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Insights into the Management of Papillary Microcarcinoma of the Thyroid

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Background: Rapid increases in the incidence of thyroid carcinoma with stable mortality rates from thyroid carcinoma have been reported from many countries, and these increases are thought to be due mostly to the increased detection of small papillary thyroid carcinomas (PTCs), including papillary microcarcinomas (PMCs; i.e., PTCs ≤10 mm). Some researchers have suggested that small PTCs have been overdiagnosed and overtreated. In Japan, the active surveillance of patients with low-risk PMCs was initiated by Kuma Hospital (1993) and Tokyo's Cancer Institute Hospital (1995) based on the extremely higher incidences of both latent thyroid carcinomas in autopsy studies and small PTCs detected in mass screening studies using ultrasound examinations compared to the prevalence of clinical thyroid carcinomas.
Methods: The above two institutions' data are summarized regarding the active surveillance of low-risk PMCs, and future prospects for their management are discussed.
Results: At 10-year observations in the Kuma Hospital series of 1235 patients, only 8% and 3.8% of the PMC patients showed size enlargement by ≥3 mm and the novel appearance of node metastasis, respectively. In contrast to clinical PTC, PMCs are most unlikely to grow in older patients (≥60 years). In the Kuma Hospital series, the 974 patients who underwent immediate surgery had significantly higher incidences of unfavorable events than the 1179 patients who chose active surveillance. The total cost of immediate surgery, including the costs for salvage surgery and postoperative care for 10 years, was 4.1 times the total cost of 10-year management by active surveillance. Only 8% of the 51 PMC patients showed tumor enlargement during pregnancy, and the rescue surgeries after delivery were successful. In the Cancer Institute Hospital series of 230 patients with 300 lesions, only 7% and 1% of the patients showed size enlargement and novel node metastasis, respectively, and that institution's analysis also revealed that macroscopic or rim calcification and poor vascularity were correlated with non-progressing disease. In both series, none of the patients who underwent rescue surgery after progression signs were detected showed significant recurrence or died of PTC.
Conclusion: Active surveillance of low-risk PMC can be the first-line management. Interestingly, older patients with low-risk PMCs are the best candidates for active surveillance.

Keywords: papillary microcarcinoma, thyroid, active surveillance, risk classification, surgery, unfavorable events, medical cost

Background

Rapid increases in thyroid cancer incidence have been reported in many countries, including the United States, Korea, and Japan (1–4). These increases are due mostly to an increase in the incidence of small papillary thyroid carcinomas (PTCs), whereas the incidences of large PTCs and malignancies of other histological types have remained stable (3). The mortality rate from thyroid cancer has remained fairly stable (1–3). Several research groups have therefore suggested that small PTCs have been overdiagnosed and overtreated (1–3). Papillary thyroid carcinomas that are ≤10 cm, which are known as papillary microcarcinomas (PMCs), were demonstrated to account for ≥50% of recent thyroid cancer series (1–3). A major clinical issue has arisen: how best to manage patients with PMCs.

The definition of PMC is a PTC measuring ≤10 mm, regardless of the presence/absence of high-risk features such as vocal cord paralysis, clinically apparent lymph node metastasis, and distant metastasis. The term ''PMC'' thus covers

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a broad range of biological characteristics. Sugitani and Fujimoto reported a striking difference in the prognosis after surgery between patients with symptomatic PMCs and those with asymptomatic PMCs. In that study, the patients with symptomatic PMC with clinically apparent lymph node metastasis and/or vocal cord paralysis group showed a 30% recurrence rate and a 74.1% rate of cause-specific survival at 10 years, whereas the asymptomatic PMCs without those features had corresponding rates of 3% and 100%, respectively (5).

As reported in 2010, patients with PMCs without clinical node or distant metastasis also had excellent prognoses after surgery without postoperative radioactive iodine treatment (6). PMCs with aggressive features should be treated appropriately depending on the extent of disease progression. However, the vast majority of PMCs are asymptomatic tumors lacking aggressive features, detected incidentally by imaging studies or thyroid screening studies. The optimal management of these incidentally detected asymptomatic PMCs is a major clinical issue, and it is the focus of this review.

In autopsy studies of individuals who died of non-thyroid diseases, latent 3–10 mm PMCs were detected in 0.5–5.2% of subjects (7). With an ultrasound examination and ultrasound-guided fine-needle aspiration biopsy (FNAB), PMCs of this size can be easily detected and diagnosed. Takebe *et al.* conducted a thyroid cancer mass screening using ultrasound and FNAB on 1048 women at Kagawa Cancer Screening Center's breast cancer screening, and thyroid carcinoma was detected in 3.5% of the otherwise healthy Japanese women aged ≥30 years (8). Of these thyroid carcinomas, 85% were ≤15 mm. This incidence was curiously almost the same as those of latent thyroid cancer in autopsy studies and >1000 times the prevalence of clinical thyroid carcinoma in Japanese women reported at that time. These findings support the concept of PMC overdiagnosis and overtreatment.

Initiation of the Active Surveillance of Low-Risk PMCs

In the early 1990s, the natural history of PMCs was unknown, and their natural history remains to be further elucidated. The most commonly held idea was that PMCs are at an early stage of clinical cancer that might kill the host if not treated appropriately. However, based on the large differences between the thyroid carcinoma incidences in autopsy studies and the screening study and the prevalence of clinical thyroid carcinoma, Miyauchi hypothesized that most PMCs do not grow or grow very slowly. He speculated that only a small minority of PMCs would grow. Any advanced cancer was of course a small cancer at its beginning. Miyauchi also suspected that a watchful follow-up (i.e., observation) could detect PMCs that grew and that rescue surgery after the detection of PMC progression signs would not be too late to control the carcinoma, and that carrying out surgery for all PMCs would result in more harm than good.

In 1993, Miyauchi proposed an observation without immediate surgery clinical trial for low-risk PMCs at a physicians' meeting at Kuma Hospital. This trial was approved and began that year. The observation without surgery design later came to be called ''active surveillance.'' In 1995, the Cancer Institute Hospital (CIH; Tokyo) also initiated an active-surveillance program for low-risk PMCs, and these two institutions have published promising data using large patient series.

The diagnosis of PMCs was made based on the results of ultrasound-guided FNABs for nodules ≥5 mm with suspicious ultrasound features, and the positive predictive value for diagnosing papillary carcinoma was approximately 98%. Surgery was recommended to patients with high-risk PMCs. For patients with low-risk PMCs, active surveillance or immediate surgery was proposed as alternatives, and the patient was asked to choose one of these options. Patients who chose active surveillance were followed with ultrasound examinations performed six months after the diagnosis and once a year thereafter. Surgery was recommended when tumors increased by ≥3 mm or when novel lymph node metastasis appeared. A few patients were prescribed levothyroxine to maintain their serum thyrotropin (TSH) at low normal or mildly suppressed levels.

When the active surveillance began, the inclusion and exclusion criteria for active surveillance were determined, and these criteria are essentially the same today. There are two types of contraindications—high-risk features and features unsuitable for active surveillance—although it remains unclear whether the latter are biologically aggressive features (Table 1). High-risk features include (i) clinical node positivity (N+; Fig. 1) or clinical distant metastasis positivity (M+; very rare); (ii) signs or symptoms of invasion to the recurrent laryngeal nerve (RLN) or trachea (Fig. 2); (iii) high-grade malignancy such as tall-cell variant on cytology (very rare for PMCs); and (iv) the presence of progression signs (i.e., size enlargement and/or the novel appearance of lymph node metastasis) during active surveillance. PMCs shown by imaging to be attached to the trachea or located on the course of the RLN are also included in the contraindication category

Table 1. Contraindications for the Active Surveillance of PMCs

Type	*Contraindications*
Clinical high-risk features	1. N1 (may present on imaging studies) or M1 (very rare) 2. Signs or symptoms of invasion to the recurrent laryngeal nerve or trachea 3. High-grade malignancy on cytology (very rare) 4. Cases showing progression signs such as size enlargement or a novel appearance of lymph node metastasis during active surveillance
Features unsuitable for observation, although it is unclear whether they are associated with biological aggressiveness	Imaging studies indicate that the tumor may invade the trachea or recurrent laryngeal nerve

PMC, papillary microcarcinoma.

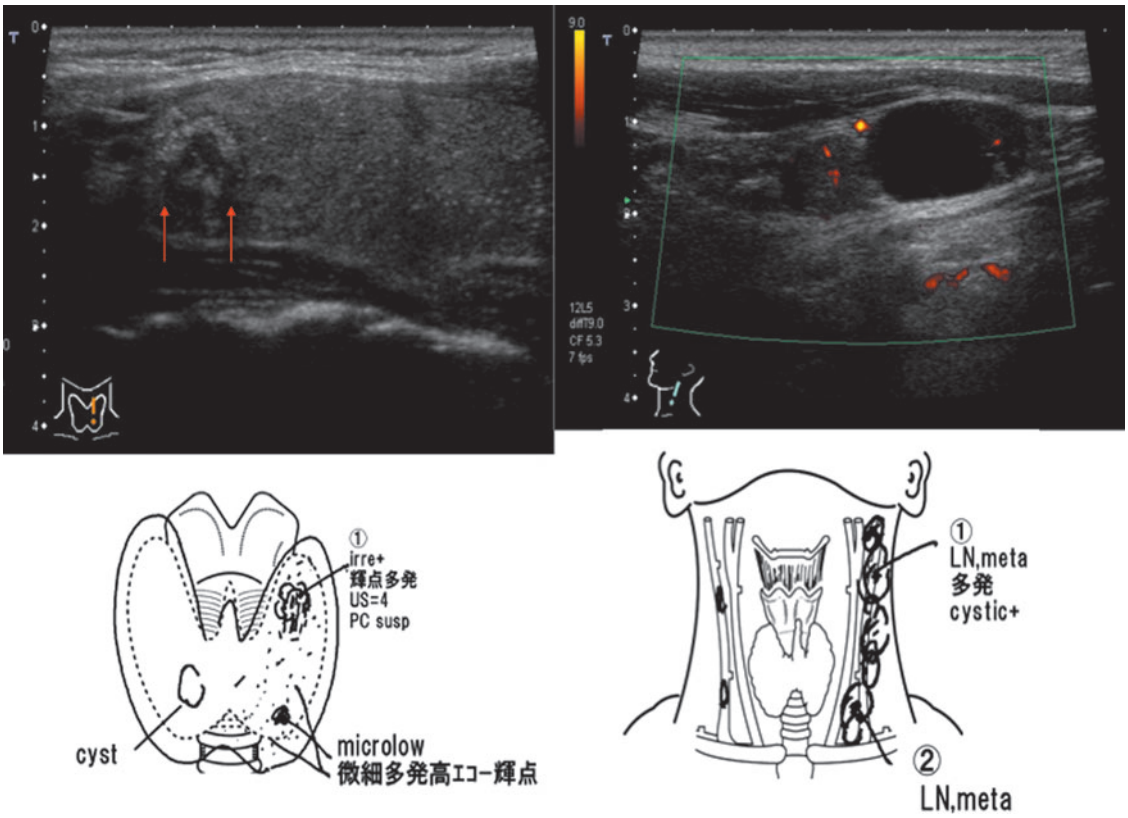

FIG. 1. Papillary microcarcinoma (PMC) with clinically apparent lymph node metastasis (41-year-old woman). Left: a tumor measuring 1 cm and multiple hyperechoic spots in the left lobe. Right: Multiple metastatic nodules in the left lateral neck compartment. LN, meta, lymph node metastasis; PC, papillary carcinoma; Irre, irregular shape; UC = 4, ultrasound classification class 4 (Kuma Hospital Classification); microlow, very small hypoechoic lesion; cystic+, presence of cystic change.

cautiously, although it is unclear whether these tumors are biologically aggressive.

Notably, tumor multiplicity and a family history of differentiated thyroid carcinoma are not included in the contraindications. Tumors in patients with a positive family history tend to be multiple, and multiple PMCs show high incidences of pathological nodal metastasis. However, the data showed that these were not strong prognostic factors. If these elements are included in the indications for surgery, the incidence of total thyroidectomy would become high, thus possibly resulting in higher rates of complications. Therefore, these features were not included in the contraindication category.

Recent Findings Regarding Thyroid Carcinoma Incidence and Mortality

As noted above, great differences between the incidence and mortality of thyroid carcinoma in various countries have been reported (1–4). In the United States, the thyroid carcinoma incidence increased by 2.4-fold and 2.9-fold between 1973 and 2002 and between 1975 and 2009, respectively (1,2). In Korea, the incidence of thyroid carcinoma increased even more radically, with a 15-fold increase between 1993 and 2011 (3). An increased thyroid carcinoma incidence was also reported in Italy, France, England, Scotland, Australia, and the Nordic countries (9). However, importantly, the thyroid carcinoma

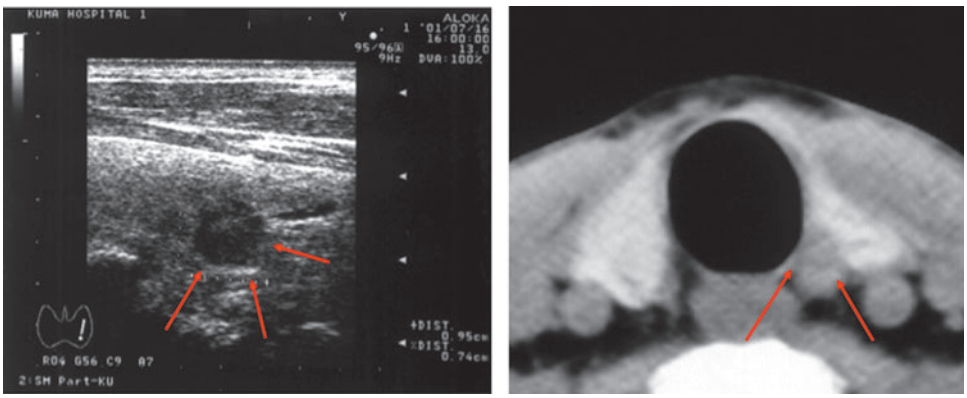

FIG. 2. PMC with left vocal cord paralysis due to carcinoma invasion (74-year-old man). Left: An ultrasonogram showing a hypoechoic tumor (arrows) extending from the dorsal surface of the left thyroid lobe. Right: A computed tomography scan revealing a low-density tumor (arrows) located on the course of the left recurrent laryngeal nerve.

mortality rate remained stable during the observation period. In the United States, an increased incidence of small papillary carcinomas, including PMC, was also reported (1,2), which was the main reason for the difference between the incidence and mortality rates. Recently, however, one study reporting that incidence-based mortality increased 1.1% per year during 1994–2013 was published (10), indicating that the change in mortality of thyroid cancer remains debatable.

Active Surveillance of Low-Risk PMC

Figure 3 illustrates the management flow for patients with low-risk PMCs. The 2015 American Thyroid Association (ATA) management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer do not recommend FNAB for nodules suspected of being low-risk PMC (11). Currently, at Kuma Hospital, PMCs ≥5 mm are diagnosed on cytology, and patients are notified of the diagnosis. There are two reasons for this approach. The size cutoff for performing FNAB for thyroid nodules with suspicious sonographic features in the Japan Association of Breast and Thyroid Sonology guidelines is 5 mm. If an FNAB is not performed, the patient might then consult another physician who might perform an FNAB, and the patients may be told both that Kuma Hospital ''missed the diagnosis'' of thyroid cancer and that they should undergo surgery immediately. This is an unacceptable scenario for the patients and Kuma Hospital. The second reason that patients are notified of the diagnosis is to encourage them to undergo regular checkups during active surveillance. Without the diagnosis of PMC, this would not be easy. Regular check-ups are considered necessary for patients with suspicious nodules, since some of these cases do show disease progression.

The most important issue is to determine whether a PMC is suitable for active surveillance based on imaging such as ultrasound and computed tomography (CT) scan if necessary. Physicians should carefully check whether a tumor shows the possibility of invading the trachea and/or RLN and whether clinical node metastasis is detected. An FNAB for suspicious nodes, together with a thyroglobulin (Tg) measurement of the FNAB needle washout (12), is useful to confirm nodal metastasis.

After diagnosing a nodule as a PMC suitable for active surveillance, in the past, two management options (active surveillance vs. immediate surgery) were presented rather equally to the patients, and the patients chose which option they wished to pursue. This was because confirmed evidence was lacking, although it was suspected that active surveillance would be better for the patients than immediate surgery. At present, active surveillance is recommended as the first-line management for low-risk PMCs based on the accumulated evidence.

Patients who choose active surveillance are followed with ultrasound at six months after the diagnosis and at least once a year thereafter. If suspicious nodes are detected, a FNAB and Tg measurement of the FNAB needle washout for these nodes (12) are performed to determine whether the nodes are metastatic or reactive. Rescue surgery is recommended when the tumor size has increased by ≥3 mm, but if the patient prefers active surveillance, it can be continued until the tumor size reaches 13 mm. Cases with newly appearing lymph node metastasis are strong candidates for rescue surgery. Without these events, patients are followed with continuing active surveillance.

Data on Active Surveillance of Low-Risk PMC

In 2003, the first report of active surveillance was published from Kuma Hospital, demonstrating that the size of >70% of the PMCs did not change or even decreased compared to that at the initial measurement (13). Kuma Hospital's second report was published in 2010, increasing the number of enrolled patients to 340 (14). It showed that various clinicopathologic features (e.g., sex, family history, and multiplicity) were not related to PMC progression, but PMCs in young patients (i.e., <45 years) were likely to progress, although the difference was not significant. The third clinical study, published in 2014 (15), enrolled 1235 patients. Only 8% of the PMC showed a size enlargement and only 3.8% were found have a novel appearance of node metastasis after a 10-year observation. Important findings about the relationship between age and PMC progression were also demonstrated.

In clinical PTCs, old age is the most important factor in terms of mortality from thyroid carcinoma (16). Another investigation showed that young age (i.e., <30 years) and old age (≥60 years) were independent prognostic factors of

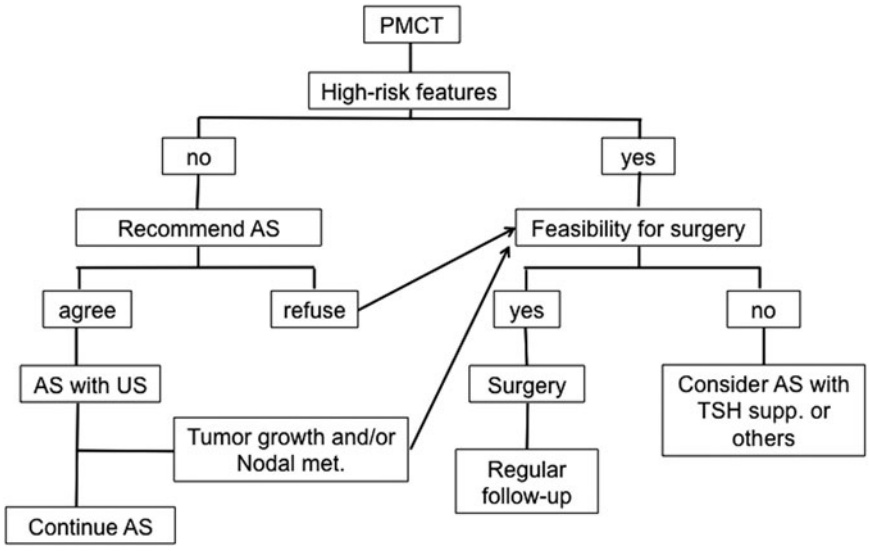

FIG. 3. Flow of the management of patients with low-risk PMC. AS, active surveillance; US, ultrasound.

Table 2. Results and Findings of Observation for Low-Risk PMC at Kuma Hospital and the Cancer Institute Hospital

Kuma Hospital	*Cancer Institute Hospital*
1. Of 1235 patients, 8% and 3.8% showed size enlargement and novel node metastasis, respectively, at 10-year observation (15).	1. Of 230 patients (300 lesions), 7% and 1% showed size enlargement and novel node metastasis, respectively, during observation (19).
2. The PMCs of young patients are likely to progress, and those of old patients are most unlikely to grow (15).	2. None of the patients who underwent surgery after the detection of progression signs showed significant recurrence or died of PTC (19).
3. None of the patients who underwent surgery after the detection of progression signs showed significant recurrence or died of PTC (15).	3. The TSH value was not linked to the progression of PMC during observation (25).
4. Only 8% of the patients showed PMC progression during pregnancy, and rescue surgery after delivery was successful (29).	4. PMCs with a rich blood supply or a lack of strong calcification on ultrasound displayed high growth activity; rich vascularity often decreased over time (23).
5. Immediate surgery and active surveillance managements had similarly excellent oncological outcomes. However, the immediate surgery resulted in significantly higher incidences of unfavorable events than the active surveillance management did (20).	
6. The Ki-67 LI was higher in PMCs resected due to tumor enlargement than in PMCs without tumor enlargement (26).	
7. The total cost of immediate surgery, including the costs for salvage surgery and postoperative care for 10 years, was 4.1 times the total cost of 10-year management for active surveillance (31).	

TSH, thyrotropin.

disease-free survival, but only old age was an independent predictor of carcinoma death in patients with clinical PTCs (17). Together, these findings indicate that older PTC patients have significantly poorer prognoses than young patients.

In 2013, Miyauchi *et al*. demonstrated that the percentages of biochemically persistent disease of PTC patients who underwent total thyroidectomy were significantly higher in patients <40 years and patients ≥60 years compared to those aged 40–60 years. The incidence of patients with a Tg doubling time (Tg-DT) <2 years, which indicates rapid tumor growth, increased with age (18). The cutoff ages of 40 and 60 years were therefore considered as appropriate to evaluate the biological characteristics of PTCs. In a 2014 study, patient ages were thus divided into three categories—young (<40 years), middle (40–59 years), and old age (≥60 years)—in order to investigate the relationship between age and PMC progression (15). In contrast to clinical PTC, the incidences of size enlargement and the novel appearance of node metastasis were significantly higher in young patients compared to middle-aged and old patients, and these incidences decreased with age at presentation. These findings were demonstrated by both univariate and multivariate analyses. Sex, family history, and multiplicity were not found to be predictors of PMC progression in the multivariate analysis. It is very interesting that although clinical PTCs in old patients are often progressive and should be treated carefully, low-risk PMCs in old patients are the best candidates for active surveillance.

In 2010, Sugitani *et al*. at the CIH reported that only 7% of 300 low-risk PMCs in a cohort of 230 patients enlarged during active surveillance (19). They also noted that only 1% of their 230 patients showed novel lymph node metastases during active surveillance. Their series included a higher percentage of old patients than the series at Kuma Hospital (15), since their patients were seen at a cancer center. However, the studies from the two institutions clearly show that during active surveillance, the incidences of tumor-size increase and the novel appearance of nodal metastasis in low-risk PMCs are low, and none of the active-surveillance patients showed distant metastasis or died of thyroid carcinoma. Both studies also showed that rescue surgery after progression signs were detected was not too late and that no life-threatening recurrence was detected thereafter. As rescue surgery for tumor enlargement, a hemithyroidectomy with paratracheal dissection was performed if the tumor was solitary. For cases with the appearance of nodal metastasis, a total thyroidectomy with dissection of the involved lateral neck compartment as well as the central neck compartment was performed. These are important points for adopting an active-surveillance policy as a low-risk PMC management option. Table 2 summarizes the two institutions' important findings regarding active surveillance.

Appearance of novel lymph node metastasis during active surveillance

In the active surveillance of 1235 low-risk PMC patients, 3.8% of patients showed novel lymph node metastasis at 10 years of active surveillance. One might think that the appearance of nodal metastasis is a failure of active surveillance. If these patients had been treated at their presentation, the most likely procedure would have been hemithyroidectomy with/without paratracheal dissection. This procedure would be unlikely to prevent the appearance of nodal metastasis in the lateral neck compartments. However, this did actually occur in the immediate-surgery series, as described later (15,20). These patients required a second operation: completion thyroidectomy with modified neck dissection. It is thought that one operation (i.e., total thyroidectomy with modified neck

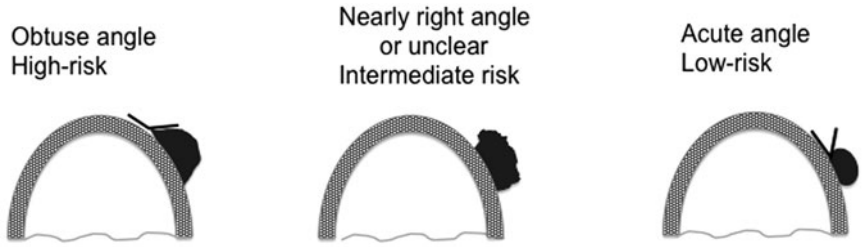

FIG. 4. Schema of typical examples of PMCs presenting a high, intermediate, and low risk for trachea invasion.

dissection) is better than two operations, since their final outcomes would be similarly excellent (21).

Active Surveillance: Clinical Topics

Evaluating the possibility of tracheal or RLN invasion

As described above, the location of PMCs is one of the most important issues in deciding whether active surveillance is appropriate. Tumors presenting tracheal invasion and/or RLN invasion should be operated on immediately. To evaluate the possibility of tracheal or RLN invasion, a CT scan is often more useful than ultrasound. For tumors located in the thyroid lobe's dorsal part, a CT scan may help during the evaluation.

The data suggest that the most important findings for evaluating the possibility of tracheal invasion are the angle formed by the tumor surface and the tracheal cartilage (Fig. 4) and the tumor size (22). In patients who underwent surgery, none of the PMCs <7 mm invaded the trachea. In the PMCs ≥7 mm, 12/51 (24%) PMCs showing obtuse angles with the tracheal cartilage required resection of part of the trachea because of invasion. Although 13/78 (17%) PMCs showed a nearly right or unclear angle, and 5/208 (2%) PMCs showed an acute angle requiring resection of peritracheal connective tissue, none of these patients required partial resection of the trachea. Thus, think that if the angle is acute, the patient could be a candidate for active surveillance, whereas an obtuse angle indicates that the patient should be surgically treated because of the suspicion for tracheal invasion.

Whether a tumor invades the RLN is judged based on whether the normal rim of the thyroid is present between the tumor and the RLN's course on ultrasound and a CT scan if necessary (22). In this study, similar to tracheal invasion, PMCs <7 mm did not invade the RLN, regardless of the risk classification. Of the PMCs ≥7 mm, 9/98 (9%) and 23/98 (23%) high-risk cases lacking the normal rim required resection of part of the RLN and sharp dissection to preserve the nerve, respectively, whereas none and only 2/28 (7%) low-risk cases with a normal rim required these procedures, respectively. Of course none of the 748 patients whose PMCs were not located on the RLN's course required these procedures (22).

Ultrasonographic findings of primary tumors

Fukuoka *et al.* showed that tumors with an initially rich vascularity had a significantly higher rate of tumor enlargement, but the vascularity of most of the tumors decreased during active surveillance (23). Their multivariate analysis showed that macroscopic or rim calcification and poor vascularity at the initial examination were significantly correlated with non-progressive disease. In a study using surgical specimens, PMCs with an ill-defined edge on ultrasonographic examination were likely to show recurrence (24). However, since no life-threatening recurrence was detected after a rescue surgery, these ultrasound findings do not prevent the inclusion of these patients in an active-surveillance program.

TSH suppression

Regarding TSH suppression, the data from Kuma Hospital and CIH have been discrepant. Sugitani *et al.* reported that the serum TSH value does not influence the progression of PMC (25). At Kuma Hospital, physicians have occasionally performed mild TSH suppression (setting the serum TSH value at low normal or slightly lower than the lower normal limit) with levothyroxine administration, especially for young patients, at the physician's discretion. Although the number of patients who underwent TSH suppression is small, none who underwent TSH suppression showed a novel appearance of node metastasis (15). Although the evidence level is not high, mild TSH suppression may be useful to prevent PMC progression, especially for young patients, who carry a higher possibility of disease progression than older patients. It is also noted that most of the patients studied by Sugitani *et al.* were old and thus had a lower possibility of disease progression. This might be why Sugitani *et al.* did not observe a significant difference among their study groups.

Lack of PMC progression markers

Active surveillance of PMCs was initiated partly because there were no markers that can be used to predict at presentation whether a PMC will progress. Active surveillance was the only method to discriminate PMCs that are progressing. This scenario has not changed. Hirokawa *et al.* reported that the Ki-67 labeling index was higher in PMCs surgically removed after size enlargement during active surveillance compared to PMCs without size enlargement on histopathological examinations, but this was not evaluated in preoperative FNAB specimens (26). The combination of *BRAF* mutation and *TERT* promoter mutations in clinical PTC was described as associated with poor prognosis (27). However, these mutations were not investigated using PMC FNAB specimens.

PMC progression and pregnancy

Low-risk PMCs are sometimes identified in young women who desire children. Shindo *et al.* reported that the PMCs of four of nine patients showed size enlargement during pregnancy (28). Although that study was reported from Kuma Hospital, it was found that there was a large selection bias in the patient series. The records of all female patients aged ≤50 years who underwent active surveillance were rechecked, and it was found that only 8% (4/51) of the low-risk PMC

patients showed size enlargement of ≥3 mm based on measurements performed before pregnancy and after delivery. None of the 51 patients showed a novel appearance of lymph node metastasis. Of the four patients whose PMCs showed size enlargement, only two underwent surgery after delivery, whereas the remaining two continued active surveillance because their tumors showed no further progression thereafter (29). Thus, young females with low-risk PMCs and the possibility of future pregnancies do not need to be excluded from active surveillance. If their tumors enlarge, rescue surgery after delivery would not be too late.

Active Surveillance as the First-Line Management for Low-Risk PMCs

The question of whether immediate surgery or active surveillance is better for managing low-risk PMC patients is important. The outcomes of these management approaches were compared (20). Among 2153 patients with low-risk PMCs seen at Kuma Hospital, 1179 (55%) patients chose active surveillance and 974 (45%) patients underwent immediate surgery. Post surgery, five patients had local recurrence that was successfully treated by salvage surgery. The remaining patients were alive without evidence of disease, but another five patients died of other causes. Of the active-surveillance patients, 94 underwent conversion thyroid surgery for various reasons, including the patient's change of mind. Although one of these patients had a local recurrence requiring salvage surgery, the 94 patients were free of disease. During surveillance, three patients died of other causes, and the remaining 1082 patients were alive without disease progression. No patients developed uncontrollable disease or died of the disease. Thus, the outcomes of these management modalities were similarly excellent.

However, the incidences of unfavorable events (e.g., temporary vocal cord paralysis, permanent or temporary hypoparathyroidism, need for levothyroxine substitution, and a surgical neck scar) were significantly higher in the immediate-surgery patients compared to those who chose active surveillance at their diagnosis. Very unfortunately, two (0.2%) of the immediate-surgery patients acquired permanent vocal cord paralysis, although their surgeries were performed by highly experienced endocrine surgeons at Kuma Hospital, a center for thyroid diseases (20). One might think that surgery for low-risk PMC would be easy, and it is indeed simple. However, human error can occur during simple and easy surgeries. It can be speculated that if non-experts had performed these patients' surgeries, the incidence of adverse events would have been much higher. This also contributes to the recommendation for active surveillance as the first-line management for low-risk PMC.

Medical Costs

Medical costs are a very important societal and individual concern. Lubitz *et al.* warned that based on the current trend in the incidence of well-differentiated thyroid cancer, the 2013 figure of US$1.6 billion as the estimated overall societal cost of well-differentiated thyroid cancer care in the United States might exceed US$3.5 billion by 2030 (30). The costs of surgery and active surveillance were analyzed based on the data of patients who underwent these management approaches. The total cost of immediate surgery, including the costs for salvage surgery and postoperative care for 10 years, was 4.1 times the total cost of 10-year management with active surveillance, including the costs for conversion surgery and salvage surgery (US$8437 vs. US$2052 per person) (31).

Costs such as those for physician visits, examinations, surgeries, and prescription medications vary greatly among countries. Insurance systems also vary greatly among countries and even within a given country. However, in Japan, the vast majority of clinical practices are conducted under the Japanese Health Care Insurance system, in which the cost for any aspect of clinical practice is the same, regardless of the experience of the physician or the size and location of the hospital. Therefore, the results of this cost analysis apply universally within Japan. If one wants to calculate the costs incurred in a given healthcare facility, the flow model and cost table provided in a previous study can be used (31).

Discussion

The prevalence of ultrasound and ultrasound-guided FNAB has greatly aided the detection and diagnosis of small nodules, including low-risk PMCs. However, ultrasound screening often detects many low-risk PMCs, which tend to be harmless. In 1997, Miyauchi contended that thyroid-screening studies using ultrasound would result in more harm than good. He proposed: (i) not using ultrasound for thyroid screening studies; (ii) that even if ultrasound is used, the threshold at which thyroid nodules should be described, even if seen on the ultrasound, should be set at a larger size; (iii) even if nodules are described, the indications for FNAB should be limited to larger and suspicious nodules; and (iv) if PMCs are diagnosed, active surveillance for low-risk PMCs should be considered (32). He also tentatively recommended that nodules ≤1 cm should not be evaluated with FNAB unless they have other malignant signs such as lymph nodes and/or distant metastasis or if the patient show symptoms such as RLN paralysis. These suggestions are similar to those in the 2015 ATA guidelines published 18 years later (11).

Several conditions are required for implementing active surveillance for low-risk PMCs. In order to implement this management, the Memorial Sloan Kettering Cancer Center group proposed a risk stratification of PMCs according to a clinical framework in collaboration with the authors (33). They divided patients into three categories: ideal, appropriate, and inappropriate candidates according to age, sex, tumor multiplicity, location of tumor, and signs of extrathyroidal extension or metastasis. This risk stratification might help physicians and patients to choose a course of management for PMC. Of course, the fully informed decision by the patient in selecting the management modality should be highly respected. However, patients' decisions are strongly influenced by how they are informed and who informs them. Clinicians should be confident about the active surveillance and immediate surgery outcomes described above. With the proper information from physicians, patients can be expected to make the decision most appropriate for them.

Educating physicians, surgeons, patients, and the public about how active surveillance of low-risk PMCs can be an excellent management modality is important. In addition, the availability of skilled sonographers is essential. Accurate ultrasonographic findings obtained by a skilled sonographer are necessary for evaluating low-risk PMC. A system for the follow-up of patients at outpatient clinics is also mandatory.

A recall system by mail or another form of contact is necessary for patients who do not comply with regular checkups.

Lastly, a simple tip for helping ensure that patients with small thyroid nodules thoroughly understand their condition and options is that the necessary information should be provided to the patient in a brochure about PMCs and treatment options *before* the FNAB is performed.

One may argue that active surveillance only delays surgical intervention. Based on the age decade–specific disease progression rate at the 10-year active surveillance point, calculated using Kaplan-Meier curves, the lifetime probability of disease progression (defined as tumor enlargement of ≥3 mm and/or the appearance of node metastasis) was estimated. The estimated values were 48.9% for patients in their 20s at presentation, 25.7% for those in their 30s, 21.4% in their 40s, 11.4% in their 50s, 8.3% in their 60s, and 3.5% for those in their 70s (Miyauchi A, Kudo T, Ito Y, *et al.* 2016 Estimation of the lifetime probability of disease progression of papillary microcarcinoma of the thyroid during active surveillance. Surgery; accepted). One might think that the values 48.9% and 25.7% in the 20s and 30s are too high to accept active surveillance. However, these estimates indicate that >50% and approximately 75% of the patients in these age decades would not require surgical intervention during their lifetimes, and the vast majority of the patients in their 40s or older would not require surgical intervention during their lifetimes. The benefits of delayed surgical intervention are also that patients can undergo surgery when their life circumstances come to be better and patients can keep normal thyroid function for many more years.

There are some therapeutic options other than active surveillance and immediate surgery such as percutaneous ethanol injection therapy (PEIT) and radiofrequency ablation (RFA) (34,35). These therapy options are adopted in order to control primary lesions. However, it was demonstrated that up to 40% of patients with PMC have pathological nodal metastases in the central compartment or even in the lateral compartment if these compartments are dissected (13). These nodal metastases cannot be treated with PEIT or RFA. Treating only primary lesions by PEIT or RFA might result in losing a biomarker of the disease. In the authors' opinion, active surveillance is more appropriate for triaging PMC that may have aggressive behavior, and a rescue surgical treatment should be done as the second line of therapy for PMCs that may grow.

Based on the accumulation of data, it can now be said that active surveillance of low-risk PMCs is a safe procedure and much more beneficial than immediate surgery for patients and for society. The data support that active surveillance of low-risk PMCs should be the first-line management modality because only a small percentage of low-risk PMCs progress, and rescue surgery after progression signs are detected has not caused significant recurrence of these carcinomas.

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