

# Active Surveillance May Be the Best Initial Management for Papillary Thyroid Microcarcinoma

Yasuhiro Ito<sup>1</sup>  and Akira Miyauchi<sup>1</sup> 

<sup>1</sup>Department of Surgery, Kuma Hospital, Kobe, Hyogo 650-0011, Japan

**Correspondence:** Yasuhiro Ito, MD, PhD, Department of Surgery, Kuma Hospital, 8-2-35, Shimoyamate-dori, Chuo-ku, Kobe, Hyogo 650-0011, Japan. E-mail: [ito01@kuma-h.or.jp](mailto:ito01@kuma-h.or.jp)

## Abstract

Active surveillance for low-risk papillary thyroid microcarcinoma (PTMC; T1aN0M0) was initiated at Kuma Hospital (Kobe, Japan) in 1993, based on a proposal by Akira Miyauchi. Favorable outcomes of such surveillance have been reported. Our latest study revealed 5- and 10-year tumor enlargement rates (by  $\geq 3$  mm) of 3.0% and 5.5% and 5- and 10-year node metastasis appearance rates of 0.9% and 1.1%, respectively. The postoperative prognosis did not differ between patients who underwent immediate surgery and those who underwent conversion surgery after progression. These findings suggest that active surveillance may be the best initial management of PTMCs.

**Key Words:** papillary thyroid microcarcinoma, active surveillance, prognosis, patient age

**Abbreviations:** AS, active surveillance; CT, computed tomography; PTMC, papillary thyroid microcarcinoma; RFA, radiofrequency ablation; TSH, thyrotropin (thyroid-stimulating hormone).

Active surveillance (AS) for low-risk papillary thyroid microcarcinoma (PTMC; T1aN0M0) was initiated in 1993 at Kuma Hospital (Kobe, Japan) based on a proposal by Dr. Akira Miyauchi. To date, favorable outcomes of this AS have been reported from Japan and abroad. This management has been adopted in the guidelines issued by the Japan Association of Endocrine Surgery and the American Thyroid Association. A consensus statement and position paper were published by the Japan Association of Endocrine Surgery and Japan Thyroid Association, respectively. We describe how to implement an AS program, and we consider clinical questions to explain how AS is the best strategy for PTMCs.

## Recommendation and Implementation of Active Surveillance for PTMC Patients

There are “for” and “against” views for diagnosing suspicious small thyroid nodules based on a cytological examination. The American Thyroid Association guidelines do not recommend a cytological examination for nodules 1 cm or smaller. This might be to avoid overtreatment with surgical intervention. However, when we initiated the AS, there were no guidelines on performing fine needle aspiration. We perform a cytological examination, diagnose them as PTMC in order to avoid the loss-to-follow-up scenario, and encourage patients to continue regular visits for monitoring. To determine whether tumors are suitable for AS, we conduct an ultrasound examination and (if necessary) computed tomography (CT) scanning: tumors attached to the trachea forming obtuse angles with a tumor surface and tumors showing no normal

thyroid tissue between the tumor and the recurrent laryngeal nerve’s course are inappropriate for AS [1].

It remains unclear whether AS of patients younger than 20 years is appropriate. Of course, PTMCs with high-risk features, such as clinical node or distant metastasis, vocal cord paralysis due to carcinoma invasion, tumor protrusion to the tracheal lumen, and suspicion of aggressive variants on cytology, are not indicated for AS. Otherwise, we recommend AS as the initial management for PTMC, although we perform surgery if patients prefer it.

Patients who choose AS are asked to visit our clinic 6 months post-diagnosis and at least once a year thereafter. We check for changes in the tumor’s size and whether novel suspicious lymph nodes have appeared. Tumors are regarded as enlarged when their maximum diameter has increased by  $\geq 3$  mm compared with the baseline, but if patients prefer continuous AS and the tumor does not have other worrisome features, they are observed until the tumor reaches 13 mm in size. For suspicious nodes, we perform a cytological examination and measure the washout’s thyroglobulin level; if either is positive for metastasis, we recommend surgery.

## Active Surveillance Patient Outcomes

Favorable outcomes of AS have been reported in prospective studies from Japan, the United States, Italy, South Korea, and Colombia. Our most recent study obtained 5- and 10-year tumor enlargement rates (by  $\geq 3$  mm) at 3.0% and 5.5% and 5- and 10-year node metastasis appearance rates at 0.9% and 1.1%, respectively [2]. A Nippon Medical school study reported a 9.9% 10-year tumor enlargement rate and a

1.4% node metastasis appearance rate [3]. Both studies [2, 3] showed that age < 40 years was a significant factor predicting PTMC progression. A thyroid-stimulating hormone (TSH) level higher than the lower normal limit and tumor size  $\geq 9$  mm are also predictors of tumor enlargement, and male gender is related to node metastasis appearance [2]. Especially for patients < 40 years old, a high TSH level independently affected tumor enlargement, and thus levothyroxine treatment for young patients to suppress TSH levels to a subnormal value might help prevent tumor growth. Importantly, in both studies, none of the patients who underwent AS showed distant metastasis or died of thyroid carcinoma during the AS or after conversion surgery conducted for various reasons.

## Clinical Questions

### Patients' Acceptance of Active Surveillance

Whether and how patients accept AS without immediate surgery is an important issue. Physicians may be concerned that patients cannot accept AS for fear of living with carcinoma, but this may be attributable to the physicians' attitudes about explaining management strategies for PTMC. Between 1993 and 1997, only 30% of the PTMC patients at our hospital chose AS, but this increased to 88% in the period from 2014 to 2016. Today, > 95% of our patients prefer AS, as the accumulation of data has enabled physicians to recommend AS with much greater confidence. We now provide a brochure to patients that depicts the merits of AS (including favorable patient outcomes) before the cytological examination, which may persuade patients of the safety of AS.

### Whether Distant Metastasis Is Evaluated Before AS

Papillary thyroid carcinoma occasionally metastasizes to distant organs. However, it was reported that lung metastasis was not detected in 1000 consecutive PTMC cases by chest CT scans conducted for preoperative screening [4]. Although physicians face tiny papillary carcinomas diagnosed based on distant metastasis, this is a very rare event (< 0.1%). We thus do not recommend imaging studies such as CT or positron emission tomography/CT scanning for screening distant metastasis before initiating AS.

### PTMC Growth and Patient Age

PTMCs in young patients are more likely to enlarge than those in older patients. Using 10-year tumor enlargement rates of each life decade from the 20s to 70s, Miyauchi et al estimated the following lifetime probabilities of disease progression: for patients in their 20s at presentation (48.6%), their 30s (25.3%), the 40s (20.9%), 50s (10.3%), 60s (8.2%), and 70s (3.5%) (5). In light of these data, almost half of PTMCs of patients in their 20s show tumor growth in their lifetime; in other words, > 50% of these patients could avoid surgery. Since conversion surgery for PTMCs after slight enlargement is not technically difficult, patients in their 20s can still be candidates for AS.

### Patients' Anxiety

While one may think that patients' anxiety is a problem for implementing AS, most studies, including ours, have demonstrated that the quality of life of patients who undergo AS is generally better than that of the patients who undergo

immediate surgery. As noted above, > 95% of our hospital's PTMC patients choose AS.

### PTMC Growth and Pregnancy

There is concern that PTMCs might enlarge during pregnancy, because human chorionic gonadotropin produced in the early phase of pregnancy is known to have weak TSH activity. However, it is reported that the PTMCs in only 4 of 50 pregnancies (8%) enlarged by  $\geq 3$  mm. Two of those 4 patients underwent conversion surgery post-delivery and no recurrence has been detected; the other 2 patients remain under continuous AS because the tumor sizes became stable post-delivery.

### Lack of Molecular Markers Predicting PTMC Growth

*BRAF* and *TERT* mutations were identified as having prognostic value, and the prognoses of clinical papillary thyroid carcinoma with both mutations are poor. However, in PTMCs, the presence of *BRAF* mutation was not associated with disease progression, and the incidence of *TERT* mutations is very low and have not been related to patients' prognoses. No markers predicting the future growth of PTMC are available, and AS is the only strategy for detecting progressive cases.

### Requirements for Implementing Active Surveillance for PTMC

Although AS is a safe management method for PTMC patients, there are some conditions for its appropriate implementation. It is very important for physicians to determine whether each PTMC is suitable for AS. Ultrasound is the most useful tool, and skillful sonographers are required for accurate evaluations of primary lesions and lymph nodes. If a tumor has strong calcification, CT might be necessary to determine the positional relationship between the tumor and surrounding organs—especially the trachea and the recurrent laryngeal nerve's course. If primary lesions and lymph nodes cannot be accurately evaluated on imaging, AS cannot be safely implemented.

Another important requirement is the patient's regular hospital visits. Regular hospital visits ( $\geq 1$ ×/year) for imaging evaluations is mandatory for implementing AS. If this cannot be done, AS cannot be implemented safely.

### Comparison of AS and Other Treatment Strategies

There are 2 other strategies for treating/managing PTMCs: surgery and radiofrequency ablation (RFA). Surgery is the classic strategy, with good prognoses; in our series, the 5- and 10-year lymph node recurrence-free survival rates, distant recurrence-free survival rates, and cause-specific survival rates were 99% and 99%, 100% and 100%, and 100% and 100%, respectively. The accumulation of AS data strongly indicates that immediate surgery for all PTMC patients is clearly over-treatment. Although the surgery for PTMC (thyroidectomy +/- level VI dissection) is not very difficult, unfavorable complications can occur. We observed that transient and permanent vocal cord paralysis due to accidental injury occurred in 8.7% and 0.9% and transient and permanent hypoparathyroidism occurred in 20.8% and 1.4% of patients who underwent immediate surgery, respectively [6]. These were

surgical results achieved by expert thyroid surgeons. If non-experts perform PTMC surgery, these incidences would be greater. Using AS can avoid such complications.

Another important clinical question for deciding the appropriateness of AS is the prognoses of patients who underwent AS vs immediate surgery and those who underwent immediate surgery vs conversion surgery. The locoregional recurrence rates of both an AS group and an immediate-surgery group were low, but the former was lower than the latter [7].

The question of whether the postoperative prognosis differs between patients who undergo conversion surgery and those who undergo immediate surgery is also important. If patients who undergo conversion surgery after progression show poorer prognoses than those who undergo immediate surgery, it would be doubtful whether AS is an appropriate strategy. We demonstrated that postoperative locoregional recurrence did not differ significantly between patients who underwent immediate surgery and those who underwent conversion surgery after progression during AS [7]. These findings also support the use of AS.

In Japan, the total cost of the 10-year management of immediate-surgery patients was 4.1 times higher than that of AS. The medical costs vary among countries because they are affected by national health insurance coverage, but at least in Japan, AS is more economical than immediate surgery.

Regarding RFA, a meta-analysis of 1770 patients showed that the pooled complete disappearance rate at the end of follow-up was 79% (95% CI, 65%-94%). The overall tumor progression rate was 1.5%; the local residual carcinoma rate was 0.4%, the new carcinoma lesion appearance rate was 0.9%, and the node metastasis appearance rate was 0.2% [8]. The overall complication rate was 2.7%, and 0.2% of the patients showed major complications (eg, voice changes, cardiac arrhythmia); these rates were lower than those of surgery. The meta-analysis authors thus concluded that RFA could be envisioned as step-up treatment after local tumor growth under AS or as the initial treatment in patients with anxiety about AS. RFA is not covered by many countries' health insurance (including Japan), and it is very costly, posing a significant problem.

## Summary

Based on the accumulation of data, it has become clear that the prognoses of PTMC patients who undergo AS are excellent. The prognosis following conversion surgery after slight progression has also been good and not different from that of immediate surgery without AS. Active surveillance for PTMCs thus provides safe management when appropriately implemented.

PTMCs in young patients are likely to grow, but TSH suppression around the lower normal limit might help prevent tumor enlargement. Some PTMCs enlarge during pregnancy, but conversion surgery after delivery is not too late. Regarding patients' anxiety, favorable results have been reported. Providing patients with a brochure about AS before the cytological examination can help remove/reduce anxiety. No molecular markers predicting future PTMC growth have been detected, and AS is the only strategy to discriminate aggressive cases. It is worth noting that none of the patients who underwent AS at our hospital showed distant metastasis or

died of thyroid carcinoma during their AS or after conversion surgery. Further, the postoperative prognosis of patients who underwent conversion surgery after progression did not significantly differ from that of the patients who received immediate surgery; this also supports the appropriateness of AS. Although PTMC surgery provides excellent prognoses and is not technically difficult, complications might occur (eg, permanent vocal cord paralysis, permanent hypoparathyroidism) that could be avoided if patients choose AS. Studies of RFA with large patient series have been conducted mainly in China and South Korea, and although they described favorable patient outcomes, studies with longer follow-up periods are necessary. The high cost of RFA also remains a problem.

## Conclusions

Active surveillance is a suitable initial management strategy for patients with PTMC. For implementing AS more efficiently, molecular markers that predict the future growth of PTMCs are necessary to identify progressive tumors in the early phase.

## Disclosures

Authors have no disclosures/conflicts.

## Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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