The American Journal of Surgery 223 (2022) 635–640

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Featured Article

Total thyroidectomy can be overtreatment in cN1a papillary thyroid carcinoma patients whose tumor is smaller than 1 cm

Kyorim Back [a], Jiyeon Lee [c], Jun-Ho Choe [b], Jung-Han Kim [b], Young Lyun Oh [c], Jee Soo Kim [b, *]

[a] Division of Endocrine Surgery, Department of Surgery, Chung-Ang University Hospital, Chung-Ang University School of Medicine, Seoul, South Korea
[b] Division of Endocrine Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University, School of Medicine, Seoul, South Korea
[c] Department of Pathology and Translational Genomics, Samsung Medical Center, Sungkyunkwan University, School of Medicine, Seoul, South Korea

ARTICLE INFO

Article history:
Received 25 May 2021
Received in revised form
19 July 2021
Accepted 10 August 2021

Keywords:
Papillary thyroid microcarcinoma
cN1a
Surgical treatment for PTMC patients with unilateral cN1a

ABSTRACT

Background: The 2015 American Thyroid Association (ATA) guidelines recommend pursuing total thyroidectomy with therapeutic central lymph-node dissection (CND) in patients with clinically apparent nodal disease (cN1a), regardless of tumor size. The aim of this study was to investigate whether total thyroidectomy is necessary for thyroid papillary microcarcinoma (PTMC) patients with preoperative unilateral cN1a.
Methods: This study included 295 papillary thyroid microcarcinoma patients who underwent total thyroidectomy with bilateral CND from January 2012 to June 2015.
Results: The median follow-up time was 42.5 months. Locoregional recurrence (LRR) was observed in only two (0.9%) patients. Among 70 cN1a patients, only 19 (27.1%) were at intermediate risk for disease recurrence and required total thyroidectomy per the ATA guidelines. Lobectomy can be considered as a treatment option for the remaining patients (72.9%).
Conclusions: Our study showed that more than two-thirds of PTMC patients with clinical nodal disease who underwent total thyroidectomy and CND were actually lobectomy candidates. Total thyroidectomy as the first surgical option for cN1a, especially in PTMC patients, should be reconsidered.

1. Introduction

In the last decade, the paradigm of treating thyroid cancer has shifted from adopting the maximum tolerated treatment to instead using the minimum necessary treatment. Recently published studies have emphasized an active surveillance strategy as the ideal treatment option for low-risk thyroid papillary microcarcinoma (PTMC) unless the patient presents with high-risk features such as clinically involved nodal disease, distant metastasis, high-grade malignancy on cytology, tumor abutting the trachea or recurrent laryngeal nerve, tumor enlargement, or novel lymph-node metastasis during observation.[1–10] According to the 2015 American Thyroid Association (ATA) guidelines, the initial surgical procedure should include total thyroidectomy with central-compartment neck dissection (CND) for thyroid cancer patients with clinically suspected nodal disease (cN1a) without a specific tumor size.[11]

It is evident that lobectomy exhibits the pros of less surgery-related complications such as vocal cord palsy or hypoparathyroidism relative to total thyroidectomy. In addition, lobectomy patients may not necessarily need to take lifelong thyroid hormones.[12–14] In a similar fashion, the extent of node dissection has an impact on the incidence of surgery-related complications and resultant discomfort. Apparently, bilateral CND leads to less favorable surgery-related complications as compared with unilateral CND.[15–17] The Updated American Joint Committee on Cancer (AJCC)/Tumor–Node–Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer (eighth edition) reported that the 10-year survival rate is not significantly affected by the stage of thyroid cancer with the exception of advanced stages in old age.[18] Thus, local recurrence and the postoperative quality of life remain important issues.[19–21]

The present study grew from the larger desire to elucidate how endocrine surgeons might decide the extent of surgery to conduct

* Corresponding author. Division of Endocrine Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University, School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul, 06351, South Korea.
E-mail address: jskim0126@skku.edu (J.S. Kim).

https://doi.org/10.1016/j.amjsurg.2021.08.015
0002-9610/

in PTMC patients with clinically involved nodal disease. Specifically, this study aimed to evaluate whether total thyroidectomy is the only treatment for PTMC patients with clinical nodal disease by analyzing the final pathology results retrospectively. Furthermore, we attempted to present clinical evidence to help better stratify the choice of surgical strategy for thyroid cancer.

2. Materials and methods

2.1. Patient selection

This study was approved by the Institutional Review Board at Samsung Medical Center, a tertiary referral center in Seoul, Korea. We conducted a retrospective study at this single institution from January 2012 to June 2015. We reviewed patients who were diagnosed with papillary thyroid carcinoma (PTC) and who underwent total thyroidectomy with bilateral CND. Patients with the following were excluded from this study: tumor size larger than 1 cm, a history of previous thyroidectomy, an age younger than 18 years or older than 80 years, cN1b confirmed by fine-needle aspiration with/without thyroglobulin(Tg) washout measurement, non-PTC carcinomas (follicular/medullary/anaplastic), PTC variants, mixed-type PTC, preoperatively detected bilateral PTC, completion thyroidectomy, distant metastasis, and follow-up duration of less than six months [residual tumor or suspicious lymph node (LN) detected within six months after the initial surgery or loss to follow-up within six months]. Finally, a total of 295 patients were chosen for the final analysis (see Fig. 1).

All patients were assessed by US preoperatively to evaluate the primary tumor and the presence of suspected nodal metastases. Suspicious thyroid lesions were diagnosed by fine-needle aspiration (FNA) or rarely core needle biopsy. Clinically involved central nodal disease (cN1a) was defined as LN metastases in the central neck compartment on preoperative US per the ATA guidelines.

2.2. Surgical methods

Surgical strategies were chosen according to the ATA guidelines. Therapeutic CND was performed after metastatic CLN was detected during preoperative US. Patients who were ruled as clinically node-negative by preoperative US underwent prophylactic CND since they had bilateral thyroid surgery. CND was defined as a level VI dissection extending superiorly to the hyoid bone, inferiorly to the innominate artery, laterally to the carotid sheaths, and dorsally to the prevertebral fascia. The central-compartment LNs included the pretracheal, prelaryngeal, and paraesophageal LNs. The term “ipsilateral” was used to indicate the same side as the main tumor, while “contralateral” referred to the opposite side of the main tumor. In cases of bilateral tumors, the largest tumor was considered to be the main tumor. Open or minimally invasive (endoscopic or robotic) thyroidectomy was chosen based on patients’ preferences after a thorough discussion of the pros and cons of each approach.

2.3. Histopathological examination of surgical specimens

Surgical specimens were microscopically examined by two or more experienced pathologists. The following histopathologic factors were assessed: main tumor size (longest diameter of the largest lesion), cell type of the main tumor, multifocality, bilaterality, extrathyroidal extension (ETE) (microscopic or gross), regional lymph-node metastasis (central or lateral compartment), and underlying conditions of the thyroid such as chronic lymphocytic thyroiditis (CLT). In our institution, the largest node among the metastatic LNs was measured. In cases of metastatic LNs with multiple tumor deposits in a single LN, the pathologist measured the largest dimension of the largest deposit. Multifocality was defined as the presence of more than two lesions in one lobe, regardless of bilaterality. ETE was defined as involvement of perithyroidal soft tissues, including fibro-adipose tissue, strap muscles, nerves, and small vascular structures by direct extension of the thyroid tumor. In addition to gross ETE, minimal (minor or micro-) ETE detected only by microscopic examination was also included. If all involved tissue was completely removed along with the tumor, the resection margin was reported as negative. The staging of thyroid cancer was determined in accordance with the seventh edition of the AJCC Cancer Staging Manual and the Future of TNM.[22]

2.4. Postoperative follow-up and management

After the initial surgery, all patients underwent regular follow-up assessments at six-to 12-month intervals with clinical evaluations including physical examinations; US, thyroid function testing

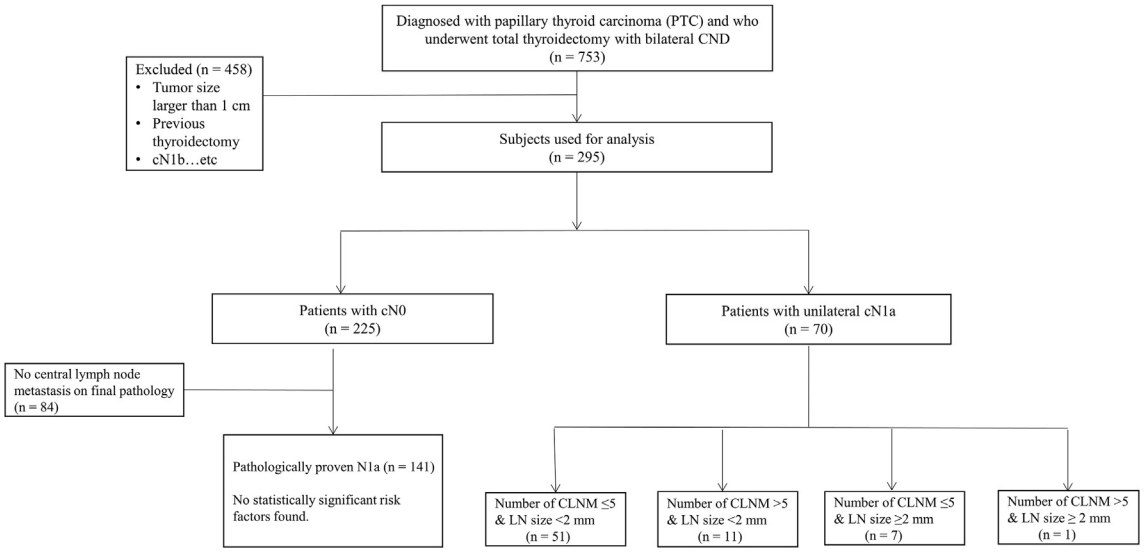

Fig. 1. Flow chart of study.

(including T3, free T4, TSH), and the measurement serum Tg level together with its antibody. CT or iodine-131 (^{131}I) scans was performed if clinically needed during follow up. Suspicious lesions for recurrence were evaluated by US-guided FNA biopsy with or without Tg washout level and/or CT or positron-emission tomography (PET). Locoregional recurrence was defined as the presence of tumors or metastatic LNs on cytology from FNA or the elevation of the Tg washout level. Radioactive iodine (RAI) therapy was performed with ^{131}I at four to 12 weeks after surgery according to the ATA guidelines. RAI was applied after thyroid hormone withdrawal or after stimulation with recombinant thyroid-stimulating hormone. When RAI treatment was no longer required, patients resumed regular follow-up.

2.5. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 24.0 software program (IBM Corporation, Armonk, NY, USA). Variables with p-values of less than 0.05 were considered to be statistically significant. The chi-squared test and Student's t-test were used to compare categorical variables between unilateral cN1a patients and cN0 patients. For multivariate analysis, we used logistic regression to identify associated variables.

3. Results

3.1. Clinicopathological characteristics of 295 PTMC patients

The 295 study participants were divided into two groups according to preoperative physical and radiologic CLN status as follows: 225 (76.3%) patients without suspected metastatic CLN (cN0) and 70 (23.7%) patients with suspicious ipsilateral metastatic CLN (cN1a). The median follow-up time was 42.5 months. The clinicopathological characteristics of the patients in the two groups are compared in Table 1. A comparison of the two groups showed that the findings concerning age ($P < 0.001$), tumor size ($P = 0.040$), multiplicity ($P < 0.001$), number of retrieved CLNs ($P < 0.001$), central LN metastasis ($P < 0.001$), number of metastatic CLNs ($P = 0.001$), and the largest LN diameter ($P = 0.044$) were significantly different. The proportion of patients with tumors larger than 0.5 cm was higher in the cN1a group than in the cN0 group (87.1% vs. 75.6%; $P = 0.040$). Central LN metastasis was more frequent in the cN1a group as compared with in the cN0 group (77.1% vs. 38.7%; $P < 0.001$). The frequency of ipsilateral metastatic CLN was 43.5% in the cN0 group and 75.7% in the cN1a group ($P < 0.001$). Contralateral central LN metastasis occurred in 11.6% of patients in the cN0 group and 12.9% in the cN1a group ($P = 0.769$). All contralateral central LN metastasis were microscopic metastasis because only unilateral cN1a patients were enrolled. The percentage of patients with more than five metastatic LNs was 4.0% in the cN0 group and 17.1% in the cN1a group ($P = 0.001$). Moreover, the largest LN diameter being at least 2 mm was occurred more in cN1a group than cN0 group (11.4% vs 4.4%; $P = 0.044$). Recurrence ($P = 1.000$) were not statistically different between the groups. LRR was observed in two (0.9%) patients in the cN0 group and none in the cN1a group (Table 1).

Factors associated with the largest metastatic central LN measuring greater than 2 mm and/or the presence more than five metastatic central LNs.

During univariate analysis, unilateral cN1a (odds ratio: 2.08; $P = 0.057$) was the most associated factor for metastatic LN size $\geq$2 mm and/or >5 LN metastasis in pathologically proven N1a (pN1a) patients, but it was not statistically significant. In multivariate analysis, no risk factors for metastatic LN size $\geq$2 mm and/or >5 LN metastasis were founded after adjusting sex, age, tumor size, multifocality, ETE, and unilateral cN1a (Table 2). We assumed that the reason why it is statistically difficult to determine intermediate risk patients based on analyzed risk factors, as presented in Table 1, there were no significant associated factors because of the small number of PTMC patients with the largest metastatic central LN measuring at least 2 mm.

3.2. Number of metastatic LNs and size distribution of patients with unilateral cN1a

In 70 PTMC patients with unilateral cN1a, the pathologic nodal status of 51 (72.9%) patients were pN0 or having five metastatic CLNs with the largest node size being less than 2 mm; thyroid lobectomy instead of total thyroidectomy could have been considered in such patients with microscopic metastatic CLN. The remaining patients (27.1%) had either largest metastatic LN sizes of at least 2 mm or more than five metastatic CLNs or had more than five metastatic CLNs with the largest node being smaller than 2 mm or pN0; of these, 11 patients (15.7%) had more than five metastatic CLNs with the largest node being smaller than 2 mm or pN0, seven patients (10.0%) had less than five metastatic CLNs with the largest node being greater than 2 mm, and one (1.4%) patient had more than five metastatic CLNs with the largest node being greater than 2 mm (Table 3). This group of patients actually belonged to the intermediate-risk category for disease recurrence according to the ATA guidelines and total thyroidectomy could have been an optimal treatment choice for these patients.

4. Discussion

Previous studies have reported that LN metastasis in PTMC patients is quite common and the proportion of metastatic CLN varies from 31% to 64%.[23–26] For thyroid cancer patients with cN1a, the 2015 ATA guidelines recommend total thyroidectomy with CND regardless of tumor size. This recommendation was made based on the recurrence rate of up to 20% found in cN1a patients. In this study, we retrospectively reviewed the final pathology results of PTMC patients with preoperative cN1a who underwent total thyroidectomy and CND. Among 70 PTMC patients with cN1a, as many as 70% of patients had less than five metastatic CLNs with the largest node size being less than 2 mm. These patients are considered at low risk for recurrence per the ATA guidelines and hemi-thyroidectomy could be sufficient treatment in this group. The rest of the patients were expected to have more than five total metastatic CLNs and/or a largest metastatic CLN size of greater than 2 mm and were categorized as at intermediate risk of recurrence; for these individuals, total thyroidectomy can be considered as a treatment option. In PTMC patients, the proportion of lobectomy candidates was about 73% even though most showed a preoperative cN1a status (Table 3).

It is known that regional LN metastasis in PTC patients is an independent predictor of a greater risk of recurrence.[27–29] Some authors have reported that LN metastasis in PTMC is associated with LRR[23,30,31]; on the other hand, others have claimed that microscopic LNM does not have an effect on LRR or decrease the survival rate.[32,33] The long-term effect of metastatic CLN on locoregional recurrence in PTMC patients has not been made clear yet. According to our results, recurrence occurred in only two patients (0.7%) in whole cohort (Table 1), and the events were inadequate to analyze for recurrence. Low-risk microscopic metastasis was predominant in PTMC patients with unilateral cN1a as the final pathology; thus, total thyroidectomy with bilateral nodal dissection for patients with cN1 disease should be reconsidered as a blanket recommendation for all patients with PTMC.

To minimize overtreatment, it would be helpful to conduct

Table 1
Clinicopathological characteristics of 295 cN0 and unilateral cN1a PTMC patients.

	cN0 no. (%)	Unilateral cN1a no. (%)	*P*-Value
Total	225 (76.3)	70 (23.7)	
Sex			0.869
Male	43 (19.1)	14 (20.0)	
Female	182 (80.9)	56 (80.0)	
Age			<0.001
Mean ± SD	50.6 ± 10.3	41.7 ± 9.7	
<55	148 (65.8)	64 (91.4)	
≥55	77 (34.2)	6 (8.6)	
Tumor size (cm)			0.040
Mean ± SD	0.70 ± 0.17	0.73 ± 0.16	
≤0.5	55 (24.4)	9 (12.9)	
>0.5	170 (75.6)	61 (87.1)	
Multiplicity			<0.001
Absent	0 (0.0)	50 (71.4)	
Present	225 (100.0)	20 (28.6)	
BRAF mutation[a]			0.254
Absent	17 (9.6)	6 (15.8)	
Present	161 (90.4)	32 (84.2)	
Gross extrathyroidal extension			1.000
Absent	210 (93.3)	65 (92.9)	
Present	15 (6.7)	5 (7.1)	
Chronic lymphocytic thyroiditis			0.819
Absent	148 (65.8)	45 (64.3)	
Present	77 (34.2)	25 (35.7)	
Retrieved central LNs (no.)			<0.001
Mean ± SD	7.0 ± 4.5	9.9 ± 4.5	
Central LN metastasis			<0.001
Absent	138 (61.3)	16 (22.9)	
Present	87 (38.7)	54 (77.1)	
Contralateral central LN metastasis			0.769
Absent	199(88.4)	61(87.1)	
Present	26 (11.6)	9(12.9)	
Number of metastatic central LNs (no.)			0.001
Mean ± SD	1.1 ± 2.2	2.7 ± 2.5	
≦ 5	216 (96.0)	58 (82.9)	
>5	9 (4.0)	12 (17.1)	
Largest size of metastatic LN(mm)			0.044
<2.0	215 (95.6)	62 (88.6)	
≧ 2.0	10 (4.4)	8 (11.4)	
Loco-regional recurrence			1.000
Absent	223 (99.1)	70 (100.0)	
Present	2 (0.9)	0 (0.0)	

PTMC indicates papillary thyroid microcarcinoma; cN0, no suspicious central lymph node metastasis; cN1a, suspicious central lymph node metastasis; no, number; SD, standard deviation; LN, lymph node; LNM, lymph node metastasis.
[a] Counted only in administered patients.

Table 2
Associations between number of CLNM >5 and/or largest central LN size ≥2 mm and clinicopathological characteristics of PTMC patients with pathologically-proven N1a (n = 141)[a].

Clinicopathological characteristics	Univariate analysis			Multivariate analysis		
	Adjusted OR	95% CI	*P*-Value	Adjusted OR	95% CI	*P*-Value
Male sex (*Ref* = female)	0.96	0.41–2.23	0.920	1.00	0.42–2.42	0.991
Age <55 (*Ref* = ≥ 55)	1.92	0.67–5.46	0.216	1.68	0.55–5.14	0.362
Tumor size (cm)			0.350			0.605
≤0.5		*Ref*			*Ref*	
>0.5	1.73	0.54–5.48		1.38	0.41–4.67	
Multifocality (*Ref* = absent)	0.86	0.40–1.87	0.709	1.01	0.45–2.27	0.981
ETE (*Ref* = absent)	0.33	0.40–2.76	0.445	1.76	0.77–4.02	0.181
Chronic lymphocytic thyroiditis (*Ref* = absent)	1.65	0.75–3.65	0.212		*N/A*	
Unilateral cN1a (*Ref* = cN0)	2.08	0.97–4.46	0.057	1.93	0.85–4.38	0.115

PTMC indicates papillary thyroid microcarcinoma; cN0, no suspicious central lymph node metastasis; cN1a, suspicious central lymph node metastasis; CLNM, central lymph node metastasis; OR, odds Ratio; CI, confidence interval; ETE, extrathyroidal extension; cN1a, clinical N1a; *Ref*, reference; *N/A*, not available.
[a] Patients without pathologically proven N1a were excluded.

intraoperative frozen-section analysis, if available. Some studies have shown the usefulness of intraoperative frozen section in determining extent of surgery, on the other hand, others have demonstrated that intraoperative frozen section has limited utility in thyroid surgery.[34,35] Although further studies are mandatory for clarifying the accuracy and effectiveness of using intraoperative

Table 3
Metastatic LN number and size distribution of 70 PTMC patients with unilateral cN1a.

N = 70	Number of CLNM ≤5 or pN0	Number of CLNM >5
Largest metastatic LN size <2 mm or pN0	51 (72.9%)	11 (15.7%)
Largest metastatic LN size ≥ 2 mm	7 (10.0%)	1 (1.4%)

PTC indicates papillary thyroid carcinoma; LN, lymph node; cN1a suspicious central lymph node metastasis; CLNM, central lymph node metastasis; LN, lymph node; pN0, pathologically proven no central lymph node metastasis.

frozen sections, intraoperative frozen section still has some advantages.[36–38] By assessing frozen sections, it is possible to discern details about the nodal status such as the LN size or number of metastatic LNs or at least metastatic status, which could help to determine the necessary extent of surgery. In addition, the examination of frozen sections would be useful especially in patients with chronic lymphocytic thyroiditis with LN enlargement. Our data indicated that 35% of patients had chronic lymphocytic thyroiditis (Table 1). In the context of this inflammatory condition, it is challenging to conduct exact differentiation of metastatic LNs from reactive ones, however, intraoperative frozen exam will be helpful for the differential diagnosis. It is no doubt that intraoperative frozen exam is more precise than intraoperative gross inspection or palpation. Although this usually takes additional time and has limit to the accuracy of diagnosis, intraoperative frozen biopsy can be helpful for determining the necessary surgical extent. Further study about predictability of intraoperative frozen biopsy is needed.

There were several limitations to this study. First, this was a nonrandomized, retrospective, relatively small cohort study performed in a single institution. Potential confounding variables may not have been identified. Since all patients in this cohort underwent total thyroidectomy and bilateral CND, this surgical intervention itself may have influenced the recurrence rate. In addition, there was a statistical limitation to clearly predict intermediate risk PTMC patients by analyzed risk factors due to a relatively small sample size of the cohort. This issue is an inevitable limitation in retrospective research, however, we consider that it doesn't invalidate our results. Larger prospective randomized controlled trials with additional intraoperative frozen data to compare the long-term effect of lobectomy to that of total thyroidectomy in cN1a PTMC patients are needed. Second, inter-observer variation in the detection and interpretation of cervical LN metastasis and inconsistent surgical management are possible concerns because of the long-term period of data collection. Third, our findings may not be applicable to all centers, especially those ranked below tertiary centers without skilled pathologists or where frozen section examination is not available.

5. Conclusion

In this study, we investigated the pathologic CLN status of PTMC patients, especially focusing on the number and size of metastatic LNs. Our retrospective data showed that about 70% of PTMC patients with preoperative cN1a who underwent total thyroidectomy actually were viable lobectomy candidates. We expect that the identification of nodal status using intraoperative frozen sections would reduce overtreatment. It should be reconsidered that total (or near-total) thyroidectomy is a mandatory surgical option in preoperative cN1a patients regardless of considering other clinicopathological factors, especially in case of PTMC. The strategy for the surgical treatment of thyroid cancer needs to be further refined. For this, careful preoperative clinical examinations, meticulous radiologic evaluations, and intraoperative frozen-section collection are prerequisites.

Author contribution statement

Study conception and design: Jee Soo Kim, Kyorim Back. Acquisition of data: Kyorim Back, Jiyeon Lee, Jun-Ho Choe, Jung-Han Kim, Young Lyun Oh. Analysis and interpretation of data: Kyorim Back. Drafting of manuscript: Kyorim Back, Jee Soo Kim. Critical revision: Kyorim Back, Jee Soo Kim.

Funding information

No funding was received for this article.

Declaration of competing interest

No competing financial interests exist.

References

1. Ito Y, Miyauchi A, Oda H. Low-risk papillary microcarcinoma of the thyroid: a review of active surveillance trials. *Eur J Surg Oncol*. 2018;44(3):307–315.
2. Brito JP, Ito Y, Miyauchi A, Tuttle RM. A clinical framework to facilitate risk stratification when considering an active surveillance alternative to immediate biopsy and surgery in papillary microcarcinoma. *Thyroid*. 2016;26(1):144–149.
3. Sugitani I, Fujimoto Y, Yamada K. Association between serum thyrotropin concentration and growth of asymptomatic papillary thyroid microcarcinoma. *World J Surg*. 2014;38(3):673–678.
4. Ito Y, Miyauchi A, Inoue H, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg*. 2010;34(1):28–35.
5. Fukuoka O, Sugitani I, Ebina A, et al. Natural history of asymptomatic papillary thyroid microcarcinoma: time-dependent changes in calcification and vascularity during active surveillance. *World J Surg*. 2016;40(3):529–537.
6. Sugitani I, Toda K, Yamada K, et al. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. *World J Surg*. 2010;34(6):1222–1231.
7. Ito Y, Tomoda C, Uruno T, et al. Papillary microcarcinoma of the thyroid: how should it be treated? *World J Surg*. 2004;28(11):1115–1121.
8. Ito Y, Miyauchi A, Kihara M, et al. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. *Thyroid*. 2014;24(1):27–34.
9. Haser GC, Tuttle RM, Su HK, et al. Active surveillance for papillary thyroid microcarcinoma: new challenges and opportunities for the health care System. *Endocr Pract*. 2016;22(5):602–611.
10. Ito Y, Uruno T, Nakano K, et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. *Thyroid*. 2003;13(4):381–387.
11. Haugen BR, Alexander EK, Bible KC, et al. American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2015;26(1):1–133, 2016.
12. Kandil E, Krishnan B, Noureldine SI, et al. Hemithyroidectomy: a meta-analysis of postoperative need for hormone replacement and complications. *ORL J Otorhinolaryngol Relat Spec*. 2013;75(1):6–17.
13. Stoll SJ, Pitt SC, Liu J, et al. Thyroid hormone replacement after thyroid lobectomy. *Surgery*. 2009;146(4):554–558. ; discussion 558-560.
14. Hauch A, Al-Qurayshi Z, Randolph G, Kandil E. Total thyroidectomy is associated with increased risk of complications for low- and high-volume surgeons. *Ann Surg Oncol*. 2014;21(12):3844–3852.
15. Son YI, Jeong HS, Baek CH, et al. Extent of prophylactic lymph node dissection in the central neck area of the patients with papillary thyroid carcinoma: comparison of limited versus comprehensive lymph node dissection in a 2-year safety study. *Ann Surg Oncol*. 2008;15(7):2020–2026.
16. Mazzaferri EL, Doherty GM, Steward DL. The pros and cons of prophylactic

central compartment lymph node dissection for papillary thyroid carcinoma. *Thyroid*. 2009;19(7):683–689.
17. Bergamaschi R, Becouarn G, Ronceray J, Arnaud JP. Morbidity of thyroid surgery. *Am J Surg*. 1998;176(1):71–75.
18. Tuttle RM, Haugen B, Perrier ND. Updated American Joint committee on cancer/tumor-node-metastasis staging System for differentiated and anaplastic thyroid cancer (eighth edition): what changed and why? *Thyroid*. 2017;27(6):751–756.
19. Vaisman F, Shaha A, Fish S, Michael Tuttle R. Initial therapy with either thyroid lobectomy or total thyroidectomy without radioactive iodine remnant ablation is associated with very low rates of structural disease recurrence in properly selected patients with differentiated thyroid cancer. *Clin Endocrinol*. 2011;75(1):112–119.
20. Nixon IJ, Ganly I, Patel SG, et al. Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy. *Surgery*. 2012;151(4):571–579.
21. Nickel B, Tan T, Cvejic E, et al. Health-related quality of life after diagnosis and treatment of differentiated thyroid cancer and association with type of surgical treatment. *JAMA Otolaryngol Head Neck Surg*. 2019;145(3):231–238.
22. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17(6):1471–1474.
23. Hay ID, Hutchinson ME, Gonzalez-Losada T, et al. Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. *Surgery*. 2008;144(6):980–987. ; discussion 987-988.
24. So YK, Son YI, Hong SD, et al. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. *Surgery*. 2010;148(3):526–531.
25. Zhao Q, Ming J, Liu C, et al. Multifocality and total tumor diameter predict central neck lymph node metastases in papillary thyroid microcarcinoma. *Ann Surg Oncol*. 2013;20(3):746–752.
26. Lim YC, Choi EC, Yoon YH, et al. Central lymph node metastases in unilateral papillary thyroid microcarcinoma. *Br J Surg*. 2009;96(3):253–257.
27. Podnos YD, Smith D, Wagman LD, Ellenhorn JD. The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. *Am Surg*. 2005;71(9):731–734.
28. Leboulleux S, Rubino C, Baudin E, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. *J Clin Endocrinol Metab*. 2005;90(10):5723–5729.
29. Lundgren CI, Hall P, Dickman PW, Zedenius J. Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based, nested case-control study. *Cancer*. 2006;106(3):524–531.
30. Pisanu A, Reccia I, Nardello O, Uccheddu A. Risk factors for nodal metastasis and recurrence among patients with papillary thyroid microcarcinoma: differences in clinical relevance between nonincidental and incidental tumors. *World J Surg*. 2009;33(3):460–468.
31. Ross DS, Litofsky D, Ain KB, et al. Recurrence after treatment of micropapillary thyroid cancer. *Thyroid*. 2009;19(10):1043–1048.
32. Wada N, Duh QY, Sugino K, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. *Ann Surg*. 2003;237(3):399–407.
33. Ito Y, Tomoda C, Uruno T, et al. Preoperative ultrasonographic examination for lymph node metastasis: usefulness when designing lymph node dissection for papillary microcarcinoma of the thyroid. *World J Surg*. 2004;28(5):498–501.
34. Trosman SJ, Bhargavan R, Prendes BL, Burkey BB, Scharpf J. The contemporary utility of intraoperative frozen sections in thyroid surgery. *Am J Otolaryngol*. 2017 Sep-Oct;38(5):614–617. https://doi.org/10.1016/j.amjoto.2017.07.003. Epub 2017 Jul 5. PMID: 28697907.
35. Marshall R, Alexander D, Fleming J, Grayson J, Peters G, Buczek E. Utility of intraoperative frozen sections of thyroid tissue in the age of molecular testing. *Clin Otolaryngol*. 2021 Apr 2. https://doi.org/10.1111/coa.13766. Epub ahead of print. PMID: 33811452.
36. Lim YS, Choi SW, Lee YS, et al. Frozen biopsy of central compartment in papillary thyroid cancer: quantitative nodal analysis. *Head Neck*. 2013;35(9):1319–1322.
37. Raffaelli M, De Crea C, Sessa L, et al. Can intraoperative frozen section influence the extension of central neck dissection in cN0 papillary thyroid carcinoma? *Langenbeck's Arch Surg*. 2013;398(3):383–388.
38. Raffaelli M, De Crea C, Sessa L, et al. Ipsilateral central neck dissection plus frozen section examination versus prophylactic bilateral central neck dissection in cN0 papillary thyroid carcinoma. *Ann Surg Oncol*. 2015;22(7):2302–2308.