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ScienceDirect

EJSO 44 (2018) 307–315

EJSO the Journal of Cancer Surgery

www.ejso.com

Review

Low-risk papillary microcarcinoma of the thyroid: A review of active surveillance trials

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Received 13 October 2016; received in revised form 1 December 2016; accepted 9 March 2017
Available online 16 March 2017

Abstract

Papillary microcarcinoma (PMC) of the thyroid is defined as papillary thyroid carcinoma (PTC) measuring ≤1 cm. Many autopsy studies on subjects who died of non-thyroidal diseases reported latent small thyroid carcinoma in up to 5.2% of the subjects. A mass screening study for thyroid cancer in Japanese adult women detected small thyroid cancer in 3.5% of the examinees. This incidence was close to the incidence of latent thyroid cancer and more than 1000 times the prevalence of clinical thyroid cancer in Japanese women reported at that time. The question of whether it was correct to treat such PMCs surgically then arose. In 1993, according to Dr. Miyauchi's proposal, Kuma Hospital initiated an active surveillance trial for low-risk PMC as defined in the text. In 1995, Cancer Institute Hospital in Tokyo, Japan, started a similar observation trial. The accumulated data from the trials at these two institutions strongly suggest that active surveillance (i.e., observation without immediate surgery) can be the first-line management for low-risk PMC. Although our data showed that young age and pregnancy might be risk factors of disease progression, we think that these patients can also be candidates for active surveillance, because all of the patients who showed progression signs were treated successfully with a rescue surgery, and none of them died of PTC. In this review, we summarize the data regarding the active surveillance of low-risk PMC as support for physicians and institutions that are considering adopting this strategy.

Keywords: Papillary microcarcinoma; Thyroid; Observation; Active surveillance; Low-risk; High-risk

The definition of papillary microcarcinoma

Papillary microcarcinoma (PMC) is defined as papillary thyroid carcinoma (PTC) measuring ≤1 cm. This definition of PMC does not depend on whether or not high-risk features such as lymph node metastasis and/or distant metastasis are present. Therefore, 'PMC' covers a broad range of biological characteristics. The prognosis of patients with PMC can be poor if they have high-risk features such as clinical node metastasis, distant metastasis, or significant extrathyroid extension such as to the trachea and recurrent laryngeal nerve, even if these patients undergo immediate and sufficient surgery. In contrast, PMCs without any high-risk features (i.e., low-risk PMCs) are generally an indolent disease, and most of them do not grow or they grow very slowly. As described next, most of the recent increase in the incidence of thyroid cancer is due to the increase in the identification of low-risk PMCs, and a major clinical issue has thus arisen: how should these low-risk PMCs be managed? This review focuses on a new management strategy for low-risk PMCs; that is, observation without immediate surgery (i.e., active surveillance).

Background based on epidemiologic data

Many autopsy studies on subjects who died of non-thyroidal diseases reported their observations of latent small thyroid carcinomas, and the incidence of latent PMCs measuring 3–10 mm — the size detectable by

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http://dx.doi.org/10.1016/j.ejso.2017.03.004

ultrasound examinations — was reported to be 0.5%–5.2%.[1] Takebe et al. conducted a screening study for thyroid cancer using an ultrasound examination and ultrasound-guided fine needle aspiration biopsy (FNAB) on women who visited the authors' center for a breast cancer screening, and they reported that thyroid carcinoma was detected in 3.5% of otherwise healthy Japanese women aged ≥30 years.[2] They also reported that 85% of these thyroid carcinomas measured ≤15 mm.[2] This incidence was oddly coincident with the incidences of latent thyroid cancer reported in autopsy studies, and was more than 1000 times the prevalence of clinical thyroid carcinoma in Japanese women reported at that time. Taking these findings together, it is apparent that small thyroid carcinomas are frequently present in otherwise healthy adult people, and most of them could be considered harmless to the health and life of their hosts.

History of active surveillance of low-risk PMC

High incidences of latent thyroid cancer in autopsy studies, a similar incidence of small thyroid cancer in the above-mentioned screening study, and the approx. 1/1000 prevalence of clinical thyroid cancer led Dr. Akira Miyauchi to hypothesize that most low-risk PMCs remain latent without progression or with very slow progression. In 1993, based on this hypothesis he proposed an observation clinical trial for low-risk PMC at a doctors' meeting at Kuma Hospital in Kobe, Japan, which obtained the approval of other surgeons and physicians, and the study was started the same year at Kuma Hospital.[3]

Dr. Miyauchi thought that a small minority of PMCs might progress, that is, show size enlargement and or the appearance of nodal metastasis, and he hypothesized that (1) active surveillance alone (observation without immediate surgery) could identify the small minority of PMCs that progress, (2) that a rescue surgery for these PMCs should be effective for these slightly progressed lesions, resulting in no influence on the patients' prognosis, and (3) that performing surgery for all PMCs might result in more harm than good. The Cancer Institute Hospital (Tokyo, Japan) started a similar observation trial for low-risk PMC in 1995, and to date, promising data drawn from a large number of patients have been published from these two institutions.

There are several contraindications for active surveillance (Table 1). We think that PMC cases with high-risk features such as clinical node metastasis, distant metastasis (very rare), and suspicion of high-grade malignancy on cytology (very rare) should not be merely observed; these cases should undergo immediate surgery. In addition, a rescue surgery should be performed for PMC showing progression signs during observation.

We think that tumors located on the course of the recurrent laryngeal nerve or attaching the trachea at an obtuse angle (Fig. 1) are also candidates for immediate surgery without observation, although it remains unknown whether they are biologically highly aggressive. However, we did not exclude patients with multiple PMCs or a family history of thyroid carcinoma originating from follicular cells from the candidates for active surveillance. Our patients with multiple PTCs and our patients with a positive family history did not show poor prognoses. We suspected that performing surgery for these patients (which would be a total thyroidectomy in these settings) might result in more harm and more complications than good. We continue to follow these strategies at present.

Table 1
Contraindications for the active surveillance of PMC.

Type	Contraindications
Clinically high-risk features	1. N1 (may present) 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 with size enlargement or novel appearance of lymph node metastasis during observation
A feature unsuitable for observation, although unclear whether it is clinically aggressive	Tumors attaching the trachea or located in the course of the recurrent laryngeal nerve

Recent epidemiologic findings about the incidence and mortality of PMC cases

Interesting data from the United States and Korea were published recently. The incidence of thyroid carcinoma increased by 2.4-fold and 2.9-fold between 1973 and 2002 and between 1975 and 2009, respectively in the U.S.[4,5] In Korea, the incidence of thyroid carcinoma showed a 15-fold increase between 1993 and 2011.[6] In both countries, the mortality rate of thyroid carcinoma did not change during these periods. These several-fold increases in incidence were due to a remarkable increase in small PTCs; especially PMCs detected by imaging studies, mainly ultrasound. Vaccarella et al. also showed that similar phenomena were observed in other countries such as Italy, France, England and Scotland, Australia, and Nordic countries.[7] In Korea, there has been an active promotion of screening examinations for thyroid cancer, and Ahn et al. reported increases

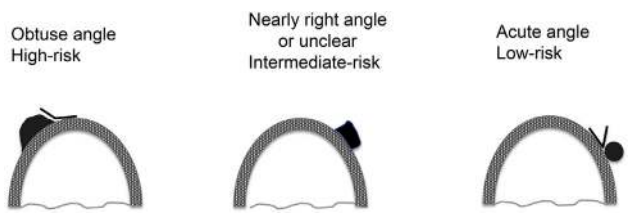

Figure 1. Schema of PMCs at high, intermediate, and low risk of tracheal invasion based on the angles formed with the tracheal cartilage and tumor surface.

in the numbers of patients suffering from hypoparathyroidism or vocal cord paralysis postoperatively.[6] These findings suggested that many harmless small carcinomas such as low-risk PMCs had been surgically treated, resulting in more harm than good without improvement in survival.[7]

Although the surgery for low-risk PMC is rather simple and fundamental in surgical technique, Oda et al. showed that permanent vocal cord paralysis due to the injury of the recurrent laryngeal nerve and permanent hypoparathyroidism occurred in 0.2% and 1.6% of patients who underwent surgery for low-risk PMC even at Kuma Hospital, a center for patients with thyroid diseases.[8] If these patients had not undergone the surgery, these unfavorable complications would have been avoided. We should take these findings into account when considering which of the two management options, observation and surgery, is better and more beneficial for patients with low-risk PMC.

The active surveillance strategy for low-risk PMC

First, it is very important to accurately evaluate a patient's PMC based mainly on imaging studies such as ultrasound and if necessary, a CT scan, to determine whether the location of the carcinoma is risky for observation and whether clinical node metastases are present. Although the most recent (2015) American Thyroid Association (ATA) guidelines do not recommend diagnosing low-risk PMC based on cytology (described below),[9] at Kuma Hospital we think that it is better to cytologically diagnose suspicious nodules as PMC and clearly disclose a diagnosis of carcinoma to patients.[10] This is to discourage the occurrence of patients going to another hospital, being diagnosed there as having thyroid carcinoma, and undergoing unnecessary surgical treatment by non-experts who assume that all thyroid carcinoma should be surgically removed. We also think that all patients with PMC should be followed up, since some PMCs show progression of the disease. Without the diagnosis of PMC, it can be very difficult to persuade patients to undergo a regular checkup.

After the diagnosis of low-risk PMC without any high-risk features or factors unsuitable for observation, in the past, we offered two management options equally, that is, active surveillance and immediate surgery, and we asked patients which option they prefer. However, at present, we recommend active surveillance as the first-line management. This is because of the favorable data regarding active surveillance, described below.

At Kuma Hospital, if a PMC case is judged as suitable for active surveillance and the patient prefers this option, the patient is followed with an ultrasound examination 6 months later and once per year thereafter. If one of these examinations reveals that the tumor size has increased by $\geq$3 mm or if lymph node metastasis appears, we recommend surgery. For the determination of whether suspicious nodes are metastatic, it is useful to perform an FNAB for the nodes and measure the thyroglobulin level in the wash-out of the needles used for the FNAB.[11] If there is no sign of progression, active surveillance is continued with annual examinations.

Results of active surveillance trials for low-risk PMCs

In 2003, the first report of the active surveillance of a small number of PMC cases was published from Kuma Hospital.[12] This study enrolled 162 patients with PMC who chose the observation option. The study's analysis revealed that in each follow-up period, >70% of the PMCs either did not change or decreased in size compared to the initial observation. A second report was published in 2004, demonstrating that size enlargement was linked only to tumor size at the initial observation ($\geq$7 mm).[13]

The third report published in 2010 showed the rate of size enlargement (by $\geq$3 mm) and the rate of novel appearance of lymph node metastasis by a Kaplan–Meier method.[14] In the fourth report on 1235 patients with low-risk PMC in 2014, we demonstrated that after a 10-year follow-up, the rates of tumor-size enlargement and the novel appearance of node metastasis were 8.0% and 3.8%, respectively. In that report, we also investigated the relationship between PMC progression and the patients' age (young, <40 years: middle-aged, 40–59 years: old, $\geq$60 years), and our analysis showed that the PMCs in the young patients were most likely to enlarge or show clinical node metastases.[15]

Old age is known as the strongest prognostic factor in clinical PTC patients especially for their cause-specific survival.[16] We were thus concerned about including old patients with PMC for the active surveillance trial.[1] However, the trial's results were different from what we expected regarding the older patients. Our findings strongly suggested that PMCs in old patients are the most unlikely (not the most likely) to progress, and that old patients are the best candidates for active surveillance. In addition, the most important finding obtained in all of the above-described surveillance studies was that all of the patients who underwent a rescue surgery for their disease with slight progression were successfully treated without further recurrence, and none of them died of PTC.[12–15] We therefore feel that PMCs at all stages of adulthood can be kept under observation without immediate surgery, and that a rescue surgery conducted after progression signs are observed during observation is not too late.

A small minority of patients with low-risk PMC developed novel lymph node metastasis during the active surveillance. This incidence was higher in the younger patients. 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 or without paratracheal dissection. However, this procedure is unlikely to prevent the appearance of nodal metastasis in the lateral neck, and these patients would thus require a second

salvage surgery. One surgery, i.e., a single rescue surgery, is better than two surgeries (i.e., a surgery at presentation and a salvage surgery for recurrent disease), since the final outcomes seam similarly excellent.[4] We therefore propose that adult patients with low-risk PMC can be candidates for watchful observation and that performing a rescue surgery only for those patients who show slight progression of the disease might not be too late.

In 2010, the Cancer Institute Hospital (CIH) in Tokyo, Japan reported that of 300 lesions of PMC, 90% were unchanged, 7% had increased in size and 9% had decreased during their active surveillance.[17] The second report from the CIH published in 2014 noted that the patients' serum thyrotropin concentration was not related to the growth of their PMCs.[18] In 2016, another CIH study revealed that ultrasound findings are important to predict the fate of PMC and that strong calcification and poor vascularity at the examination at presentation were significantly correlated with non-progressive disease.[19] In that patient series, none of the patients who underwent a rescue surgery showed further recurrence or died of PTC.[17–19] Table 2 summarized the findings in the publications from Kuma Hospital and the CIH.

Overseas movement

Following the persuasive reports of the effectiveness of active surveillance of low-risk PMC from the two Japanese institutions described above, the most recent (2015) version of the ATA management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer discourage the performance of an FNAB on thyroid nodules $\leq$1 cm even if an ultrasound examination shows features suspicious for malignancy, unless there are aggressive features such as extrathyroid extension or nodal metastasis.[9] The intention of this statement is to avoid overtreatment for PMCs. The guideline committee might have thought that patients in the U.S. would find it difficult to accept that their carcinomas simply be followed up without any direct therapies. After the publication of the ATA guidelines, we discussed this issue and decided to implement a policy of performing FNABs for suspicious nodules. We think that PMCs should be diagnosed as PTC on cytology before observation because some of these carcinomas show progression of the disease and that regular follow-up would be difficult without a clear diagnosis.

The ATA guidelines also adopted an active surveillance approach as a management option for low-risk PMC. The guidelines state that an active surveillance management approach can be considered as an alternative to immediate surgery in patients with several conditions, including patients with "**very low risk tumors**." The ATA's definition of this category is basically the same as our definition of low-risk PMC.

In a study conducted at the Memorial Sloan-Kettering Cancer Center in New York, in collaboration with Kuma Hospital, Brito et al. constructed a risk-stratified approach to decision-making in probable or proven PMC for American patients.[20] They classified PMC into three categories: ideal, appropriate, and inappropriate as candidates for active surveillance. The risk stratification included tumor/neck ultrasound characteristics (tumor location, FNAB findings, and N status), patient characteristics (patient age, childbearing potential, and intelligence of patients) and medical team characteristics (availability of high-quality neck ultrasonography, and experienced multidisciplinary management team).

Haser et al. published a review article concluding that with proper patient selection, organization, and patient support, active surveillance has the potential to be a long-term management strategy for select patients with PMC.[21] They also proposed that the patients' quality of life (including psychological aspects), cultural differences, and the patients' clinical status should be taken into consideration.

It thus seems that an active surveillance management approach for PMC is gradually being adopted, on a global basis. However, the currently available data on the outcome of active surveillance of PMC are only from Japan, and further data should be collected in various populations in different countries with different cultures, diet habits, and attitudes. We believe that education for physicians and surgeons, patients with the disease, and the general public will

Table 2
Results and findings of observation for low-risk PMC at Kuma Hospital and the Cancer Institute Hospital.

Kuma Hospital[12–15]	Cancer Institute Hospital[17–19]
1. Of 1235 patients, 8% and 3.8% showed size enlargement and novel node metastasis, respectively, at 10-year observation. 2. The PMC of young patients are likely progress, and those of old patients are most unlikely to grow. Although the number of patients is small, none of the young patients with TSH suppression showed progression. 3. Only 8% of the patients showed PMC progression during pregnancy, and rescue surgery after delivery was successful. 4. In Japan, the medical cost of observation was lower than that of immediate surgery. 5. None of the patients who underwent surgery after the detection of progression signs showed significant recurrence or died of PTC.	1. Of 230 patients (300 lesions), 7% and 1% showed size enlargement and novel node metastasis, respectively, during observation. 2. The TSH value was not linked to the progression of PMC during observation. 3. PMC with rich blood supply or lack of strong calcification on ultrasound were signs of high growth activity. Rich vascularity often decreased over time. 4. None of the patients who underwent surgery after the detection of progression signs showed significant recurrence or died of PTC.

be the key point for implementing this new strategy. Shared decision-making between patients and their doctors is very important. Without sufficient knowledge and confidence, doctors cannot give proper information to their patients.

Clinical issues concerning observation of PMC

Several clinical issues are present before and during observation for PMC. Here we list the clinical issues that physicians may encounter, along with our comments.

(1) The determination of possible tracheal (TR) invasion or recurrent laryngeal nerve (RLN) invasion

The tumor location of PMC is one of the most important issues in deciding whether active surveillance is indicated. Tumors presenting the possibility of TR invasion, RLN invasion or risk of RLN invasion in case of future progression should be immediately operated without observation. To accurately evaluate the relationship between PMC and the TR or the RLN, a CT scan may be necessary in addition to an ultrasound examination. Ultrasound is not suitable for tumors located at the dorsal side of the thyroid or tumors with fine strong echoes. For such tumors, a CT scan is useful for an accurate evaluation.

The most important finding to consider in the diagnosis of TR invasion is the angle formed by the tumor surface and the TR cartilage (Fig. 1). 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. In our patient series, none of the PMCs <7 mm invaded the trachea, and we observed that the angle between the TR cartilage and the tumor surface of the PMCs that were ≥7 mm was significantly related to the presence or absence of TR invasion. We also reported that significant invasion to the TR requiring airway resection was present in 24% of PMCs ≥7 mm showing obtuse angles with TR cartilage.[22]

Whether a tumor invades the RN or not is judged based on whether the normal rim of the thyroid is present between the tumor and the course of the RN. However, since the appearance of RN paralysis during active surveillance causes great stress for patients, it may be better to surgically treat tumors located on the course of the RLN with a possible risk of future RLN invasion. In one study, 9% of patients judged as at risk for RLN showed RLN invasion, but not in other patients.[22] Tables 3 and 4 summarize these findings.

(2) Cytological diagnosis of PMC

Whether tumors suspected of PMC are diagnosed by cytology might depend on the country. The ATA guidelines do not recommend performing an FNAB for nodules <1 cm, including nodules suspected of being PMC on ultrasonography.[9] This may be because patients in the U.S. are less willing to undergo only active surveillance without surgery for low-risk PMC, and more likely to undergo unnecessary surgical treatment. The guidelines issued by the Japan Association of Endocrine Surgeons/Japanese Society of Thyroid Surgery (JAES/JSTS) state that PMC should be diagnosed by FNAB.[10] This is to prevent patients from undergoing unnecessary surgery in another hospital by non-experts. It is better that physicians tell their patients the cytological results of their PMC and recommend observation as the first line of management. In addition, disclosing the diagnosis of PMC makes the patient much more likely to return for the follow-up examinations.

Table 3
Relationship between preoperative and postoperative findings of tracheal invasion in the subset of PMCs ≥7 mm.

Risk grade/TR invasion	Surgical and pathological tracheal invasion		
	No or minimal	Significant	Total
High-risk	39 (76%)	12 (24%)	51
Intermediate-risk	78 (100%)	0	78
Low-risk or no-risk	745 (100%)	0	745
Total	862	12	874

No or minimal: no invasion or invasion to adventitia dissection only.
Significant: laminate dissection or dissection of tracheal cartilage and mucosa.
Source: Reference No, 22

(3) Pathological characteristics of PMCs that showed progression on observation

We studied the pathological characteristics of three groups of PMC patients who were surgically treated following some periods of active surveillance.[23] Group 1 was 18 patients with PMCs that enlarged in size by ≥3 mm during observation. One of these patients showed the appearance of novel lymph node metastasis as well. Group 2 was 11 patients with PMCs that showed the appearance of novel lymph node metastasis without tumor enlargement during observation. Group 3 was 160 patients with PMCs that did not show tumor progression, but for whom a thyroidectomy was performed after a ≥1-year observation based on other reasons such as enlargement of associated nodules or the appearance of primary hyperparathyroidism.

Table 4
Relationship between preoperative and postoperative findings of RLN invasion in the subset of PMCs ≥7 mm.

Risk grade/RLN invasion	Surgical and pathological RLN invasion		
	No or minimal	Significant	Total
High-risk	89 (91%)	9 (9%)	98
Low-risk or no-risk	776 (100%)	0	776
Total	865	9	874

No or minimal: No invasion or minimal invasion requiring RLN shaving.
Significant: Invasion requiring partial layer dissection or segmental resection of the RLN with reconstruction of the resected RLN.
Source: Reference No. 22

On pathological examination, intraglandular dissemination was observed in 22.2% and 36.4% of the Group 1 and 2 patients, respectively; these rates are significantly higher than that of the Group 3 patients (2.5%) ($p < 0.001$). Psammoma bodies in normal thyroid tissue were detected at a significantly higher incidence in Group 2 patients (18.2%) compared to the Groups 1 and 3 patients (5.6% and 1.3%, respectively) ($p < 0.001$). The Ki-67 labeling index of the Group 1 patients (>5% in 50.0% and >10% in 22.2% of patients) was significantly higher than that of the Group 3 patients (>5% in 5.0% and >10% in 1.9% of patients) ($p < 0.001$). These three characteristics (intraglandular dissemination, psammoma bodies in normal thyroid tissue, and a high Ki-67 labeling index) were identified as indicators of progressive PMC. The former two features were mostly associated with appearance of node metastasis, while a high KI-67 labeling index was mostly associated with tumor growth. These features may possibly be identified cytologically or ultrasonographically in future studies.

(4) Relationship between the patient's background, ultrasound findings or molecular markers, and PMC growth

There are three types of markers potentially related to PMC progression: the patient's background, ultrasound findings, and molecular markers.

In our recent study, as described above, patient age was regarded as a predictor of PMC progression. PMCs in the young patients (<40 years) were most likely to grow and show novel nodal metastasis, whereas the PMCs in the old patients (≥60 years) were the most indolent.[15] These findings are in contrast to clinical PTCs, in which old age is an important predictor of carcinoma recurrence and death.[16]

In a series of low-risk PMC patients who underwent surgery, we observed PMCs with an ill-defined edge on ultrasound examination.[24] Fukuoka et al. demonstrated that a rich blood supply or lack of strong calcification on ultrasound is signs of PMCs' high growth activity.[19] They also showed that rich vascularity in many cases decreased over time during observation.

BRAF mutations and *TERT* promoter mutations are known to have prognostic values in PTC. Xing et al. showed that *BRAF* and *TERT* promoter mutations cooperatively affect the prognosis of PTC patients, and they demonstrated that PTCs with both of these two mutations show the most aggressive characteristics.[25] Lee et al. reported that the identification of *TERT* promoter mutations in preoperative FNAB helped to better characterize the prognosis and the triage of PTC patients in Korea, where a large proportion of PTCs showed *BRAF* mutations.[26] In Japan, *BRAF* mutations have had no prognostic significance, except for high-risk PTC,[27,28] and studies on *TERT* promoter mutations have not been published; there are also no studies regarding the relationships between these mutations and PMC growth.

Although there are some potential markers that may predict mild progression activity of PMC, these are not sufficient to preclude the active surveillance approach to low-risk PMC. In our previous studies, none of the adult patients of any age showed life-threatening growth or metastasis during observation, and all of the patients who showed slight progression were successfully treated with a rescue surgery without recurrence after surgery. Therefore, we conclude that regardless of these characteristics, all adult patients with low-risk PMC according to our definition provided above can be candidates for active surveillance.

(5) Effect of TSH suppression for observation of low-risk PMC

Thyroid-stimulating hormone (TSH) suppression is a common strategy to avoid the recurrence or the progression of a recurred lesion of differentiated thyroid carcinoma, including papillary carcinoma. In Japan, however, no studies on a large number of patients have been published to examine the efficacy of TSH suppression. In the most recent ATA guidelines, TSH suppression is not routinely recommended for low-risk differentiated thyroid carcinoma after surgery, because it may induce osteoporosis — especially in elderly female patients.[9] One retrospective analysis demonstrated that the serum TSH value was not related to the progression of low-risk PMC during observation.[17] Ito et al. showed that, although the number of patients in their study was small, none of the patients whose serum TSH was low showed PMC progression.[18] Therefore, observation under TSH suppression may be effective to some extent for PMCs in young patients whose PMCs are slightly more progressive,[15] but further studies (e.g., prospective studies) are needed to draw any confirmative conclusions.

(6) Pregnancy and low-risk PMC

Regarding the observation of low-risk PMC in young females, pregnancy is a very important issue. In the first report from our group at Kuma Hospital, Shindo et al. reported that 49.4% of PMCs monitored during pregnancy showed size enlargement.[29] If these data are representative, it is possible that low-risk PMCs in young females who may become pregnant should be surgically treated at their presentation. To clarify this issue, we searched our entire series of patients with PMC for female patients (aged ≤40 years) who had a pregnancy and a delivery during active surveillance, and we found that only 8% of the PMCs (on 4 of 51 patients with 52 pregnancies/deliveries) enlarged in size, and none of the patients showed the novel appearance of lymph node metastasis during pregnancy.[30] We concluded that the Shindo et al. report with the 49.4% result was based on a strong selection bias. Two of our four patients showing enlargement of their PMC during pregnancy underwent a rescue surgery after delivery, and showed no recurrence after surgery. The remaining two patients continued observation after the delivery, and no further progressive signs has been detected. Taking these

findings together, we can conclude that the possibility of pregnancy is not a reason for declining active surveillance of low-risk PMCs. Even though some of these PMCs might enlarge during pregnancy, a rescue surgery after delivery can solve the problem.

(7) Costs of observation for low-risk PMC

The rapidly increasing medical costs for the treatment of thyroid cancer have presented a major societal issue, since the numbers of patients with thyroid cancer are increasing rapidly in many countries. Lubitz et al. warned that the US$ 1.6 billion of the societal medical costs for thyroid cancer treatment in 2013 might expand to US$ 3.5 billion in 2030.[31] Medical costs are also a great concern for individual patients.

Whether the medical cost of observation significantly differs from that of immediate surgery will vary from country to country. Lang et al. in Hong Kong compared the costs between a non-surgical approach and early surgery, they and concluded that the non-surgical approach was cost-saving in the initial 16 years and cost-effective thereafter, regardless of patient age, complication rate, or rate of PMC progression.[32]

In Japan, the vast majority of clinical practices including surgeries are performed under the country's health care insurance system. Under this system, each cost of any clinical practice including examinations and surgeries is the same regardless of the hospital, the location of the hospital and the experience level of the physician(s). Oda et al. analyzed the costs for immediate surgery and active surveillance performed under this system, and they showed that the simple cost of immediate surgery with 10-year management after surgery was 4.7–6.5 times the simple cost of active surveillance for 10 years.[8] Here, 'simple costs' did not include the costs of salvage surgery for recurrence after surgery or the costs of conversion surgery during the surveillance. 'Total costs' meant all costs including costs for these events.

Oda et al. also demonstrated that the 10-year total cost of immediate surgery with 10-year postoperative management was 4.1 times the total cost of active surveillance for 10 years when the costs of salvage surgery for recurrence and conversion surgery were considered.[8] These data suggest that the total amount of medical cost-saving for a society could be huge if the active surveillance approach is adopted instead of immediate surgery. On the other hand, one might think that the income of a hospital or a surgeon decreases if active surveillance is used instead of immediate surgery for low-risk PMC. However, at Kuma Hospital we feel that our priority should be patients' good health and happiness.

(8) Active surveillance as the first line of management for low-risk PMC

Some endocrinologists and endocrine surgeons might consider surgical treatment to be better than observation even for low-risk PMC. This is because follow-up is easy and simple (Tg monitoring and TSH suppression). However, such an attitude is not beneficial for patients. First, the accumulated data regarding the natural history of low-risk PMC clearly show that most low-risk PMCs do not grow or grow very slowly, indicating that many PMC patients have undergone unnecessary surgery. More importantly, rescue surgery after the detection of progression signs was demonstrated to be adequate for low-risk PMC patients.[15,17]

Secondly, although surgery for low-risk PMC is not difficult for experienced surgeons, significant complications of surgery can occur. Even at Kuma Hospital, the rate of permanent recurrent laryngeal nerve paralysis has been 0.2%, and that of permanent hypoparathyroidism has been 1.6%; moreover, 66% of the patients have been administered L-thyroxine during their lifetime.[8] At the least, the incidence of permanent recurrent laryngeal nerve paralysis and permanent hypoparathyroidism should be expected to be higher than those indicated above if patients undergo surgery by non-experts. Such surgical complications can be avoided if observation is chosen as the first line of management.

The costs of surgery and active surveillance vary from country to country, but as indicated above, active surveillance is more cost-effective than immediate surgery (at least in Japan and Hong Kong[32,33]). It is unlikely that surgery is much more cost-effective than observation in any country. Taking all of the existing data into account, we can conclude that observation is more suitable as the first-line management for low-risk PMC than immediate surgery.

(9) Other therapeutic strategies for low-risk PMC

There are some therapeutic options other than observation and immediate surgery. Some physicians have used percutaneous ethanol injection therapy (PEIT) and radiofrequency ablation (RFA).[34,35] The purpose of these therapies is to control the primary PMC lesions. It is well known that up to 40% of patients with PMC have pathological nodal metastases in the central compartment or even in the lateral compartment, if these areas are surgically dissected.[12] These nodal metastases cannot be treated with PEIT or RFA. Some of the PMCs might progress, as mentioned above. Treating the primary lesion with PEIT or RFA might result in losing a biomarker of the disease. We think that observation 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.

Limitations and discussion

One might think that making diagnosis of a small thyroid nodule is not easy. However, it is actually rather

easy to make diagnosis especially of PTC with US-guided FNAB. The positive predictive value reached 98.9% in our series.[12] This was probably one of the major reasons why only the incidence of small PTC increased in many countries.[4–6] If a nodule is suspected of PMC on ultrasound but is not diagnosed as PTC on cytology, we usually do not repeat FNAB and just follow the nodule as suspicious of PMC. If it shows progression, we perform FNAB again. However, these suspicious cases were not included in our previous studies of active surveillance.[12–15]

To date, the results of active surveillance of patients with low-risk PMC have been reported exclusive from Japanese two institutions, Kuma Hospital in Kobe and Cancer Institute Hospital in Tokyo.[1,3,8,15,17] Although these data convinced many doctors that the active surveillance is a safe alternative to the immediate surgery, one might argue that the biological characteristics of PMCs in other countries might differ from those in Japan. However, the large difference between the incidence of latent carcinoma and the prevalence of clinical thyroid carcinoma is a universal phenomenon.[1] Therefore, it is speculated that the biological nature and natural history of low-risk PMCs in other countries should be mostly similar to that of Japanese PMCs.

When we talked on active surveillance of low-risk PMCs, the most popular arguments by other doctors included: 1. Most PMCs can be easily treated with a simple surgery, lobectomy with or with out paratracheal dissection, 2. Their patients will not accept the surveillance policy, 3. The cost of active surveillance might be higher than that of immediate surgery, and 4. Some or many physicians do not have access to high quality ultrasound examination and FNAB as we have in Kuma Hospital.

Although one might think lobectomy is sufficient for most PMCs, 44% of our PMC patients underwent total thyroidectomy with central node dissection, because of multiple PMCs, associated significant nodules or suspicious nodules in the contralateral lobe or other reasons.[12] Total thyroidectomy naturally associates with low but significantly higher incidences of complications than hemithyroidectomy. Therefore we did not exclude patients with multiple foci or positive family history for papillary cancer from the candidates of active surveillance. Even hemithyroidectomy associated significantly higher incidences of unfavorable events than active surveillance.[8] Regarding patient's preference, this should be largely influenced on the information, education and physician's explanation to the patient. We think that education to physicians, surgeons, and patients as well as genera public people is very important. Medical costs are important issue for the society and also for the individual patient. We reported the cost of immediate surgery with 10-year postoperative management was 4.1 times the cost of active surveillance for 10 years under the Japanese Health Care Insurance System.[33] Access to high quality ultrasound examination and FNAB are necessary for the appropriate active surveillance. In a setting without these access, not making cytological diagnosis for small suspicious nodules as the 2015 ATA management guidelines recommend[9] might be a practical approach. However, we think that following such patients with suspicious nodules is necessary, since a small minority of the patients with PMCs did show disease progression. We doubt that this is possible without an accurate diagnosis. When we order US-guided FNAB for patients with a suspicious nodule, we give a brochure on the managements of PMCs to the patients and ask them to read it carefully. Giving sufficient information in advance to telling the FNAB diagnosis helps the patients choosing their optimal option of the managements.

Conclusions

At present, we conclude that active surveillance is the optimal first line of management for all adult patients with low-risk PMCs. None of our patients who underwent observation showed life-threatening metastases to the distant organs or died of PTC. The small minority of the patients whose PMCs progressed were adequately treated with a rescue surgery, without further recurrence of the disease. Surgery for low-risk PMCs is not difficult, but surgery still presents the possibility of complications such as permanent vocal cord paralysis and permanent hypoparathyroidism. In our series, up to 60% of the patients who underwent surgical treatment required L-thyroxine administration postoperatively. Thus, the oncological outcomes of active surveillance and immediate surgery were similarly excellent, regardless of patient background factors such as age, gender and family history. However, immediate surgery was associated with significantly higher incidences of unfavorable events compared to active surveillance. The medical costs for immediate surgery with 10-year postoperative management were 4.1 times the medical costs of active surveillance for 10 years. Taken together, the accumulated data indicate that observation can be applied for all adult patients with low-risk PMC regardless of background factors such as age, gender and family history. Future studies may identify PMCs with possible high growth activity, which are suitable for immediate surgery at the diagnosis.

Conflict of interest statement

No conflicts of interest to declare.

References

1. Ito Y, Miyauchi A. A therapeutic strategy for incidentally detected papillary microcarcinoma of the thyroid. *Nat Clin Pract Endocrin Metab* 2007;**3**:240–8.
2. Takebe K, Date M, Yamamoto Y. Mass screening for thyroid cancer with ultrasonography [in Japanese]. *KARKINOS* 1994;**7**:309–17.
3. Miyauchi A. Clinical trials of active surveillance of papillary microcarcinoma of the thyroid. *World J Surg* 2016;**40**:516–22.
4. Davies L, Welch HG. Increasing incidence of thyroid cancer in the Unites States, 1973–2002. *JAMA* 2006;**595**:2164–7.

5. Davies L, Welch HG. Current thyroid cancer trends in the United States. *JAMA Otolaryngol Head Neck Surg* 2014;**140**:317–22.
6. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic" — screening and overdiagnosis. *N Engl J Med* 2014;**371**:1765–7.
7. Vaccarelia S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L. Worldwide thyroid-cancer epidemic? The increasing impact of overdiagnosis. *N Engl J Med* 2016;**375**:614–7.
8. Oda H, Miyauchi A, Ito Y, et al. Incidences of unfavorable events in the management of low-risk papillary microcarcinoma of the thyroid by active surveillance *vs*. immediate surgery. *Thyroid* 2016;**26**:150–5.
9. 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.
10. Takami H, Ito Y, Okamoto T, Onoda N, Noguchi H, Yoshida A. Revisiting the guidelines issued by the Japanese Society of Thyroid Surgeons and Japan Association of Endocrine Surgeons: a gradual move towards consensus between Japanese and western practice in the management of thyroid carcinoma. *World J Surg* 2014;**38**:2002–10.
11. Uruno T, Miyauchi A, Shimizu K, et al. Usefulness of thyroglobulin measurement in fine-needle aspiration biopsy specimens for diagnosing cervical lymph node metastasis in patients with papillary thyroid cancer. *World J Surg* 2005;**29**:483–5.
12. 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.
13. Ito Y, Tomoda C, Uruno T, et al. Papillary microcarcinoma of the thyroid: how should it be treated? *World J Surg* 2004;**28**:1115–21.
14. Ito Y, Miyauchi A, Inoue H, et al. An observation trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg* 2010;**34**:28–35.
15. 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.
16. Ito Y, Kudo T, Kobayashi K, Miya A, Ichihara K, Miyauchi A. Prognostic factors for recurrence of papillary thyroid carcinoma in the lymph nodes, lung, and bone: analysis of 5,768 patients with average 10-year follow-up. *World J Surg* 2012;**36**:1274–8.
17. Sugitani I, Toda K, Yamada K, Yamamoto 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**:1222–31.
18. Sugitani I, Fujimoto Y, Yamada K. Association between thyrotropin concentration and growth of asymptomatic papillary thyroid microcarcinoma. *World J Surg* 2014;**38**:573–8.
19. Fukuoka O, Sugitani I, Ebina A, Toda K, Kawabata K, Yamada K. Natural history of asymptomatic papillary thyroid microcarcinoma: time-dependent changes in calcification and vascularity during active surveillance. *World J Surg* 2016;**40**:529–37.
20. Brito J, Ito Y, Miyauchi A, Tuttle RM. A clinical framework to facilitate risk stratification when considering an active surveillance alternative to immediate biopsy and surgery in papillary microcarcinoma. *Thyroid* 2016;**26**:144–9.
21. Haser TC, Tuttel M, 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.
22. Ito Y, Miyauchi A, Oda H, Kobayashi K, Kihara M, Miya A. Revisiting low-risk thyroid papillary microcarcinomas resected without observation: was immediate surgery necessary? *World J Surg* 2016;**40**:523–8.
23. Hirokawa M, Kudo T, Ota H, Suzuki A, Miyauchi A. Pathological characteristics of low-risk papillary thyroid microcarcinoma with progression during active surveillance. *Endocr J* 2016;**63**:805–10.
24. Ito Y, Kobayashi K, Tomoda C, et al. Ill-defined edge on ultrasonographic examination can be a marker of aggressive characteristic of papillary thyroid microcarcinoma. *World J Surg* 2005;**29**:1007–11.
25. Xing M, Liu B, Liu X, et al. *BRAFV600E* and *TERT* promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. *J Clin Oncol* 2014;**32**:2716–26.
26. Lee SE, Hwang TS, Choi YL, et al. Prognostic significance of TERT promoter mutations in papillary thyroid carcinomas in a BRAF(V600E) mutation-prevalent population. *Thyroid* 2016;**26**:901–10.
27. Ito Y, Yoshida H, Maruo R, et al. BRAF mutation in papillary thyroid carcinoma in a Japanese population: its lack of correlation with high-risk clinicopathological features and disease-free survival of patients. *Endocr J* 2009;**56**:89–97.
28. Ito Y, Yoshida H, Kihara M, Kobayashi K, Miya A, Miyauchi A. BRAF(V600E) mutation analysis in papillary thyroid carcinoma: is it useful for all patients? *World J Surg* 2014;**38**:679–87.
29. Shindo H, Amino N, Ito Y, et al. Papillary thyroid microcarcinoma might progress during pregnancy. *Thryoid* 2014;**24**:840–4.
30. Ito Y, Miyauchi A, Kudo T, et al. Effects of pregnancy on papillary microcarcinoma of the thyroid re-evaluated in the entire patient series at Kuma Hospital. *Thyroid* 2016;**26**:156–60.
31. Lubitz CC1, Kong CY, McMahon PM, et al. Annual financial impact of well-differentiated thyroid cancer care in the United States. *Cancer* 2014;**120**:1345–52.
32. 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.
33. Oda H, Miyauchi A, Ito Y, 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.
34. Lim CY, Yun JS, Lee J, et al. Percutaneous ethanol injection therapy for locally recurrent papillary thyroid carcinoma. *Thyroid* 2007;**17**:347–50.
35. Dupuy DE, Monchik JM, Decrea C, et al. Radiofrequency ablation of regional recurrence from well-differentiated thyroid malignancy. *Surgery* 2001;**130**:971–7.