



Active Surveillance of Papillary Thyroid Microcarcinoma: A Mini-Review from Korea

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In Korea, the incidence of thyroid cancer increased explosively in the early 2000s, and reached a plateau in the early 2010s. Most cases of newly diagnosed thyroid cancer are small indolent microcarcinoma and could be good candidates for active surveillance (AS) instead of immediate surgery. Many considerations must be taken into account for establishing selection criteria for candidates for AS of papillary thyroid microcarcinoma (PTMC), including the characteristics of the tumor, the patient, and the medical team. If possible, AS of PTMC should be a part of a prospective clinical trial to ensure long-term safety and to identify clinical and/or molecular markers of the progression of PTMC. In this review, we discuss lessons regarding surgical interventions for PTMC, and then describe the concept, application, caveats, unanswered questions, and future perspectives of AS of PTMC. For appropriately selected patients with PTMC, AS can be a good alternative to immediate surgery.

Keywords: Thyroid neoplasms; Active surveillance

INTRODUCTION

In Korea, the incidence of thyroid cancer increased explosively starting in 2004, and reached a plateau in 2012. The incidence of thyroid cancer in 2014 was 51.6 per 100,000 persons [1]. Whether there was a true increase in thyroid cancer or this exponential increase of incidence of thyroid cancer merely reflected the screening effect due to the widespread use of ultrasonography (US) is beyond the scope of this review. However, it is evident that most of the cases of newly diagnosed thyroid cancer can be attributed to the recent increase in the use of various neck imaging modalities, mostly US, because most cases of newly diagnosed thyroid cancer are small papillary thyroid carcinoma (PTC) and cancer mortality did not increase despite the sudden increase in thyroid cancer. Furthermore, over-diagnosis became somewhat of an epidemic in Korea, which might be ex-

plained by the introduction of a nation-wide cancer screening program [2]. At the beginning of the current century, we did not have adequate knowledge regarding the real biological behavior of these small PTCs, and were surprised to find that these small PTCs had similar clinicopathological parameters to their larger counterparts, such as regional lymph node metastasis, extrathyroidal extension (ETE), and multifocality [3,4]. These findings led us to perform surgery for cases of papillary thyroid microcarcinoma (PTMC) and were responsible for the epidemic rise in the incidence of thyroid cancer in Korea.

However, the increased incidence of thyroid cancer is a worldwide phenomenon, and the necessity of active surveillance (AS) was proposed by a group of surgeons from Japan. The 2015 American Thyroid Association (ATA) guidelines suggested AS as an alternative option for PTMC. However, the concept of AS of PTMC has only been recently introduced, so

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only sparse clinical data have been published and more research is needed to prove its long-term clinical safety. In this review, we discuss the lessons learned regarding surgical interventions of PTMC, followed by a description of the concept, application, caveats, unanswered questions, and future perspectives of AS of PTMC.

LESSONS FROM SURGICAL INTERVENTIONS FOR PTMC: EXPERIENCES FROM ASAN MEDICAL CENTER

During the last 20 years, PTMCs larger than 6 mm usually underwent surgical intervention at Asan Medical Center, even before the 2009 ATA recommendations. We knew that nodules smaller than 5 mm could be observed without harm to the patient. We have found that delaying surgery for PTMC by more than 18 months was not associated with a higher risk of recurrence than immediate surgery [5].

We found that unilateral surgery to treat PTMC did not pose a significantly higher risk of recurrence (3.8%) than bilateral surgery (1.6%) during a median of 8.5 years of follow-up [6]. Most of the cases of recurrence in the hemithyroidectomy group were in the contralateral lobe, and recurrence in the lateral neck lymph node was quite rare (0.58% in the hemithyroidectomy group and 1.45% in the total thyroidectomy group) and usually occurred in patients whose neck nodes were not thoroughly searched by US before surgery.

We also found that PTMC patients who underwent total thyroidectomy had equivalent outcomes, regardless of radioactive iodine remnant ablation [7]. Additionally, postoperative thyrotropin suppression therapy for PTMC did not improve patients' outcomes. We found that the recurrence rate was not significantly different according to whether thyroxine suppression therapy was administered during a median follow-up of 8.6 years [8].

Our data also showed that young age (<40 years) and male sex were predictors of large-volume (equal or more than 5) central neck lymph node metastasis in clinical N0 PTMC [9]. Our PTMC data showed that young (<50 years) or male patients, those with a tumor located within the upper lobe or in a subcapsular location, and those with a tumor with microcalcifications had a higher risk of lateral neck lymph node metastasis [10]. Due to these findings, we perform immediate surgery for young (<40 years) male patients after a thorough US examination of the entire neck.

DEFINITION AND BACKGROUND OF ACTIVE SURVEILLANCE

Definition

AS refers to the life-long application of meticulous diagnostic modalities to check for changes in the status of a disease without immediate therapeutic measures until the progression of the disease is evident [11]. Regular follow-up modalities must be provided to the patient to ensure that the progression of the disease is tolerable. AS has been applied to urethral cancer, intraocular melanoma, and prostate cancer. Prostate cancer is the most widely researched and applied area of AS.

Most cases of prostate cancer are detected by an early detection program measuring prostate-specific antigen. Prostate cancer is biologically indolent and complications of prostate surgery, such as urinary incontinence and impotence, are relatively common. Prostate cancer develops mainly in older men, and the average age at the time of diagnosis is the late 60s. This means that the expected duration of life-long surveillance is shorter than for other cancers with a younger age peak, such as thyroid or breast cancer. Thus, prostate cancer may be the best candidate model for AS, as recommended by many guidelines [11,12].

Active surveillance of papillary thyroid microcarcinoma

The traditional cancer staging system for thyroid cancer is the American Joint Committee on Cancer TNM (tumor, node, metastasis) system, which regards microscopic ETE as a risk factor. Thus, even small thyroid cancers with microscopic ETE are classified as stage III in patients older than 45 years [13]. Microscopic ETE very frequently accompanies small thyroid cancers; therefore, many surgeons have preferred total or near total thyroidectomy even for PTMC, and previous guidelines supported somewhat aggressive surgery [14]. However, total or near total thyroidectomy, especially performed by low-volume surgeons, can cause substantial postsurgical complications, such as vocal cord paralysis and hypoparathyroidism, resulting in a decreased quality of life (QoL) and an increased socioeconomic burden [15]. These unfavorable results are evident in the USA, where thyroid operations are performed at low-volume centers and medical costs are high.

A group of surgeons from Japan introduced the concept of AS for thyroid cancer and started an observational trial for PTMC as an alternative to immediate surgery. Ito et al. [16] at Kuma hospital in Japan reported the first observational trial of 162 PTMC patients (mean follow-up period of 46.5 months; range, 18 to 113). During the follow-up period, 56 patients underwent

delayed surgery; seven had a final size of at least 1 cm, and another two showed lateral neck metastasis, and the remaining 47 underwent surgery for various reasons. Among the 56 patients who received delayed surgery, 13 patients (23.3%) showed an increase in tumor size. They subsequently published follow-up reports in 2010 and 2014 analyzing larger groups of patients (340 and 1,235 patients, respectively) [17,18]. Their report in 2014 found that 191 patients (15.4%) out of the 1,235 patients received delayed surgery (mean follow-up period of 60 months; range, 18 to 227) [18]. Fifty-eight patients (4.6%) showed a size increase of 3 mm or more, 19 patients (1.5%) had new neck node metastasis, and 43 patients (3.5%) showed a size increase to larger than 12 mm. Among the 191 patients who underwent a delayed operation, only one showed recurrence at 75 months of follow-up after surgery, and they concluded that delayed surgery was not associated with a worse prognosis [18]. Sugitani et al. [19] also reported similar results among 230 patients with a mean 5 years of follow-up. Seven percent of those patients received surgery during follow-up, and none experienced recurrence and/or cancer-specific death [19]. We reported the retrospective cohort data of 192 PTMC patients under AS who refused to undergo surgery or had medical conditions making them not suitable for surgery [20]. Twenty-seven of the patients (14%) showed a volume increase of 50% or more after a median of 31.2 months of follow-up. Four of them (2%) showed a size increase of at least 3 mm, and only one had new neck node metastasis.

The 2015 ATA guidelines adopted AS of PTMC as a reasonable option [21], and the Korean Thyroid Association (KTA) issued the same recommendation [22]. However, recent clinical guidelines from American Association of Clinical Endocrinologists and the British Thyroid Association do not discuss AS, meaning that there is still controversy regarding AS as a standard alternative for surgery for PTMC [23,24].

CLINICAL APPLICATION OF ACTIVE SURVEILLANCE

Selection criteria for candidates

The 2015 ATA guidelines define the candidate patients for AS of PTMC as follows [21]: patients with very low risk tumors, patients at high surgical risk because of comorbid conditions, patients expected to have a relatively short remaining lifespan, or patients with concurrent medical or surgical issues that need to be addressed prior to thyroid surgery. The KTA has recommended using the same criteria for AS of PTMC. Brito et al.

[25] suggested useful guidelines based on characteristics of the tumor, patient, and medical team, as shown in Table 1. Thus, not only the size of the tumor, but also many other aspects of the clinical situation should be considered before recommending AS to a PTMC patient.

Ito et al. [26] emphasized that tracheal invasion and/or recurrent laryngeal nerve involvement can be more precisely predicted using neck computed tomography. Thus, for tumors located adjacent to the trachea or tracheal groove, computed tomography can be performed to exclude unfavorable candidates for AS of PTMC.

Once a patient is identified as a candidate, informed consent should be obtained after a thorough explanation of the risks and benefits of AS over immediate surgery. In Korea, it has been very difficult to obtain informed consent for AS of PTMC, because the public believed that all cancer must be removed as early as possible. Recently, changes have taken place in the recognition of the risk of small thyroid cancer, because the Korean mass media has repeatedly emphasized the possibility of overdiagnosis of thyroid cancer in our country and that many cases of thyroid cancer are safe even without surgery. In any case, it is critical to obtain informed consent from patients to prevent future medico-legal issues, because AS of PTMC is still not an established option; it is currently under investigational use, and more data are needed to ensure the clinical safety of AS.

Follow-up methods and schedule

Meticulous repeated US is the method of choice for AS of PTMC. According to the protocol of Kuma hospital, initial follow-up US is performed 6 months after the initiation of AS, and every year thereafter [26]. The protocol of Memorial Sloan-Kettering Center in the USA uses a stricter schedule; they perform US every 6 months during the first 2 years of surveillance and every 1 or 2 years; thereafter, if there is no evidence of disease progression. Thyroid function tests are recommended every year, although there is no role for serum thyroglobulin measurements as part of AS of PTMC [25].

The definition of disease progression requiring delayed surgery is still debatable, but Kuma hospital used the following criteria: a tumor size increase of at least 3 mm, new neck node metastasis, and/or a tumor size increase to at least 12 mm [18]. Recently, Kwon et al. [20] added tumor volume increase by at least 50% as another criterion of progression. It is surprising that these PTMCs may grow at an earlier stage than expected, but another group also confirmed the same finding [27]. However, the clinical significance of those findings should be confirmed

Table 1. A Risk-Stratified Approach to Decision-Making for Probable or Proven Papillary Microcarcinoma

| Candidate for observation | Ideal | Appropriate | Inappropriate |
|------------------------------|---|--|---|
| Tumor characteristics | Solitary thyroid nodule Well-defined margins Surrounded by at least 2 mm of normal thyroid parenchyma No evidence of extrathyroidal extension Previous US documenting stability cN0 cM0 | Multifocal PTMCs Subcapsular locations not adjacent to RLN without evidence of extrathyroidal extension Ill-defined margins Background US findings that will make follow-up difficult FDG-avid PTMCs | Evidence of aggressive cytology on FNA Subcapsular locations adjacent to RLN Evidence of extrathyroidal extension Clinical evidence of invasion of RLN or trachea N1 disease at initial evaluation or identified during follow-up M1 disease Documented increase in size of 3 mm or more in a confirmed PTC |
| Patient characteristics | Older patients (at least 60 years) Willing to accept an active surveillance approach Understanding that surgical intervention may be necessary in the future Expected to be compliant with FU plans Supportive significant others Life-threatening comorbidities | Middle-aged patients (18–59 years) Strong family history of PTC Childbearing potential | Young patients (less than 18 years) Unlikely to be compliant with FU plans Not willing to accept an observation approach |
| Medical team characteristics | Experienced multidisciplinary management team High-quality neck US Prospective data collection Tracking/reminder program to ensure proper FU | Experienced endocrinologist or thyroid surgeon Neck US routinely available | Reliable neck US not available Little experience with thyroid cancer management |

Adapted from Brito et al., with permission from Mary Ann Liebert Inc. [25].

US, ultrasonography; PTMC, papillary thyroid microcarcinoma; RLN, recurrent laryngeal nerve; FDG, fluorodeoxyglucose; FNA, fine-needle aspiration; PTC, papillary thyroid carcinoma; FU, follow-up.

by a further prospective observational trial, since it is uncertain whether these small growths of PTMCs are in fact harmful.

Miscellaneous considerations

AS of PTMC is not a simple decision to avoid performing surgery; instead, it should be thought of as establishing a follow-up period to determine the best tailored option for each patient. The safety and cost-effectiveness of AS of PTMC has not been established. The characteristics of the patient and the medical team should be considered in order to obtain the best clinical outcome. The single most important thing to do to be sure that patients to receive regular follow-up to ensure the safety of AS. If patients are expected to be lost during follow-up, AS is not a good option for them. Haser et al. [28] suggested the following important points regarding AS of PTMC to provide continuity of care as patients move or change physicians/hospitals, to store US data in a detailed and uniform format to identify and report

changes readily, to educate clinicians and patients about entry/exclusion criteria and follow-up, to evaluate patients' QoL during AS, and to conduct research on outcomes for patients undergoing AS.

CAVEATS AND UNANSWERED QUESTIONS FOR ACTIVE SURVEILLANCE

To biopsy or not to biopsy

The 2015 ATA guidelines do not recommend cytological examination for any suspicious nodules smaller than 1.0 cm [21]. However, without confirmation by cytological and/or histological diagnosis, how can we be certain that a patient truly has cancer? Even for the nodules that are highly suspicious on US, nodules, the malignancy rate is around 80% [29]. Without confirmation, patients with only a suspicious nodule identified on US may undergo repeated US follow-up. Another consideration

is the occasional finding of small medullary thyroid carcinoma, which is indistinguishable from PTC by US [30,31] and rarely small anaplastic carcinoma, which can be cured by early surgery alone [32]. In this regard, we think that it may be appropriate for a fine needle aspiration biopsy to be performed on suspicious nodules larger than 5 mm in size that are under consideration for AS.

Lack of evidence

The meta-analysis performed by Alhashemi et al. [33] only included reports from two institutions in Japan, because those were the only reports available at that time. The prognosis of PTC is excellent, and it is necessary to have a long period of follow-up and a large number of patients to discriminate differences due to the treatment strategy. Nilubol and Kebebew [34] analyzed the Surveillance, Epidemiology, and End Results database records of 61,523 thyroid cancer patients between 1988 and 2007, of whom 1,753 died. Among them, 7.7% of patients with a thyroid cancer sized less than 1.0 cm and 12.8% of those with a thyroid cancer sized between 1.0 and 2.0 cm died; that is, 20.5% of mortality came from small thyroid cancers measuring 2.0 cm or smaller. These findings also provide for the idea that some small thyroid cancers require surgery to prevent possible mortality from cancer and that further large-scale, long-term, prospective studies are needed to prove the long term safety of AS.

Excluding inappropriate candidates

Many recent reports have focused on how to find ideal and inappropriate subgroups of patients for AS of PTMC.

Age might be the most important clinical factor predicting future progression during AS of PTMC. Ito et al. [18] reported that a size increase of at least 3 mm, neck node metastasis, and a size increase to at least 12 mm were found in 4%, 0.5%, and 2.5% of those aged older than 60 years old, respectively, in contrast to 12.1%, 16.1%, and 22.5%, respectively, among those aged less than 40 years old. These findings suggest that immediate surgery might be more favored for younger patients, because they have a higher chance of exhibiting disease progression. Our experiences of surgical interventions for PTMC also showed that young age (<40 years) is a predictor of large-volume (5 or more) central neck lymph node metastasis in clinical N0 PTMC [9].

Fukuoka et al. [35] reported that the US findings were different between PTMC patients with progression during AS and those without progression. They found that smaller increases in peritumoral vascularity and higher densities of tumor calcifica-

tion predicted no tumor progression. Hirokawa et al. [36] also found that a Ki-67 labeling index of 5% or more and the presence of psammoma bodies in the thyroid parenchyma were more prevalent in the tumor tissue of patients who showed progression during AS. Our surgical data showed that PTMC patients with microcalcifications had a higher risk of lateral neck lymph node metastasis [10]. Thus, further prospective trials should be performed to identify high-risk US features capable of excluding inappropriate candidates for AS.

Quality of life

Another important aspect of AS is QoL. In the field of prostate cancer, QoL is not significantly different between patients who receive AS and those who undergo immediate surgery. Carter et al. [37] performed a meta-analysis finding that there were no significant differences in anxiety, depression, or general QoL between immediate surgery and AS. Venderbos et al. [38] also reported that anxiety and fear diminished over time in patients under AS. The most frequent reason to withdraw from AS of PTMC has been found to be the patient's anxiety regarding progression [16-18,20]. Thus, QoL is a very important issue for AS of PTMC.

Surgical complications have a major impact on QoL. Oda et al. [39] compared the complications between 1,179 patients under AS of PTMC and 94 patients who received immediate surgery. They concluded that complications, such as temporary vocal cord paralysis, temporary/permanent hypoparathyroidism, skin wounds, and/or postsurgical hematoma were more prevalent among those who underwent immediate surgery. Some surgeons and physicians argued that their conclusion was misleading. Oda et al. [39] used all patients who received AS of PTMC as a denominator to calculate the complication rate. Instead, only patients who received delayed surgery during AS of PTMC should be considered as the denominator, and when their data was reanalyzed, the complication rate was higher among patients who received delayed surgery than among those who underwent immediate surgery. Most cases of PTMC have a very slight chance of gross ETE and/or lateral neck node metastasis, and can be easily removed by hemithyroidectomy alone. However, if lateral neck node metastasis develops during AS, those patients should receive more extensive surgery, such as total thyroidectomy and modified radical neck dissection. Thus, delayed surgery during AS of PTMC might have a higher chance of involving extended surgery than immediate surgery; thereby, resulting in a decrease in QoL due to the increase in surgical complications.

Cost-effectiveness analysis

Lang and Wong [40], from Hong-Kong, used a standard model of 40-year-old women to analyze the cost-effectiveness of AS of PTMC and found that AS of PTMC was more cost-effective during the first 16 years of follow-up than immediate surgery. The cost-effectiveness was lower in the AS group after 17 years of follow-up than in the immediate surgery group. However, they also found that QoL was still high enough to compensate for the decrease in the cost-effectiveness of AS of PTMC. Oda et al. [41], from Japan, used their cohort to analyze cost-effectiveness and found that immediate surgery cost 4.1 times more than AS during the first 10 years of follow-up.

Venkatesh et al. [42], from the USA, introduced two concepts for the cost-effectiveness analysis of AS of PTMC. The first is that patients who choose AS might have more anxiety. The second is that patients can be treated by hemithyroidectomy as an option for immediate surgery, which is an operation with lower chances of surgical complications than near or total thyroidectomy. They demonstrated that the cost-effectiveness of hemithyroidectomy of PTMC was dependent largely on the health utility associated with AS of individual patients, as well as the remaining life expectancy of the patient after diagnosis. They concluded that PTMC patients with even a modest decrement in QoL may benefit from early hemithyroidectomy as the more cost-effective strategy.

The cost of surgery is much lower in Korea than in the USA. Thus, immediate hemithyroidectomy might be more cost-effective in Korea than in the USA. For this reason, conclusions from cost-effectiveness analysis from other countries should only be applied to one's own clinical practice after a consideration of country-specific medical costs.

FUTURE PERSPECTIVES

It is rare, but a very small portion of PTMCs grow and metastasize to a distant site. If we can find a biomarker that would predict the growth and/or metastasis of PTMC, it would become possible to identify the subset of patients with a high probability of disease progression, and their cancer could be removed at an early stage by immediate hemithyroidectomy. The other subset of PTMC patients, with a lower probability of progression, could then be safely followed by AS.

BRAF and/or TERT are well known molecular prognostic markers for thyroid cancer, but their role in PTMC patients has not been established yet [43]. Thyroid-stimulating hormone was not found to be a prognostic marker for PTMC progression [44].

Tumor calcification patterns varied across age groups [35], and showed an association with lateral neck metastasis [10], but no confirmatory data regarding their relationship with the disease progression of PTMC have been found. Thus, future research should focus on finding novel prognostic markers of PTMC progression.

CONCLUSIONS

For appropriately selected PTMC patients, AS can be a good alternative to immediate surgery and surgery can be safely delayed until progression occurs. The selection criteria must consider many aspects, including characteristics of the tumor, the patient, and the medical team. If possible, AS of PTMC should be evaluated in a prospective clinical trial to ensure its long-term safety and to find prognostic markers for the progression of PTMC.

CONFLICTS OF INTEREST

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

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