Surgical Outcomes in Patients With Low-risk Papillary Thyroid Microcarcinoma From MAeSTro Study

Immediate Operation Versus Delayed Operation After Active Surveillance A Multicenter Prospective Cohort Study

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Objective: To investigate surgical, and clinical outcomes in patients with low-risk papillary thyroid microcarcinoma (PTMC) according to treatment options [immediate operation (IOP) vs delayed operation after active surveillance (AS) (DOP)].

Background: AS has been adopted as an alternative to immediate surgery in patients with low-risk PTMC. Although some patients undergo surgery during AS, there is little information on surgical, and clinical outcomes after delayed operation after AS.

Methods: A multicenter prospective cohort study including 1177 patients was conducted at 3 tertiary hospitals in Korea from June 2016 to January 2020. Patients with low-risk PTMC were enrolled. The participants were self-assigned into AS or IOP, and during AS, the patients underwent surgery if there were signs of disease progression or if the patient's choice changed.

Results: A total of 516 patients underwent operation; 384 (74.4%) in the IOP group and 132 (25.6%) in the DOP group. Compared with the IOP group, the DOP group was significantly associated with a larger tumor size ($P=0.002$), higher rates of lymphatic invasion ($P=0.002$), and multifocality ($P=0.008$). However, the rates of total thyroidectomy, postoperative hypoparathyroidism and vocal cord palsy did not differ significantly between the groups ($P=0.283$, $P=0.184$, and $P=0.284$, respectively). Of the 132 patients in the DOP group, disease progression was present in 39 (29.5%) patients. The DOP group with disease progression had a significantly higher rate of lymph node metastasis ($P=0.021$) and radioiodine therapy ($P=0.025$) than the DOP group without disease progression.

Conclusions: These results suggest that AS might be considered an alternative treatment option for patients with low-risk PTMC regarding the extent of thyroidectomy and postoperative complications in the DOP group. To assess oncologic outcomes, long-term follow-up will be needed.

Trial registration: ClinicalTrials.gov Identifier: NCT02938702.

Keywords: active surveillance, immediate surgery, papillary thyroid microcarcinoma, postoperative complication; surgical outcome

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The incidence of thyroid cancer has been increasing in most areas of the world,[1] and this increase is mainly due to an increase in the number of patients diagnosed with papillary thyroid microcarcinoma (PTMC), which is defined as papillary

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H.H. and S.K. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: S.-J.K., Y.J.P., Y.S.J. Acquisition of data: H.W.Y., J.K., Y.K.K., C.Y.L., S.W.C., E.J.C., C.H.R., J.R., K.H. Y., D.J.P., K.E.L. Analysis, and interpretation of data: H.H., J.Y.C., S.K., J.H.M., E.K.L. Drafting the article: H.H., J.Y.C., S.K., Y.S.J Statistical analysis: H.H.

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thyroid cancer (PTC) with a maximum diameter of 1 cm or less.[2] Several studies have reported that the ease of medical access and widespread high-resolution ultrasonography have enabled the early diagnosis of papillary thyroid cancer.[3,4] With the exception of those patients with high-risk features, most patients with PTMC have excellent clinical outcomes.[5] In a study of 18,445 patients with PTMC between 1988 and 2007, the disease-specific 10 and 15 year survival rates were 99.5% and 99.3%, respectively.[6] Given the indolent nature of PTMCs, it is anticipated that most PTMCs would not progress to clinically significant disease during the patient's lifetime.[7]

As active surveillance (AS) was proposed as an alternative to immediate surgery in patients with low-risk PTMC in 1993,[8] AS was adopted in the guidelines by the Japan Association of Endocrine Surgeons (JAES) in 2011,[9] the American Thyroid Association (ATA) in 2015 [2] and the Korean Thyroid Association in 2016.[10] To date, several studies have reported clinical results, including local recurrence, mortality, and other oncologic outcomes, between AS and immediate surgery in PTMC patients.[11,12] During AS, the patients underwent surgery if there were signs of tumor progression or if the patient's choice changed, and some cohort studies reported that the rate of conversion surgery was 7% to 16%.[13–15] However, few studies have evaluated the surgical outcomes or postoperative complications in patients who underwent immediate operation (IOP) and delayed operation after AS (DOP). Oda et al[11] studied the incidence of unfavorable events in 2153 patients with low-risk PTMC who received AS (n = 1179) and immediate surgery (n = 974). During the follow-up, 94 patients (8.0%) underwent surgery after a period of observation longer than 1 year. They reported that surgical complications, including vocal cord palsy, hypoparathyroidism and surgical scarring, were more frequent in the IOP group. However, they analyzed the incidence of surgical complications in the entire AS group, including 1085 patients who did not undergo surgery.[11]

Therefore, the aim of this multicenter prospective cohort study was to evaluate clinical and surgical outcomes, including the extent of surgery and postoperative complications, in patients with low-risk PTMC who underwent surgery according to their treatment modality (IOP vs DOP groups). In addition, we also analyzed the clinical and surgical outcomes according to disease progression in the DOP group.

METHODS

Study Design

This study is part of a Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma (MAeSTro), in which the recruitment of participants has been completed. The cohort protocols, including the diagnosis and enrollment criteria for the patients, have been described previously.[16] Patients aged 18 or more who were diagnosed with PTMC by fine needle aspiration or core needle biopsy between June 2016 and January 2020 were included. Patients with suspected major organ involvement or lymph node/distant metastasis were excluded.

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (1603-044-747), Seoul National University Bundang Hospital (B-1605-348-402), and National Cancer Center (NCC2016-0183). Informed consent was obtained from all study participants.

Participants and Procedures

The participants were allowed to choose AS or immediate operation after careful consideration of the benefits and risks of each treatment modality. During AS, some patients underwent surgery if they changed their preference in the absence of progression or if disease progression was detected. Disease progression was defined as a size increase of ≥ 3 mm in at least 1 dimension, or ≥ 2 mm in at least 2 dimensions, suspected organ involvement during a follow-up imaging study, including neck ultrasonography, and a pathologic diagnosis of lymph node/distant metastasis. These disease progression criteria were established with reference to previous studies.[13,17–20] . Recent studies have shown that the change in tumor volume (TV) is sensitive for detecting tumor progression.[18,21–23] When we designed the MAeSTro study, the TV change was not included in the definition of disease progression. Therefore, we also analyzed the clinicopathologic features between DOP groups based on disease progression, including TV change in disease progression criteria. The TV was calculated as follows:[24] TV (mm^3) = length (mm) X width (mm) X thickness (mm) X $\pi/6$. The TV change was calculated using the following equation: [final TV (mL) − initial TV (mL)] × 100/initial TV (mL), and the TV increase was defined as an increase of $> 50\%$. The patients who underwent IOP or DOP were scheduled for follow-up visits every 6 months during the first 2 years after surgery, and then every 1 year thereafter. The follow-up visits included a physical examination, thyroid ultrasonography, and thyroid function tests, including serum thyroglobulin and anti-thyroglobulin antibodies.

Study Population

A total of 1177 patients with low-risk PTMC were finally enrolled in the MAeSTro study between June 2016 and January 2020 (Fig. 1). Among these patients, 755 (64.1%) patients chose AS and 422 (35.9%) patients chose immediate operation as their initial treatment option. Of the 755 patients in the AS group, 546 patients (72.3%) who continued with AS, 45 patients (6.0%) who were lost to follow-up, and 32 patients (4.2%) who underwent surgery at outside hospitals were excluded. In addition, among the patients who decided to pursue IOP, 38 patients (0.9%) underwent surgery at outside hospitals and were excluded. Finally, 516 patients were analyzed in this study; 384 patients (74.4%) in the IOP group and 132 patients (25.6%) in the DOP group.

Statistical Analysis

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the mean and standard deviation or the median and interquartile range (IQR). Pearson $\chi 2$ test and Fisher exact test were used to compare categorical variables. Student t test was used to compare continuous variables with a normal distribution, and the Mann-Whitney U test was used for variables with a non-normal distribution. P value of < 0.05 were considered to represent statistical significance. All statistical analyses were performed with SPSS software (version 28.0; SPSS, Chicago, IL).

RESULTS

IOP Group Versus DOP Group

The clinical and operative characteristics of the 516 patients are shown in Table 1. The groups had similar age and sex distributions ($P = 0.131$ and $P = 0.105$, respectively). The patients' mean age at diagnosis was 46.3 ± 10.5 years in the IOP group and 47.9 ± 10.6 years in the DOP group, and there were 308 females (80.2%) in the IOP group and 97 females (73.5%) in the DOP group. However, the IOP group had a significantly larger initial tumor size [median: 6.8 mm (IQR, 5.4–8.2) vs 6.4 mm (IQR, 5.2–7.7),

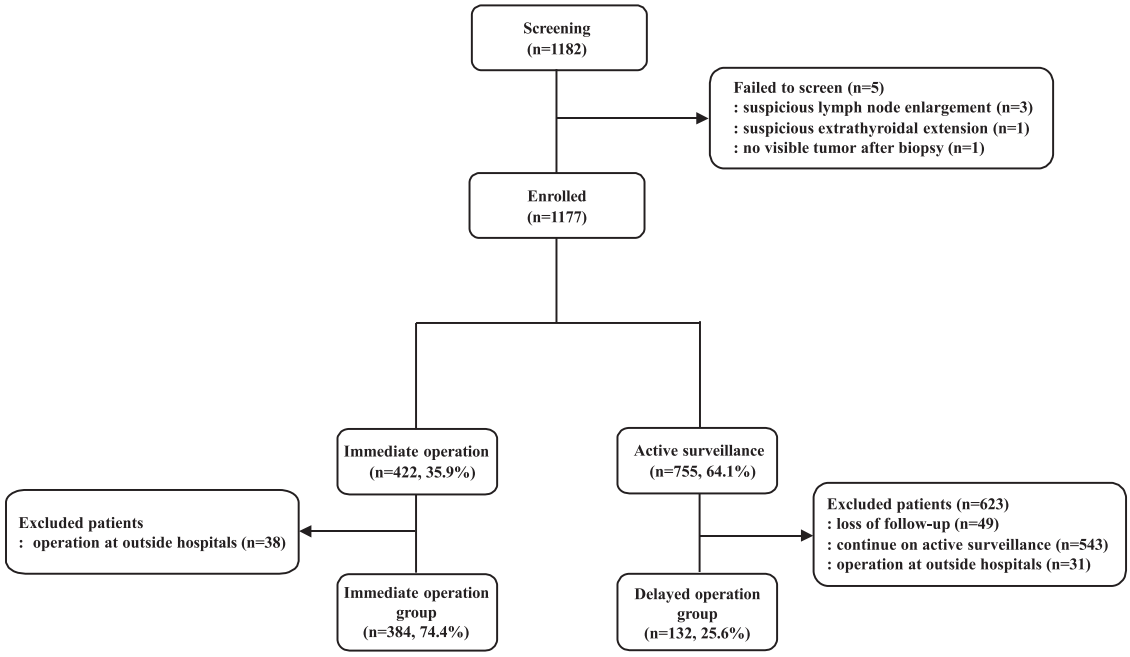

FIGURE 1. Flowchart of patients enrolled.

$P = 0.037$] and volume [median: 102.0 mm^3 (IQR, 51.7–185.1) vs 88.9 mm^3 (IQR, 46.7–155.5), $P = 0.034$] than the DOP group. The median follow-up periods after the operation in the IOP and DOP groups were 46 months (IQR, 36–51 months) and 28 months (IQR, 13–39 months) ($P < 0.001$), respectively. The extent of lymph node dissection was significantly different between the IOP and DOP groups (central and lateral lymph node dissection: 1.6% in IOP vs 6.1% in DOP, $P = 0.020$); however, there were no significant differences in the extent of thyroidectomy (total thyroidectomy: 28.4% in IOP vs 33.3% in DOP, $P = 0.283$) and radioiodine therapy (14.6% in IOP vs 18.9% in DOP, $P = 0.235$) after surgery between the groups.

The median tumor size in the DOP group was significantly larger than that in the IOP group [median: 6.0 mm (IQR, 5.0–8.0) vs 7.0 mm (IQR, 6.0–9.0), $P = 0.002$), and the T stage (American Joint Committee on Cancer; AJCC 8th edition) was significantly higher in the DOP group ($\geq$T1b: 8.9% vs 15.2%, $P = 0.041$). In addition, the DOP group was significantly associated with the rate of histologic subtype confirmed pathologically (classic: 93.2% in IOP vs 85.6% in DOP; follicular variant: 2.9% vs 4.5%; tall cell variant: 3.4% vs 9.1%, $P = 0.018$), and higher rate of lymphatic invasion (31.5% vs 46.2%, $P = 0.002$) and multifocality (28.4% vs 40.9%, $P = 0.008$) than the IOP group (Table 2). In the case of postoperative complications, including hypoparathyroidism and vocal cord palsy, there were no significant differences between the two groups (Table 1). There was 1 patient (IOP: 0.3%; DOP: 0.8%) in each group with permanent hypoparathyroidism, and there was only 1 patient (0.3%) in the IOP group with permanent vocal cord palsy.

DOP With or Without Disease Progression Groups

The clinical and operative characteristics of the DOP group are shown in Table 3. Of the 132 patients in the DOP group, 93 patients (70.5%) underwent surgery during AS based on the patient's decision (DOP group without progression), whereas 39 patients (29.5%) underwent surgery because of disease progression (DOP group with progression), including size enlargement (n = 29, 74.4%), suspected new extrathyroidal extension (n = 3, 7.7%) and pathologic diagnosis of regional lymph node metastasis (n = 7, 17.9%). In the DOP group with progression, the proportion of males was significantly higher than that in the DOP group without progression (43.6% vs 19.4%, $P = 0.004$). In addition, the last tumor size [median: 8.9 mm (IQR, 7.7–9.6) vs 6.0 mm (IQR, 4.8–7.4), $P < 0.001$] and volume [median: 233.1 mm^3 (IQR, 127.1–322.0) vs 66.5 mm^3 (IQR, 31.8–130.7), $P < 0.001$] based on preoperative neck ultrasonography in the DOP group with progression were significantly larger than those in the DOP group without progression.

The tumor size in the DOP group with progression was significantly larger than that in the DOP group without progression [median: 8.0 mm (IQR, 7.0–9.0) vs 7.0 mm (IQR, 5.5–8.0), $P = 0.038$], and the patients in the DOP group with progression were significantly associated with a higher rate of lymph node metastasis (N1a/N1b: 51.3% vs 30.1%, $P = 0.021$) and radioiodine therapy (30.8% vs 14.0%, $P = 0.025$) after surgery than those in the DOP group without progression (Tables 3, 4). However, there were no significant differences in the extent of thyroidectomy and lymph node dissection, extrathyroidal extension, lymphatic invasion and multifocality. In addition, in the case of postoperative complications, there were no significant differences between the two groups. (Table 3)

IOP Group Versus DOP Group Without Disease Progression

The clinicopathologic findings and postoperative complications were analyzed between the IOP group and the DOP group without progression. The IOP group had a larger initial tumor size [median: 6.8 mm (IQR, 5.4–8.2) vs 6.0 mm (IQR, 5.1–7.7), $P = 0.026$] and a higher rate of extrathyroidal extension (55.7% vs 44.1%, $P = 0.043$) than the DOP group

TABLE 1. Clinical and Operative Characteristics Between the IOP and DOP Groups

Variable	IOP (n = 384)	DOP (n = 132)	*P*
Age at diagnosis, yr, mean (SD)	46.3 (10.5)	47.9 (10.6)	0.131
Sex, n (%)			0.105
Male	76 (19.8)	35 (26.5)	
Female	308 (80.2)	97 (73.5)	
Initial tumor size, mm, median (IQR)	6.8 (5.4–8.2)	6.4 (5.2–7.7)	0.037
Initial tumor volume, mm^3, median (IQR)	102.0 (51.7–185.1)	88.9 (46.7–155.5)	0.034
Period between enrollment and operation, months, median (IQR)	0 (0–1)	15 (7–28)	< 0.001
Follow-up duration after operation, months, median (IQR)	46 (36–51)	28 (13–39)	< 0.001
Extent of thyroidectomy, n (%)			0.283
Lobectomy/Isthmectomy	275 (71.6)	88 (66.7)	
Total thyroidectomy	109 (28.4)	44 (33.3)	
Lymph node dissection, n (%)			0.020
None	23 (6.0)	6 (4.5)	
Central only	355 (92.4)	118 (89.4)	
Central and lateral	6 (1.6)	8 (6.1)	
Purpose of central lymph node dissection, n (%)			0.802
None	23 (6.0)	6 (4.5)	
Prophylactic	318 (82.8)	110 (83.3)	
Therapeutic	43 (11.2)	16 (12.1)	
RAI, n (%)	56 (14.6)	25 (18.9)	0.235
Hypoparathyroidism, n (%)			0.184
No	340 (88.5)	111 (84.1)	
Transient/Permanent*	44 (11.5)	21 (15.9)	
Vocal cord palsy, n (%)			0.284
No	372 (96.9)	125 (94.7)	
Transient/Permanent†	12 (3.1)	7 (5.3)	
Postoperative complication, n (%)			0.271
No	382 (99.5)	130 (98.5)	
Yes	2 (0.5)‡	2 (1.5)§	

*In the case of permanent hypoparathyroidism, there was 1 patient in each group.
†In the case of permanent vocal cord palsy, there was only 1 patient in the IOP group.
‡Wound infection (n = 1), seroma (n = 1).
§Postoperative bleeding (n = 2)
RAI indicates radioactive iodine.

TABLE 2. Pathologic Features Between the IOP and DOP Groups

Variable	IOP (n = 384)	DOP (n = 132)	*P*
Subtype, n (%)			0.018
Classic	358 (93.2)	113 (85.6)	
Follicular variant	11 (2.9)	6 (4.5)	
Tall cell variant	13 (3.4)	12 (9.1)	
Others	2 (0.5)	1 (0.8)	
Size of tumor, mm, median (IQR)	6.0 (5.0–8.0)	7.0 (6.0–9.0)	0.002
Extrathyroidal extension, n (%)			0.197
None	170 (44.3)	67 (50.8)	
Microscopic/gross	214 (55.7)	65 (49.2)	
Lymphatic invasion, n (%)	121 (31.5)	61 (46.2)	0.002
Multifocality, n (%)	109 (28.4)	54 (40.9)	0.008
AJCC (8th, T stage), n (%)			0.041
T1a	350 (91.1)	112 (84.8)	
≥ T1b	34 (8.9)	20 (15.2)	
AJCC (8th, N stage), n (%)			0.255
N0/NX	265 (69.0)	84 (63.6)	
N1a/N1b	119 (31.0)	48 (36.4)	
$BRAF^{V600E}$ mutation, n (%)			0.097
Not done	2 (0.5)	4 (3.0)	
Positive	343 (89.3)	108 (81.8)	
Negative	39 (10.2)	20 (15.2)	

AJCC indicates American Joint Committee on Cancer.

without progression. However, other factors, including the extent of thyroidectomy and lymph node dissection, tumor size, lymphatic invasion and multifocality, were not significantly different between the two groups (Table 5). In addition, there were no significant differences in the postoperative complications.

IOP Group Versus DOP Group With Disease Progression

In the IOP group and the DOP group with progression, the DOP group with progression had a higher proportion of males than the IOP group (19.8% vs 43.6%, $P = 0.001$). The patients with DOP group with progression had a higher T (≥ T1b: 8.9% vs 20.5%, $P = 0.042$) and N stage (N1a/N1b: 31.0% vs 51.3%, $P = 0.012$), and a higher rate of lymphatic invasion (31.5% vs 56.4%, $P = 0.002$), multifocality (28.4% vs 48.7%, $P = 0.008$), and radioiodine therapy (14.6% vs 30.8%, $P = 0.009$) than the IOP group. In addition, the extent of lymph node dissection (central and lateral lymph node dissection: 1.6% in IOP vs 10.3% in DOP group with progression, $P = 0.014$) and the rate of histologic subtype (classic: 93.2% in IOP vs 82.1% in DOP group with progression; follicular variant: 2.9% vs 2.6%; tall cell variant: 3.4% vs 12.8%, $P = 0.040$) were significantly different between the two groups (Table 6). However, there were no significant differences in the postoperative complications.

TABLE 3. Clinical and Operative Characteristics Between the DOP Groups Based on Disease Progression

Variable	With progression (n = 39)	Without progression (n = 93)	*P*
Age at diagnosis, yr, mean (SD)	49.1 (12.0)	47.4 (10.0)	0.403
Sex, n (%)			0.004
Male	17 (43.6)	18 (19.4)	
Female	22 (56.4)	75 (80.6)	
Initial tumor size, mm, median (IQR)	7.0 (6.0–7.6)	6.0 (5.1–7.7)	0.238
Initial tumor volume, mm^3, median (IQR)	105.5 (57.9–156.0)	79.2 (43.0–154.6)	0.523
Period between enrollment and operation, months, median (IQR)	18 (7–29)	15 (7–27)	0.391
Disease progression, n (%)			
Size enlargement	29 (74.4)		
New ETE	3 (7.7)		
Regional lymph node metastasis	7 (17.9)		
Distant metastasis	0		
Last tumor size, mm, median (IQR)	8.9 (7.7–9.6)	6.0 (4.8–7.4)	< 0.001
Last tumor volume, mm^3, median (IQR)	233.1 (127.1–322.0)	66.5 (31.8–130.7)	< 0.001
Follow-up duration after operation, months, median (IQR)	33 (12–39)	26 (14–38)	0.580
Extent of thyroidectomy, n (%)			0.225
Lobectomy/Isthmectomy	23 (59.0)	65 (69.9)	
Total thyroidectomy	16 (41.0)	28 (30.1)	
Lymph node dissection, n (%)			0.367
None	1 (2.6)	5 (5.4)	
Central only	34 (87.2)	84 (90.3)	
Central and lateral	4 (10.3)	4 (4.3)	
Purpose of central lymph node dissection, n (%)			0.155
None	1 (2.6)	5 (5.4)	
Prophylactic	30 (76.9)	80 (86.0)	
Therapeutic	8 (20.5)	8 (8.6)	
RAI, n (%)	12 (30.8)	13 (14.0)	0.025
Hypoparathyroidism, n (%)			0.145
No	30 (76.9)	81 (87.1)	
Transient/permanent	9 (23.1)	12 (12.9)	
Vocal cord palsy, n (%)			0.104
No	39 (100.0)	86 (92.5)	
Transient/Permanent	0	7 (7.5)	
Postoperative complication, n (%)			0.505
No	38 (97.4)	92 (98.9)	
Yes	1 (2.6)	1 (1.1)	

ETE indicates extrathyroidal extension; RAI, radioactive iodine.

DOP With or Without Disease Progression Groups Including TV Change

In the DOP group, 48 patients (36.4%) showed a TV increase, of which 20 patients only had an increase in TV without other disease progression. Of the remaining 28 patients, 27 patients had both an increased TV and tumor size enlargement, and 1 patient had both an increased TV and a suspected new extrathyroidal extension. When the DOP group was divided into 2 groups according to disease progression, including the TV changes, the proportions of males (35.6% vs 19.2%, $P = 0.034$), patients with total thyroidectomy (42.4% vs 26.0%, $P = 0.048$) and N stage (N1a/N1b: 50.8% vs 24.7%, $P = 0.002$) were significantly higher in the DOP group with progression than in the group without progression (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/SLA/E473); however, there were no differences in the postoperative complications between the two groups.

DISCUSSION

In 2003, Kuma Hospital published the first study regarding AS,[8] since then, several studies have analyzed the natural course of PTMC, risk factors for disease progression, clinical outcomes, and changes in the quality of life between AS and IOP groups for low-risk PTMC.[13,14,21,22,25–31] The present study is the first to compare surgical outcomes, including surgical extent and postoperative complications, between the IOP and DOP groups, as a part of the MAeSTro study. We revealed that the extent of thyroidectomy and postoperative complications (vocal cord palsy, and hypoparathyroidism) were not significantly different between the IOP and DOP groups

There have been only a few studies evaluating the clinicopathologic findings or postoperative complications in patients who underwent DOP during AS. Kwon et al[21] reported the clinical outcomes of 24 patients (13%) who underwent DOP among 192 patients who had AS.[21] Total thyroidectomy was performed in 9 patients (37.5%), and DOP was performed due to disease progression in 9 patients (37.5%). In addition, in a multicenter cohort study of 370 patients with low-risk PTMC who had AS reported by Oh et al[22], 58 patients (15.7%) underwent DOP. Total thyroidectomy was performed in 17 patients (29.3%), and DOP was performed due to disease progression in 13 patients (22.4%) with tumor size enlargement and 5 patients (8.6%) with lymph node metastasis. However, these studies were conducted in a retrospective setting, and there were no results on the extent of lymph node dissection or the postoperative complications in the patients who underwent DOP. In addition, Oda et al[11] analyzed the incidences of postoperative complications,

TABLE 4. Pathologic Features Between the DOP Groups Based on Disease Progression

Variable	With progression (n = 39)	Without progression (n = 93)	*p*
Subtype, n (%)			0.568
Classic	32 (82.1)	81 (87.1)	
Follicular variant	1 (2.6)	5 (5.4)	
Tall cell variant	5 (12.8)	7 (7.5)	
Others	1 (2.6)	0	
Size of tumor, mm, median (IQR)	8.0 (7.0–9.0)	7.0 (5.5–8.0)	0.038
Extrathyroidal extension, n (%)			0.067
None	15 (38.5)	52 (55.9)	
Microscopic/Gross	24 (61.5)	41 (44.1)	
Lymphatic invasion, n (%)	22 (56.4)	39 (41.9)	0.128
Multifocality, n (%)	19 (48.7)	35 (37.6)	0.237
AJCC (8th, T stage), n (%)			0.266
T1a	31 (79.5)	81 (87.1)	
≥T1b	8 (20.5)	12 (12.9)	
AJCC (8th, N stage), n (%)			0.021
N0/NX	19 (48.7)	65 (69.9)	
N1a/N1b	20 (51.3)	28 (30.1)	
$BRAF^{V600E}$ mutation, n (%)			0.571
Not done	1 (2.6)	3 (3.2)	
Positive	31 (79.5)	77 (82.8)	
Negative	7 (17.9)	13 (14.0)	

AJCC indicates American Joint Committee on Cancer.

such as hypoparathyroidism and vocal cord palsy, between AS (including 94 DOP patients) and IOP patients; however, the histopathologic outcomes were not compared between the IOP and DOP groups.[11]

Our study has several strengths. The present study is a part of the MAeSTro study, the first prospective multicenter cohort study for low-risk PTMC in Korea, and this study was designed to evaluate the disease course of PTMC through follow-up visits using the same intervals in three tertiary hospitals. When designing this cohort study, the definition of disease progression was established,[16] and surgery is recommended if disease progression is detected. This protocol would be helpful to precisely compare the surgical outcomes, and disease course of the IOP and DOP groups. In addition, we collected detailed information focused on the surgical extent, including the extent of thyroidectomy and lymph node dissection, the purpose of lymph node dissection, the histopathologic characteristics and the postoperative complications, and compared these parameters between the IOP and DOP groups. Therefore, this study provides useful information for the consideration of treatment options in patients with low-risk PTMC and for determining whether there are unfavorable events in patients who underwent DOP compared with IOP. Furthermore, we also performed a subgroup analysis based on disease progression to investigate how disease progression influences surgical outcomes, and the postoperative management to evaluate the safety of AS.

In the results between the IOP and DOP groups, the initial tumor size was larger in the IOP group than in the DOP group; however, the tumor size that was confirmed in the pathologic outcomes after surgery was larger in the DOP group than in the IOP group. This may be because the median period between enrollment and operation of the DOP group [15 months (IQR, 7–28 months)] was longer than that of the IOP group [0 month (IQR, 0–1 month)]. However, the extent of thyroidectomy and the proportion of therapeutic central neck dissection were not different between the two groups, even though there was a significant increase in tumor size at the initial assessment and the time of operation in DOP group [6.4 mm (IQR, 5.2–7.7) vs 7.0 mm (IQR, 6.0–9.0), $P < 0.001$]. We postulated that increased tumor size during AS in DOP group may not affect the extent of operation because we enrolled the PTMC patients with scheduled follow-up intervals to identify the disease progression, and there were no patients who had large-sized tumor at the time of operation to affect the extent of operation.

The extent of lymph node dissection was significantly different between the IOP and DOP groups ($P = 0.020$), especially in the central and lateral lymph node dissection (IOP: n = 6, 1.6%; DOP: n = 8, 6.1%). In the IOP group, all the 6 patients who underwent lateral lymph node dissection were confirmed lateral lymph node metastasis before surgery. However, the 8 patients in the DOP group did not have any suspicious features of lateral lymph node metastasis at the initial assessment. During active surveillance, lateral lymph node metastasis was suspected or confirmed in these patients at the time of operation, and we performed lateral lymph node dissection. Among the definition of disease progression including size enlargement, new extrathyroidal extension, regional lymph node metastasis, and distant metastasis, especially regional lymph node metastasis is thought to be an important factor to affect the extent of operation in the present study.

In addition, the ratio of histologic subtype was different between the IOP and DOP groups. In particular, the proportion of tall cell variants was higher in the DOP group (9.1%) than in the IOP group (3.4%). In addition, the proportion of tall cell variants was higher in the DOP group with progression (12.8%) than in the IOP group (3.4%). The tall cell variant of papillary carcinoma presents at an older age and at a more advanced stage than classical papillary carcinoma and demonstrates a higher rate of recurrence and decreased disease-specific survival.[2] These results suggest that an aggressive histologic subtype may be associated with disease progression, so it is necessary to take this factor into account when determining the treatment options for low-risk PTMC. However, it is difficult to confirm the histologic subtype before surgery.

Hypoparathyroidism, or vocal cord palsy, is one of the most common surgical complications of thyroid surgery and may severely impair the patient's quality of life. Permanent hypoparathyroidism was present in 0.3% of the patients in the IOP and 0.8% of DOP groups, and permanent vocal cord palsy was present in 0.3% of the patients in the IOP group. In addition, some patients developed wound infections (n = 1, 0.3%) and seromas (n = 1, 0.3%) in the IOP group, and postoperative bleeding occurred in 2 patients (1.5%) in the DOP group. Interestingly, the postoperative complications did not differ significantly between the two groups. This may be because the extent of thyroidectomy, and rate of central neck dissection were not different between the two groups. In order more accurately to compare the postoperative complications in both groups, further evaluation of more patients will be needed in the future because the patients experienced a relatively low rate of complications in each group.

During the follow-up period after surgery, there were recurrences in 3 patients (0.8%) in the IOP group, and they underwent reoperation because of locoregional recurrence on the

TABLE 5. Clinicopathologic Features Between the IOP Group and the DOP Group Without Disease Progression

Variable	IOP (n = 384)	DOP Without progression (n = 93)	*P*
Age at diagnosis, yr, mean (SD)	46.3 (10.5)	47.4 (10.0)	0.359
Sex, n (%)			0.924
Male	76 (19.8)	18 (19.4)	
Female	308 (80.2)	75 (80.6)	
Initial tumor size, mm, median (IQR)	6.8 (5.4–8.2)	6.0 (5.1–7.7)	0.026
Initial tumor volume, mm^3, median (IQR)	102.0 (51.7–185.1)	79.2 (43.0–154.6)	0.054
Period between enrollment and operation, months, median (IQR)	0 (0–1)	15 (7–27)	< 0.001
Follow-up duration after operation, months, median (IQR)	46 (36–51)	26 (14–38)	< 0.001
Extent of thyroidectomy, n (%)			0.742
Lobectomy/Isthmectomy	275 (71.6)	65 (69.9)	
Total thyroidectomy	109 (28.4)	28 (30.1)	
Lymph node dissection, n (%)			0.251
None	23 (6.0)	5 (5.4)	
Central only	355 (92.4)	84 (90.3)	
Central and lateral	6 (1.6)	4 (4.3)	
Purpose of central lymph node dissection, n (%)			0.736
None	23 (6.0)	5 (5.4)	
Prophylactic	318 (82.8)	80 (86.0)	
Therapeutic	43 (11.2)	8 (8.6)	
Subtype, n (%)			0.093
Classic	358 (93.2)	81 (87.1)	
Follicular variant	11 (2.9)	5 (5.4)	
Tall cell variant	13 (3.4)	7 (7.5)	
Others	2 (0.5)	0	
Size of tumor, mm, median (IQR)	6.0 (5.0–8.0)	7.0 (5.5–8.0)	0.107
Extrathyroidal extension, n (%)			0.043
None	170 (44.3)	52 (55.9)	
Microscopic/gross	214 (55.7)	41 (44.1)	
Lymphatic invasion, n (%)	121 (31.5)	39 (41.9)	0.056
Multifocality, n (%)	109 (28.4)	35 (37.6)	0.081
AJCC (8th, T stage), n (%)			0.235
T1a	350 (91.1)	81 (87.1)	
≥ T1b	34 (8.9)	12 (12.9)	
AJCC (8th, N stage), n (%)			0.869
N0/NX	265 (69.0)	65 (69.9)	
N1a/N1b	119 (31.0)	28 (30.1)	
$BRAF^{V600E}$ mutation, n (%)			0.248
Not done	2 (0.5)	3 (3.2)	
Positive	343 (89.3)	77 (82.8)	
Negative	39 (10.2)	13 (14.0)	
RAI, n (%)	56 (14.6)	13 (14.0)	0.882

AJCC indicates American Joint Committee on Cancer; RAI, radioactive iodine.

lateral lymph nodes. However, there were no patients with recurrence in the DOP group during the follow-up period, which is thought to be because the DOP group (28 months) had a relatively shorter follow-up period after operation than the IOP group (46 months). Therefore, a long-term follow-up period will be needed to evaluate oncologic outcomes, such as recurrence and mortality, in both groups.

In the subgroup analyses based on disease progression, interestingly, the DOP group with disease progression had a higher proportion of males than the DOP group without progression. This result is consistent with the findings in the MAeSTro study by Lee et al[32] that male sex was significantly associated with progression; therefore, we need to exercise caution when male patients choose AS for PTMC. In the DOP group with progression, the N stage and rate of radioiodine therapy after total thyroidectomy were significantly higher than those in the DOP group without progression. These findings suggest that additional treatment is required in patients who undergo surgery because of disease progression. Radioiodine therapy was administered after total thyroidectomy in the intermediate- or high-risk patients according to the ATA guidelines.[2] Between the IOP group and DOP group without progression, the extent of surgery and clinicopathologic features were not different. However, in the IOP group and the DOP group with progression, the number of aggressive clinicopathologic features were higher in the DOP group with progression. Therefore, we need to evaluate the predictive factors for disease progression to improve the clinical outcomes in patients who underwent AS for low-risk PTMC.

Tuttle et al analyzed 291 patients who underwent AS instead of immediate operation for low-risk PTMC and reported that the serial measurements of TV can facilitate early identification of tumor growth. When we evaluated the surgical outcomes and postoperative complications between the DOP groups according to disease progression, including TV changes, the rate of extent of thyroidectomy was significantly higher in the DOP group with disease progression ($P = 0.048$). These results suggest

TABLE 6. Clinicopathologic Features Between the IOP Group and the DOP Group With Disease Progression

Variable	IOP (n = 384)	DOP With progression (n = 39)	*P*
Age at diagnosis, yr, mean (SD)	46.3 (10.5)	49.1 (12.0)	0.117
Sex, n (%)			0.001
Male	76 (19.8)	17 (43.6)	
Female	308 (80.2)	22 (56.4)	
Initial tumor size, mm, median (IQR)	6.8 (5.4–8.2)	7.0 (6.0–7.6)	0.702
Initial tumor volume, mm^3, median (IQR)	102.0 (51.7–185.1)	105.5 (57.9–156.0)	0.368
Period between enrollment and operation, months, median (IQR)	0 (0–1)	18 (7–29)	< 0.001
Follow-up duration after operation, months, median (IQR)	46 (36–51)	33 (12–39)	< 0.001
Extent of thyroidectomy, n (%)			0.099
Lobectomy/Isthmectomy	275 (71.6)	23 (59.0)	
Total thyroidectomy	109 (28.4)	16 (41.0)	
Lymph node dissection, n (%)			0.014
None	23 (6.0)	1 (2.6)	
Central only	355 (92.4)	34 (87.2)	
Central and lateral	6 (1.6)	4 (10.3)	
Purpose of central lymph node dissection, n (%)			0.201
None	23 (6.0)	1 (2.6)	
Prophylactic	318 (82.8)	30 (76.9)	
Therapeutic	43 (11.2)	8 (20.5)	
Subtype, n (%)			0.040
Classic	358 (93.2)	32 (82.1)	
Follicular variant	11 (2.9)	1 (2.6)	
Tall cell variant	13 (3.4)	5 (12.8)	
Others	2 (0.5)	1 (2.6)	
Size of tumor, mm, median (IQR)	6.0 (5.0–8.0)	8.0 (7.0–9.0)	0.001
Extrathyroidal extension, n (%)			0.486
None	170 (44.3)	15 (38.5)	
Microscopic/Gross	214 (55.7)	24 (61.5)	
Lymphatic invasion, n (%)	121 (31.5)	22 (56.4)	0.002
Multifocality, n (%)	109 (28.4)	19 (48.7)	0.008
AJCC (8th, T stage), n (%)			0.042
T1a	350 (91.1)	31 (79.5)	
≥ T1b	34 (8.9)	8 (20.5)	
AJCC (8th, N stage), n (%)			0.012
N0/NX	265 (69.0)	19 (48.7)	
N1a/N1b	119 (31.0)	20 (51.3)	
$BRAF^{V600E}$ mutation, n (%)			0.166
Not done	2 (0.5)	1 (2.6)	
Positive	343 (89.3)	31 (79.5)	
Negative	39 (10.2)	7 (17.9)	
RAI, n (%)	56 (14.6)	12 (30.8)	0.009

AJCC indicates American Joint Committee on Cancer; RAI, radioactive iodine.

that the TV change needs to be considered a parameter to evaluate disease progression during AS.

Our study has several limitations. This study was not a randomized study because the participants had a chance to choose their initial treatment modality. Therefore, the results could potentially be influenced by self-selection bias. In addition, the follow-up period might not be sufficient to evaluate recurrence or cancer-specific mortality; however, the present study is sufficient to analyze surgical outcomes, including surgical extent and postoperative complications, especially for considering the treatment options for low-risk PTMC.

CONCLUSION

The extent of thyroidectomy and postoperative complications did not differ between the IOP and DOP groups. These results suggest that AS might be considered an alternative treatment option for patients with low-risk PTMC. However, unfavorable pathologic features were significantly higher in the DOP group than in the IOP group. In addition, among the DOP groups, the rates of lymph node metastasis and radioiodine therapy were higher in the patients who underwent surgery due to disease progression. Therefore, long-term follow-up will be needed to evaluate oncologic outcomes, including recurrence and mortality.

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