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Active Surveillance of Papillary Thyroid Microcarcinoma: Where Do We Stand?

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Abstract
The recent sharp increase in thyroid cancer incidence is mainly due to increased detection of small papillary thyroid microcarcinoma (PTMC). Due to the indolent nature of the disease, active surveillance (AS) of low-risk PTMCs is suggested as an alternative to immediate surgery to reduce morbidity from surgery. For appropriately selected PTMC patients, AS can be a good management option and surgical intervention can be safely delayed until progression occurs. Many considerations must be taken into account at the time of initiation of AS, including radiological tumor characteristics and clinical characteristics of the patient. A specialized medical team should be assembled to monitor patients during AS with an appropriate follow-up protocol. The fact that some patients require surgery for disease progression after long-term follow-up is a major drawback of the current AS protocol. Evaluation of tumor kinetics by three-dimensional tumor volume measurement during the initial 2–3 years of AS may be helpful for discrimination of PTMCs that need early surgical intervention. In this review, we will discuss the clinical outcomes of surgical intervention and AS, considerations during AS, and unresolved questions about AS.

Introduction

The incidence of thyroid cancer has increased all over the world. The age-standardized incidence of thyroid cancer in Korea has also increased sharply since 2000 and reached 49.1 per 100,000 in 2015 [1]. It is apparent that the recent increased use of various neck images, mostly ultrasonography (US) and US-guided aspiration, is the major factor underlying the increasing incidence of thyroid cancer. Indeed, most of the newly diagnosed thyroid cancers are small papillary thyroid carcinomas (PTCs) including papillary thyroid microcarcinomas (PTMCs) [1, 2].

For the last several decades, we did not have sufficient knowledge of the biological behavior of PTMCs, and were surprised to find that many of these PTMCs have similar pathological characteristics to larger PTCs such as the

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presence of cervical lymph node (LN) metastases, extrathyroidal extension (ETE), and multifocal tumors [3, 4]. These findings have led to more diagnosis and surgery for them. However, we now realize that most PTMCs have a very indolent nature and excellent outcomes [2, 5, 6].

Recently, active surveillance (AS) instead of immediate surgery was suggested as a management option for PTMCs [6–8]. By definition, AS means applying life-long diagnostic modalities to evaluate changes in disease status without treatment, until progression of the disease becomes clinically apparent [9, 10]. Regular follow-up should be provided for the patient to ensure that disease progression is tolerable without any additional therapeutic options, such as surgery. AS is most widely studied in prostate cancer [11]. Prostate cancers are biologically indolent in many cases, but complications with prostate operations such as urinary incontinence and erectile dysfunction are relatively common. Furthermore, prostate cancer usually develops in the elderly. These suggest that prostate cancer could be the best disease context in which to apply AS [9, 12].

Since most PTMCs also have a very indolent nature, immediate surgery may not be a good treatment option because surgical complications, although very rare with experienced surgeons, are inevitable. Conceptually, PTMCs can be safely left untreated with AS and only those progressing need surgery. AS has only been introduced recently, and more studies are needed to prove long-term clinical safety. However, it is clear that AS may be beneficial for some PTMC patients. In this review, we will discuss the clinical outcomes of PTMCs after surgical intervention and AS, considerations during AS, and unresolved questions about AS.

Clinical Outcomes of PTMC after Early Surgical Intervention

During the past several decades, patients with PTMC >6 mm usually underwent immediate surgery at our center. Lessons were learned. First, patients with PTMC may have distant metastases and die of their disease. We found that 12 out of 8,808 (0.14%) patients with PTMC had distant metastases and 4 patients among them died of thyroid cancer [13]. However, all of the patients who developed distant metastases had clinically apparent cervical LN metastases, mostly involving the lateral cervical area, and 1 patient had clinically evident distant metastasis before the initial surgery. Therefore, those who developed distant metastases from primary PTMC already had advanced clinical disease, and were not stratified in the low-risk group.

Next, analyses focused on low-risk PTMCs. In these patients, delays in surgery by more than 18 months were not associated with any increased risk of recurrence compared with those who underwent immediate surgery [14]. Lobectomy for the treatment of PTMC did not pose any significantly higher risk of recurrence (3.8%) than total thyroidectomy (1.6%) during 8.5 years of follow-up, after controlling for various clinicopathological characteristics [15]. Most of the recurrences in the lobectomy group occurred in the contralateral remaining lobe. Recurrences at lateral cervical LNs were rare (0.6% in the lobectomy group and 1.5% in the total thyroidectomy group). This suggested that lobectomy was sufficient as the initial treatment for PTMC. Furthermore, PTMC patients who had undergone total thyroidectomy had excellent clinical outcomes independent of radioactive iodine remnant ablation [16] or postoperative thyrotropin (TSH) suppression therapy [17]. These findings suggested that most low-risk PTMCs had an indolent nature with an excellent outcome. The conclusion was drawn that more conservative treatment approaches, including AS, may be safe.

Importantly, we found that young age (<40 years) and male sex were predictors of large-volume LN metastasis (≥5 metastatic LNs) in clinical N0 PTMC patients [18]. We also identified predictors of lateral cervical LN metastasis in PTMC: young age (<50 years), male sex, subcapsular or upper thyroid tumor location, and microcalcification [19]. These findings suggested that young male patients may not be good candidates for AS.

AS for Patients with PTMC

A group of Japanese surgeons introduced the concept of AS for PTMCs and began observational trials as an alternative to immediate surgery. In their first observation trial from Ito et al. [7], 162 PTMC patients at Kuma Hospital were followed over a mean period of 46.5 months (range: 18–113) and 56 patients among them ended up receiving surgery. Among these 56 patients, only 13 (23.3%) showed a significant increase in the size of their tumors. Tumor size increased to >1.0 cm in 7 patients, and new lateral cervical LN metastases developed in 2 patients. In 2010 and 2014, the group published follow-up reports analyzing larger numbers of patients (340 and 1,235, respectively) [6, 8]. According to their 2014 report, 191 out of 1,235 patients received delayed surgery during a mean follow-up of 60 months (range: 18–227) [6]; 58

(4.6%), 43 (3.5%), and 19 patients (1.5%) underwent surgery for an increase in tumor size >3 mm, tumors reaching >12 mm, and new cervical LN metastases, respectively. Among these 191 patients, only 1 patient showed recurrent disease 75 months after the surgery, and the authors concluded that delayed surgery after AS did not worsen prognosis. Another Japanese group reported similar results. Among 230 PTMC patients, only 7% underwent surgery during a mean follow-up of 5 years, and no patient experienced recurrence and/or cancer-specific death [20].

We also reported a single-center study analyzing 192 PTMC patients under AS [21]. Twenty-seven patients (14%) showed an increase in tumor volume (TV) greater than 50% during a median follow-up period of 31.2 months. Four of them (2%) showed an increase in maximal tumor diameter of at least 3 mm, and only 1 patient (0.5%) showed new cervical LN metastases. Another retrospective observational study from a single center in Korea analyzed 127 PTMCs and showed PTMC progression, defined by an increase in TV greater than 50%, in 28 patients (20%) during a median follow-up of 26 months [22]. The first multicenter study in Korea supported these results [23]. During a median follow-up period of 32.5 months, 86 of 370 patients (23.2%) showed an increase in TV greater than 50%, and 13 patients (3.5%) showed an increase in maximal tumor diameter [23].

A cohort study in the USA included 291 patients undergoing AS for low-risk PTCs (<1.5 cm). In that study, only 12 and 25% of the tumors showed a growth in tumor diameter of 3 mm or more and a TV increase greater than 50% at 5 years, respectively [24]. Table 1 summarizes recently published reports about AS in PTMCs.

Considerations during AS

At the Time of Initiation of Active Surveillance: Selection Criteria for Candidates

The 2015 American Thyroid Association (ATA) guidelines define the following patients as eligible for AS in PTMC [5]: patients with very low-risk PTMCs, patients in whom comorbidities render surgery high risk, patients expected to have a relatively short life expectancy, or patients with simultaneous medical or surgical problems that need to be addressed before thyroid surgery. Patients should be willing to accept an AS approach, understand that surgical intervention may be necessary in the future, and be compliant with follow-up plans. In addition, pathological and radiological characteristics of tumors and clinical characteristics of patients should be used as eligibility criteria for AS. Finally, a specialized medical team should be assembled to monitor patients during AS.

With regard to tumor characteristics, solitary PTMC is an ideal candidate for AS, rather than multifocal tumors [25]. The tumor should have well-defined margins surrounded by at least 2 mm of normal thyroid parenchyma rather than a subcapsular location, adjacent to the recurrent laryngeal nerve, or with evidence of extrathyroidal extension. Finally, the tumor should have been confirmed stable by previous US. There should be no evidence of clinical LN or distant metastasis [25]. Ito et al. [26] emphasized that tracheal invasion and/or recurrent laryngeal nerve involvement can be more precisely evaluated by neck computed tomography (CT) than by US. Thus, in the case of a tumor adjacent to the trachea or tracheoesophageal groove, additional CT should be applied to exclude unfavorable candidates for AS.

Some studies reported that thyroid cancers with a size of 1–2 cm can also be safely managed by AS. A previous study of AS from Memorial Sloan Kettering Cancer Center (MSKCC) included patients with PTCs ≤1.5 cm in maximal diameter and confirmed the low likelihood of growth of these tumors [24]. A recent study from Japan compared AS clinical outcomes in patients with T1a and T1b disease. T1b PTCs with a mean size of 1.2 cm showed the same excellent outcomes as T1a PTMCs, and only 7% showed a diameter increase >3 mm during 7 years of follow-up [27]. These studies suggest that the eligibility criteria for AS can be broadened.

With regard to patient characteristics, age seems to be the most important factor predicting progression of PTMC during AS. Ito et al. [6] reported that a size increase of at least 3 mm, development of new cervical LN metastasis, and a size increase to at least 12 mm were detected in 4, 0.5, and 2.5% of older PTMC patients (>60 years), respectively. However, in younger PTMC patients (<40 years), the incidence was 12.1, 16.1, and 22.5%, respectively. These findings suggest that immediate surgery may be more beneficial for younger patients, since they are more likely to exhibit disease progression during AS. A recent study from that group reported age-specific disease progression rates in PTMC. The disease progression rates after 10 years of AS were 37% for patients in their 20s and 3.5% for patients in their 70s [28]. Our experience of surgical intervention for PTMC suggests that young age is an important predictor of large-volume LN metastasis in clinical N0 PTMC, as described above [18]. However, the patient's preference should be considered. Even if the tumor or patient characteristics indicate a high risk of progression, patients can

Table 1. Summary of previous studies of active surveillance in thyroid cancer

	Patients, *n*	Inclusion criteria	Follow-up, months	Primary outcome	Special points
Ito et al. [6], 2014	1,235	**PTMC (≤10 mm) without:** – Regional LN metastasis or distant metastases – Signs or symptoms of invasion to the RLN or trachea, – FNAB findings suggesting high-grade malignancy – Tumors located adjacent to the RLN or trachea **Patients under observation ≥18 months**	Range 18–227	**Size enlargement (>3 mm)** – 58 patients (4.6%) **Novel appearance of LN metastasis** – 19 patients (1.5%) **Progression to clinical disease (tumor >12 mm or novel appearance of LN metastasis)** – 43 (3.5%)	PTMC in young patients (<40 years) may be more progressive than in older patients (>60 years)
Kwon et al. [21], 2017	192	**PTMC (≤10 mm) without:** – Initial lateral LN metastasis or distant metastases – Clinical evidence of macroscopic invasion into the perithyroidal soft tissue or invasion into the trachea or the RLN – FNAB or CNB findings suggesting aggressive variants of PTC **Patients under observation ≥12 months**	Median 30.1	**Volume increase ≥50%** – 27 patients (14%) **Size enlargement (>3 mm)** – 4 patients (2%)	Tumor volume is more sensitive in detecting PTMC progression than the change in tumor diameter
Tuttle et al. [24], 2017	291	**PTC (≤15 mm) without:** – Clinical or radiological evidence of ETE, invasion of local structures, or regional or distant metastases, – FNAB findings suggesting high-grade malignancy **Patients having TSH level within the reference interval and under observation ≥6 months**	Median 25	**Volume increase ≥50%** – 36 patients (12%) **Size enlargement (>3 mm)** – 11 patients (4%)	PTCs appear to follow predictable growth kinetics
Kim et al. [22], 2018	126	**PTMC (≤10 mm) without:** – Initial lateral LN metastasis or distant metastases, – Clinical evidence of RLN or trachea invasion **Patients without LT4 treatment and on follow-up ≥12 months**	Median 26	**Volume increase ≥50%** – 28 patients (20%)	Sustained elevation of serum TSH is associated with PTMC progression
Oh et al. [23], 2018	370	**PTMC (≤10 mm) without:** – Initial lateral LN metastasis or distant metastases – Clinical evidence of macroscopic invasion into the perithyroidal soft tissue, trachea, or the RLN – FNAB or CNB findings suggesting aggressive variants of PTC **Patients under observation ≥12 months**	Median 32.5	**Volume increase ≥50%** – 86 patients (23%) **Size enlargement (>3 mm)** – 13 patients (4%)	The risk of volume increase in patients <45 years of age was twice as high as in older patients

choose AS if they are in complete agreement and fully understand the risks associated with AS. Informed consent should be obtained to confirm the patient's agreement with AS as part of the standard process.

Institutes that perform AS should have experienced multidisciplinary teams and high-quality neck US machines. Prospective data collection is recommended and a tracking/reminder program to ensure proper follow-up is mandatory, because the single most important criterion for the safety and success of AS is regular follow-up. [25, 29]. Healthcare providers should remind patients of appointments in advance to avoid patient loss.

During Follow-Up

Follow-Up Protocol

Meticulously repeated US is mandatory for patients on AS for PTMC. At Kuma Hospital, follow-up is carried out 6 months after AS initiation and annually thereafter [26]. The MSKCC has a stricter protocol; US examination is recommended every 6 months for the first 2 years and thereafter every year or two [24]. If there is no evidence of progression, the follow-up interval may be longer. Thyroid function testing does not have a definitive role in AS, but is recommended annually. Measurement of serum thyroglobulin is not recommended [25, 26].

Although the definition of progression requiring surgical intervention is still controversial, Kuma Hospital uses the following criteria: tumor size increase >3 mm, appearance of new cervical LN metastases, and/or tumor size increase to a minimum of 12 mm [6].

Examination of Cervical LN during AS

Examination of cervical LNs is extremely important for the determination of disease progression during AS and also for the decision of surgical extent when thyroidectomy is planned for PTC. Loss of the fatty hilum, rounded rather than oval shape, hyperechogenicity, microcalcification, cystic changes, or increased vascularity noted by US may suggest tumor involvement of the cervical LNs [5, 30]. It is still unclear whether small but suspicious LNs detected by US are to be aspirated or left undiagnosed. Current guidelines suggest not doing biopsy for suspicious LNs <8–10 mm in the smallest diameter [5, 30]. However, we have reported that aspirating the suspicious small LNs in the lateral cervical area significantly improved surgical outcome when lateral neck dissection was performed [31].

Given the presence of the thyroid gland, US may not be accurate to evaluate cervical LN metastasis in the central neck area during AS. Neck CT with intravenous contrast was reported to be more sensitive than US for evaluating cervical LNs preoperatively, especially with locally invasive tumors or bulky thyroid cancer [5, 32]. However, the role of CT for PTMC patients under AS is not well elucidated.

Tumor Kinetics Assessment with TV Measurement

PTMC tumor growth is usually very slow and some patients develop clinically problematic tumor growth after many years of observation. If we can reliably predict future tumor growth in advance, we may recommend immediate surgery, rather than AS, for those whose tumor will ultimately grow to a significant size. We need sensitive markers to assess tumor growth.

We added TV increase by at least 50% as a definition of tumor growth [21]. It is surprising that these PTMCs may grow at an early stage by TV measurement even when the maximal diameter remains stable. We noticed that PTMC that is initially vertically slender, a shape that is also called taller-than-wide, becomes globular with time, causing TV to change without altering the maximal diameter. This finding suggests that TV measurement is more sensitive than maximal diameter measurement and may reveal early progression of PTMCs. The study from MSKCC had similar findings [24]. It also showed that TV increased linearly up to 5 years. We also showed that PTMC assessed by TV measurement grows linearly up to 5 years in a Korean multicenter study [23]. In another recent study, we found that TV doubling time, assessed by at least three US follow-up datasets, is a good indicator of PTMC growth. In that study, PTMCs with TV doubling time <5 years were significantly associated with maximal diameter increase ≥3 mm, and they were also associated with young age and macrocalcification [33].

In summary, PTMC growth velocity, assessed by TV measurement, may predict early on which patients ultimately progress after long-term AS. However, so far, tumor kinetics have been studied for a limited period of time. Although PTMCs show linear growth up to 5 years, it is not clear whether such growth velocity will remain constant beyond 5 years and ultimately cause clinically significant disease necessitating surgery.

Unsolved Questions concerning AS

Size Criteria for Cytologic Evaluation of Thyroid Nodules

The 2015 ATA guidelines do not recommend fine-needle aspiration biopsy (FNAB) for suspicious thyroid nodules <1.0 cm [5]. However, it is impossible to confirm cancer without cytological and/or historical diagnosis. Despite showing very suspicious features by US, the malignancy rate of thyroid nodules is about 80% [34]. Without FNAB, patients with benign thyroid nodules that have only suspicious US features may undergo repeated US. In this regard, we cautiously think that it may be appropriate to perform FNAB on thyroid nodules >5 mm with suspicious US features, especially in patients under consideration for AS.

The size criteria for FNAB of cervical LNs are also unclear, as described above. We still do not know how cancer cells metastasize, or what the ultimate fate of very small LN metastases is [30]. Whether the small metastatic LNs might be good candidates for AS is probably beyond the scope of this review, but it should be addressed.

Quality of Life

The most common reason for surgery during AS of PTMC was patients' anxiety about disease progression [6–8, 21]. Therefore, quality of life (QoL) is a very important issue in PTMC AS. In our recent study, we compared the QoL of PTMC patients under AS with that of those who underwent lobectomy using three different questionnaires. After adjusting for age, sex, and serum TSH levels, patients who underwent lobectomy showed more health-related problems, which may be related to surgery, than those managed by AS. The analysis of anxiety and fear related to disease progression showed no significant differences between the two groups [35]. A study from Japan also reported that cancer concerns in patients with AS was comparable to those in actively treated patients [36].

Surgical complications have a great effect on QoL. One study confirmed that surgical complications were more common in patients who underwent immediate surgery than in those under AS [37]. However, this result is somewhat biased, since all patients who received AS were grouped together to calculate the complication rate. When the patients who received delayed surgery were considered as a subgroup, the complication rate was found to be higher among them than among those who underwent immediate surgery [37]. Most PTMCs have a very slight chance of gross extrathyroidal extension and/or clinical cervical LN metastasis, and can be easily cured by lobectomy alone. However, if clinical cervical LN metastasis develops during AS, patients should receive more extensive therapy [38], causing more complications. Thus, delayed surgery during AS of PTMC is more likely to be associated with extended surgery than immediate surgery and, therefore, result in a decreased QoL related to the increase in surgical complications. More studies are needed.

Cost-Effectiveness

Since medical costs and clinical practice are different in each country, country-specific cost-effectiveness analysis is needed. In one study analyzing the cost-effectiveness of AS of PTMC using the standard model of a 40-year-old woman in Hong Kong [39], AS was more cost-effective than immediate surgery for 16 years, and the cost efficiency became lower in the AS group after 17 years of follow-up. However, the QoL of patients undergoing AS may be superior enough to compensate for the reduction in cost-effectiveness. Oda et al. [40] also analyzed cost-effectiveness in Japan and found that immediate surgery costs 4.1 times more than AS during 10 years of follow-up. In the USA, Venkatesh et al. [41] also calculated the cost-effectiveness of AS using the reference case of a 40-year-old patient with low-risk PTMC treatable by lobectomy. They demonstrated that cost-effectiveness was largely dependent on the patient-specific decrease in QoL that occurs upon PTMC diagnosis and on the remaining life expectancy of the patient after initiation of AS. They suggested that early lobectomy is more cost-effective than AS in PTMC patients in whom the diagnosis of PTMC is associated with a decrease in QoL.

Age is also an important factor in determining the cost-effectiveness of AS in PTMC. The lifetime disease progression probability during AS is related to the decade of life [28]. Since the estimated lifetime disease progression rate is 60% for patients in their 20s, early surgical intervention may be more cost-effective in these young patients. Since most young patients show excellent response after initial surgery, the cost of following patients after surgery may be minimized.

Biomarker

BRAF and/or *TERT* promoter mutations are well-known molecular prognostic markers in thyroid cancer, but their prognostic role in the progression of PTMC has not been established [42, 43]. In addition, there are no reports showing whether these events are associated with tumor progression during AS. The Ki-67 labeling index is reported to be associated with progression during AS [44]; however, it is usually measured by histopathology after surgery and therefore cannot be used as a biomarker of progression during AS.

TSH was not found to be a prognostic marker of PTMC progression in one study [45] but was related to progression in another study [22]. In the former study, the patients were older and the investigators used the increase in maximal diameter as a criterion for progression [45]. In the latter one, the patients were younger and the authors used TV increase >50% as a criterion for tumor progression [22]. Since PTMC in the older age group rarely progresses and the maximal diameter increase is not a sensitive measurement, these differences in study popula-

tion and design may explain the different results. The tumor calcification pattern was associated with lateral cervical LN metastasis and was also dependent on age [19, 46], but this result has not been confirmed in the context of PTMC progression.

US-Guided Ablation Therapies for PTMC

Although current guidelines do not recommend ablation therapies for PTMC [47], some studies reported the safety and effectiveness of localized minimally invasive therapies, such as microwave ablation and radiofrequency ablation (RFA), for PTMC. Teng et al. [48] reported that microwave ablation significantly decreased TV without the development of LN metastasis or distant metastasis during 21 months of follow-up. The mean volume reduction rate was approximately 99% at the last follow-up. Another study evaluating RFA for PTMC showed that PTMC nodules were nearly completely resolved in 96% of patients at 12 months after RFA without recurrence during a mean follow-up of 8 months [49]. Complications associated with ablation were minimal and transient in both studies. It is clear that these tumor ablation therapies are effective and safe approaches to control the tumor itself. However, even small PTMCs frequently have LN metastases in the central compartment that cannot be detected preoperatively. Although these therapies can resolve the tumor itself, residual disease at LNs can cause disease progression. Another recent study did not detect any recurrences during a mean follow-up of 4 years after RFA in PTMC patients who were ineligible for surgery [50]. However, longer follow-up studies are necessary to validate the clinical value of ablation therapies for PTMC.

Conclusions

For some appropriately selected PTMC patients, AS can be a good alternative to immediate surgery. Choosing AS is not a simple decision to avoid surgery for patients with PTMC, and establishing an appropriate protocol is necessary to balance the risk, benefits, and cost-effectiveness of AS. Initial selection criteria for suitability should consider many aspects, including the characteristics of tumors and patients, and the availability of specialized medical teams. However, patients with a higher risk of progression are not absolutely contraindicated for AS. Biomarkers and tumor kinetics measurements may be helpful to predict early on which PTMCs are at risk of future progression, and thereby decrease the burden of long-term follow-up. Ideally, patients at high risk of progression can undergo immediate surgery rather than AS, and those with a very low possibility of tumor progression can receive AS with a lower frequency of follow-up, adjusted to risk. Future research should focus on developing new predictive early markers of PTMC progression during AS.

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No potential conflict of interest relevant to this article was reported.

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