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Study Protocol of Expanded Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma (MAeSTro-EXP)

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Background: Active surveillance (AS) has emerged as a viable management strategy for low-risk papillary thyroid microcarcinoma (PTMC), following pioneering trials at Kuma Hospital and the Cancer Institute Hospital in Japan. Numerous prospective cohort studies have since validated AS as a management option for low-risk PTMC, leading to its inclusion in thyroid cancer guidelines across various countries. From 2016 to 2020, the Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma (MAeSTro) enrolled 1,177 patients, providing comprehensive data on PTMC progression, sonographic predictors of progression, quality of life, surgical outcomes, and cost-effectiveness when comparing AS to immediate surgery. The second phase of MAeSTro (MAeSTro-EXP) expands AS to low-risk papillary thyroid carcinoma (PTC) tumors larger than 1 cm, driven by the hypothesis that overall risk assessment outweighs absolute tumor size in surgical decision-making.

Methods: This protocol aims to address whether limiting AS to tumors smaller than 1 cm may result in unnecessary surgeries for low-risk PTCs detected during their rapid initial growth phase. By expanding the AS criteria to include tumors up to 1.5 cm, while simultaneously refining and standardizing the criteria for risk assessment and disease progression, we aim to minimize overtreatment and maintain rigorous monitoring to improve patient outcomes.

Conclusion: This study will contribute to optimizing AS guidelines and enhance our understanding of the natural course and appropriate management of low-risk PTCs. Additionally, MAeSTro-EXP involves a multinational collaboration between South Korea and Australia. This cross-country study aims to identify cultural and racial differences in the management of low-risk PTC, thereby enriching the global understanding of AS practices and their applicability across diverse populations.

Keywords: Thyroid cancer, papillary; Watchful waiting; Immediate surgery; Study protocol

INTRODUCTION

Active surveillance (AS) for low-risk papillary thyroid microcarcinoma (PTMC) was introduced after two Japanese institutions, Kuma Hospital and the Cancer Institute Hospital, initiated clinical trials [1,2]. Since then, several prospective cohort studies and uncontrolled treatment series have reported outcomes of AS for patients with low-risk PTMC [3-9]. These studies suggest that AS can be considered as a treatment option for the disease. As a result, many countries have specified in their thyroid cancer treatment guidelines that AS can be considered for low-risk PTMC [10-15]. We conducted a Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma (MAeSTro) that enrolled 1,177 patients with low-risk PTMC from 2016 to 2020 [16]. Our study reported on various outcomes, including the progression rate of PTMC, sonographic features associated with progression, quality of life (QoL), surgical outcomes, and cost, comparing AS to surgery [6,17-22]. We continue to monitor and observe relevant indicators.

Current guidelines from most professional societies recommend applying AS primarily to PTMCs measuring 1 cm or less. This is because AS was initially introduced in Japanese studies for low-risk PTMCs under 1 cm, and subsequent research has built upon this foundation. However, the use of the 1 cm size criterion was based on the belief at the time that the prognosis of T1a (≤1 cm) and T1b (1–2 cm) tumors was different. Recently, several studies have reported that when adjusting for factors including treatment range, there is no difference in prognosis between T1a and T1b tumors [23-27]. These studies suggest that tumor size should not be the sole determinant. Other factors, such as more aggressive histological features or evidence of extrathyroidal extension (ETE), may play a more significant role in patient outcomes than size alone. Therefore, the focus is shifting towards a more comprehensive evaluation of tumor characteristics beyond just size [24,26-28]. Based on this evidence, the American Thyroid Association recommends thyroid lobectomy as sufficient treatment for low-risk, unifocal, intrathyroidal papillary and follicular carcinomas ≤4 cm. This perspective has also influenced the criteria for AS, and recently, studies on AS for low-risk papillary thyroid carcinoma (PTC) larger than 1 cm are underway [5,8,29-34]. This expansion of size criteria is based on the hypothesis that the comprehensive risk assessment of 'low-risk' is a more important factor than the absolute size of 1 cm in determining the immediate need for surgery for PTC. In studies that include PTC up to 1.5 cm as candidates for AS, initial tumor size (<1.0 cm vs. 1.0–1.5 cm) was not associated with the tumor progression of thyroid cancer during AS [7], and the results of studies published to date indicate that the progression rate of thyroid cancer is not different when comparing studies that observed PTMC (≤1.0 cm) with those that observed PTC up to 1.5 cm [7,30]. Furthermore, studies observing the

natural course of PTC have reported that the growth rate of tumor may significantly slow down after reaching a size of approximately 1.0 to 1.5 cm, compared to the initial stages of development [33,35]. Taking this into consideration, if the criterion for applying AS is restricted to the conventional tumor size of 1 cm, there is a risk of performing surgery in cases of low-risk PTC which were detected too early during the initial phase of rapid growth, and show an increase in size during the subsequent follow-up period. To avoid such situations, there is a growing need to expand the size criteria.

Therefore, the aim of the second phase of the MAeSTro (MAeSTro-EXP), is to expand the inclusion criteria, to include tumors up to 1.5 cm and to clarify unclear aspects of the protocol from the original MAeSTro study. This phase will enable a comprehensive evaluation of progression free survival, surgical outcomes, risk factors for disease progression, QoL, medical costs, and factors influencing treatment decisions in patients with low-risk PTCs. The findings from this study may provide the clinical evidence needed to potentially expand the size criteria in current guidelines, which currently recommend AS for low-risk PTMCs measuring 1.0 cm or less. Additionally, MAeSTro-EXP plans to compare outcomes not only between institutions but also based on racial and socio-cultural differences, with participation from four institutions in South Korea and five institutions in Australia as part of this multinational, multicenter study.

METHODS

Study design and setting

MAeSTro-EXP is a multinational prospective cohort study conducted in Korea and Australia. Data are collected for patients who were diagnosed with low-risk PTC and included cancer progression, QoL questionnaires, imaging results, and specimens of blood and thyroid tissues. The participants were recruited from Seoul National University Hospital (SNUH, Seoul, Korea), Seoul Metropolitan Government Seoul National University Boramae Medical Center (SMG-SNU BMC, Seoul, Korea), Seoul National University Bundang Hospital (SNUBH, Seongnam, Korea), the National Cancer Center (NCC, Goyang, Korea), Royal North Shore Hospital (RNSH, Sydney, New South Wales, Australia), Westmead Hospital (WH, Sydney, New South Wales, Australia), Canberra Hospital (CH, Australian Capital Territory, Australia), Princess Alexandria Hospital (PAH, Brisbane, Queensland, Australia), and St Vincent's Hospital Melbourne (SVHM, Melbourne, Victoria, Australia). SNUH, SNUBH, RNSH, PAH, and SVHM are tertiary referral hospitals. SMG-SNU BMC, NCC, and WH are secondary referral hospitals. The study protocol was registered on Clinicaltrials.gov (trial registration number, NCT06261190) and approved by the ethics committee of SNUH (IRB number, 2308-182-1463), SNUBH (IRB number, B-2312-873-405), SMG-SNU BMC (IRB number, 30-2024-13), NCC (IRB number, 2024-0044), RNSH, CH, and WH (IRB number, 2024/ETH 00762), PAH (IRB number, TBD), and SVHM (IRB number, 132/34). All participants provide informed consent and are informed that they could withdraw or change between the AS and surgery group at any time. According to the International Conference on Harmonization Good Clinical Practice Guidelines, all recorded data were anonymized.

Participants

Patients with low-risk PTCs with the tumor size of ≤1.5 cm are considered eligible. Eligible participants received sufficient information regarding AS and immediate surgery. After careful consideration about the pros and cons of each modality, participants are allowed to select their preferred management. When participants choose immediate surgery, optimal types and extent of surgery is decided by their surgeons based on the 2024 Korean Thyroid Association guidelines [15] or 2015 American Thyroid Association guidelines [12].

Participants are included if all following criteria are met:

(1) Subjects, including those who are 18 years old or older, with a thyroid nodule of ≤1.5 cm in maximum diameter and a Bethesda category V (suspicious for PTC) or VI (PTC) diagnosis on cytopathology. Additionally, patients with a Bethesda category III diagnosis who are positive for the BRAF V600E mutation are also eligible for inclusion.

(2) Subjects without high-risk features, including lymph node (LN) metastasis, distant metastasis, signs or symptoms of invasion to the recurrent laryngeal nerve or trachea, high-risk ultrasound (US) features indicating gross ETE of the tumor to the strap muscle or to the trachea, high-risk US features indicating minor ETE to the posterior thyroid capsule, high-risk US features of minor ETE to recurrent laryngeal nerve in tumors located near tracheoesophageal (TE) groove or a high-grade malignancy diagnosis on cytopathology

- Definition of LN metastasis:
  - LN metastasis proven by cytopathology.
  - LN aspiration or biopsy should be considered in any suspicious LNs or intermediate LNs with a short di-

ameter over 0.5 cm on imaging (either US or CT).
- LN metastasis includes cases that are highly suspected on imaging studies.
- CT scanning is not mandatory, but it is performed if possible.

• Definition of distant metastasis:
- Clinical or radiological suspicion of a distant metastasis.
- A separate imaging test to assess distant metastasis is not mandatory, but if feasible, it is recommended to perform a low-dose chest CT.

• Definition of signs or symptoms of invasion to the recurrent laryngeal nerve:
- If a patient complains of voice changes, an evaluation of possible involvement of the recurrent laryngeal nerve through laryngoscopy is necessary.

• Definition of high-risk US features of gross ETE to the strap muscle:
- Tumors with a US feature of replacement of the strap muscle.
- Tumors with US features of capsular abutment, capsular disruption, or bulging of the thyroid contour are not considered as tumors with high-risk US features.

• Definition of high-risk US features of gross ETE to the trachea:
- Tumors with a maximum diameter of ≥0.7 cm that are in contact with tracheal wall at an obtuse angle.
- Tumors with a maximum diameter of ≥0.7 cm that are in contact with tracheal wall at an acute or right angle are not considered as tumors with high-risk US features.
- Tumors with a maximum diameter of <0.7 cm that are in contact with tracheal wall are not considered as tumors with high-risk US features, regardless of the angle of contact.

• Definition of high-risk US features of minor ETE to posterior thyroid capsule:
- Tumors with a maximum diameter of ≥0.7 cm and a US feature of dorsal capsular abutment.
- Tumors with a maximum diameter of ≥0.7 cm and without a US feature of dorsal capsular abutment are not considered as tumors with high-risk US features.
- Tumors with a maximum diameter of <0.7 cm and a US feature of dorsal capsular abutment are not considered as tumors with high-risk US features.

• Definition of high-risk US features of minor ETE to recurrent laryngeal nerve in tumors located near TE groove:
- Any tumors with absence of intervening thyroid parenchyma between tumor and TE groove.
- Any tumors, regardless of its size, with presence of intervening thyroid parenchyma between tumor and TE groove are not considered as tumors with high-risk US features.

• Definition of high-grade malignancy diagnosis on cytopathology:
- Poorly- or de-differentiated thyroid carcinoma, differentiated high-grade thyroid carcinoma, or subtypes with a poor prognosis, such as the tall cell, diffuse sclerosing, columnar cell, or solid subtype.

The overall exclusion criteria were:
(1) Subjects who are unable or unwilling to attend regular follow-ups.
(2) Subjects with a diagnosis of benign, atypia of undetermined significance, or follicular neoplasm (Bethesda category II, III, or IV) based on fine-needle aspiration or, or benign, indeterminate by core needle biopsy.

Enrollment and follow-up

In patients given the option to choose between AS and immediate surgery for PTC, a shared decision-making approach is employed. In Korean study sites, patients are provided with informational materials before making their decisions, ensuring a balanced presentation of the risks and benefits of both AS and immediate surgery, based on published results. This approach aims to minimize inter-physician variability and maintain consistency in the information provided to each patient, facilitating their decision-making process. The interview time for each patient is at least 15 minutes, and a consideration period of 1 to 2 weeks is allowed for discussions with their families. In Australian study sites, patients are recruited out of another randomized control trial that is designed to evaluate a web-based clinical support tool in selecting patients who are appropriate for AS. Clinicians who are recruiting patients will either be assigned to the clinical support tool or a control tool. Patients are provided information regarding AS and surgery and make a shared decision with their clinician whether they pursue AS or surgery.

For the early detection of potential progression in participants opting for AS instead of surgery, their PTCs are closely monitored following the protocol outlined below. Participants who undergo immediate surgery are also followed post-surgery in accordance with the protocol.

For the participants choosing AS, the following protocols are

implemented to monitor the progression of PTCs. During the initial 2 years, participants in the study undergo US follow-ups at 6-month intervals. If there is a volume increase of less than 50% during both the most recent 6 and 12 months, the follow-up frequency changes to annual [29,32]. However, the follow-up schedule reverts to 6-month intervals if there is instance of volume increase of 50% or more within a year or if the tumor diameter reaches 1.3 cm. If the schedule reverts to 6-month intervals, this frequency is maintained for an additional 2 years. Depending on the researcher's discretion, follow-ups of less than 6 months may be conducted if deemed necessary. Follow-ups encompass a physical examination involving the palpation of the thyroid and neck, high-resolution thyroid US, and thyroid function tests. Questionnaires assessing QoL (Supplemental Material S1), anxiety and depression (Supplemental Material S2), and the decision-making process (Supplemental Material S3) are administered at baseline. Subsequently, during follow-up, questionnaires evaluating QoL, anxiety and depression, and satisfaction with the treatment (Supplemental Material S4) are also administered. Additional imaging or biopsy is conducted as deemed necessary, and patients undergo surgery if the indications for conversion surgery are met during these monitoring processes.

Indications for conversion surgery during AS

(1) Absolute indications

- Newly developed LN or distant metastasis.
- Newly developed gross ETE to the strap muscle or trachea, or minor ETE to dorsal capsule or TE groove.
- When there are symptoms such as hoarseness or dysphagia, indicating involvement of the recurrent laryngeal nerve, and it has been confirmed through vocal cord inspection.
- A PTC with a maximum diameter ≥1.3 cm and a rapid volume increase during AS.
- Even if it does not meet the indications mentioned above, if the size of the tumor exceeds 2 cm.
- Definition of rapid volume increase:
  - For a tumor with maximum diameter ≥1.3 cm and calculated volume <600 mm^3 using 3 axis diameters: two consecutive volume increases of ≥50% at 6-month intervals.
  - For a tumor with maximum diameter ≥1.3 cm and calculated volume ≥600 mm^3: a single volume increase of ≥50% at 6-month interval.
  - If there is a US examination result at 6-month interval prior to evaluating the tumor size, it should be included when applying the aforementioned criteria.
  - Volume calculation using 3 axis diameters:
    - ✓ Tumor volume=axis1 (in millimeters, up to the first decimal place)×axis2×axis3×0.524
    - ✓ Volume increase (%)=($volume_{after}$ −$volume_{before}$)/$volume_{before}$×100 (%)

(2) Relative indications

- A PTC size increase of ≥3 mm in maximum diameter confirmed in two consecutive US examinations.
- A PTC size increase of ≥2 mm in at least two dimensions confirmed in two consecutive US examinations.
- A newly identified PTC, which is cytopathologically confirmed in the ipsilateral or contralateral lobe and smaller than the existing PTC under active AS. If AS is maintained for the newly identified PTC, the indications for surgery applies to both the newly arising PTC and the original one.
- When a patient chooses to undergo surgery in the absence of progression.
- Combined Graves' disease is suitable for radioactive iodine ablation therapy or surgery.

Participants who undergo immediate surgery or transition from the AS to surgery are scheduled for follow-up visits every 6 months during the first 2 years post-surgery and then annually thereafter. These follow-ups include the same examinations as those for the AS group, along with laboratory testing of serum thyroglobulin and anti-thyroglobulin antibodies. Participants who have undergone surgery may receive radioactive iodine therapy if indicated, following the 2024 Korean Thyroid Association guidelines [36] or American Thyroid Association 2015 guidelines [12]. Participants will be monitored for at least 10 years or until death.

Study outcomes

The primary outcome of MAeSTro-EXP is progression free survival of the patients with low-risk PTC who choose AS as their treatment modality. Disease progression in the study patients undergoing AS was defined by any of the following criteria: (1) a PTC size increase of ≥3 mm in maximum diameter confirmed in two consecutive US examinations; (2) a size increase of ≥2 mm in at least two dimensions confirmed in two consecutive US examinations; (3) a cytopathological diagnosis of a new PTC; (4) a cytopathological diagnosis of a cervical LN metastasis; or (5) clinical or radiological suspicion of a distant metastasis; and (6) suspected organ involvement during the follow-up, such as trachea, esophagus, nerves, vessels, or muscles in imaging study

including high-resolution US. However, this definition of disease progression is intended for the analysis of the natural course of thyroid cancer and is separate from the criteria for determining whether to continue AS. The decision to continue AS will be based on the indication for conversion surgery.

For secondary outcomes, we will compare surgical outcomes, including surgical extent, postoperative staging, and complications, as well as long-term overall and disease-specific mortality between the immediate surgery and delayed surgery groups. Risk factors for disease progression during AS will be evaluated, considering various parameters such as US findings, epidemiological factors, and pathological features. Furthermore, a comparison of QoL parameters and medical costs between the AS and immediate surgery groups will be conducted. Finally, we will explore factors influencing patients' decisions regarding PTC management, including the impact of socio-cultural backgrounds in this multinational study conducted in Korea and Australia.

Surveys from study participants and physicians

We collect survey results from study participants and physicians. The surveys for the study participants include questionnaires assessing QoL, anxiety and depression, decision-making process, and satisfaction with the treatment. The QoL survey utilized a Korean version of a thyroid-specific QoL questionnaire originally developed by Dow et al. [37,38] and further refined and validated by Ryu et al. [39]. The hospital anxiety and depression scale [40] was used to assess patients' anxiety and depression. Surveys for the decision-making process and satisfaction with treatment, as well as the physician survey, were developed by the endocrinologists (J.H.M., E.K.L., M.J.K., and Y.J.P.) and preventive medicine doctors (S.K.P., K.K.) on the research committee of MAeSTro-EXP. All committee members, including endocrinologists, thyroid surgeons, radiologists, and preventive medicine doctors, approved the final versions. Some survey items were adopted from previous studies [19,41,42]. However, these surveys are conducted in Korea, while a separate survey is used in Australia to measure QoL. Since the QoL survey is conducted to compare the longitudinal changes in the QoL between the surgery group and the AS group during the follow-up period after the diagnosis of thyroid cancer, we plan to compare QoL scores between the Korean and Australian participants as supplementary information. For this cross-sectional comparison, the scores will be standardized using the z-score. The survey for satisfaction with treatment is conducted identically in both countries.

Sample size

This study is an observational cohort study targeting patients with low-risk PTC who opted for AS or immediate surgery based on a sufficient understanding of the treatment options. The primary objective of the study is to evaluate progression free survival of the patients with low-risk PTC who choose AS, in other words, to observe the natural course of low-risk PTC.

The minimum number of study subjects required for the study was calculated from the perspective of securing statistical power in comparing the progression rates to clinically significant thyroid cancer between the two groups.

In a study conducted in Japan, the 5-year progression rate in the AS group and the 5-year recurrence rate in the immediate surgery group were reported as 6.8% and 1.5%, respectively. Similar rates are expected in Korea. The expected ratio of patients choosing AS to immediate surgery is approximately 1:1 to 1:2, with an anticipated 10% dropout rate in the 5-year follow-up for each group. Therefore, assuming a 1:1 or 1:2 ratio between the AS group and the immediate surgery group, a total of 442 patients (221 in each group) or 453 patients (151 in the AS group and 302 in the immediate surgery group) would be required for the study to achieve 80% power with a significance level of 0.05 for a two-sided test comparing the 5-year progression rate difference between the two groups. Considering a 10% follow-up failure rate, a total of 499 patients with low-risk PTC are planned to be enrolled. This study will be conducted in both Korea and Australia, with each country recruiting 400 patients to allow for independent statistical analysis in each nation.

Statistical analysis

The categorical variables were presented as numbers and percentages, while continuous variables with normal distribution were expressed as mean±standard deviation and variables with nonnormal distribution were expressed as median values (interquartile ranges). Associations are examined through multivariate regression analyses, adjusting for potential confounders. Cox proportional hazard models and Kaplan-Meier curves are employed to assess time-to-event outcomes such as recurrence, metastasis, and mortality. Stratification and sensitivity analyses are planned to further assess demographic and clinical characteristics among patients who experienced recurrence, metastasis, or mortality in the AS and surgery groups. Variables measured multiple times during follow-up are analyzed using repeated measures regression analyses. All tests utilize a significance level of 0.05, and IBM SPSS software version 22.0 (IBM Co., Armonk, NY, USA) is used for all analyses.

DISCUSSION

In MAeSTro-EXP, the inclusion criteria for AS has expanded tumor size from MAeSTro, a previously conducted multicenter prospective cohort study, to include low-risk PTC with maximum diameter of 1.5 cm. Additionally, we clarified previously ambiguous inclusion criteria. Specific criteria for evaluating the US feature of ETE have now been outlined. ETE to the strap muscle is defined as the presence of strap muscle replacement on US. This definition stems from previous research, where the diagnostic accuracy of determining gross ETE to the strap muscle using a US finding of strap muscle replacement, was found to be higher compared to using US findings such as capsular abutment, disruption, and contour bulging [43]. According to the findings reported by Ito et al. [44], invasion into the trachea or recurrent laryngeal nerve was not observed in low-risk PTC cases with a size of less than 0.7 cm. Additionally, even in cases where the tumor size is 0.7 cm larger, tracheal invasion was not observed when the tumor interfaces with the tracheal wall at an acute or right angle. Therefore, in this study, tumors with a size equal to or greater than 0.7 cm and interfacing with the tracheal wall at an obtuse angle are defined as high-risk features and excluded from consideration for AS. To minimize or exclude the risk of invasion into the recurrent laryngeal nerve, stricter criteria were established. In cases where the tumor is located in the TE groove, it is excluded from consideration for AS regardless of its size if there is no intervening thyroid parenchyma between the tumor and the thyroid capsule. For tumors located near the thyroid dorsal capsule, exclusion from AS is implemented if the tumor is 0.7 cm or larger and exhibits the US finding of dorsal capsule abutment.

With the inclusion of low-risk PTC up to 1.5 cm in size as candidates for AS, determining the appropriate time to transition to surgery when the tumor size increases poses a challenge. Previous prospective cohort studies, including our original study MAeSTro [1,2,16,34], adopted identical criteria for disease progression and the transition from AS to surgery. This creates a dilemma where low-risk PTCs of the same size can become candidates for AS or targets for surgical removal based on the timing of their discovery. Most previous studies that considered low-risk PTMC as AS candidates focused on tumors with sizes ranging from 0.5 to 1.0 cm. In our original study, MAeSTro, the baseline tumor size in the AS group was 0.6±0.2 cm. Similarly, other studies reported an initial tumor size in the range of 0.6–0.8 cm [1,2]. Consequently, applying the widely recognized progression criteria for tumor size, which is an increase of 3 mm or more in the maximum diameter, indicates that most tumors requiring surgical removal are larger than 1 cm. This aligns well with the criterion for applying AS to tumors with a size of ≤1 cm. However, in MAeSTro-EXP, which allows low-risk PTC with a 1.5 cm size as AS candidates, a PTC starting at 0.8 cm and growing to 1.2 cm during AS may qualify for surgery if the criteria for progression and transitioning to surgery remain the same. Conversely, if the same low-risk PTC is initially found at a size of 1.2 cm, it could be considered eligible for AS. Therefore, in the MAeSTro-EXP protocol, two-step surgical indications are established as relative and absolute indications for surgery.

In this study protocol, we incorporated widely accepted progression criteria, including a 3 mm increase in the maximum diameter of the tumor, LN metastasis, distant metastasis, and the occurrence of new PTC, enabling comparability with other studies. We also included the criteria a 2 mm increase in at least two diameters of the tumor, which is one of the progression criteria adopted in our previous study, MAeSTro. The absolute indications for transitioning from AS to surgery align with the progression criteria for LN and distant metastasis, applying the same criteria. However, we have included tumor size and newly occurring PTC in the relative indications for surgery, allowing for a more flexible transition from AS to surgery. Meanwhile, invasion into cervical structures has been included in the absolute indications for surgery, leading to a more stringent approach. This approach ensures that surgery is not pursued merely based on progression but is reserved for cases where surgery is deemed necessary. Kinetic analyses of low-risk PTMC under AS conducted in Japan showed a significant decrease in growth activity after enlargement, and many cases entered a stabilized stage [35,45]. Therefore, Japan groups applying AS for low-risk PTMC do not immediately transition to surgery based solely on tumor size increase. AS can be maintained based on patient preference until the tumor reaches 1.3 cm. To date, when applying these criteria, there have been no reports of life-threatening recurrences or deaths from thyroid carcinoma [45]. Based on these research results, The consensus statements from Japan Associations of Endocrine Surgery indicated that AS could be allowed to continue until the tumor diameter reached 1.3 cm [10]. Additionally, a prospective study from Italy includes low-risk PTC up to 1.3 cm in size in AS on the basis of significant variations in US measurements and the contraction of paraffin-fixed tissue, which typically results in an underestimation of the actual histological size. Building on these previous studies and guidelines, the MAeSTro-EXP protocol allows for the continuation of

AS for low-risk PTC until it reaches 1.3 cm. For tumors 1.3 cm or larger, if they do not stabilize and show rapid growth, we transition to surgery. However, if the growth rate is not rapid and does not meet other absolute indications for surgery, AS can be maintained until the tumor reaches 2.0 cm. If the tumor size surpasses 2.0 cm, we opt for transitioning to surgery, even if it does not meet the criteria for other surgical indications. This decision is based on ongoing prospective studies that set 2.0 cm as the maximum size for applying AS to low-risk PTC [29,32]. The criterion for rapid tumor growth rate was a 50% or more increase in volume change over a 6-month period. Previous studies suggested that changes in the maximum diameter were more useful than volume due to reported fluctuations [46]. However, this observation was made for small tumors with an average diameter of around 5 mm, where the baseline volume is very small. If the sum of the three axes is 1.5 cm or more, volume fluctuation is relatively small [46]. Therefore, we apply volume change when the maximum diameter is 1.3 cm or larger, ensuring no issues with this criterion.

The potential limitation of this study protocol is selection bias. Randomly assigning the treatment strategy for low-risk PTC for a clinical study could raise ethical concerns, as decisions regarding the treatment plan involve a shared decision-making process between patients and the medical team. Therefore, selection bias is unavoidable, and the outcomes of MAeSTro revealed that treatment decision was influenced by factors such as the patients' baseline QoL and the attitudes of the consulting medical team towards AS. In this study, to conduct a more in-depth analysis of these influencing factors, we have prepared a more detailed patient and medical team survey than in previous studies.

Despite the aforementioned limitations, MAeSTro-EXP will be the first multinational prospective study of AS in patients with low-risk PTCs. It is a multidisciplinary study involving endocrinologists, thyroid surgeons, radiologists, and preventive medicine specialists from eight specialized referral hospitals in Korea and Australia. As a multinational study, MAeSTro-EXP provides a unique opportunity to investigate how socio-cultural backgrounds and racial characteristics influence management decisions for low-risk PTC. The outcomes of MAeSTro-EXP will contribute to the development of more optimal management strategies for low-risk PTC, aligning with the clinical, socioeconomic, and radiologic characteristics of the affected patients. Moreover, the results will offer definitive evidence that could validate the role of AS in the management of low-risk PTCs.

In conclusion, we have initiated a multinational, multicenter prospective cohort study, named MAeSTro-EXP, focusing on low-risk PTCs in Korea and Australia. This study compares AS with surgery. The outcomes from this prospective study will validate the role of AS and contribute to the development of personalized management approaches for low-risk PTC patients.

CONFLICTS OF INTEREST

Young Joo Park is an editor-in-chief and Sun Wook Cho is a deputy editor of the journal. But they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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