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Active Surveillance of Papillary Thyroid Cancer: Past, Present, and Future

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Active surveillance (AS) of papillary thyroid microcarcinoma was first suggested by Dr. Akira Miyauchi at Kuma Hospital in 1993. Based on several subsequent evidences, AS was approved by the American Thyroid Association in 2015. AS is no longer an experimental treatment but has become an acceptable standard of care for patients with low-risk thyroid cancers. No molecular markers, such as BRAF mutations, have been identified to predict the prognosis of papillary thyroid cancer. However, future molecular studies may reveal the relationship between genetic mutations and thyroid cancer prognosis. AS involves closely monitoring thyroid cancer over time, instead of immediately treating it with surgery. Patients and medical doctors should consider these two options: observation or surgery. **(Ewha Med J 2021;44(2):37-40)**

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Introduction

The incidence of thyroid cancer has tripled or increased even more in many developed countries over the past 30 years, and this has been attributed, at least in part, to overdiagnosis [1]. This is because most papillary thyroid cancers (PTCs) diagnosed incidentally by imaging are papillary thyroid microcarcinoma (PTMC), which is defined as a tumor with a diameter of 1 cm or less [2,3]. The most common presentation of incidental thyroid cancer is PTMC that measures less than 2 mm in 60% of patients, in patients older than 45 years [4,5]. Mortality from PTC remains low and stable [6].

Active surveillance (AS) of low-risk PTMC was first suggested by Dr. Akira Miyauchi at Kuma Hospital in 1993 [7]. Patients who chose AS were observed with ultrasound examination once a year, unless signs of progression were apparent, such as size enlargement of ≥3 mm compared to the size at AS initiation and/or novel appearance of lymph node metastasis on imaging studies [8]. Ito et al. [8] compared the outcomes of 340 patients with PTMC who underwent observation and 1,055 patients who underwent immediate surgery without observation. The proportion of patients who's PTMC had grown by 3 mm or more was 6.4% and 15.9% at the 5 and 10-year follow-up, respectively. Novel nodal metastasis was detected in 1.4% and 3.4% of patients at 5 and 10 years, respectively. After observation, 109 of the 340 patients underwent surgical treatment for various reasons, none of whom suffered showed cancer recurrence [8]. Ito et al. [9] also showed the feasibility of AS for low-risk PTC as a treatment method to avoid unnecessary surgery.

Based on these promising results, AS was approved by the American Thyroid Association (ATA) in 2015 [10]. Further-

more, some researchers have tried to apply AS even in patients with PTC over 1 cm. Here, we review the current treatment trends for PTC with AS.

Definition of Low-risk PTC

Low-risk PTCs are defined as small, intrathyroidal lesions without gross extra-thyroidal extension (ETE), clinically apparent lymph node metastasis, or distant metastasis. They do not invade surrounding structures such as the recurrent laryngeal nerve, esophagus, or trachea. Additionally, most low-risk PTCs remain indolent over time without any overt disease [11]. In the present review, the definition of low-risk PTMC was PTC measuring ≤1 cm with no high-risk features unsuitable for AS, that is: (1) the presence of cervical lymph node metastasis or distant metastasis, (2) fine-needle aspiration results suggesting high-grade malignancy, and (3) tumors that may possibly extend the trachea or recurrent laryngeal nerve.

Current Treatment Policy of PTC

Certain trends in treatment and outcomes over the last few decades favor conservative therapeutic approaches for PTC [11]. The incidence of thyroid cancer has nearly tripled since 1975, increasing from 4.9 to 14.3 per 100,000 individuals in the United States. However, the mortality rate from thyroid cancer remained stable between 1975 and 2009 (approximately 0.5 deaths per 100,000 individuals) [12]. These results can be inferred that aggressive treatment does not increase the survival rate of patients with PTMC. According to the 2015 ATA management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer, if surgery is chosen for patients with PTMC without ETE and cervical lymph node metastasis, the initial operation should be a thyroid lobectomy if there are not clear indications of total thyroidectomy. Thyroid lobectomy alone is sufficient treatment for small, solitary, and subcapsular carcinomas in the absence of prior head and neck radiation therapy, familial thyroid cancer, or clinically detectable cervical lymph node metastasis [10].

History of AS

AS for PTMC was first suggested in 1993 by Ito et al. [7], whose proposal became the basis for performing AS rather than immediate surgery at Kuma Hospital, Kobe, Japan. They published the results of a large prospective study of patients who underwent AS over 22 years [9,13]. In their trial, which included 2,153 patients, 1,235 patients underwent AS instead of immediate surgery. In the AS group, 8% and 3.8% of patients showed tumor enlargement by 3 mm or more and the novel appearance of lymph node metastasis at 10 years, respectively. However, the incidences of unfavorable events, such as temporary vocal cord paralysis (VCP) and temporary and permanent hypoparathyroidism, were significantly higher in the immediate surgery group than in the AS group (4.1% vs. 0.6%, $P<0.0001$; 16.7% vs. 2.8%, $P<0.0001$; and 1.6% vs. 0.08%, $P<0.0001$, respectively). No patients in either group died of the disease.

Another prospective trial performed AS of 230 patients with PTMC [14]. No patients developed extrathyroidal invasion or distant metastasis. Three patients (1%) who developed apparent lymph node metastasis and nine patients (4%) in whom the tumor increased in size eventually underwent surgery after 1 to 12 years of follow-up. No recurrences were identified postoperatively. Retrospective study from the Republic of Korea reported experience with AS of 192 patients with PTMC [15]. In that study, 24 patients (13%) underwent delayed thyroid surgery at a median of 31.2 months and seven (29%) had cervical lymph node metastasis on pathologic examination. A cohort study of 291 patients undergoing AS was recently conducted at the Memorial Sloan Kettering Cancer Center in New York, the United States. Tuttle et al. [16] analyzed the findings who underwent AS instead of immediate surgery for PTC or suspicious PTC (Bethesda category V or VI) based on fine-needle aspiration and ultrasonography findings, with a tumor size of up to 1.5 cm. In that study, the rates of tumor growth during AS were low.

Establishment of AS

The results of previous studies demonstrated the usefulness of AS. The ATA guidelines were updated in 2015 to incorporate AS as an option within the management paradigm of PTC [10]. Therefore, AS is no longer an experimental treatment and has become an acceptable standard of care for patients with low-risk thyroid cancers. Based on the update to the ATA guidelines in 2015, Brito et al. [17] suggested categories for risk

stratification of patients with PTC when considering. These categories include the characteristics of the tumor, the patient, and the medical staff. The patient is classified as "ideal", "appropriate", or "inappropriate". Ideal patients are older patients with a solitary thyroid nodule within the thyroid gland, and no evidence of nodal or distant metastasis. Appropriate patients are younger patients with multifocal PTMC and no evidence of ETE. Inappropriate patients include those who are young (<18 years), with tumors in a subcapsular location near the recurrent laryngeal nerve, evidence of ETE, and aggressive features in cytological studies.

At the Memorial Sloan Kettering Cancer Center, researchers enrolled patients with Bethesda V or VI tumors on an AS approach who underwent baseline ultrasonography to measure tumor volume [16]. Currently, operation is recommended when the tumor exhibits an increase in size as defined by (1) a 3-mm growth in axial dimension or (2) a >50% increase in tumor volume with a short-term or in cancers located immediately near to the thyroid capsule [11]. No molecular markers, such as BRAF mutations, have been identified to predict the prognosis of PTC. Tuttle et al. [16] insisted that there were no clear molecular differences between indolent PTCs and those that exhibit lateral neck lymph nodal metastasis. However, future molecular studies may reveal the relationship between genetic mutations and thyroid cancer prognosis.

Contribution of AS to Surgeon's Decision to Perform Surgery

AS involves closely monitoring the thyroid cancer over time, instead of immediately treating it with surgery. Thyroid surgery is not without risk even when conducted by the most experienced surgeons. These risks include temporary or permanent hypoparathyroidism, temporary or permanent VCP, and the need for lifetime thyroid hormone replacement. As mentioned earlier, Miyauchi [13] reported significantly higher rates of complications in patients with immediate surgery, compared with those with AS. Moreover, Griffin et al. [18] retrospectively reported the proportion of thyroid cancer patients who met the criteria for AS and the number of surgeries and complications that could have been avoided. In that study, three of 56 patients who met the criteria for AS suffered permanent complications from surgery, including VCP, hypoparathyroidism, and a chipped tooth during intubation. Although the complication rates were low in both studies, complications could have been avoided because some patients did not require surgery (in the short-term and potentially long-term). The rate of complications was unacceptably high because they were all avoidable.

Another consideration for AS is the risk of tumor progression including higher risk of local recurrence. Oda et al. [19] studied 2,153 patients with low-risk PTMC who underwent immediate surgery or AS. In that study, five (0.51%) of the 974 patients developed local recurrence, requiring reoperation who underwent immediate surgery. In the AS group, 94 (8.0%) of the 1,179 patients who chose AS had a conversion surgery. After the conversion surgery, one patient (0.08%) required reoperation for local recurrence. This study indicated that the risk of developing nodular metastasis for AS might be minimal.

Davies et al. [20] evaluated the experience of patients undergoing AS. They reported that cancer concerns were common among thyroid cancer patients who underwent AS, which is like the concerns of patients who underwent immediate surgery. The level of cancer worries reported by AS patients declined over time, and patients expressed satisfaction with their disease management decisions. These findings suggest the likelihood of cancer worries should not be considered as hindering successful AS in PTC.

Future research is needed to identify clinical, radiologic, and molecular biomarkers for better risk stratification to help determine suitability for AS. More prospective data are necessary to better define the optimal AS protocols regarding scans, clinical examinations, and surgical intervention if necessary.

Conclusion

AS is a safe alternative to immediate surgery for patients with low-risk PTC. Patients with low-risk PTC should consult a surgeon to discuss AS options. Further prospective studies may support AS and broaden the application range of AS.

References

1. Roman BR, Morris LG, Davies L. The thyroid cancer epidemic, 2017 perspective. *Curr Opin Endocriol Diabetes Obes* 2017;24:332-336.
2. Hirokawa M, Kudo T, Ota H, Suzuki A, Miyauchi A. Pathological

chracteristics of low-risk papillary thyroid microcarcinoma with progression during active surveillance. *Endocr J* 2016;63:805-810.
3. Ito Y, Miyauchi A, Oda H. Low-risk papillary microcarcinoma of the thyeoid: A review of active surveillance trials. *Eur J Surg Oncol* 2018;44:307-315.
4. Hughes DT, Haymart MR, Miller BS, Gauger PG, Doherty GM. The most commonly occurring papillary thyroid cancer in the United States is now a microcarcinoma in a patient older than 45 years. *Thyroid* 2011;21:231-236.
5. Altekruse S, Das A, Cho H, Petkov V, Yu M. Do US thyroid cancer indidence rates increase with socioeconomic status among people with health insurance? An observational study using SEER population-based data. *BMJ Open* 2015;5:e009843.
6. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA* 2006;295:2164-2167.
7. Ito Y, Miyauchi A, Kudo T, Oda H, Yamamoto M, Sasai H, et al. Trends in the implementation of active surveillance for low-risk papillary thyroid microcarcinomas at Kuma Hospital: Gradual increase and heterogenity in the acceptance of this new management option. *Thyroid* 2018;28:488-495.
8. Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg* 2010;34:28-35.
9. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of pipillary microcarcinoma of the thyroid under observation. *Thyroid* 2014;24:27-34.
10. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nififorov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guideleines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016;26:1-133.
11. Lohia S, Hanson M, Tuttle RM, Morris LGT. Active surveillance for patients with very low-risk thyroid cancer. *Laryngoscope Investig Otolaryngol* 2020;5:175-182.
12. Davies L, Welch HG. Current thyroid cancer trends in the United States. *JAMA Otolaryngol Head Neck Surg* 2014;140:317-322.
13. Miyauch A. Clinical trials of active surveillance of papillary microcarcinoma of the thyroid. *World J Surg* 2016;40:516-522.
14. Sugitani I, Toda K, Yamada K, Tamamoto N, Ikenaga M, Fujimoto Y. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. *World J Surg* 2010;34:1222-1231.
15. Kwon H, Oh HS, Kim M, Park S, Jeon MJ, Kim WG, et al. Active surveillance for patients with papillary thyroid microcarcinoma: A single center's experience in Korea. *J Clin Endocrinol Metab* 2017;102:1917-1925.
16. Tuttle RM, Fagin JA, Minkowitz G, Wong RJ, Roman B, Patel S, et al. Natural history and tumor volume kinetics of papillary thyroid cancers during active surveillance. *JAMA Otolaryngol Head Neck Surg* 2017;143:1015-1020.
17. Brito JP, Ito Y, Miyauchi A, Tuttle RM. A clinical framework to gacilitate risk stratification when considering an active surveillance alternative to immediate biopsy and surgery in papillary microcarcinoma. *Thyroid* 2016;26:144-149.
18. Griffin A, Brito JP, Bahl M, Hoang JK. Applying criteria of active surveillance to low-risk papillary thyroid cancer over a decade: How many surgeries and complications can be avoided? *Thyroid* 2017;27:518-523.
19. Oda H, Miyauchi A, Ito Y, Sasai H, Masuoka H, Yabuta T, et al. Comparison of the costs of active surveillance and immediate surgery in the management of low-risk papillary microcarcinoma of the thyroid. *Endocr J* 2017;64:59-64.
20. Davies L, Roman BR, Fukushima M, Ito Y, Miyauchi A. Patient experience of thyroid cancer active surveillance in Japan. *JAMA Otolaryngol Head Neck Surg* 2019;145:363-370.