Editorial

Active surveillance or surgery for papillary thyroid microcarcinoma: a current dilemma

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Thyroid cancer has been increasing rapidly worldwide with incidence that has doubled in the last two decades. Papillary carcinomas account approximately 85% of thyroid tumors (1). Despite this increase, the thyroid cancer-mortality remained stable, due to the improvement of imaging techniques, to the increased use of ultrasound guided fine-needle biopsy which facilitated the detection and diagnosis of very small tumors and to widespread thyroid-cancer screening (2). Papillary thyroid carcinomas with a maximum diameter of 10 mm or less are called microcarcinomas (PTMC), comprising nearly 50% of the newly diagnosed cases. The incidence of these small tumors is increasing globally, making its management an important clinical issue (1,2).

Surgery is the standard of care current treatment for thyroid cancer and prognosis is generally favorable (3). In US more than 90% of thyroid cancer patients undergo surgery as the primary oncologic treatment and 85% of these patients undergo total thyroidectomy (1). Papillary microcarcinomas have low disease-specific mortality, low recurrence rate, and in view of potential complications after surgery, their management with immediate surgery is being reconsidered, in the last years (4-6).

However, for selected PTMC patients there has been an increasing interest in active surveillance or delaying surgery in favor of observation with serial ultrasonography. Trials from Japan, of active surveillance of asymptomatic PTMC, have revealed that nonsurgical management of low-risk microcarcinomas showed excellent outcome, is a safe approach and a cost-effective long-term management option than immediate surgery with postsurgical follow-up. Additionally, during active surveillance program those patients who showed signs of disease progression, such as tumor enlargement and lymph node metastasis, underwent surgery without increased risk of disease recurrence (7-9).

In 1993, Ito, Miyauchi and their team proposed a clinical trial comparing surgery and observation for low-risk PTMC, at a doctors' meeting at Kuma Hospital and the trial started in the same year. Patients choose immediate surgery or observation after thorough discussion with surgeons about pros and cons of the two proposed management options. Their paper published in 2010 shares their 22-year experience with the active surveillance program, comprising more than 2,000 patients with low-risk PTMC and compares the outcomes of immediate surgery with that of active observation (7).

PTMCs were divided in two groups based on the ultrasonographic and cytological findings. High-risk PTMC was defined as a microcarcinoma having one or more of the following characteristics: lymph node or distant metastasis, high-grade cytology, extra-thyroid extension or significant growth during a previous observation. For patients with high-risk microcarcinomas the author recommended surgery.

Low-risk PTMC was defined a microcarcinoma having none of the afore-mentioned features. For patients with low-risk PTMC the author proposed two options, immediate surgery or observation. The patients who chose observation were followed with ultrasound examination 6 months later and once a year thereafter. In those cases where tumor has grown by 3 mm or more, or a novel lymph node metastasis appeared, surgery was recommended.

The outcome of the two groups of patients were similarly

excellent. In the active surveillance group of 1,235 patients, 8% of patients showed tumor enlargement by 3 mm or more at 10 years of observation, and 3.8% of the patients showed novel appearance of lymph node metastasis at 10 years of follow-up. During this period, younger patients (<40 years) observed showed a significant higher incidence of tumor size enlargement (P=0.0014), lymph nodes metastases appearance (P<0.0001) and progression to clinical disease when compared to the older one (>60 years) (P<0.0001). PTMCs in patients 60 years or older rarely increased in size neither showed nodal metastasis. In the age group of 40–59 years, PTMCs were in between.

Multivariate analysis for size enlargement of microcarcinoma and novel appearance of lymph node metastasis revealed that age younger than 40 years was the only significant factor, and that family history and multiple foci were not significant factors.

From the oncological outcome, active surveillance of low-risk PTMC patients showed that those aged 40 and older are better candidates for observation than young patients. Although the progression rates are slightly higher in young patients, it was suggested that they also can be candidates for observation, since the final outcome was excellent. Based on the afore-mentioned conclusions, active surveillance is now recommended as the best choice for patients with low-risk PMC at Kuma Hospital.

Moreover, based on Dr. Miyauchi results, Japanese Thyroid Tumor Management Guidelines 2010 published by the Japanese Association of Endocrine Surgeons and the Japanese Society of Thyroid Surgery accepted "observation for low-risk PTMC" as a management option (10). This became the first-published guidelines that accepted observation for low-risk PTMCs.

Active surveillance has also been advised by the most recent American Thyroid Association (ATA) 2015 Guidelines as a safe possible alternative to immediate surgery in low-risk PTMC patients (3).

A recent cohort study in US by Tuttle *et al.* reported that the rates of tumor growth during active surveillance with papillary thyroid carcinomas measuring 1.5 cm or less, were low. The authors also recommended serial measurement of tumor volume to facilitate early identification of tumors that will continue to grow and would require further intervention. Although it is a well-designed study, the number of patients was relatively small and the follow-up period was only 25 months (11).

Although the oncological outcomes of the immediate surgery and active surveillance groups were similarly excellent, the incidence of postoperative complications were higher in the immediate surgery group according to Kuma's hospital results. Temporary vocal cord paralysis (VCP) and temporary and permanent hypoparathyroidism were significantly higher in the immediate surgery group than in the observation 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). Permanent VCP occurred in two patients of the surgery group. Active surveillance in appropriately selected patients, certainly eliminates the risk of the tragedy of bilateral VCP.

Patients with incidentally found papillary microcarcinoma (discovered during surgery for benign thyroid disease or during histopathology) had a lower (5.2%) risk for tumor recurrence than the patients with nonincidental disease. Whether the tumor was found incidentally or not was a more important predictor of outcome than was the primary tumor size. Some studies have shown that a significant proportion of nonincidental papillary microcarcinomas can have aggressive features and disease recurrence similar to conventional papillary thyroid carcinomas. Arora *et al.* reported that there was no statistically significant difference between nonincidental PTMC and conventional PTC (>1 cm) with regards to recurrence incidence (12). In our retrospective study including 539 thyroid PTMC patients, Karatzas *et al.* found that incidental microcarcinomas had significantly fewer aggressive tumor features and an indolent clinical behavior. On the contrary, we found that the incidence of lymph node metastasis at diagnosis and disease recurrence rate between non-incidental PTMCs and PTCs showed no significant differences. Based on these findings, we suggested that nonincidental PTMC patients and conventional PTCs should be treated likewise (13).

Another study by Karatzas *et al.* including 319 patients with PTMC, showed that tumor size ≥5 mm was an independent risk factor for bilaterality (14). Other authors also reported that PTMCs with a primary tumor >5 or 7 mm were independent predictive factors for bilateral tumor site and occult central lymph node metastasis, so total thyroidectomy should be considered for these patients (15,16).

Pellegriti *et al.* argued that total thyroidectomy is the treatment of choice for papillary microcarcinoma, and this policy finds in agreement the majority of surgeons (17). It is questionable that lobectomy preserves thyroid function, since L-thyroxine therapy is required in 50% of patients immediately after lobectomy and is ultimately required in the majority of surgeries. Total thyroidectomy

compared to lobectomy is more likely to result in hypoparathyroidism and recurrent laryngeal nerve injury. In hands of experienced thyroid surgeons, postoperative hypocalcemia, which is usually transient, occurs in only 6% of patients and recurrent laryngeal injury in about 1%. The high incidence of multifocality and bilaterality in series with PTMC patients suggests that, even when papillary carcinomas are small, residual tumor may frequently be left behind in the contralateral lobe if a lobectomy is performed (12,13,16). Pellegriti *et al.* also reported that in patients with nonincidental microcarcinomas, a more extensive surgery with central lymph node dissection at the time of thyroidectomy should be performed routinely (17). Also, Wada *et al.* followed the same surgical approach in a group of 259 patients with PTMC, and he concluded that patients with palpable lymph nodes at presentation should be treated with total thyroidectomy and therapeutic lymph node dissection, whereas no prophylactic dissection was essential in patients without palpable lymphadenopathy (18). In our series, we suggested total thyroidectomy and prophylactic central neck dissection should be considered for all patients with PTMC >5 mm (13).

Taking into consideration all the afore-mentioned, we believe that carefully selected low-risk patients along with longstanding follow-up should be the key factors for active surveillance and should be pursued following a well-designed prospective clinical trial. With proper patient selection, organization and support, active surveillance has the potential to be a strategy for the management of low-risk patients with papillary microcarcinomas. Moreover, before we consider patients as candidates for longstanding observation, we need to assess carefully their psychological status, quality of life and medical co-morbidity. Obviously, because of different disease approach mentality between populations, patients may experience anxiety from living with cancer. However, for the implementation of active surveillance in a country, specific measures should be considered, such as, the involved clinicians should develop systems to standardize thyroid ultrasound tests and record keeping, so that PTMCs can be tracked consistently over time. Also, the clinicians must be familiar with active surveillance protocols and be capable to evaluate the factors which would make a patient eligible or ineligible for continued observation. Patients eligible to observation should be able to make regular appointments and to comply with lifelong follow-up. All patients should be screened for anxiety and tolerance for uncertainty before active surveillance is recommended (14).

Various staging systems have been designed to try to identify patients with papillary carcinoma who are most likely to have poor outcomes. Tumor size has traditionally been viewed as an important prognostic factor and papillary thyroid carcinomas less than 1 cm in size are considered to be associated with lower risk. The finding that aggressiveness of PTMCs increased with increasing size suggests that in a larger case series, or in a cohort study with longer follow-up, a gradation in risk for tumor recurrence based on tumor size has been observed.

In a study that followed 162 PTMC patients who chose observation, 70% of tumors were stable over a mean follow-up of 3.8 years. It is worth noting that of a total of 732 patients included in this study, 570 patients preferred surgery to observation, and another 56 who initially elected observation, ultimately underwent surgery (19).

A recent study in Korea showed that some PTMCs grow significantly after a relatively short period of active surveillance. The authors also showed that the change in tumor volume was more sensitive in detecting tumor progression than the change in the maximal tumor diameter (20).

Recently, the ATA introduced guidelines for active surveillance management as an alternative to immediate thyroid surgery for patients with very low-risk tumors, patients with high surgical risk due to co-morbidity, and those who are expected to have a relatively short life expectancy. Referring to tumor growth, ATA guidelines define tumor enlargement as a 20% increase in at least 2 nodule dimensions with a minimal increase of 2 mm or more than a 50% change in volume (3). Previous studies of active surveillance in PTMC patients defined tumor enlargement as an increase in tumor diameter of 3 mm or more, compared with that of initial diagnosis (8). Kwon *et al.* (20) found that changes of tumor volume detect more sensitively tumor progression than changes in the maximal tumor diameter. Currently, there is no consensus on what is considered a clinically significant increase in tumor size in patients under active surveillance. Future studies should focus on the characteristics of serial neck ultrasonographic imaging that would predict a clinically significant increase in tumor size and possible cervical lymph node metastasis.

A study on active surveillance reported that the proportion of patients with PTMC progression was lower in the elderly compared to young patients (21). Another study showed that PTMCs in younger patients tended to increase in size more than those in the elderly (8). From all these studies appears that the most common reason for choosing thyroid surgery was not an increase in tumor

size, but the patient's anxiety. Patients with PTMC under active surveillance felt anxiety during observation, even though their tumor remained stable following US neck examinations. Anxiety also may have an effect on these patients quality of life (20,22).

In conclusion, papillary thyroid microcarcinoma is being diagnosed with increasing frequency. Recent studies have shown that the oncological outcome of immediate surgery and active surveillance in microcarcinoma patients were equally excellent. In many countries, active surveillance is offered optionally to patients for their low-risk PTMC management. It is of paramount importance that the two management options should be discussed with the patient, as both benefits and risks should be weighed before a decision is made. An active surveillance program must focus on proper patient selection based on specific features, such as appropriate ongoing monitoring, psychological evaluation and support, as well as prompt decision to stop surveillance and proceed to surgery for those showing progression of tumor during the monitoring period. We think that, a realistic patient selection program with appropriate surveillance strategy adopted by the health system of a country, are of paramount importance for the management of low-risk PTMC patients.

Finally, further clinical trials would study the safety of active surveillance as strategy for the management of low-risk patients in comparison with immediate surgery risks and benefits, in integrative programs, providing patients quality of life and long-term outcome.

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Footnote

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References

1. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 2014;140:317-22.
2. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic": screening and overdiagnosis. N Engl J Med 2014;371:1765-7.
3. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1-133.
4. Ito Y, Higashiyama T, Takamura Y, et al. Prognosis of patients with benign thyroid diseases accompanied by incidental papillary carcinoma undetectable on preoperative imaging tests. World J Surg 2007;31:1672-6.
5. Hotomi M, Sugitani I, Toda K, et al. A novel definition of extrathyroidal invasion for patients with papillary thyroid carcinoma for predicting prognosis. World J Surg 2012;36:1231-40.
6. Ito Y, Fukushima M, Kihara M, et al. Investigation of the prognosis of patients with papillary thyroid carcinoma by tumor size. Endocr J 2012;59:457-64.
7. Ito Y, Miyauchi A, Inoue H, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. World J Surg 2010;34:28-35.
8. Sugitani I, Toda K, Yamada K, et al. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. World J Surg 2010;34:1222-31.
9. Lang BH, Wong CK. A cost-effectiveness comparison between early surgery and non-surgical approach for incidental papillary thyroid microcarcinoma. Eur J

Endocrinol 2015;173:367-75.
10. Yoshida A, Okamoto T. Japanese management guidelines for thyroid tumors 2010. Edited by the Japanese Association of Endocrine Surgeons and the Japanese Society of Thyroid Surgery. Kanehara Shuppan, Tokyo.
11. Tuttle RM, Fagin JA, Minkowitz G, et al. Natural history and tumor volume kinetics of papillary thyroid cancers during active surveillance. JAMA Otolaryngol Head Neck Surg 2017;143:1015-20.
12. Arora N, Turberndian HK, Kato MA, et al. Papillary thyroid carcinoma and microcarcinoma: is there a need to distinguish the two? Thyroid 2009;19:473-7.
13. Karatzas T, Vasileiadis, Kapetanakis S, et al. Risk factors contributing to the difference in prognosis for papillary versus micropapillary thyroid carcinoma. Am J Surg 2013;206:586-93.
14. Karatzas T, Vasileiadis I, Charitoudis G, et al. Bilateral versus unilateral papillary thyroid microcarcinoma: predictive factors and associated histopathological findings following total thyroidectomy. Hormones 2013;12:529-36.
15. Zhou YL, Gao EL, Zhang W, et al. Factors predictive of papillary thyroid micro-carcinoma with bilateral involvement and central lymph node metastasis: a retrospective study. World J Surg Oncol 2012;10:67.
16. Miccoli P, Minuto MN, Ugolini C, et al. Intrathyroidal differentiated thyroid carcinoma: tumor size-based surgical concepts. World J Surg 2007;31:888-94.
17. Pellegriti G, Scollo C, Lumera G, et al. Clinical behavior and outcome of papillary thyroid cancers smaller than 1.5 cm in diameter: study of 299 cases. J Clin Endocrinol Metab 2004;89:3713-20.
18. Wada N, Duh QY, Sugino K, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. Ann Surg 2003;237:399-407.
19. Ito Y, Uruno T, Nakano K, et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. Thyroid 2003;13:381-7.
20. Kwon H, Oh HS, Kim M, et al. Active surveillance for patients with papillary thyroid microcarcinoma: A single center's experience in Korea. J Clin Endocrinol Metab 2017;102:1917-25.
21. Ito Y, Miyauchi A, Kihara M, et al. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid 2014;24:27-34.
22. Haser GC, Tuttle RM, Su HK, et al. Active surveillance for papillary thyroid microcarcinoma: New challenges and opportunities for the health care system. Endocr Pract 2016;22:602-11.

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