Active Surveillance for T1bN0M0 Papillary Thyroid Carcinoma

Toshihiko Sakai,¹ Iwao Sugitani,^{1,2} Aya Ebina,¹ Osamu Fukuoka,³ Kazuhisa Toda,¹ Hiroki Mitani,¹ and Keiko Yamada⁴

Background: Prospective trials of active surveillance for asymptomatic papillary microcarcinoma (T1aN0M0) since the 1990s have shown progression rates of only 5–10%. Late rescue surgery after progression had no deleterious effects on mortality and morbidity. The 2015 American Thyroid Association guidelines approved active surveillance for very low-risk papillary thyroid carcinoma (PTC) as an alternative method to immediate surgery. However, there is no study that evaluates long-term active surveillance for T1b tumors.

Methods: A prospective trial of active surveillance with 360 very low-risk PTC (T1aN0M0) patients has been conducted since 1995. Of the 392 T1bN0M0 patients, 61 selected active surveillance over surgery and eventually participated in this trial, while the remaining 331 patients underwent surgery. To find an appropriate management strategy for patients with T1bN0M0 PTC, the outcomes of active surveillance for T1bN0M0 to T1aN0M0 PTC were investigated and compared, and the outcomes of surgery for T1bN0M0 PTC were studied.

Results: After a mean of 7.4 years of active surveillance, 29 (8%) T1aN0M0 tumors and four (7%) T1bN0M0 tumors had increased in size ($p=0.69$). Development of lymph node metastasis was seen in three (0.8%) patients and two (3%) patients, respectively ($p=0.10$). No significant difference in progression rate was seen between groups. Among T1bN0M0 tumors, weak calcification and rich vascularity were risk factors for tumor-size increase, and younger age was a predictor for the development of lymph node metastasis. Mean initial tumor size was significantly greater in T1bN0M0 patients who underwent immediate surgery (14.5 ± 2.8 mm) than it was in patients who chose observation (11.7 ± 1.1 mm; $p<0.0001$). No postoperative recurrence was seen in patients with tumor <15 mm in diameter.

Conclusions: Active surveillance is an option for selected patients with T1bN0M0 PTC.

Keywords: active surveillance, observation, thyroid cancer, microcarcinoma, overtreatment

Introduction

IN THE LAST FEW DECADES, rapid increases in the incidence of thyroid carcinoma have been reported from many developed countries, including the United States and South Korea (1–3). These increases are mainly due to increases in the incidence of small papillary thyroid carcinomas (PTC). This is generally attributed to the widespread use of more sensitive diagnostic procedures, including high-resolution ultrasonography (US). Autopsy series have indicated a frequency of latent papillary microcarcinoma (PMC) of at least 4–11% in the general population (4). Aggressive evaluation of small thyroid nodules with US and US-guided fine-needle aspiration (FNA) can find these very large subclinical reservoirs. Mortality rates from thyroid cancer have remained largely stable, despite the marked increases in incidence

rates. Currently, preventing overdiagnosis and overtreatment of these very low-risk PTCs is becoming one of the most important issues in the management of thyroid carcinoma.

At two Japanese institutions, Kuma Hospital and Cancer Institute Hospital, prospective clinical trials have been conducted to verify the safety of active surveillance for patients with asymptomatic PMC (T1aN0M0) since the 1990s. As reported in 2010, active surveillance was carried out for 300 lesions in 230 patients at the Cancer Institute Hospital between 1995 and 2008 (5). Among those lesions, 7% had increased in size, 90% were unchanged, and 3% had decreased. Three (1%) patients developed apparent lymph node metastasis (LNM), but no patients showed extrathyroidal invasion or distant metastasis. None of the patients treated with surgery after progression developed tumor recurrence. The report from Kuma Hospital in 2014 showed that 8% and 3.8% exhibited

¹Division of Head and Neck and ⁴Department of Ultrasonography, Cancer Institute Hospital, Tokyo, Japan.

²Department of Endocrine Surgery, Nippon Medical School, Tokyo, Japan.

³Department of Otolaryngology and Head and Neck Surgery, University of Tokyo, Tokyo, Japan.

tumor size enlargement and novel node metastasis, respectively, among 1235 patients at the 10-year observation (6). Delayed rescue surgery after detection of signs of progression did not lead to significant recurrence or mortality. According to these favorable outcomes, the Japanese Clinical Guidelines for treatment of thyroid tumor published in 2010 approved a policy of active surveillance for patients with asymptomatic PMC for the first time in the world (7). Subsequently, the American Thyroid Association (ATA) management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer revised in 2015 also endorsed active surveillance as an alternative to immediate surgery for properly selected patients with very low-risk tumors (8).

The American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) system for differentiated thyroid carcinoma (DTC) classifies T1a as a tumor ≤ 1 cm without extrathyroidal extension and T1b as a tumor >1 cm but ≤ 2 cm in greatest dimension without extrathyroidal invasion (9,10). Several studies have pointed out that patients with a T1 tumor without clinically apparent nodal metastasis or distant metastasis (T1N0M0) show excellent prognoses after surgery without postoperative radioactive iodine treatment (11,12). Although active surveillance for patients with T1aN0M0 tumor has been accepted as appropriate management, little research has reported on the long-term validity of active surveillance for T1bN0M0 tumors. To establish an appropriate management strategy for patients with T1bN0M0 PTC, the present study investigated and compared outcomes of active surveillance for patients with T1bN0M0 to T1aN0M0 tumors. The outcomes of immediate surgery for patients with T1bN0M0 PTC were also studied.

Methods

A prospective trial of active surveillance for patients with low-risk PTC has been conducted since 1995 at the Cancer Institute Hospital, a tertiary cancer referral center in Tokyo, Japan. As of 2016, a total of 798 patients had been diagnosed with clinical T1N0M0 PTC by US-guided FNA cytology. All patients are evaluated for the presence of clinically apparent extrathyroidal invasion, lymphadenopathy (maximum diameter ≥ 1 cm), and distant metastasis using neck US and lung computed tomography (CT). Patients with asymptomatic PMC (T1aN0M0) were considered as candidates for the clinical trial of active surveillance. Detailed information was provided regarding the option of nonsurgical observation in addition to immediate surgery, and the patients chose the treatment themselves (5). For patients with T1bN0M0 PTC, surgery was generally recommended, but if the patient requested active surveillance, the final decision was made by the physician, taking into consideration the patient's age, tumor size, and other risk factors.

Among 406 patients with T1aN0M0 PTC, 360 (89%) chose active surveillance and 46 (11%) underwent immediate surgery. On the other hand, 331/392 (84%) patients with T1bN0M0 PTC underwent immediate surgery, and 61 (16%) chose active surveillance.

Patients who participated in the active surveillance program were followed with palpation, US, and chest radiography every 6 or 12 months after diagnosis to check for tumor enlargement, development of LNM, or distant metastasis. Diagnostic B-mode gray-scale US (5.0–13.0 MHz linear

transducer) was performed by a single experienced radiologist (K.Y.) who specializes in thyroid US to evaluate tumor status and cervical LNM. Calcification patterns and vascularity were also recorded using both gray-scale and color Doppler US (13). Increased or decreased tumor size was defined as a change in maximum tumor diameter ≥ 3 mm on US from the start of observation. At the same time, the tumor volumes were calculated using the ellipsoid equation: $\pi/6 \times \text{length} \times \text{width} \times \text{height}$ and calculated relative to the baseline. A relevant change in volume was defined as $>50\%$ increase from baseline (14). Either tumor enlargement or development of metastasis was defined as "progression." Surgery was recommended during follow-up if the patient met the following criteria: (i) change in patient preference; (ii) tumor at risk for extrathyroidal extension to the recurrent laryngeal nerve, trachea, and esophagus; or (iii) signs of progression were detected. These protocols were approved by the ethics committee of the Cancer Institute Hospital in 1994. Written informed consent for participation in this study was obtained after agreement based on the informed decision of the patient.

In the case of immediate or delayed rescue surgery, lobectomy was carried out as a principal procedure according to a risk-adapted management policy (5,15,16). Total thyroidectomy was conducted only for patients with bilateral lesions or autoimmune thyroid disease. As for lymph node dissection, prophylactic central node dissection and selective therapeutic lateral neck dissection were performed (17). Patients who underwent surgery were followed by US and chest radiography or lung CT every year to check for recurrence.

Statistical analysis

Data are expressed as the mean $\pm$ standard deviation. Comparison of clinical characteristics between groups was performed using the chi-square test for categorical variables and the *t*-test for continuous variables. Time-dependent variables were analyzed using the Kaplan–Meier method and were compared using the log-rank test. All analyses were performed using JMP for Windows v10.0.2 (SAS Institute, Cary, NC). *p*-Values of <0.05 were considered statistically significant.

Results

Clinical characteristics

The clinical characteristics and outcomes of patients with T1aN0M0 PTC and T1bN0M0 PTC are shown in Table 1. Comparing the active surveillance groups of T1a and T1b, the male-to-female ratio was significantly greater for T1b than for T1a ($p=0.02$). No significant differences in age or follow-up period were seen between the same groups. Comparing the clinical characteristics of T1bN0M0 patients who had active surveillance and those who underwent immediate surgery, no significant differences in sex or age were evident between groups. Mean tumor size was significantly larger in the surgery group (14.5 mm) than in the active surveillance group (11.7 mm; $p<0.0001$).

Outcomes of active surveillance

The mean observation period was 7.4 years (range 0.5–25 years) in T1N0M0 PTC, 7.3 years (range 0.5–25 years) in T1aN0M0 PTC, and 7.9 years (range 1–17 years) in T1bN0M0 PTC. There were no differences in the prevalence of

TABLE 1. CLINICAL CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH T1a AND T1b PTC

		<i>T1a</i>		<i>T1b</i>
		Active surveillance (n = 360)	Active surveillance (n = 61)	Surgery (n = 331)
Sex	Male (rate)	41 (11%)	14 (23%)*	52 (16%)
Age	<i>M</i> ± <i>SD</i> (range)	53.9 ± 12.0 (23–84)	54.4 ± 10.7 (32–78)	51.9 ± 12.6 (17–82)
Tumor size (mm)	<i>M</i> ± <i>SD</i> (range)	7.6 ± 1.8 (2–10)	11.7 ± 1.1**	14.5 ± 2.8***
Comorbidity of malignant tumor		88 (24%)	13 (21%)	71 (21%)
Follow-up period (years)	<i>M</i> ± <i>SD</i> (range)	7.3 ± 4.3 (0.5–25)	7.9 ± 4.0 (1–17)	
Diameter increase of ≥3 mm		29 (8%)	4 (7%)	
Volume increase of ≥50%		74 (21%)	7 (11%)	
Development of clinical LNM		3 (1%)	2 (3%)	

*T1a vs. T1b; $p=0.02$.**T1a vs. T1b; $p<0.001$.***Active surveillance vs. surgery; $p<0.0001$.

PTC, papillary thyroid carcinoma; LNM, lymph node metastasis.

comorbidity of malignant tumors between T1a active surveillance cases, T1b active surveillance cases, and T1b surgery cases. After active surveillance, 29 (8%) patients with T1aN0M0 PTC and four (7%) patients with T1bN0M0 had shown an increase in maxima tumor diameter of ≥3 mm ($p=0.69$). Seventy-four (21%) patients with T1aN0M0 PTC and seven (11%) patients with T1bN0M0 had shown an increase in tumor volume ≥50% ($p=0.10$). Development of LNM was seen in three (1%) patients with T1aN0M0 and two (3%) patients with T1bN0M0 ($p=0.10$). None of the events showed a significant difference between T1a and T1b. The five-year progression rate was 5% for both T1a and T1b, and the 10-year progression rate was 12% for both. No significant difference in time-dependent progression rate was evident between groups.

Predictors of tumor size enlargement and development of LNM from T1b PTC are shown in Table 2. Univariate analysis among T1bN0M0 tumors revealed that non-calcification pattern and rich vascularity in the tumor were associated with a higher rate of tumor enlargement, while lower age was a risk factor for LNM development.

Outcomes of immediate surgery for T1b

Among patients who received immediate surgery for T1b PTC, eight patients showed recurrence, at the remnant

thyroid in two (0.6%) cases, at lymph nodes in five (1.3%) cases, and at distant sites in one (0.3%) case. Recurrence did not occur in patients with a maximal tumor diameter <15 mm. The five-year disease-free survival (DFS) rate for PTC ≥15 mm was 99%, and the 10-year DFS was 95%. The recurrence rate for PTC ≥15 mm was significantly higher than that for PTC <15 mm ($p=0.017$).

Outcomes of surgery after active surveillance for T1b

Eleven patients underwent surgery after active surveillance. None of these patients showed recurrence during the follow-up period. The treatment strategy was switched to surgery for several reasons. The most common reason was a request from the patient (five cases), followed by tumor enlargement (four cases), and development of LNM and extrathyroidal infiltration (one case each).

No significant differences in surgical procedures, complications, or overall rate of recurrence were seen between the surgery after active surveillance group and the immediate surgery group.

Discussion

Recently, it has been realized that detecting and treating small, intrathyroidal PTC does not result in decreased

TABLE 2. RISK FACTORS FOR TUMOR SIZE ENLARGEMENT AND DEVELOPMENT OF LNM IN T1b (UNIVARIATE ANALYSIS)

Risk factor	Size change			Development of LNM		
	No change (n = 57)	Enlargement (n = 4)	p	Development of LNM– (n = 59)	Development of LNM+ (n = 2)	p
Sex (Male)	14 (25%)	0	0.26	14 (24%)	0	0.43
Age (Mean ± SD)	54.7 ± 10.8	49.5 ± 6.2	0.35	55.0 ± 10.3	37.5 ± 7.8	0.02
Tumor size (Mean ± SD)	11.7 ± 1.1	11.5 ± 0.6	0.69	11.7 ± 1.1	11.0 ± 0	0.37
Non-calcification pattern	3 (5%)	3 (75%)	<0.0001	6 (10%)	0	0.63
Rich vascularity	10 (18%)	3 (75%)	0.01	12 (20%)	1 (50%)	0.31

mortality from thyroid cancer. Overdiagnosis and overtreatment of very low-risk PTC has thus been an emerging issue not only for patient quality of life, but also for public health management. To prevent overdiagnosis of subclinical PTC, the U.S. Preventive Services Task Force recommended against screening for thyroid cancer in asymptomatic adults using either neck palpation or US in 2017 (18). The ATA management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer do not recommend FNA cytology for sub-centimeter thyroid nodules, even if the nodule shows a suspicious pattern on ultrasonography (8). The Japan Society of Ultrasonics in Medicine and the Japan Association of Breast and Thyroid Sonology recommend observation for solid thyroid nodules with a diameter of ≤ 5 mm. For solid nodules measuring 5–10 mm, FNA is advocated only when features highly suggestive of malignancy are present on US (19).

As a modality to reduce overtreatment for patients who have been already diagnosed with asymptomatic PMC, the policy of active surveillance has been accepted as a safe procedure in both Japanese and U.S. guidelines (7,8). Based on the accumulated data, this approach could be more beneficial and cost-effective for patients and society than immediate surgery (5,6,20,21). Clinical trials of active surveillance for patients with T1aN0M0 PTC have been conducted in Japan since the 1990s. Subsequently, similar studies have also been launched in the United States and Korea (14,22).

Usually, the indication for active surveillance is limited to T1aN0M0 PTC, excluding T1bN0M0. However, Anderson *et al.* (12) reported similar overall and disease-specific survival rates after surgery between patients with T1a and T1b tumors who underwent surgery using a large pool of data from the National Cancer Data Base (98,111 cases of T1a and 51,801 cases of T1b) and the Surveillance, Epidemiology, and End Results program (11,208 cases of T1a and 7,173 cases of T1b). Few published studies to date have evaluated long-term active surveillance for T1b tumors. A trial from the Memorial Sloan Kettering Cancer Center included 59 patients with intrathyroidal T1b (≤ 1.5 cm) tumors (14). Among those, two (3.4%) patients showed a tumor diameter increase of ≥ 3 mm. This was not significantly different from patients with T1a tumors (9/232; 3.9%), but the median follow-up period was only 25 months (range 6–166 months).

The present study was a prospective trial of active surveillance for 61 patients with T1bN0M0 PTC. The mean observation period was 7.9 years (range 1–17 years). Although a greater number of patients and longer follow-up period are needed, the progression rate did not differ significantly from that of T1aN0M0 PTC, and delayed rescue surgery was not associated with any deleterious outcomes. This represents the first report to suggest the safety of long-term active surveillance for patients with T1bN0M0 PTC. This study also examined the risk of progression under active surveillance for T1b tumors. Risk factors for tumor size enlargement were a non-calcification pattern and rich vascularity, and the only risk factor identified for LNM was younger age. These results were almost the same as findings from previous studies for T1a tumors (5,6,13,23). It has previously been shown that the grade of tumor calcification correlated with age at diagnosis, and that the majority of tumors exhibited an upgraded calcification pattern during observation. Moreover, the incidence of tumor enlargement tended to be inversely related to the grade of calcification (13). Investigators from Kuma Hospital also

reported age as an independent predictor of progression by multivariate analysis (6). Miyauchi *et al.* (23) recently estimated lifetime disease progression probabilities as 60% for the 20s, 37% for 30s, 27% for 40s, 15% for 50s, and 10% for 60s according to the age at the start of active surveillance for T1aN0M0 PTC. Even for T1bN0M0 PTC, older patients with a strong calcification pattern would be good candidates for active surveillance rather than immediate surgery.

Expanding the indications for active surveillance to T1b tumor might lead to reductions in surgery and avoid the risk of surgical complications. Griffin *et al.* (24) examined the proportion of PTC that would meet the criteria for active surveillance as proposed by the Memorial Sloan Kettering Cancer Center with Kuma Hospital (25). Among 243 patients with PTC who underwent surgery, 27 had nodules ≤ 1 cm, and 15 of these would have been appropriate for active surveillance according to the criteria. Fifty patients had nodules 1.1–1.5 cm in diameter, of whom 41 would have been ideal or appropriate for active surveillance. Of these 56 patients who met the criteria for active surveillance, 52 had undergone total thyroidectomy, and 45 had elective central nodal dissection. Eventually, three patients developed permanent complications from surgery, including vocal cord paralysis, hypoparathyroidism, and a chipped tooth from intubation. No patients died or developed recurrent disease. Griffin *et al.* concluded that increasing the size threshold for active surveillance of PTC to 1.5 cm led to a quarter of patients being eligible compared to only 6% with the 1 cm threshold. Without an active surveillance program, the majority of patients with low-risk cancer undergo thyroidectomy, which carries a small risk of permanent surgical complications.

As mentioned above, the thyroid cancer disease management team at Memorial Sloan Kettering Cancer Center collaborated with Kuma Hospital to develop a risk-stratified clinical decision-making framework for selecting candidates for active surveillance of PMC (25). The risk-stratification framework comprised three domains: tumor/neck US characteristics (size of the primary tumor, location of the tumor within the thyroid gland), patient characteristics (age, comorbidities, willingness to accept observation), and medical team characteristics (availability and experience of the multidisciplinary team). Based on these criteria, patients with probable or proven PTC can then be classified as ideal, appropriate, or inappropriate candidates for active surveillance. In this study, active surveillance was applied to the patients with the smaller T1b tumors. The mean tumor size was 11.7 mm (range 11–16 mm), and two patients with ≥ 15 mm tumors underwent active surveillance. Our study also shows favorable outcomes of immediate surgery for patients with T1bN0M0 PTC. Particularly, patients with tumor size < 15 mm never showed recurrences. They may represent very low-risk cancer, and it may be possible to conclude that adoption of active surveillance for PTCs < 15 mm in diameter is safe and reasonable. Careful risk stratification using the proposed decision-making framework is clearly important to improve patient outcomes and safety with the active surveillance management option.

Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
 Toshihiko Sakai, MD
 Division of Head and Neck
 Cancer Institute Hospital
 3-8-31 Ariake
 Koto-ku
 Tokyo 135-8550
 Japan

E-mail: tsakai8312@gmail.com