nodules had a high-risk sonographic pattern according to the ATA classification (11). Thirty-three nodules (29%) were assessed by FNA before surgery and were benign (Bethesda category II). Data on postoperative Tg and TgAb values were available for 89 patients (76%), with a mean (\pm standard deviation) Tg level of 12.5 \pm 21.2 ng/mL (median, 4.4 ng/mL; range, 0 to 86.7 ng/mL) and for 12 patients (11%) with elevated TgAb titers. Nine patients (8%) had Tg levels > 30 ng/mL, the suggested threshold for excellent response to therapy after lobectomy (24).

Follow-up and outcome

Over a median follow-up of 6 years (range, 2 to 17.5 years; mean, 6.75 years), the median size change of contralateral

nodules was 0 mm (range, –20 to 19 mm), and in 26 patients (23%) contralateral nodules increased ≥ 3 mm in size (median growth of 6.5 mm; range, 4 to 19 mm) (Fig. 2). Expressed as percentage change, median growth was 0% (mean, $14\% \pm 80\%$), with stable nodules (size change $< 20\%$) in 46 patients (41%), a decrease of $\geq 20\%$ in 29 patients (26%), and an increase $\geq 20\%$ in 37 patients (33%). Of the patients with nodule growth of $\geq 20\%$ (range, 20% to 400%), in 11 patients the absolute size change was < 3 mm (within interobserver variability range). The largest percentage increase (400%) was in a 4-mm nodule that grew to 16 mm, which was biopsied during follow-up and found to be benign. Twenty patients (19%) developed new nodules in the remaining lobe. In 16 patients (14%), the nodule that was detected before surgery (initial size, 9 ± 4 mm) was not present at the last US (expressed as negative size change); 13 of these patients had Hashimoto thyroiditis with presumably regenerative nodules (25). Four patients (3%) had growth of > 1 cm, all of whom underwent FNA, which was benign, and two patients had completion thyroidectomy with benign histology. In the subgroup of patients with contralateral nodules ≥ 1 cm at the time of the initial surgery, growth was detected in 17% (eight of 46 patients), all of whom had completion thyroidectomy (Table 2). Mean TSH level (from all measurements during follow-up) was 2.37 ± 1.3 mIU/L, with mean maximal TSH level (highest TSH per patient) of 6.1 ± 7.4 mIU/L. There was no correlation between mean TSH or maximal TSH level and nodule growth.

Sixty-five patients had FNA of contralateral nodules during follow-up, with benign cytology in 54 patients

(83%), Bethesda III in four patients (6%), Bethesda IV in three patients (3%), Bethesda V in two patients (2%), Bethesda I in one patient (1%), and Bethesda VI cytology diagnostic of PTC in one patient. Twelve patients (11%) underwent completion thyroidectomy because of substantial growth of contralateral nodules (three patients), intermediate to suspicious risk of malignancy on FNA (Bethesda categories III to V; seven patients), malignancy (one patient), or other unknown reasons (one patient), as detailed in Table 2. No surgical difficulties or local complications were related to completion surgery.

After completion thyroidectomy, six patients (5%) were diagnosed with contralateral PTC: five patients with micropapillary tumors (< 1 cm) and one patient with a multifocal tumor up to 20 mm confined to the thyroid gland. Median time to contralateral PTC diagnosis was 5.5 years (range, 2.5 to 7.5 years). Of these six patients, one had FNA before the initial surgery for a 20-mm nodule that was benign, and after 7 years of follow-up a repeated FNA was due to an 8-mm growth that was reported as Bethesda IV category. The other five patients had FNA during follow-up because of growth in three patients (size change, 4 to 8 mm) and at the discretion of the physician in two cases. Contralateral PTC was diagnosed in the index nodule detected before initial lobectomy in five patients, and in one case incidental findings of multifocal PTC up to 0.12 mm were detected adjacent to the known lesion (Bethesda IV lesion that was benign on final histology). Five patients with contralateral PTC received RAI therapy (range, 30 to 150 mCi) with no evidence of disease after an additional median follow-up of 6 years (range, 3.5 to 10 years). The size of

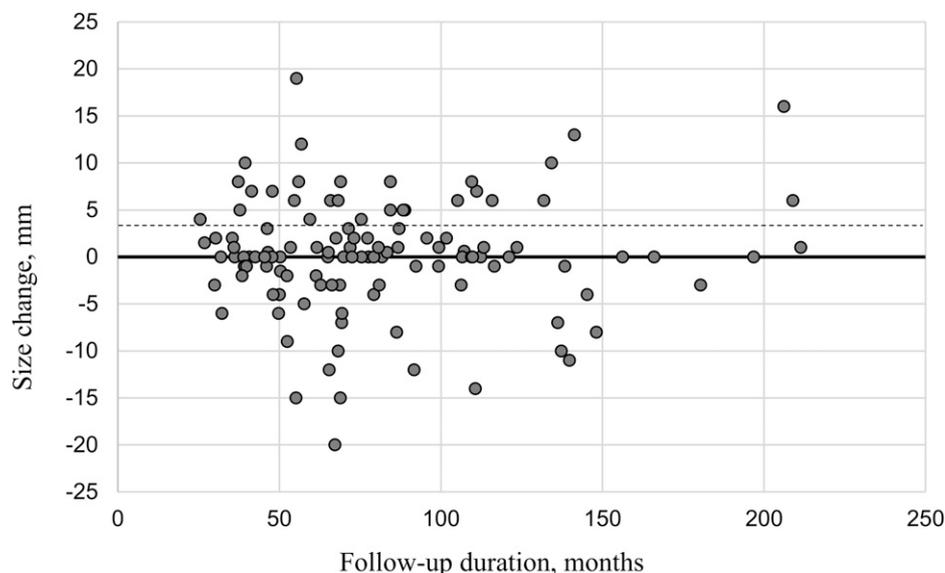


Figure 2. Contralateral nodule size change during follow-up. Each point represents size change (mm), plotted according to the time of last follow-up (months). The solid line indicates no change; the dotted line indicates 3-mm growth.

Table 2. Completion Cases

No.	Age, y	Primary Tumor	Contralateral Nodule, mm	Size Change, mm	FNA	Max Tg, ng/mL	Time to Completion, mo	Pathology	RAI Therapy, mCi	Follow-Up After Completion, mo	Outcome
1	75	FVPTC, 15 mm	10	+4	Bethesda V	20.5	59	Multifocal PTC, largest 10 mm	30	45	NED
2	60	PTC, 3 mm	12	+4	Bethesda III	0	26	Benign	—	67	NED
3	70	FVPTC, 5 mm	15	≤3	Bethesda III	86.7	68	Benign	—	72	NED
4	39	FVPTC, 8 mm	6.5	≤3	Bethesda III	37.2	27	PTC, 5 mm	No treatment	59	NED
5	53	FVPTC, 11 mm	6	≤3	Bethesda IV	ND	75	Multifocal PTC, largest 5 mm, ETE	100	86	NED
6	25	FVPTC, 10 mm	20	+8	Bethesda IV	65.3	84	Multifocal FVPTC, largest 1.2 mm	30	43	NED
7	54	PTC, 1 mm	20	+10	—	0	39	Benign	—	145	NED
8	73	PTC, 4 mm	20	+8	Bethesda VI	ND	37	Multifocal PTC, largest 20 mm	150	83	NED
9	55	FVPTC, 4 mm	22	+19	Bethesda II	ND	55	Benign	—	5	NED
10	45	PTC, 13 mm	4	≤3	Bethesda V	9.3	87	Multifocal PTC, largest 5 mm	100	120	NED
11	44	PTC, 10 mm	14	−4	Bethesda II	9.1	50	Benign	—	72	NED
12	36	FVPTC, 10 mm	6	+12	Bethesda II	16.5	57	Benign	—	24	NED

Abbreviations: FVPTC, follicular variant papillary thyroid carcinoma; Max, maximal; ND, no data; NED, no evidence of disease.

the primary tumor and its histopathological characteristics were not associated with nodule growth or development of malignancy. Similarly, no correlation was found between age, background of Hashimoto thyroiditis, or presence of macrocalcifications in the contralateral nodules and risk of malignancy.

Discussion

The decision to perform lobectomy or total thyroidectomy in patients with PTC is multifactorial and requires thorough understanding of the natural history of the disease. Our study describes the outcomes of contralateral benign-appearing nodules after lobectomy. After a median follow-up of 6 years, 23% of nodules increased in size and 22% decreased in size or disappeared. Twelve patients (11%) underwent completion thyroidectomy because of either a growth or suspicious FNA result or patient preference (Table 2). In six patients (5%), PTC was diagnosed in the contralateral lobe (five with microscopic disease and one with macroscopic disease). After additional treatment with RAI ablation in five patients, all had no evidence of disease. These findings suggest that with appropriate selection and follow-up, lobectomy in the presence of bilateral nonsuspicious nodularities is a safe option, though it requires routine US examinations and FNA when a growth or suspicious features are demonstrated.

Previous studies reported that thyroid lobectomy can be performed in properly selected patients with low recurrence/persistence rates of 1% to 5% and completion thyroidectomy rates of <10% (26–32). Vaisman *et al.* (27) reported outcomes for patients with differentiated thyroid cancer treated with either lobectomy or total

thyroidectomy at Memorial Sloan Kettering Cancer Center. In patients treated with lobectomy (in the presence of a normal contralateral lobe), the rate of completion thyroidectomies was 9.7%, and the rate of contralateral cancer was 4.1% after a mean follow-up of 6.8 years. In agreement with these findings, the current study showed a completion thyroidectomy rate of 11% and a contralateral PTC rate of 5%. Patients were diagnosed with contralateral disease after a median of 5.5 years (range, 2.5 to 7.5 years). Survival analysis revealed a 5-year overall survival rate of 100% and disease-free survival rate of 99.2%. Long-term US surveillance after lobectomy allows early detection of recurrence with no effect on survival compared with total thyroidectomy (26, 27, 33).

The diameter growth of 23% in the contralateral nodule reported in our study is higher than that reported by Durante *et al.* (34) in a large study of 992 patients with benign nodules followed up for >5 years; they reported a 15.4% growth rate (but using a different definition of 20% increase ≥2 nodule diameters, with a minimum increase of 2 mm). This difference may reflect a predisposition for growth in patients with PTC, possibly related to genetic, environmental, or microenvironmental factors (35, 36). However, the long-term significance of this growth tendency is unknown because growth is not a major predictor of malignancy (37).

Of note, 58% of our patients had FNA during follow-up, a high number given the preoperative consideration of these nodules as benign. It is reasonable to assume that with a current paradigm of less aggressive treatment in patients with low-risk PTC, the need for FNAs during follow-up would be lower.

According to the 2015 ATA guidelines, contralateral thyroid nodules may be an indication for a bilateral

procedure (Recommendation 35); the National Comprehensive Cancer Network clinical practice guidelines (version 1.2017) use similar wording (11, 38). The 2012 European Society for Medical Oncology clinical practice guidelines together with a 2006 European consensus do not address the issue, as total thyroidectomy is recommended for most patients (39, 40). The arguments underlying these recommendations favoring total thyroidectomy include the need for RAI therapy to facilitate follow-up and the risk for contralateral malignancy. However, recent data call this approach into question. First, the use of RAI ablation in low-risk PTC is decreasing, and according to the ATA guidelines, it is “not routine.” Therefore, the need to remove the contralateral lobe depends on its own characteristics, rather than on the necessity for RAI therapy. Second, several recent studies demonstrated that follow-up after lobectomy is safe and effective in detecting clinically significant recurrences (26, 27, 33). Our results support this conclusion even in the presence of contralateral nodules, with an excellent outcome after a median of 6 years of follow-up. Third, bilateral multifocality is common in patients with PTC, with rates up to 44%. With the use of high-resolution US and performance of FNA for suspicious nodules, the risk of missing clinically relevant disease is low, though not zero.

Despite our results showing that follow-up of contralateral nodules is safe in selected patients, lifelong follow-up can be cumbersome and a major cause of stress for both the patient and the treating physician. As with other aspects of managing low-risk PTC, the patient’s preferences, the physician’s approach, the availability of good quality US, and the patient’s adherence to follow-up are key considerations in choosing the right surgical approach. Compared with total thyroidectomy, lobectomy carries less risk of surgical complications and sometimes obviates the need for long-term levothyroxine therapy (31, 41, 42); nevertheless, lobectomy poses a risk for completion thyroidectomy and requires more follow-up in the presence of benign-appearing contralateral nodules.

The major limitation of our work is its retrospective design. US examinations were performed by several radiologists during follow-up for a median of 6 years. This could have affected the proportion of patients reported to have nodule growth or shrinkage but had limited effect on the final outcome of completion thyroidectomies (which were based on FNA results or clear nodule growth) or on the detection of contralateral cancer. The criterion for growth (≥ 3 mm in the largest diameter) was intentionally chosen to minimize the effect of these variations. Data on nodule volume were not available, as most US reports did not include three axis measurements.

Notably, disappearance of 14% of nodules in our study is higher than that described by Durante *et al.* (34), who reported 18.5% shrinkage of nodules (with a mean reduction in the largest diameter of 3.7 mm) and nodule disappearance in 2.3% of patients. In our study, all but one of the nodules that disappeared were in patients with Hashimoto thyroiditis and apparently represent hyperplastic nodules (sometimes termed *pseudonodules*) related to scarring and local areas of thyroid hyperplasia (43, 44). The detection and reporting of these hyperplastic nodules may vary considerably between radiologists. Nevertheless, we decided to include these patients because at the time of the initial surgery, these nodules were considered a possible indication for total thyroidectomy and were relevant for decisions on the extent of surgery.

Other limitations of our study include the duration of follow-up (median of 6 years), which may not reflect the lifelong risks and benefits of this less-aggressive approach, and the characteristics of the patients included in the study. Most patients had a small PTC (60% smaller than 1 cm) and low-risk disease (93%), so our conclusions should be applied to similar groups of patients. Of note, data on vascular invasion were not available for most patients because these data were not routinely reported in patients with microscopic PTCs. Because the presence of vascular invasion is an intermediate risk feature according to the 2015 ATA guidelines, some patients in our study may have been misclassified as low risk.

In conclusion, for low-risk patients with small PTC tumors and nonsuspicious contralateral thyroid nodules, lobectomy alone is a safe option, provided that regular US follow-up is available to detect the small proportion of patients who may need completion thyroidectomy. Our results enable informed decision-making on the extent of surgery by patients and physicians for low-risk PTC and bilateral nodularity.

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