High Serum TSH Level Is Associated With Progression of Papillary Thyroid Microcarcinoma During Active Surveillance

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Objective: Thyroid-stimulating hormone (TSH) is a growth factor affecting initiation or progression of papillary thyroid cancer (PTC), which supports TSH suppressive therapy in patients with PTC. In patients with papillary thyroid microcarcinoma (PTMC) during active surveillance, however, the association between serum TSH level and growth of PTMC has not been demonstrated.

Patients: We analyzed 127 PTMCs in 126 patients under active surveillance with serial serum TSH measurement and ultrasonography.

Design: The patients were categorized into groups with the highest, middle, and lowest time-weighted average of TSH (TW-TSH). PTMC progression was defined as a volume increase of ≥50% compared with baseline. Kaplan-Meier survival analysis according to TW-TSH groups and Cox proportional hazard modeling was performed. We identified the cutoff point for TSH level by using maximally selected log-rank statistics.

Results: During a median follow-up of 26 months, PTMC progression was detected in 28 (19.8%) patients. Compared with the lowest TW-TSH group, the adjusted hazard ratio (HR) for PTMC progression in the highest TW-TSH group was significantly higher [HR 3.55; 95% confidence interval (CI), 1.22 to 10.28; $P = 0.020$], but that in the middle TW-TSH group was not (HR 1.52; 95% CI, 0.46 to 5.08; $P = 0.489$). The cutoff point for the serum TSH level for PTMC progression was 2.50 mU/L.

Conclusions: Sustained elevation of serum TSH levels during active surveillance is associated with PTMC progression. Maintaining a low-normal TSH range with levothyroxine treatment during active surveillance of PTMC might be considered in future studies. (***J Clin Endocrinol Metab*** **103: 446–451, 2018)**

Recently, the incidence of thyroid cancer has been rising worldwide because of increased detection of papillary thyroid microcarcinoma (PTMC) (1, 2). Most PTMCs are indolent and easily monitored by neck ultrasonography (US) (3, 4). Clinical trials in Japan reported that the oncological outcomes of active surveillance for

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Abbreviations: CI, confidence interval; DTC, differentiated thyroid cancer; HR, hazard ratio; IQR, interquartile range; LN, lymph node; LT4, levothyroxine; PTC, papillary thyroid cancer; PTMC, papillary thyroid microcarcinoma; TSH, thyroid-stimulating hormone; TW-TSH, time-weighted average of thyroid-stimulating hormone; US, ultrasonography.

PTMC were as good as those of immediate surgery (5–7). Informed by these data, the 2015 American Thyroid Association/American Association of Clinical Endocrinologists guidelines for differentiated thyroid cancer (DTC) proposed active surveillance as an alternative treatment option to surgery for PTMC (8). The selection of appropriate patients and management of the patients during active surveillance is thus becoming an important clinical issue (9).

Some previous studies have suggested that younger age is a predictive factor for PTMC progression, but it is not a modifiable factor (10, 11). It is noteworthy that thyroid-stimulating hormone (TSH) has a potential role in the initiation or progression of DTC (12–16). Previous studies have shown that the incidence of papillary thyroid cancer (PTC) is related to the serum TSH levels in large benign thyroid nodules (14), and preoperative serum TSH levels are higher in patients with more advanced tumors and larger tumors (15). Based on these findings, TSH suppressive therapy has been widely used in patients with DTC, especially in patients with advanced and metastatic DTC, to prevent disease progression (8).

Some experts have suggested that mild TSH suppression by levothyroxine (LT4) administration might be useful for preventing PTMC progression (17). However, the association of PTMC progression with serum TSH levels during active surveillance has not been demonstrated. The aim of this study was to investigate the association between serum TSH levels and PTMC progression.

Patients and Methods

Study subjects

We enrolled patients who received a diagnosis of PTMC from April 2011 to March 2016 and continued active surveillance with serial serum TSH measurements at Samsung Medical Center (Seoul, Korea) without immediate surgery for >12 months (N = 142). Patients who had initial advanced disease with lateral lymph node (LN) metastasis or distant metastasis and clinical evidence of recurrent laryngeal nerve or trachea invasion (N = 2) and patients with LT4 treatment (N = 14) were excluded. A total of 127 PTMC nodules in 126 patients were studied. This retrospective cohort study was approved by the Institutional Review Board of Samsung Medical Center (no. 2017-06-131).

Follow-up protocol for active surveillance

All enrolled PTMC nodules were measured as ≤10 mm and were cytopathologically diagnosed as Bethesda category (18) V or VI by fine needle aspiration at baseline. The PTMC nodules were regularly monitored with US of both transverse and longitudinal planes. Follow-up took place every 6 to 12 months at the physician's discretion. Tumor size was defined as the maximum diameter on US, and tumor volume (mm^3) was calculated as length (mm) × width (mm) × thickness (mm) × $\pi/6$ (19). Newly developed highly suspicious LN was assessed by fine needle aspiration and thyroglobulin measurement. We used HDI 5000 (Advanced Technology Laboratories, Bothell, WA) or LOGIQ700 ultrasound scanners (GE Medical Systems, Milwaukee, WI) equipped with 12-50 MHz linear array transducers. All US images were reviewed by experienced radiologists and endocrinologists. Serum TSH was measured with a commercialized immunoradiometric assay kit (Immunotech, Czech Republic) (reference range of 0.30 to 6.00 mU/L for men and 0.30 to 6.50 mU/L for women).

Study design and definition

Serum TSH level in this study was not always measured at the same interval because of more frequent measurements in patients with high or low serum TSH levels and clinician preference. To avoid potential bias, we used a time-weighted average of serum TSH (TW-TSH) for quantitative evaluation of TSH exposure during observation instead of simple mean serum TSH (20). TW-TSH was calculated with the formula TW-TSH = $\sum_2^n (T \times TSH)$ + (initial $T \times m$TSH)/$\sum_1^n T$, where mTSH is the mean TSH level between the last measurement before and the first measurement after the start of active surveillance, and T is the time interval between the measurements (21). We categorized PTMC nodules into three groups according to TW-TSH tertile: first (lowest), second (middle), and third (highest).

The primary outcome of the study was PTMC progression, defined as a volume increase of ≥50% compared with baseline. We adopted the criteria from the definition of thyroid nodule growth in the recent American Thyroid Association guidelines (recommendation 23) (8), which is also applied as more sensitive indicator of PTMC growth than size criteria in a recent study (22). In addition, we separately assessed size increase (≥3 mm) and new appearance of LN metastasis compared with baseline because it has been widely used to define PTMC progression during active surveillance in previous studies. The cutoff point for size (3 mm) is based on the fact that ≤2 mm could be inaccurate because of observer variation or ultrasound resolution (9, 10). Other clinical and sonographic factors such as age at diagnosis, sex, subcapsular location, and parenchymal disease were also evaluated. Nodules abutting the thyroid capsule were considered to have a subcapsular location (23). Parenchymal disease was defined as having any abnormal thyroid autoantibodies including anti-TSH receptor antibody, antithyroid peroxidase antibody, and antithyroglobulin antibody, or changes in parenchymal echo pattern on US.

Statistics

All variables (including baseline characteristics) are presented as numbers with percentages for categorical variables, mean ± standard deviation values for continuous variables following a normal distribution, and median with interquartile range (IQR) for continuous variables not following a normal distribution. The Kaplan-Meier cumulative event curve with log-rank test was used to compare PTMC progression between the three groups. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for PTMC progression according to patient, tumor, and treatment factors. We calculated the optimal cutoff point of serum TSH level by selecting a TW-TSH level with maximum log-rank statistics ($P < 0.0005$) on Kaplan-Meier curves (24, 25). All statistical analyses were performed in IBM

SPSS Statistics for Windows (Version 22.0; IBM, Armonk, NY). Significance was defined as $P < 0.05$ for two-sided tests.

Results

Patient characteristics

The baseline characteristics for the PTMC nodules (N = 127) are presented in Table 1. Most patients were female (N = 100, 78.7%), and the median age at diagnosis was 51.0 years (IQR, 44.0 to 58.0 years). The most common reason to choose active surveillance was patient preference (N = 104, 81.8%). The remaining patients opted for active surveillance because of pregnancy (N = 2, 1.5%), other malignancy (N = 16, 12.5%), and high risk for operation (N = 5, 3.9%). The median baseline tumor size was 5.7 mm (IQR, 4.7 to 6.7 mm), and tumor volume was 60.3 mm^3 (IQR, 35.7 to 96.7 mm^3). Baseline serum TSH level was 1.85 mU/L (IQR, 1.26 to 2.74 mU/L).

Characteristics of three groups according to serum TSH level during follow-up

Table 2 provides the clinical characteristics of the lowest (N = 42, range 0.16 to 1.58), middle (N = 43, range 1.58 to 2.38), and highest (N = 42, range 2.39 to 9.16) TW-TSH groups. Baseline characteristics did not differ between the three groups except initial serum TSH level and proportion of LT4 treatment; the median initial TSH levels in the lowest, middle, and highest TW-TSH groups were 1.05 mU/L (IQR 0.75 to 1.33 mU/L), 2.08 mU/L (IQR 1.62 to 2.38 mU/L), and 3.11 mU/L (IQR 2.40 to 3.95 mU/L), respectively ($P < 0.001$).

PTMC progression during follow-up according to serum TSH level

During follow-up, 25 patients developed PTMC progression as defined previously: 5 patients (11.9%) in the lowest, 6 patients (14.0%) in middle, and 14 patients (33.3%) in the highest TW-TSH group. In addition, 7 PTMC nodules increased in size by ≥3 mm, and 1 PTMC nodule showed new metastatic LN. All concurrently fulfilled the criteria for PTMC progression (volume increase of ≥50%). Figure 1 shows Kaplan-Meier survival curves for PTMC progression according to the three TW-TSH groups (log-rank P = 0.007). In multivariate analysis, higher TW-TSH was an independent risk factor for PTMC progression; the adjusted HR for PTMC progression in the highest TW-TSH group was 3.55 (95% CI, 1.22 to 10.28) compared with the lowest TW-TSH group (P = 0.020). However, the HR of middle TW-TSH group was not significantly different from that of lowest TW-TSH group (1.52; 95% CI, 0.46 to 5.08; P = 0.489) (Table 3). Age <55 at diagnosis was also a prognostic factor for PTMC progression (HR 0.26; 95% CI, 0.07 to 0.88; P = 0.031) in univariate analysis, although the P value in multivariate analysis did not reach statistical significance (HR 0.29; 95% CI, 0.08 to 1.01; P = 0.052) (Table 3). Similar results were obtained when we categorized patients according to initial TSH tertile [log-rank P = 0.013; Supplemental Fig. 1(a)].

Among 18 patients who underwent surgery during follow-up, the majority selected surgery for reasons other than PTMC progression, such as patient preference (10 patients, 55.5%) or cure of other malignancy (4 patients, 22.2%). Only 4 patients (22.2%) underwent to surgery because of PTMC progression.

Table 1. Baseline Characteristics of Enrolled Patients

Characteristic	All PTMC Nodules (N = 127)
Median age, y (IQR)	51.0 (44.0–58.0)
Age ≥55 y, n (%)	42 (33.1%)
Female sex, n (%)	100 (78.7)
Tumor diameter at diagnosis, mm	5.7 (4.7–6.7)
Tumor volume at diagnosis, mm^3	60.3 (35.7–96.7)
Initial TSH level, mU/L	1.85 (1.26–2.74)
Subcapsular location, n (%)	27 (21.3%)
Parenchymal disease, n (%)	24 (18.9%)
Reason for active surveillance	
Preference, n (%)	104 (81.8%)
Medical reason	
Pregnancy, n (%)	2 (1.5%)
Other malignancy, n (%)	16 (12.5%)
High risk of operation, n (%)	5 (3.9%)
Median follow-up, mo (IQR)	25.0 (17.0–37.0)

Cutoff point evaluation of serum TSH level for PTMC progression

Having demonstrated that serum TSH level is an independent factor for PTMC progression, we wanted to identify the cutoff point for predicting PTMC progression. The results of the maximally selected log-rank statistics are presented in Fig. 2. For predicting PTMC progression, the optimal cutoff point of TW-TSH that maximized the log-rank statistic was 2.50 mU/L ($P <$ 0.001). In addition, the cutoff point of the initial serum TSH level for PTMC progression was 3.92 mU/L [Supplemental Fig. 1(b)].

Discussion

The current study demonstrated that high serum TSH level is associated with PTMC progression during active surveillance. The association remained significant after adjustment for age, sex, and other factors. We also identified the theoretical optimal cutoff of serum TSH level for PTMC progression.

TSH is a pituitary hormone that promotes thyroid hormone synthesis and growth of thyrocytes. The role of

Table 2. Clinical Characteristics of Three TW-TSH Groups According to TW-TSH Value Tertiles

Characteristic	Lowest (N = 42)	Middle (N = 43)	Highest (N = 42)	*P*
Median age, y (IQR)	52.0 (44.7–59.2)	51.0 (44.0–58.0)	48.5 (41.7–54.7)	0.319
Age ≥55 y, n (%)	16 (38.1%)	16 (37.2%)	10 (23.8%)	0.295
Female sex, n (%)	29 (69.0%)	34 (79.1%)	37 (88.1%)	0.103
Tumor diameter at diagnosis, mm	5.45 (4.50–7.10)	5.50 (4.60–6.20)	6.00 (4.95–7.40)	0.207
Tumor volume at diagnosis, mm^3	61.60 (32.61–95.67)	47.84 (36.71–89.46)	73.03 (36.59–128.72)	0.258
Initial TSH level, mU/L	1.05 (0.75–1.33)	2.08 (1.62–2.38)	3.11 (2.40–3.95)	<0.001
Time-weighted TSH level, mU/L	1.15 (0.86–1.47)	1.94 (1.79–2.23)	3.11 (2.58–3.87)	<0.001
Subcapsular location, n (%)	7 (16.7%)	7 (16.3%)	13 (31.0%)	0.172
Parenchymal disease, n (%)	8 (19.0%)	7 (16.3%)	9 (21.4%)	0.832
Reason for active surveillance				0.127
Preference, n (%)	31 (73.8%)	39 (90.7%)	34 (81.0%)	
Medical reason, n (%)	11 (26.2%)	4 (9.3%)	8 (19.0%)	
PTMC progression,[a] n (%)	5 (11.9%)	6 (14.0%)	14 (33.3%)	0.024
Size increase by ≥3 mm, n (%)	0 (0.0%)	3 (7.0%)	4 (9.5%)	0.140
New appearance of LN, n (%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	—
Surgery during active surveillance, n (%)	7 (16.7%)	8 (18.6%)	3 (7.1%)	0.270
Median follow-up, mo (IQR)	28.0 (18.5–44.2)	23.0 (15.0–34.0)	24.0 (16.7–36.2)	0.220

[a]Defined as volume increase by ≥50% compared with baseline.

TSH in the initiation or progression of PTC has been well demonstrated (12, 16). Considering these biological backgrounds, results of this study regarding the association between high serum TSH level and PTMC progression seems reasonable. In a previous study of patients with PTMC, however, there was not an association of PTMC progression with serum TSH level (26). This discordance could be explained by a different definition of PTMC progression. In contrast to previous studies that used size criteria for PTMC progression, we defined PTMC progression as a tumor volume increase of >50%, which is more sensitive for detecting tumor progression than diameter change (22). Similar to the volume criterion for PTMC progression, the number of patients with a diameter increase of ≥3 mm also increased with higher levels of TW-TSH (0, 3, and 4 patients in the lowest, middle, and highest TW-TSH tertiles, respectively). However, as in the previous study, we could not demonstrate the association between serum TSH level and size increase of PTMC nodules because of the small number of outcomes. In addition to the difference in definition of PTMC progression, the former study had a low proportion of patients with high serum TSH levels or young age, which is the condition supporting PTMC progression, leading to the null result (10).

In this study, we could not investigate the association between LT4 treatment and PTMC progression because of the small number of patients with LT4 treatment and inadequate TSH suppression in patients with PTMC treated with LT4. The TW-TSH level in LT4-treated patients was higher than in patients without LT4 treatment, which means that serum TSH suppression was inadequate. In fact, one patient with appropriate TSH suppression by LT4 administration showed a considerable reduction in tumor volume in this study. Additionally, a previous study by Ito *et al.* (10) reported a lower progression of PTMC in the TSH-suppressive therapy group (2%) than in other patients without

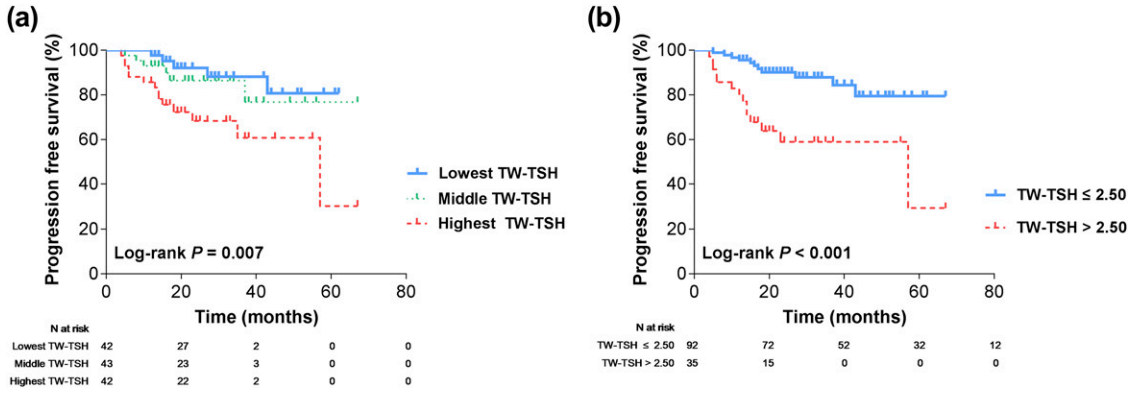

Figure 1. Kaplan-Meir graphs according to (a) tertile of TW-TSH and (b) cutoff point of TW-TSH.

Table 3. Univariate and Multivariate Cox Proportional Hazard Models for PTMC Progression

	Univariate		Multivariate[a]	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age ≥55 y	0.26 (0.07–0.88)	0.031	0.29 (0.08–1.01)	0.052
Female sex	1.07 (0.40–2.86)	0.890	0.78 (0.28–2.18)	0.644
Subcapsular location	1.37 (0.54–3.45)	0.499	1.18 (0.44–3.12)	0.732
Parenchymal disease	1.21 (0.48–3.06)	0.675	1.49 (0.57–3.88)	0.412
Tumor size at diagnosis, mm	0.68 (0.05–9.14)	0.771	0.48 (0.03–6.49)	0.581
TW-TSH group		0.020		0.041
Lowest (first tertile)	—	—	—	—
Middle (second tertile)	1.52 (0.46–5.01)	0.490	1.52 (0.46–5.08)	0.489
Highest (third tertile)	3.75 (1.34–10.49)	0.011	3.55 (1.22–10.28)	0.020

[a]Model: adjusted for age ≥55 years, sex, subcapsular location, parenchymal disease, tumor size at diagnosis (mm), TW-TSH group.

TSH suppression (4.8%), although the difference did not reach statistical significance because of the small number of enrolled patients.

We found that younger age at diagnosis (<55 years) was associated with lesser PTMC progression than older age at diagnosis in the current study. The association between young age and PTMC progression has been demonstrated in another report (10), which supports our findings. Interestingly, previous autopsy studies have shown that the incidence of latent carcinoma was lower in childhood than in adulthood but did not increase with age in adulthood (27, 28). Based on the aforementioned evidence, we speculate that the majority of PTMCs arise while patients are young and remain stable, with very low propensity to increase to a clinically apparent disease.

Because profound TSH suppression has been revealed to be a risk factor for cardiovascular events in older patients, osteoporosis, or arrhythmia (29), the recent guidelines do not recommend full suppression of TSH levels for low-risk patients with PTC (8). In this study, PTMC progression in the middle TW-TSH group was not different from that in the lowest TW-TSH group, and the optimal cutoff point of serum TW-TSH level for PTMC progression was 2.50 mU/L. These results suggest that a low-normal TSH level, which is not related to adverse events of excess thyroid hormone, is low enough to prevent PTMC progression. This cutoff point is consistent with the results from the study by Gao *et al.* (30), which proposed a TSH level ≥2.5 mU/L as a predictor of central node metastasis in patients with PTMC with immediate surgery. Considering both the risk of full TSH suppression and the benefit of maintaining serum TSH levels <2.50 mU/L, the "mild TSH suppression target (0.5–2.0 mU/L)" proposed by a recent guideline (8), or a little bit higher, appears to be a suitable range for the target TSH level during PTMC active surveillance.

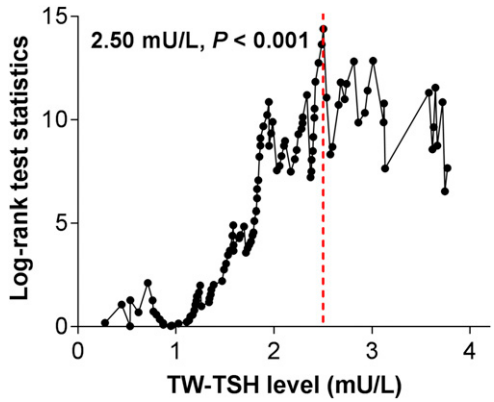

Figure 2. Evaluating the cutoff point of TW-TSH level with maximally selected log-rank statistics.

This topic has clinical implications because more and more patients with PTMC opt for active surveillance instead of immediate surgery for various reasons. Although many experts suggest that mild TSH suppression by LT4 administration might be useful to prevent PTMC progression (31), there is little evidence to support this notion. This study presents indirect evidence that LT4 treatment to maintain a low-normal TSH range might be helpful in preventing PTMC progression in some patients with high TW-TSH during active surveillance. However, TW-TSH level is difficult to apply in a clinical setting. Instead, the initial TSH level could be considered a clinically useful indicator of PTMC progression or LT4 treatment at the start of observation because higher initial TSH level was also associated with PTMC progression in this study. The retrospective, single-center study design, small sample size, and low event rate are also limitations of this study. In addition, statistical comparison between the groups with or without LT4 treatment was not done. Thus, a prospective study with an appropriate study design to evaluate the effectiveness of LT4 treatment during active surveillance of PTMC is necessary.

In conclusion, a higher level of serum TSH during active surveillance was associated with volume increase of PTMC in the first 2 years, and this result provides grounds for future studies to evaluate LT4 treatment to maintain a low-normal TSH range during active surveillance of PTMC.

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References

1. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic"–screening and overdiagnosis. *N Engl J Med*. 2014;**371**(19):1765–1767.
2. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA*. 2006;**295**(18):2164–2167.
3. Siddiqui S, White MG, Antic T, Grogan RH, Angelos P, Kaplan EL, Cipriani NA. Clinical and pathologic predictors of lymph node metastasis and recurrence in papillary thyroid microcarcinoma. *Thyroid*. 2016;**26**(6):807–815.
4. Yu XM, Wan Y, Sippel RS, Chen H. Should all papillary thyroid microcarcinomas be aggressively treated? An analysis of 18,445 cases. *Ann Surg*. 2011;**254**(4):653–660.
5. Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, Tomoda C, Takamura Y, Kobayashi K, Miya A. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg*. 2010;**34**(1):28–35.
6. Ito Y, Uruno T, Nakano K, Takamura Y, Miya A, Kobayashi K, Yokozawa T, Matsuzuka F, Kuma S, Kuma K, Miyauchi A. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. *Thyroid*. 2003;**13**(4):381–387.
7. Miyauchi A. Clinical trials of active surveillance of papillary microcarcinoma of the thyroid. *World J Surg*. 2016;**40**(3):516–522.
8. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 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*. 2016;**26**(1):1–133.
9. Haymart MR, Miller DC, Hawley ST. Active surveillance for low-risk cancers: a viable solution to overtreatment? *N Engl J Med*. 2017;**377**(3):203–206.
10. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. *Thyroid*. 2014;**24**(1):27–34.
11. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M, Fujimoto Y. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. *World J Surg*. 2010;**34**(6):1222–1231.
12. Cooper DS, Specker B, Ho M, Sperling M, Ladenson PW, Ross DS, Ain KB, Bigos ST, Brierley JD, Haugen BR, Klein I, Robbins J, Sherman SI, Taylor T, Maxon HR III. Thyrotropin suppression and disease progression in patients with differentiated thyroid cancer: results from the National Thyroid Cancer Treatment Cooperative Registry. *Thyroid*. 1998;**8**(9):737–744.
13. Fiore E, Rago T, Provenzale MA, Scutari M, Ugolini C, Basolo F, Di Coscio G, Berti P, Grasso L, Elisei R, Pinchera A, Vitti P. Lower levels of TSH are associated with a lower risk of papillary thyroid cancer in patients with thyroid nodular disease: thyroid autonomy may play a protective role. *Endocr Relat Cancer*. 2009;**16**(4):1251–1260.
14. McLeod DS, Watters KF, Carpenter AD, Ladenson PW, Cooper DS, Ding EL. Thyrotropin and thyroid cancer diagnosis: a systematic review and dose-response meta-analysis. *J Clin Endocrinol Metab*. 2012;**97**(8):2682–2692.
15. Haymart MR, Repplinger DJ, Leverson GE, Elson DF, Sippel RS, Jaume JC, Chen H. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. *J Clin Endocrinol Metab*. 2008;**93**(3):809–814.
16. Fiore E, Vitti P. Serum TSH and risk of papillary thyroid cancer in nodular thyroid disease. *J Clin Endocrinol Metab*. 2012;**97**(4):1134–1145.
17. Haymart MR, Esfandiari NH, Stang MT, Sosa JA. Controversies in the management of low-risk differentiated thyroid cancer. *Endocr Rev*. 2017;**38**(4):351–378.
18. Cibas ES, Ali SZ; NCI Thyroid FNA State of the Science Conference. The Bethesda System for Reporting Thyroid Cytopathology. *Am J Clin Pathol*. 2009;**132**(5):658–665.
19. Jeong WK, Baek JH, Rhim H, Kim YS, Kwak MS, Jeong HJ, Lee D. Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. *Eur Radiol*. 2008;**18**(6):1244–1250.
20. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA*. 2003;**290**(15):2041–2047.
21. Lichtenberg S, Rahamimov R, Green H, Fox BD, Mor E, Gafter U, Chagnac A, Rozen-Zvi B. The incidence of post-transplant cancer among kidney transplant recipients is associated with the level of tacrolimus exposure during the first year after transplantation. *Eur J Clin Pharmacol*. 2017;**73**(7):819–826.
22. Kwon H, Oh HS, Kim M, Park S, Jeon MJ, Kim WG, Kim WB, Shong YK, Song DE, Baek JH, Chung KW, Kim TY. Active surveillance for patients with papillary thyroid microcarcinoma: a single center's experience in Korea. *J Clin Endocrinol Metab*. 2017;**102**(6):1917–1925.
23. Oh HS, Kim WG, Park S, Kim M, Kwon H, Jeon MJ, Lee JH, Baek JH, Song DE, Kim TY, Shong YK, Kim WB. Serial neck ultrasonographic evaluation of changes in papillary thyroid carcinoma during pregnancy. *Thyroid*. 2017;**27**(6):773–777.
24. Contal C, O'Quigley J. An application of changepoint methods in studying the effect of age on survival in breast cancer. *Comput Stat Data Anal*. 1999;**30**(3):253–270.
25. Visvanathan K, Fackler MS, Zhang Z, Lopez-Bujanda ZA, Jeter SC, Sokoll LJ, Garrett-Mayer E, Cope LM, Umbricht CB, Euhus DM, Forero A, Storniolo AM, Nanda R, Lin NU, Carey LA, Ingle JN, Sukumar S, Wolff AC. Monitoring of serum DNA methylation as an early independent marker of response and survival in metastatic breast cancer: TBCRC 005 prospective biomarker study. *J Clin Oncol*. 2017;**35**(7):751–758.
26. 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.
27. Franssila KO, Harach HR. Occult papillary carcinoma of the thyroid in children and young adults. A systemic autopsy study in Finland. *Cancer*. 1986;**58**(3):715–719.
28. Lang W, Borrusch H, Bauer L. Occult carcinomas of the thyroid. Evaluation of 1,020 sequential autopsies. *Am J Clin Pathol*. 1988;**90**(1):72–76.
29. Biondi B, Cooper DS. Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer. *Thyroid*. 2010;**20**(2):135–146.
30. Gao Y, Qu N, Zhang L, Chen JY, Ji QH. Preoperative ultrasonography and serum thyroid-stimulating hormone on predicting central lymph node metastasis in thyroid nodules as or suspicious for papillary thyroid microcarcinoma. *Tumour Biol*. 2016;**37**(6):7453–7459.
31. Miyauchi A, Ito Y, Oda H. Insights into the management of papillary microcarcinoma of the thyroid. *Thyroid*. 2017;thy.2017.0227.