Active Surveillance for Patients With Papillary Thyroid Microcarcinoma: A Single Center's Experience in Korea

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Context: Papillary thyroid microcarcinoma (PTMC) usually has an excellent prognosis.

Objective: To evaluate the three-dimensional structures of PTMCs, using serial neck ultrasonography (US) in patients under active surveillance.

Design and Setting: A retrospective cohort study.

Participants: In total, 192 patients diagnosed with PTMC under active surveillance for >1 year were included in a median 30-month follow-up. Changes in tumor size were evaluated not only using the maximal tumor diameter but also the tumor volume.

Results: The median age of patients was 51.3 years and 145 patients (76%) were female. The median initial maximal tumor diameter and tumor volume were 5.5 mm and 48.8 mm^3, respectively. The tumor size increased in 27 patients (14%); 23 patients showed a tumor volume increase >50% without a maximal diameter increase of ≥3 mm. The other four patients had both an increasing tumor volume and increasing maximal tumor diameter ≥3 mm. One patient (0.5%) had newly appeared cervical lymph node (LN) metastasis at 3 years after the initial diagnosis. There were no significant risk factors associated with increased tumor size, such as age, sex, or Hashimoto thyroiditis. Twenty-four patients (13%) underwent delayed thyroid surgery at a median of 31.2 months and seven (29%) had cervical LN metastasis on pathologic examination.

Conclusion: Some PTMCs could grow significantly after a relatively short period of active surveillance. We also found that the change in tumor volume was more sensitive to detect tumor progression than the change in the maximal tumor diameter. (***J Clin Endocrinol Metab*** **102: 1917–1925, 2017)**

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The incidence of thyroid cancer has been increasing worldwide in recent years (1–7). Most of this increase is due to an increased incidence of papillary thyroid cancer (PTC)—predominantly small PTC (1–4). Several studies have shown that widespread use of high-resolution neck ultrasonography (US) has enabled the early detection of small PTCs (1–3). Most small PTCs usually have an indolent clinical course and an excellent prognosis (8–13). In particular, papillary thyroid microcarcinoma (PTMC), defined as a PTC ≤1 cm in maximal diameter, shows low rates of locoregional recurrence, distant metastases, and disease-specific mortality (8–11).

Active surveillance was initially used in patients with localized prostate cancer and has been applied to several

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Abbreviations: CNB, core-needle biopsy; FNAC, fine-needle aspiration cytology; IQR, interquartile range; LN, lymph node; PTC, papillary thyroid cancer; PTMC, papillary thyroid microcarcinoma; Tg, thyroglobulin; TSH, thyroid-stimulating hormone; US, ultrasonography.

cancers, such as urethral cancer and intraocular melanoma (14–16). It is a treatment plan with a curative intent in which active treatment, such as surgery or radiation therapy, is delayed to avoid or delay treatment adverse effects until the cancer shows significant progression (16, 17). During active surveillance, the patient's condition should be closely monitored and certain examinations and tests should be performed on a regular schedule (16).

Recently, American Thyroid Association guidelines introduced active surveillance management as an alternative to immediate thyroid surgery in patients with very low-risk tumors, those who are at high surgical risk because of comorbidity, and those who are expected to have a relatively short life expectancy (18).

A few studies from Japan reported the results of active surveillance in patients with cytopathologically proven PTMC (19–22). One study, which included 1,235 patients under active surveillance, suggested that the tumor size was stable in most patients (20). However, 5% and 10% of patients had an increase in tumor size at 5- and 10-year follow-up, respectively (10). Another study reported that tumor size was stable in 93% patients during 5 years of follow-up (19). To the best of our knowledge, no study, except for those of two centers in Japan, has evaluated the clinical outcomes of active surveillance in patients with PTMC.

In this study, we aimed to evaluate the changes in the three-dimensional structure of PTMCs based on neck US in Korean patients followed up by active surveillance without immediate surgery for PTMC. We also evaluated the clinicopathological features and clinical outcomes in patients who underwent delayed thyroid surgery.

Methods

Study design and patients

This retrospective cohort study included 192 patients cytopathologically diagnosed with PTMC and followed up by active surveillance without immediate surgery for >1 year from 2002 to 2015 at Asan Medical Center, Seoul, Korea. These patients did not undergo immediate thyroid surgery, either because they refused surgery despite the physician's recommendation, had other malignancies that were not cured, or were at high risk for general anesthesia because of a cardiopulmonary disease such as heart failure, asthma, or chronic obstructive pulmonary disease. Patients with lateral cervical lymph node (LN) metastasis or distant metastasis were not included. Patients with any clinical evidence of macroscopic invasion into the perithyroidal soft tissue or invasion into the trachea or the recurrent laryngeal nerve also were not included. Patients with an aggressive variant of PTC in fine-needle aspiration cytology (FNAC) or core-needle biopsy (CNB) were excluded from active surveillance. This study was approved by the institutional review board of Asan Medical Center.

Neck US examination and cytopathological diagnosis of PTMC

Neck US images were evaluated with an iU22 unit (Philips Healthcare, Bothell, WA) or a EUB-7500 unit (Hitachi Medical Systems, Tokyo, Japan) equipped with a linear high-frequency probe (5 to 14 MHz). All neck US examinations and US-guided FNAC and CNB procedures were performed by experienced radiologists. FNAC procedures were performed with a 23-gauge needle connected to a 10-mL syringe as previously reported (23). US-guided CNB procedures were performed with an 18-gauge, 1.1-cm or 1.6-cm excursion, double-action, spring-activated needle (TSK Ace-cut; Create Medic, Yokohama, Japan) as previously reported (24). The follow-up US protocol is well established and was performed as previously reported (25), with interobserver variations in measurements of the diameter and volume of thyroid nodules of about 13% and 7%, respectively. All neck US images were reviewed by an experienced radiologist (J.H.B) and endocrinologist (H.M.K).

Cytopathological diagnoses were made by pathologists experienced in thyroid cytopathology. FNAC diagnoses were classified into six categories according to the Bethesda System (26). CNB specimens were evaluated on the basis of the criteria proposed by the Korean endocrine pathology thyroid CNB study group (27).

Management and follow-up protocol for active surveillance

The patients were regularly followed-up with physical examinations and neck US every 6 to 12 mo. All thyroid nodules in US images were evaluated with both transverse and longitudinal planes for the three-dimensional evaluation and tumor volume measurement. The maximal tumor diameter was measured from one outer margin to the other outer margin of the nodule. All patients were evaluated for both central and lateral cervical LNs by neck US. When a suspicious LN was found, FNAC of the LN and assessment of the thyroglobulin (Tg) level in the washout of the needles was performed.

When delayed thyroid surgery was chosen during follow-up, the patients underwent routine prophylactic central compartment neck dissection. After the initial surgical treatment, patients were regularly followed up as previously reported (28, 29).

Analysis of US imaging during follow-up and definition

We evaluated the changes in tumor size not only using the maximal tumor diameter but also using the tumor volume. An increase in the maximal tumor diameter was defined as an increase of ≥3 mm (19, 20), whereas a decrease in the maximal tumor diameter was defined as a decrease of ≥3 mm. A change in tumor volume was defined as an increase or decrease in volume of >50% compared with that of the initial diagnosis (18). Tumor volume was calculated as [tumor volume (mm^3) = length (mm) × width (mm) × thickness (mm) × $\pi/6$] (30). Volume change was calculated by the following equation: [initial volume (mL) − final volume (mL)] × 100/initial volume (mL) (30).

An increasing tumor size was defined as an increase in the maximal tumor diameter or tumor volume. A decreasing tumor size was defined as a decrease in the maximal tumor diameter or tumor volume.

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Hashimoto thyroiditis was defined as serum antithyroid peroxidase antibody levels >60 IU/mL or serum anti-Tg antibody >60 IU/mL, with diffuse parenchymal heterogeneity on US.

Thyroid function tests

As previously reported (31), serum thyroid-stimulating hormone (TSH) concentrations (reference range, 0.3 to 4 mIU/L; lower detection limit, 0.01 mIU/L) were measured by an immunoradiometric assay (TSH-CTK-3; DiaSorin, Saluggia, Italy) with a functional sensitivity of 0.07 mIU/L. The serum free T4 level (normal range, 10.30 to 24.45 pmol/L) was measured with the free T4 radioimmunoassay kit (Immunotech, Prague, Czech Republic). The serum total T3 level (reference range, 1.51 to 2.77 nmol/L) was measured by radioimmunoassay using T3-CTK (DiaSorin).

Statistical analysis

All statistical analyses were performed with R (version 3.1.0) and the R library package (R Foundation for Statistical Computing, Vienna, Austria; http://www.*R*-project.org). Continuous variables are presented as medians with interquartile ranges (IQRs). Categorical variables are presented as numbers with corresponding percentages. The Wilcoxon rank-sum test, Wilcoxon signed-rank test, or Kruskal-Wallis test was used to compare continuous variables. The χ^2 test or Fisher exact test was used to compare categorical variables. $P < 0.05$ was considered to indicate statistical significance. All P values were two-sided.

Results

Baseline clinical features of patients with PTMC under active surveillance

The clinical features of the 192 patients under active surveillance are listed in Table 1. The median age of the patients was 51.3 y (IQR, 42.9 to 59.5 y). When we classified patients into three categories according to their age at diagnosis, 61 patients (32%) were <45 years old (young), 99 patients (52%) were 45 to 64 years old (middle aged), and 32 patients (17%) were ≥65 years (old). In total, 145 patients (76%) were female. The median maximal tumor diameter at initial diagnosis was 5.5 mm (IQR, 4.2 to 6.9 mm), and 114 patients (59%) had tumors >5.0 mm in diameter. The median tumor volume at diagnosis was 48.8 mm^3 (IQR, 23.1 to 100.6 mm^3). Hashimoto thyroiditis was found in 42 patients (22%). The median serum TSH concentration was 2.0 mIU/L (IQR, 1.2 to 3.2 mIU/L), the median serum free T4 level was 15.5 pmol/L (IQR, 16.7 to 18.0 pmol/L), and the median serum total T3 level was 2.0 nmol/L (IQR, 1.8 to 2.2 nmol/L). Twelve patients (6%) took levothyroxine for hormone replacement therapy, and eight (4%) took levothyroxine for TSH suppressive therapy. The most common reason for active surveillance was the patient's refusal to have surgery despite the physician's recommendation. In addition, 48 patients (25%) had other malignant disease, four patients (2%) had cardiopulmonary disease, and four (2%) had systemic disease, such as poorly controlled systemic lupus erythematosus or multiple sclerosis. *BRAF* mutational analysis was performed in 17 patients and six patients had the *BRAF V600E* mutation.

Table 1. Baseline Clinical Features of Patients (N = 192) With PTMC Under Active Surveillance

	Value
Age at diagnosis, y	51.3 (42.9–59.5)
<45	61 (32)
45–64	99 (52)
≥65	32 (17)
Female sex	145 (76)
Maximal tumor diameter at diagnosis, mm	5.5 (4.2–6.9)
>5	114 (59)
Tumor volume at diagnosis, mm^3	48.8 (23.1–100.6)
Hashimoto thyroiditis	42 (22)
Thyroid function test	
TSH, mIU/L	2.0 (1.2–3.2)
Free T4, pmol/L	15.5 (16.7–18.0)
Total T3, nmol/L	2.0 (1.8–2.2)
Levothyroxine replacement	20 (10)
Hormone replacement therapy	12 (6)
TSH suppressive therapy	8 (4)
Reasons for active surveillance	
Refusal of patient	136 (71)
Comorbidities	
Malignant disease	48 (25)
Cardiopulmonary disease	4 (2)
Systemic disease	4 (2)

Continuous variables are presented as median (IQR). Categorical variables are presented as no. (%).

Clinical features of patients with PTMC according to the change in tumor size

During a median of 30.1 mo (IQR, 21.4 to 43.7 mo) of follow-up, 27 patients (14%; increasing group) had an increase in tumor size (Table 2). Tumor volume increased in 27 patients (14%) and the maximal tumor diameter increased in four patients (2%) during follow-up (Supplemental Table 1). There was no significant change in tumor size in 132 patients (69%; stable group), and 33 patients (17%; decreasing group) had decreases in tumor size. Changes in the maximal tumor diameter and tumor volume during follow-up in the three groups according to the change in tumor size are shown in Figure 1.

There were no significant differences in the median age of the patients between the groups: 53.6 y (IQR, 41.6 to 60.3 y) in the decreasing group, 51.8 y (IQR, 43.5 to 59.7 y) in the stable group, and 47.3 y (IQR, 41.2 to 58.7 y) in the increasing group ($P = 0.5$). There were no significant differences in age categories and the proportion of women according to the change in tumor size ($P = 0.8$ and $P = 0.2$, respectively).

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Table 2. Clinical Features in Patients With PTMC Under Active Surveillance, According to Change in Tumor Size

	Decreasing (n = 33; 17%)	Stable (n = 132; 69%)	Increasing (n = 27; 14%)	*P*
Age at diagnosis, y	53.6 (41.6–60.3)	51.8 (43.5–59.7)	47.3 (41.2–58.7)	0.5[a]
<45	10 (30)	40 (30)	11 (41)	0.8[b]
45–64	16 (48)	71 (54)	12 (44)	
≥65	7 (21)	21 (16)	4 (15)	
Female sex	28 (85)	95 (72)	22 (81)	0.2[b]
Maximal tumor diameter at diagnosis, mm[c]	6.0 (5.0–7.7)*d*	5.5 (4.5–6.7)[d]	4.5 (3.5–5.8)*e*	0.002[a]
>5	24 (73)[d]	82 (62)[d]	8 (30)[e]	0.002[b]
Tumor volume at diagnosis, mm^{3}[c]	79.6 (48.5–125.8)[d]	47.5 (26.5–100.6)[d]	23.0 (12.9–54.0)[e]	0.001[a]
Hashimoto thyroiditis	7 (21)	29 (22)	6 (22)	0.9[b]

Continuous variables are presented as median (IQR). Categorical variables are presented as no. (%).

[a] *P* value estimated by Kruskal-Wallis test.

[b] *P* value estimated by χ^2 or Fisher exact test.

[c–e] Post hoc analysis was evaluated by Bonferroni correction method. The same letters indicate nonsignificant difference between groups.

The median maximal tumor diameter at initial diagnosis was larger in the decreasing group than in the other groups: 6.0 mm (IQR, 5.0 to 7.7 mm) in the decreasing group, 5.5 mm (IQR, 4.5 to 6.7 mm) in the stable group, and 4.5 mm (IQR, 3.5 to 5.8 mm) in the increasing group (P = 0.002). There were significant differences in the proportion of patients with a maximal tumor diameter >5 mm between the groups: 73% in the decreasing group, 62% in the stable group, and 30% in the increasing group (P = 0.002). There were significant differences in the median maximal tumor volume: 79.6 mm^3 (IQR, 48.5 to 125.8 mm^3) in the decreasing

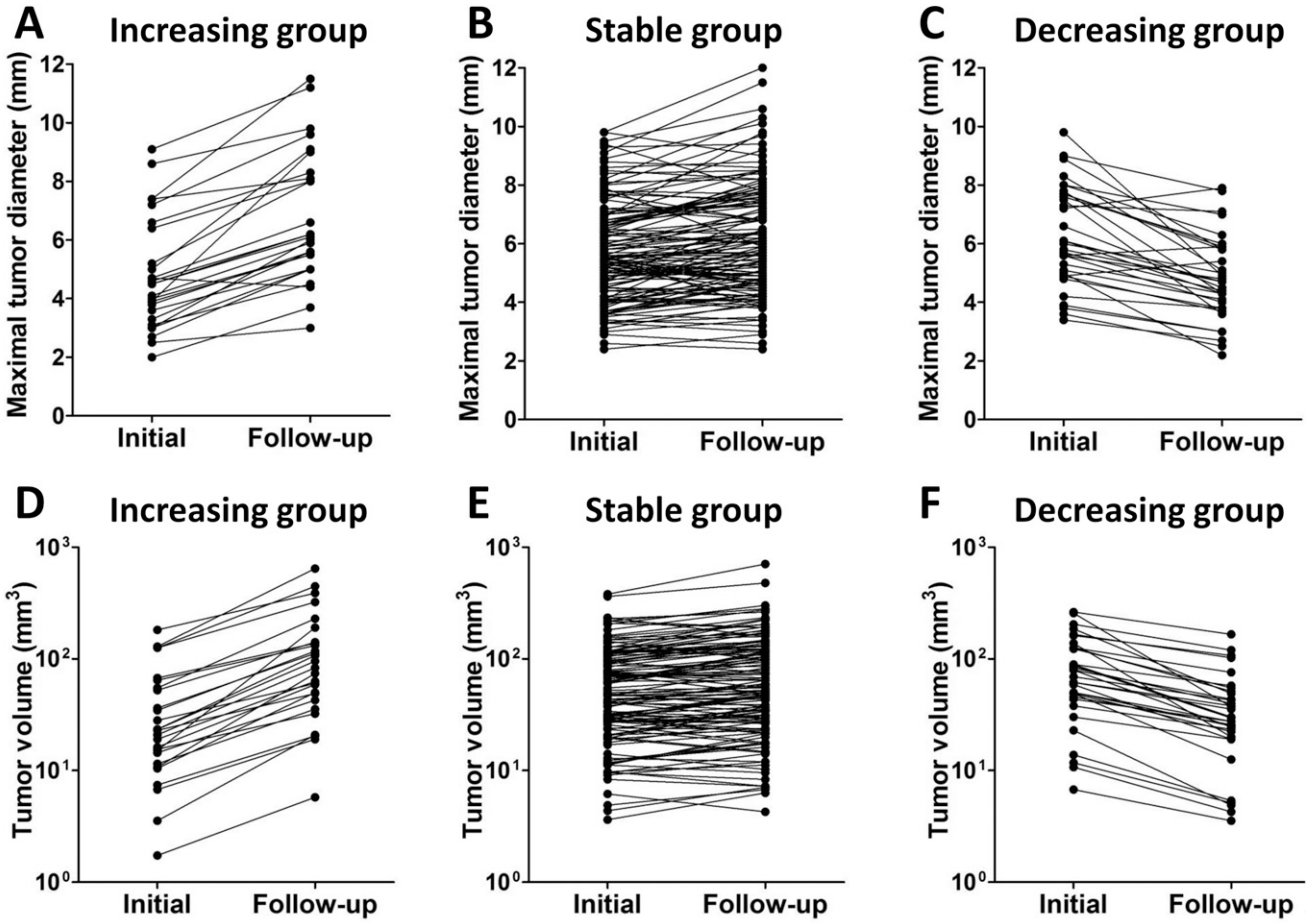

Figure 1. Changes in maximal tumor diameter and tumor volume during follow-up in the three groups according to the changes in tumor size. Changes in maximal tumor diameter in (A) the increasing group, (B) the stable group, and (C) the decreasing group. Changes in tumor volume in (D) the increasing group, (E) the stable group, and (F) the decreasing group.

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group, 47.5 mm^3 (IQR, 26.5 to 100.6 mm^3) in the stable group, and 23.0 mm^3 (IQR, 12.9 to 54.0 mm^3) in the increasing group ($P = 0.001$). In post hoc analysis, there were no significant differences in maximal tumor diameter and tumor volume between the decreasing and stable groups. The median tumor diameter and tumor volume were lower in the increasing group than in the decreasing and stable groups. Most patients in the decreasing group had tumors with cystic features on neck US [Supplemental Fig. 1(A) and 1(B)].

In the increasing group, a 45-year-old woman had a newly apparent central cervical LN at 3 years after initial diagnosis. She had a 5.0-mm hypoechoic tumor in the right lobe of the thyroid [Fig. 2(A)]. The tumor had increased to 9.1 mm in maximal diameter 31.4 mo after the initial diagnosis [Fig. 2(B)]. The tumor volume increased by 76% and a new cervical LN was detected at right level 6 [Fig. 2(C)]. Cervical LN metastasis of PTMC was confirmed after thyroid surgery.

In the increasing group, all patients had increases in tumor volume of >50%. However, in 23 patients (85%), the maximal tumor diameter remained stable (an increase of <3 mm). In these 23 patients, tumor volume increased by 50% to 60% in six patients (26%), 60% to 70% in eight patients (35%), 70% to 80% in eight patients (35%), and more than 80% in one patient (4%). For example, a 58-year-old woman had a 7.2-mm hypoechoic solid tumor in the left lobe of the thyroid [Fig. 2(D)]. The maximal tumor diameter was stable because it increased to 9.6 mm during a follow-up of 21.6 mo [Fig. 2(E)]. However, the tumor volume significantly increased by 61.2% (from 124.7 mm^3 to 321.1 mm^3).

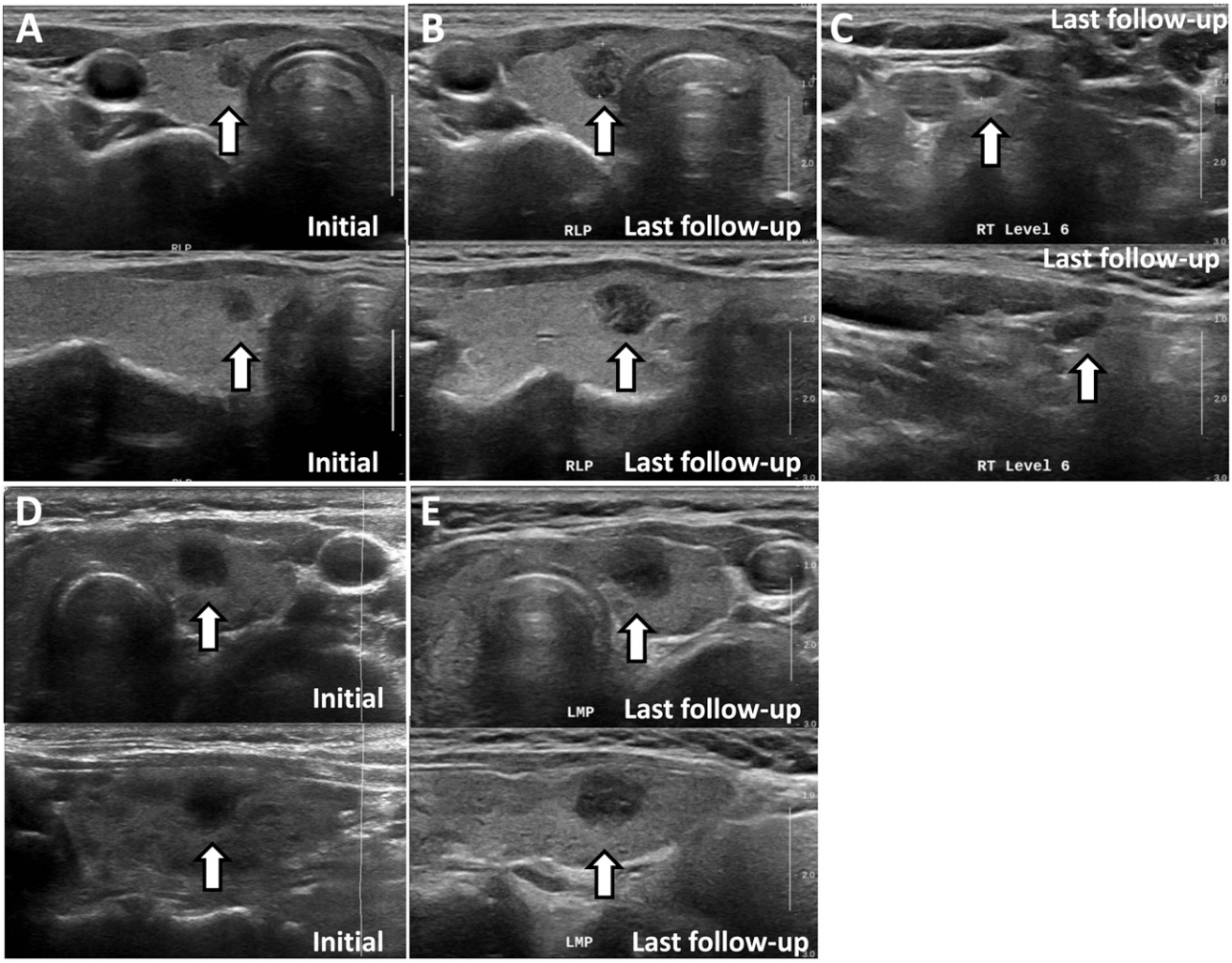

Figure 2. A 45-year-old woman had a newly apparent central cervical LN at 3 years after initial diagnosis. (A) She had a 5.0-mm hypoechoic tumor in the right lobe of the thyroid. (B) The tumor increased to 9.1 mm in maximal diameter. The tumor volume increased by 75.9% and (C) a new cervical LN was detected in right level 6. Cervical LN metastasis of PTC was confirmed after thyroid surgery. (D, E) Images from patients with increasing tumor volume and stable state, based on the maximal tumor diameter. (D) A 58-year-old woman had a 7.2-mm hypoechoic solid tumor in the left lobe of the thyroid. (E) The maximal tumor diameter was stable because it increased to 9.6 mm during the follow-up. However, tumor volume significantly increased by 61.2% (from 124.7 mm^3 to 321.1 mm^3).

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Clinicopathological features of patients who underwent delayed thyroid surgery

Among the 192 patients, 24 (13%) underwent delayed thyroid surgery during the study period (Table 3). The median period from diagnosis to surgery was 31.2 mo (IQR, 20.7 to 42.1 mo). The median age of the patients was 51.8 y (IQR, 46.8 to 58.8 y) and 21 patients (88%) were female. The median maximal tumor diameters at initial diagnosis, at last follow-up, and based on surgical pathology were 6.2 mm (IQR, 5.2 to 7.7 mm), 7.3 mm (IQR, 6.3 to 9.0 mm), and 7.0 mm (IQR, 6.0 to 8.0 mm), respectively. There was a significant difference in the maximal tumor diameter between the initial diagnosis and last follow-up before surgery in patients who underwent delayed thyroid surgery ($P = 0.001$). The median tumor volume at initial diagnosis was 96.3 mm^3 (IQR, 52.9 to 124.6 mm^3). Among 24 patients who underwent delayed thyroid surgery, 19 (79%) were confirmed to have classical PTC. However, two patients (8%) had the tall-cell variant of PTC, and three patients (13%) had the infiltrative subtype of the follicular variant of PTC. Multifocal PTMCs were present in 15 patients (63%) and nine patients (34%) had extrathyroidal extension. Seven patients (29%) had central cervical LN metastasis (pN1a). The median number of metastatic LNs was 2.0 (IQR, 1.5 to 3.0). The median metastatic LN diameter was 2.0 mm (IQR, 0.9 to 3.5 mm) and two patients (29%) had extranodal extension. There were no significant differences in age, proportion of women, maximal tumor diameter, tumor volume, multifocality, extrathyroidal extension, and Hashimoto thyroiditis between patients with or without central cervical LN metastasis (Supplemental Table 2).

Fifteen patients (63%) underwent lobectomy and nine patients (38%) underwent total thyroidectomy (Table 3). No patient had recurrence after initial thyroid surgery during a median of 7.2 mo (IQR, 5.9 to 13.8) of follow-up. The most common reason for the decision to undergo thyroid surgery was patient anxiety (n = 12; 50%). Eight patients (33%) underwent surgery because of an increase in tumor size. One patient (0.5%) had newly apparent cervical LN metastasis at 3 years after the initial diagnosis. Two patients (8%) in the stable group underwent surgery because the tumors were located close to the posterior capsule. One patient underwent diagnostic surgery because of the increasing size of another thyroid nodule according to serial neck US.

Table 3. Clinicopathological Features of Patients (n = 24) Who Underwent Delayed Thyroid Surgery for PTMC

	Value
Duration from diagnosis to surgery, mo	31.2 (20.7–42.1)
Age, y	51.8 (46.8–58.8)
Female sex	21 (88)
Maximal tumor diameter, mm	
At diagnosis	6.2 (5.2–7.7)
At last follow-up	7.3 (6.3–9.0)
Surgical pathology	7.0 (6.0–8.0)
Tumor volume at diagnosis, mm^3	96.3 (52.9–124.6)
Multifocality	15 (63)
Extrathyroidal extension	9 (34)
Cervical LN metastasis	
pN0	17 (71)
pN1a	7 (29)
pN1b	0
Metastatic LN numbers	2.0 (1.5–3.0)
Metastatic LN diameter, mm	2.0 (0.9–3.5)
Extranodal extension	2 (29)
Surgical extent	
Lobectomy	15 (63)
Total thyroidectomy	9 (38)
Duration of no evidence of disease, mo	7.2 (5.9–13.8)
Reasons for the decision of thyroid surgery	
Anxiety of patients	12 (50)
Tumor size enlargement	8 (33)
Appearance of LN metastasis	1 (4)
Tumor location near posterior capsule	2 (8)
Coexistence of benign thyroid nodule	1 (4)

Continuous variables are presented as median (IQR). Categorical variables are presented as no. (%).

Discussion

In this study, we evaluated the three-dimensional structures of PTMCs based on serial neck US in patients under active surveillance without immediate surgery. During a median of 30 mo of follow-up, tumor size increased in 27 patients (14%), and one patient (0.5%) had newly apparent cervical LN metastasis. There were no significant risk factors associated with an increased tumor size, such as age, sex, or Hashimoto thyroiditis. In our series, 33 patients (17%) had a decreasing tumor size. Twenty-four patients (13%) underwent delayed thyroid surgery. No patient had recurrence after initial thyroid surgery.

We evaluated the changes in tumor size not only using the maximal tumor diameter but also using the tumor volume. The American Thyroid Association guidelines define tumor enlargement as a 20% increase in at least two nodule dimensions, with a minimal increase of 2 mm or >50% change in volume (18). Previous studies of active surveillance of patients with PTMC defined tumor enlargement as an increase in the tumor diameter of ≥3 mm compared with that at initial diagnosis (19, 20). We found that the tumor volume change more sensitively detected tumor progression than changes in the maximal tumor diameter. In this study, the maximal tumor diameter increased ≥3 mm in only four patients (2%), whereas the tumor volume increased >50% in 27 patients. Of all of the patients with an increasing tumor volume, the maximal tumor diameter remained stable (increase of <3 mm) in 23 patients (85%). On neck US,

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changes in tumor volume may reflect tumor progression more sensitively than changes in maximal tumor diameter. However, not all patients with a tumor volume increase >50% will be likely to have clinically significant disease progression over time. The changes in tumor volume would be more convincing if the serial increases in tumor volume were noted in follow-up US examination. Currently, there is no consensus on what is considered a clinically significant increase in tumor size in patients under active surveillance. Further studies should focus on characteristics of serial neck US for predicting a clinically significant increase in tumor size and cervical LN metastasis.

Thirty-three patients (17%) had decreases in tumor size. Most patients in the decreasing group had tumors with cystic features on neck US [Supplemental Fig. 1(A) and 1(B)]. Ultrasonographic features should also be considered as well as tumor size by neck US examination. Previous studies suggested that FNAC could lead to the obliteration of thyroid nodules (32–34). FNAC-induced reactive changes include necrosis, hemorrhage, infarction, fibrosis, vascular thrombosis/proliferation, and formation of granulation tissue (32–34).

A previous study of active surveillance reported that the proportion of patients with PTMC progression was lowest in the elderly and highest in young patients (20). Another study showed that PTMCs in younger patients tended to increase in size more than those in older patients (19). In our study, there were no significant associations between age and changes in tumor size (Table 2; Supplemental Table 1). However, four patients with a significantly increasing maximal tumor diameter were younger than 65 years (Supplemental Table 1). Active surveillance might be carefully considered for younger and middle-aged patients. Because of the retrospective nature and relatively short follow-up period of this study, further prospective research is required.

Previous studies from South Korea reported that the incidence of thyroid cancer has increased rapidly as a result of screening for thyroid cancer with neck US (1, 2). In the current study, 44% of patients had tumors ≤5 mm in diameter, because patients from the early 2000s were included. In 2010, the Korean Thyroid Association revised guidelines for the diagnosis and management of thyroid nodules and cancer, and recommended FNAC to be performed for nodules >5 mm in patients with risk factors for thyroid cancer or malignant features on neck US (35). The numbers and proportions of PTMCs ≤5 mm in diameter have decreased since 2010 when the revised guidelines were announced (36). The efforts of physicians to apply neck US and FNAC based on the guidelines could lead to a decrease in the overdetection of small PTCs (36).

In this study, the most common reason for choosing to undergo thyroid surgery was patient anxiety, not an increase in tumor size. Patients with PTMC under active surveillance felt anxiety during follow-up, even though their tumors remained stable according to neck US. This anxiety could have an effect on the quality of life of these patients. A previous study reported that the incidence of unfavorable events, such as vocal cord paralysis, hypoparathyroidism, and postoperative hematoma, was higher in patients who had immediate surgery than in patients under active surveillance (21). One prospective study suggested that the quality of life of patients with low-risk prostate cancer who were under active surveillance did not differ from that of a noncancer comparison group (37). However, there have been no studies of the quality of life or anxiety of patients with PTMC who are undergoing active surveillance.

Active surveillance should be applied carefully and followed up thoroughly in selected patients with PTMC. Although the prognosis of PTMC is favorable, some patients with PTMC suffer from locoregional recurrence and distant metastasis (9–11). In this study, 27 patients (14%) had an increase in tumor size despite a relatively short follow-up period. However, none of the 24 patients who underwent delayed surgery had expansion in the extent of surgery. There is a possibility of an expansion of the operative field in patients with delayed thyroid surgery after active surveillance. Some patients with newly apparent lateral cervical LN metastasis during active surveillance need to receive modified radical neck dissection. This could increase the risk of surgical complications. Moreover, distant metastases cannot be easily detected in patients under active surveillance because diagnostic whole-body scans cannot be done for these patients. Imaging studies such as computed tomography, magnetic resonance imaging, or whole-body fluorodeoxyglucose-positron emission tomography cannot be routinely performed in all patients under active surveillance at diagnosis and follow-up because of their cost and the risk of radiation exposure. In this study, 24 patients (13%) were evaluated with chest computed tomography scan at the initial diagnosis of PTC. However, there is no consensus on the extent of radiologic studies to evaluate distant metastases of PTMC. Further research is needed on how to effectively detect and monitor distant metastasis. Medical cost is another problem. A previous study suggested that the 10-year total cost of immediate surgery was 4.1 times greater than that of active surveillance (38). Considering that medical costs vary among countries and health-care systems, further study is required for patients with PTMCs.

This retrospective study had some limitations. The possibility of a selection bias cannot be ruled out because only patients in a single tertiary referral center were enrolled. Patients who refused thyroid surgery or had

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other underlying comorbid or malignant diseases were included. The study had a relatively short follow-up period. In this study, most PTMC patients were detected by thyroid US screening or incidentally diagnosed because of other malignancies. We could not compare characteristics or behaviors between PTMCs detected by screening and those detected clinically. Serum Tg levels in patients under active surveillance were not available in this study because the health insurance system in Korea dose not reimburse the cost of serum Tg measurement before thyroid surgery for patients with differentiated thyroid cancer. Molecular analyses were performed in a limited number of patients because molecular testing panels such as the seven-gene and ThyroSeq panels (University of Pittsburgh Medical Center, Pittsburgh, PA) were not widely available in Korea. Because the *BRAF* mutational analysis was performed only in a few patients and data were incomplete, we could not analyze the effect of *BRAF* mutation on tumor progression. However, to our knowledge, this is the first study of patients with PTMC under active surveillance outside of the two centers from Japan. Moreover, we evaluated the three-dimensional structures and tumor volume as well as the maximal tumor diameter in the patients under active surveillance. Using neck US, we demonstrated that the change in tumor volume could reflect tumor progression more sensitively than the change in the maximal tumor diameter.

In conclusion, some PTMCs can grow significantly after a relatively short period of active surveillance. For active surveillance, serial examination of neck US to identify tumor progression and changes in the three-dimensional structure is important. Changes in tumor volume could reflect tumor progression more sensitively than changes in the maximal tumor diameter based on neck US. About 13% of patients underwent delayed thyroid surgery during a median of 31.2 mo of follow-up, and 29% of them had cervical LN metastasis in this study. Further prospective research with large numbers of patients with PTMCs and a longer follow-up period of active surveillance is required.

Acknowledgments

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