Position paper from the Japan Thyroid Association task force on the management of low-risk papillary thyroid microcarcinoma (T1aN0M0) in adults

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Abstract. The incidence of thyroid carcinoma has been increasing worldwide. This is interpreted as an increase in the incidental detection of papillary thyroid microcarcinomas (PTMCs). However, mortality has not changed, suggesting overdiagnosis and overtreatment. Prospective clinical trials of active surveillance for low-risk PTMC (T1aN0M0) have been conducted in two Japanese institutions since the 1990s. Based on the favorable outcomes of these trials, active surveillance has been gradually adopted worldwide. A task force on the management of PTMC in adults organized by the Japan Thyroid Association therefore conducted a systematic review and has produced the present position paper based on the scientific evidence concerning active surveillance. This paper indicates evidence for the increased incidence of PTMC, favorable surgical outcomes for low-risk PTMC, recommended criteria for diagnosis using fine needle aspiration cytology, and evaluation of lymph node metastasis (LNM), extrathyroidal extension (ETE) and distant metastasis. Active surveillance has also been reported with a low incidence of disease progression and no subsequent recurrence or adverse events on survival if conversion surgery was performed at a slightly advanced stage. Active surveillance is a safe and valid strategy for PTMC, because it might preserve physical quality of life and reduce 10-year medical costs. However, some points should be noted when performing active surveillance. Immediate surgery is needed for PTMC showing high-risk features, such as clinical LNM, ETE or distant metastasis. Active surveillance should be performed under an appropriate medical team and should be continued for life.

Key words: Papillary thyroid microcarcinoma, Active surveillance, Japan Thyroid Association, Position paper
IN RECENT YEARS, the incidence of thyroid carcinoma has been increasing rapidly worldwide. This increase is mainly due to the widespread adoption of imaging tests such as ultrasonography (US), the improvement of diagnostic accuracy, and increasing opportunities for these tests, and the incidental detection of small papillary thyroid carcinomas (PTCs) is thus considered to be increasing. On the other hand, the mortality of thyroid carcinoma has not changed, suggesting that small PTCs may be overdiagnosed and overtreated.

The “Thyroid Ultrasound-A guidebook for diagnosis and management, 2nd edition” published by the Japan Association of Breast and Thyroid Sonology (JABTS) in 2012 therefore did not recommend screening for small papillary carcinomas [1]. In 2017, the United States Preventive Service Task Force (USPSTF) also published a statement that thyroid carcinoma screening using cervical palpation and US was not recommended for asymptomatic adults without a history of radiation exposure to the neck or a family history of thyroid carcinoma [2]. In addition, the Japanese Thyroid Association (JTA) and American Thyroid Association (ATA) management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer set a lower limit on the diameter of tumors to be examined with fine needle aspiration cytology (FNAC) in cases where PTC is suspected based on US findings [3, 4].

Prospective clinical trials, in which low-risk (T1aN0M0) papillary thyroid microcarcinomas (PTMCs) without clinical apparent metastasis and invasion is followed-up using US instead of immediate surgery after diagnosis, have been conducted at two Japanese institutions, Kuma Hospital and Cancer Institute Hospital, since the 1990s. This management policy is called active surveillance. Based on the favorable outcomes of these clinical trials, “Japanese clinical guidelines for treatment of thyroid tumor” published in 2010 by the Japan Association of Endocrine Surgeons and the Japanese Society of Thyroid Surgery (those two associations combined to form the present Japan Association of Endocrine Surgery (JAES) in 2018) allowed active surveillance for patients with low-risk PTMCs under sufficient explanation and consent alternative to immediate surgery [5]. In 2015, ATA management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer also acknowledged a policy of active surveillance for low-risk PTMCs [4].

In this situation, the JTA decided to issue a position paper based on the current scientific evidence by means of a systematic search of relevant articles with the aim of presenting the scientific evidence concerning active surveillance for adult patients with low-risk PTMCs to the general public and physicians. It is hoped that this position paper will provide a better understanding and widespread recognition of the concept of overdiagnosis and overtreatment of thyroid carcinomas and the appropriate indications and methods for the safe implementation of a new management policy called active surveillance.

Methods

The committee to prepare this position paper was established in November 2018. Committee members were assigned by the JTA and consisted of 13 endocrinologists, 3 endocrine/thyroid surgeons, 1 head and neck surgeon and 1 research scientist specializing in thyroid diseases. We referred to Minds Manual for Guideline Development 2017 published by the Japan Council for Quality Health Care [6] and The Grading of Recommendations Assessment, Development and Evaluation (GRADE) method published internationally to prepare this paper.

Determination of clinical question (CQ)

Clinically important issues regarding the treatment of low-risk PTMC in adults were divided into epidemiology, surgical outcome, diagnosis, and active surveillance. Finally, a total of six CQs were selected: 1 regarding epidemiology, 1 regarding surgical outcome, 3 regarding diagnosis, and 1 regarding active surveillance. The committee examined each CQ and set keywords for the literature search.

Literature search

A literature search was conducted by the Japan Medical Library Association. A comprehensive search of the literature published from January 1st, 1990 to June 30th, 2019 was performed. The databases searched were PubMed, Ichushi-web from NPO Japan Medical Abstracts Society, and the Cochrane Library. The search languages were English and Japanese. The search formula for each CQ is described in the Appendix.

Primary screening

Two members (CQ1-3: I.S. and K.H., CQ4: I.S and Y.Y.) in charge of each CQ independently examined the title and abstract of the reports collected in the literature search, and excluded those reports that did not fit the purposes of the CQ. Results from each member were queried, and a secondary screening data set was created. The full texts of the identified reports were collected according to the dataset.

Secondary screening

For each CQ, two members independently examined the full texts of the reports selected by primary screening.
and excluded those reports that did not fit the purpose of the CQ. In addition, reports that the committee deemed necessary for the purpose of the CQ were additionally investigated. A table of patients, interventions, comparisons and outcomes (PICO) or patients, exposures, comparisons and outcomes (PECO) was prepared for each report from the literature.

**Preparation of drafts**

Based on the tables created in the secondary screening, reports with a high level of evidence were selected from those reports that fit the purpose of each CQ. The committee in charge of each CQ (3 or 4 individuals for each CQ) drafted the position paper based on the selected literature.

**Consensus building**

To prepare this position paper, a consensus was built on the statement for each CQ by convening the committee and gathering opinions through e-mail deliberations.

**Evaluation of the position paper**

After preparing the final draft of this position paper, public comments on the final draft were invited from members of the JTA and JAES. The final draft was revised based on the comments and obtained endorsement from both societies.

**Funds**

This position paper was created through the general account budget of the JTA and had no interest in other specific organizations, products or technologies.

**Conflict of interest (COI)**

Appropriate management of COI was implemented for all members of the committee in accordance with common guidelines for COI in clinical research by the Japan Endocrine Society. No member had COI regarding the preparation or content of this position paper.

**CQ 1: Has the incidence of PTC increased in recent years?**

**Summary**

While the incidence of small PTCs has increased worldwide since the 1980s, mortality from thyroid carcinomas during the same period has remained almost unchanged. Autopsy studies on patients with no known history of thyroid pathology found that about 10% of PTCs were unrelated to the cause of death, and the incidence has not changed since the 1970s. On the other hand, the times during which US and FNAC spread rapidly and the time when the incidence of PTC increased were coincident. These facts suggest that most of the small PTCs comprising the perceived increase in recent years do not affect lifespan, and were instead found due in large part to improvements in examination accuracy and increased opportunities for examinations.

**Comments**

In recent years, the incidence of thyroid carcinomas has increased worldwide, as shown in Table 1 [7-35]. The histopathological type of increased thyroid carcinoma was mostly PTC, especially small PTC with tumor diameter <20 mm [8, 11, 13, 19, 22, 25, 27-29, 32, 34, 36-39]. For example, Davies et al. reported that the incidence of PTC increased 2.9-fold between 1988 and 2002, with 49% showing a tumor size <10 mm and 87% with tumor size <20 mm [19]. Du et al. reported that 94.9% of thyroid carcinomas diagnosed in China between 1972 and 2014 were PTCs, of which 70.4% had tumor size <10 mm [8].

Excessive iodine intake (especially in iodine-deficient areas) [9, 12, 16, 22, 23, 28, 31, 34, 40], obesity [7, 11, 16, 20, 22], dietary habits such as intake of nitrates, nitrites, and specific trace elements [26], chemical substances such as dioxins [41] and polybrominated diphenyl ethers [18, 24], impacts of the Chernobyl nuclear accident [7, 12, 27, 32], environmental factors such as living in an area near a nuclear power plant [24] or living in volcanic areas [42], and exposure to medical radiation [8, 11, 16-18, 35] have been mentioned as causes of increased PTC, but the extent of their involvement in tumor development remains uncertain.

Few reports have described increasing mortality of PTC, despite the increasing incidence [7-21]. The increased incidence of PTC is interpreted as resulting from the overdiagnosis of small PTC that do not affect lifespan [8, 11, 13, 15, 16, 19, 24, 27, 31, 32, 42-45]. Indeed, Furuya-Kanamori et al. analyzed 12,834 autopsies of patients with no known history of thyroid pathology in 38 regions of 25 countries from 1949 to 2007, and reported that the prevalence of incidental thyroid carcinoma among the partial and whole examination subgroup were 4.1% and 11.2%, respectively, showing no change since 1970 [46].

The reason why the number of small PTCs is increasing is considered to involve increased examination opportunities for the thyroid gland due to the widespread adoption of thyroid US and FNAC that can easily diagnose PTC [8, 11, 12, 15, 16, 18-21, 23-25, 27, 29, 34, 44]. Comparing the ability to detect thyroid nodules by palpation and thyroid US, 93.6% of nodules <5 mm and 51.8% of nodules ≥20 mm cannot be detected by palpation. Therefore, US has been reported to have high sensitivity to detect thyroid nodules compared to palpation.
| Ref | Country or region | Sex | Type | Age-adjusted incidence rate per 100,000 people | Age-adjusted mortality rate per 100,000 people |
|-----|------------------|-----|------|-----------------------------------------------|-----------------------------------------------|
|     |                  |     |      | Observation period | Incidence rate | Observation period | Incidence rate | Observation period | Mortality rate | Observation period | Mortality rate |
| 7   | Spain            | Male | PTC  | 1985–1987 | 1.3 (3.5) | 2009–2013 | 3.9 (10.2) | 2000–2004 | 0.28 (3.4) | 2005–2009 | 0.26 (3.3) |
|     |                  | Female |      |           |             |             |             | 2000–2004 | 0.2 (2.3) | 2005–2012 | 0.2 (2.0) |
| 8   | China            | TC   |      | 2000     | 2.75 (2012 | 19.42 (9.4) | 2000–2013 | 0.2 (2.3) | 2005–2012 | 0.2 (2.0) |
| 9   | Singapore        | Male | TC   | 1974     | 1.5 (3.7) | 2013     | 2.7 (8.4) | 1974–1978 | <1.0 (1.0) | 2009–2013 | <1.0 (1.0) |
|     |                  | Female |      |           |             |             |             | 1974–1978 | <1.0 (1.0) | 2009–2013 | <1.0 (1.0) |
| 10  | Italy            | Male | TC   | 1998–2002 | 5.3 (16.2) | 2008–2012 | 10.1 (28.2) | 1998–2002 | 0.87 (0.94) | 2008–2012 | 0.76 (0.77) |
|     |                  | Female |      |           |             |             |             | 1998–2002 | 0.87 (0.94) | 2008–2012 | 0.76 (0.77) |
| 11  | Switzerland      | Male | PTC  | 1998     | 1.59 (2.93) | 2012     | 0.56 (0.42) | 1998     | 0.67 (0.48) | 2012     | 0.48 (0.48) |
|     |                  | non-PTC |      |           |             |             |             | 1998     | 0.67 (0.48) | 2012     | 0.48 (0.48) |
|     |                  | Female |      |           |             |             |             | 1998     | 0.67 (0.48) | 2012     | 0.48 (0.48) |
| 12  | Croatia          | Male | TC   | 1988     | 1.9 (4.5) | 2010     | 3.2 (13.2) | 1988     | 0.7 (0.7) | 2010     | 0.6 (0.6) |
|     |                  | Female |      |           |             |             |             | 1988     | 0.7 (0.7) | 2010     | 0.6 (0.6) |
| 13  | United States    | TC   |      | 1990     | 5.43 (2009 | 14.1 (4.1) | 1990     | 0.37 (0.37) | 2009     | 0.5 (0.5) |
| 14  | Korea            | Male | TC   | 1996–2000 | 2.3 (21) | 2006–2010 | 13.5 (100) | 1996–2000 | 0.3 (0.4) | 2006–2010 | 0.5 (0.6) |
|     |                  | Female |      |           |             |             |             | 1996–2000 | 0.3 (0.4) | 2006–2010 | 0.5 (0.6) |
| 15  | United States    | PTC  |      | 1973     | 3.5 (2009 | 12.5 (12.5) | Mortality rate around 0.5 and decreasing by 0.11%/year since 1975 |
| 16  | Brazil           | Male | PTC  | 1997–2000 | 2.15 (4.31) | 2005–2008 | 4.09 (8.18) | 1997–2000 | 0.37 (0.37) | 2005–2008 | 0.3 (0.3) |
|     |                  | TC   |      | 1997–2000 | 3.64 (5.49) | 2005–2008 | 8.36 (18.81) | 1997–2000 | 0.53 (0.37) | 2005–2008 | 0.37 (0.37) |
|     |                  | Female |      | 1997–2000 | 14.8 (23.11) | 2005–2008 |                 | 1997–2000 | 0.53 (0.37) | 2005–2008 | 0.37 (0.37) |
| 17  | Puerto Rico      | Male | TC   | 1985     | 1.1 (4.7) | 2004     | 3.0 (10.5) | 1985     | 0.2 (0.6) | 2004     | 0.3 (0.4) |
|     |                  | Female |      |           |             |             |             | 1985     | 0.2 (0.6) | 2004     | 0.3 (0.4) |
| 18  | United States    | Male | PTC  | 1985–1989 | 3.0 (7.3) | 2000–2004 | 4.6 (13.0) | 1985–1989 | 0.4 (0.47) | 2000–2004 | 0.46 (0.47) |
|     |                  | Female |      |           |             |             |             | 1985–1989 | 0.4 (0.47) | 2000–2004 | 0.46 (0.47) |
| 19  | United States    | TC   |      | 1973     | 3.6 (2.7) | 2002     | 8.7 (7.7) | 1973     | 0.57 (0.57) | 2002     | 0.47 (0.47) |
|     |                  | PTC  |      |           |             |             |             | 1973     | 0.57 (0.57) | 2002     | 0.47 (0.47) |
| 20  | Korea            | Male | PTC  | 1997     | 1.11 (19.2) | 2011     | 19.22 (20.01) | changed by 0.03% per year |
|     |                  | TC   |      | 1997     | 1.48 (20.01) | 2011     | 94.15 (96.08) | changed by 0.4% per year |
|     |                  | Female |      |           |             |             |             | 1997     | 1.48 (20.01) | 2011     | 94.15 (96.08) |
| 21  | United States    | TC   |      | 1974–1977 | 4.56 (2010–2013 | 14.42 (3.2) | increased by 1.1% per year (1994–2003) |
| 22  | Denmark          | TC   |      | 1980     | 0.62 (2014 | 3.2 (2.2) |
| 23  | Sri Lanka        | Male | PTC  | 2001     | 1.55 (2.45) | 2010     | 1.89 (5.6) |
|     |                  | Female |      |           |             |             |             | 2001     | 1.55 (2.45) | 2010     | 1.89 (5.6) |
| 24  | Republic of China| Male | TC   | 1997     | 1.93 (9.3) | 2012     | 5.62 (18.81) |
|     |                  | Female |      |           |             |             |             | 1997     | 1.93 (9.3) | 2012     | 5.62 (18.81) |
| 25  | Spain            | Male | TC   | 1986–1990 | 2.24 (9.05) | 2006–2010 | 5.85 (14.04) |
|     |                  | Female |      |           |             |             |             | 1986–1990 | 2.24 (9.05) | 2006–2010 | 5.85 (14.04) |
Table 1 Cont.

| Ref | Country or region | Sex | Type | Age-adjusted incidence rate per 100,000 people | Age-adjusted mortality rate per 100,000 people |
|-----|-------------------|-----|------|-----------------------------------------------|-----------------------------------------------|
|     |                   |     |      | Observation period | Incidence rate | Observation period | Incidence rate | Observation period | Mortality rate | Observation period | Mortality rate |
| 26  | United States     |     | TC   | 1988–1992 | 3.1 | 2003–2007 | 26.4 |
|     |                   | Male |      | 2.0      | 2.4 |           |     |
|     |                   | Female |     | 5.8      | 6.7 |           |     |
|     |                   | Male |      | 1.0      | 1.7 |           |     |
|     |                   | Female |     | 2.5      | 4.7 |           |     |
|     |                   | Male |      | 2.1      | 5.3 |           |     |
|     |                   | Female |     | 6.9      | 16.0 |          |     |
|     | Italy             | Male | TC   | 1988–1992 | 8.2 | 2003–2007 | 6.2 |
|     |                   | Female |     | 3.4      | 6.2 |           |     |
|     |                   | Male |      | 9.1      | 19.2 |          |     |
|     |                   | Female |     | 2.2      | 4.3 |           |     |
|     |                   | Male |      | 5.6      | 13.4 |          |     |
|     |                   | Female |     | 1.7      | 2.3 |           |     |
|     |                   | Male |      | 6.6      | 7.6 |           |     |
|     |                   | Female |     | 2.6      | 11.3 |          |     |
|     | Korea             | Male | TC   | 1993–1997 | 12.2 | 2003–2007 | 59.9 |
|     |                   | Female |     | 6.7      | 7.6 |           |     |

PTC, Papillary thyroid carcinoma; TC, Thyroid carcinoma; DTC, Differentiated thyroid carcinoma; PMC, Papillary microcarcinoma

[47]. Takebe et al. reported that PTC was found in 3.5% of subjects after active screening for thyroid carcinoma using US and FNAC in adult women (FNAC was conducted for nodules $\geq 3$ mm) [48]. In the United States, the number of US examinations has been reported to have increased 5-fold and the number of FNAC procedures...
increased 7-fold, resulting in a 2-fold increase in the incidence of thyroid carcinoma in 2012 compared to 2000 [49]. In Korea, the policy of general cancer screening with no charge has led to the active use of thyroid US, resulting in a 15-fold increase in the incidence of PTC between 1993 and 2011, and most of those cases involved a tumor <10 mm in maximal diameter [44]. A greater number of opportunities for examinations, such as thyroid US, is reportedly associated with a greater incidence of PTC, but most are small, unpalpable carcinomas [15]. In addition, computed tomography (CT), magnetic resonance imaging (MRI) and fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT carried out for the purpose of screening or evaluation of other diseases has led to the increased detection of incidental thyroid carcinoma [13, 50-53].

CQ2: What is the surgical outcome of low-risk PTMC (T1aN0M0)?

Summary
Postoperative outcomes for PTC with tumor size ≤10 mm and no clinical invasion or metastasis (low-risk PTMC: T1aN0M0) are extremely favorable.

Comments
Yu et al. reported that the 10- and 15-year disease-specific survival rates were 99.5% and 99.3%, respectively, in 18,445 cases of PTMC with a tumor size <10 mm (including 2,294 cases with lymph node metastasis [LNMI]) in a retrospective study using the Surveillance, Epidemiology and End Results Cancer Database (SEER), and the prognostic of PTMC was good regardless of the presence or absence of LNM [54]. In Japan, Ito et al. reported no recurrence at distant sites or cause-specific death 10 years after surgery among 1,034 patients of PTMC, with no clinical LNM or extrathyroidal extension (ETE) [55]. Similarly, Sugitani et al. reported that although lymph node recurrence was observed in 4 cases (2.7%), no distant recurrence or cause-specific death was observed among 148 cases of asymptomatic PTMC (T1aN0M0). On the other hand, 30 cases of symptomatic PTMC with clinical LNM or recurrent laryngeal nerve palsy at the time of diagnosis showed 9 cervical recurrences, 4 distant recurrences, and 4 cause-specific deaths [56]. Noguchi et al. examined 2,070 cases of PTMC including incidentaloma and reported that the 35-year recurrence-free survival rate was 80.4% in 791 patients with clinical LNM, compared with 94.7% in 137 patients without clinical LNM. They also reported that the 25-year recurrence-free survival rates were 73.8% and 60.5% in patients with recurrent laryngeal nerve invasion or esophageal muscle layer invasion, respectively, compared with 94.3% and 94.0% in patients without those invasions, respectively [57].

The postoperative prognosis for PTC with tumor size ≤10 mm and no clinical invasion or distant metastasis (low-risk PTMC: T1aN0M0) is therefore extremely good.

Postoperative prognoses of PTC were compared between tumor size ≤5 mm and tumor size 5–10 mm using data from small retrospective studies. Survival rates were extremely good in both groups, although the recurrence rate for PTC with tumor size ≤5 mm was slightly lower than that for PTC with tumor size 5–10 mm [58-60]. Based on a meta-analysis by Mehanna et al., the recurrence rate for incidental carcinoma (854 cases; mean tumor size, 4.6 mm) discovered on postoperative pathological examination of Graves’ disease or benign tumor was 0.5%, significantly better than the 7.9% for non-incidental carcinoma (2,669 cases; mean tumor size, 6.9 mm) diagnosed preoperatively (odds ratio [OR] 14.7, 95% confidence interval [CI] 5.6–54.8) [61].

CQ3: Diagnosis of PTMC

CQ 3-1: Is FNAC recommended when a nodule of size ≤10 mm is found on US?

Summary
FNAC is recommended for nodules 5–10 mm in size that are strongly suspected to represent malignancy on US, while observation without FNAC is recommended for nodules ≤5 mm. However, FNAC should be considered when there is clinical LNM or ETE (particularly posterior extension), hoarseness due to recurrent laryngeal nerve palsy, or distant metastasis.

Comments
Actively searching for PTMC in health screenings is not preferable. The demerits of detecting PTMC in screening tests have already been emphasized in the Thyroid Ultrasound-A guidebook for diagnosis and management, 2nd edition published by the JABTS [1]. In addition, they recommend the necessity of considering the examination procedures and criteria sufficiently, so as not to bring about any disadvantages to the examinee when health examinations are consciously performed. In 2017, the USPSTF also published a statement that thyroid carcinoma screening using cervical palpation or US was not recommended for asymptomatic adults without a history of radiation exposure to the neck or a family history of thyroid carcinoma [2].

According to the second edition of the “Japanese guidebook for the thyroid ultrasound diagnosis” and the third edition revised in 2016 [1, 62], FNAC is recommended for a solid lesion with a tumor size of 5–10 mm, only when the nodule meets almost all signs suggesting a
high suspicion for malignancy. Observation without FNAC is usually recommended for solid lesions with tumor size ≤5 mm, but FNAC should be considered when there is clinical LNM, hoarseness due to recurrent laryngeal nerve palsy or distant metastasis, or when medullary thyroid carcinoma is suspected due to high serum carcinoembryonic antigen (CEA)/calcitonin. For patients with a history of high-dose radiation exposure, surgical history of thyroid carcinoma, or family history of thyroid carcinoma, FNAC could be considered when determining the malignant risk of thyroid nodules. A similar policy for FNAC is also recommended in the practice guideline for thyroid nodule treatment 2013 published by the JTA [3]. The ATA [4], National Comprehensive Cancer Network (NCCN) [63], American College of Radiology (ACR) [64], European Society for Medical Oncology (ESMO) [65] and European Thyroid Association (ETA) [66] have also published guidelines for thyroid nodule treatment. The criteria for FNAC in various guidelines are summarized in Table 2. In all guidelines, FNAC is recommended for thyroid nodules 10–15 mm in size that have US findings suspicious of malignancy, and FNAC is not recommended for thyroid nodules with diameter ≤10 mm in principle. However, FNAC is considered for nodules with all malignant US signs (ATA) and high-risk nodules that are suspected to have LNM, ETEs, or distant metastases (ATA and ETA).

Many studies have examined what kind of US findings are suggestive of malignancy for thyroid nodules. A multicenter study by Shimura et al. reported that border characteristics, shape, and internal echo level of thyroid nodule as US findings were important characteristics to differentiate PTC from benign nodules [67].

Table 2 Criteria for fine-needle aspiration cytology on thyroid nodules in various guidelines

| 5–10 mm | 10–15 mm | 15–20 mm | >20 mm |
|---------|----------|----------|--------|
| JABTS (2016) | Highly suspicious (Meets most suspicious US findings including shape, boundary, internal echo, high echo level, and halo sign) | Suspicious (Meets any suspicious US features) (Except for spongiform) | Recommend FNAC |
| JTA (2013) | Sonographically suspicious subcentimeter thyroid nodule without evidence of extrathyroidal extension or sonographically suspicious lymph nodes may be observed. FNA can be considered at lower size cutoffs for all sonographic appearances | High-suspicion pattern (Solid hypoechoic nodule or solid component of a partially cystic nodule with one or more suspicious US features) Intermediate-suspicion pattern (Hypoechoic solid nodule) | Low-suspicion pattern (Iso- or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas) Very low-suspicion pattern (Spongiform pattern or partially cystic nodule without suspicious US features) |
| ATA (2016) | Not recommended | 1. Solid nodule with suspicious US features 2. Mixed cystic-solid nodule with suspicious US features if solid component >1 cm | |
| NCCN (2019) | Not recommended | Highly suspicious (≥7/14 points) (15–25 mm) Moderately suspicious (4–6/14 points) (≥25 mm) | Spongiform nodule |
| ACR (2017) | Preoperative FNAC for cytology not required for nodules measuring ≤1 cm | Similar to ATA | Similar to ATA |
| ESMO (2019) | Patients with <1-cm nodules with highly suspicious US features and no abnormal lymph nodes can have the choice of FNA or observation. In case of proven growth or detection of a suspicious lymph node, FNA should be performed. | Nodule with high-risk US features | Nodule with intermediate-risk US features Nodule with low-risk US features |
| ETA (2017) | | |

JABTS, Japan Association of Breast and Thyroid Sonology; JTA, Japan Thyroid Association; ATA, American Thyroid Association; NCCN, National Comprehensive Cancer Network; ACR, American College of Radiology; ESMO, European Society for Medical Oncology; ETA, European Thyroid Association; US, ultrasonography; FNAC, fine needle aspiration cytology
was reflected in the “Japanese guidebook for the thyroid ultrasound diagnosis, 2nd edition” published by JABTS [1]. Recent meta-analyses [68-70] have reported useful US findings contributing to the diagnosis of benign and malignant thyroid nodules (Table 3). Common malignant US findings in these reports included taller-than-wide shape, microcalcification, irregular border, internal low echo, solid nodule, and internal blood flow.

CQ 3-2: Is evaluation of LNM and ETE for PTMC recommended?

Summary

As clinical LNM and ETE are important risk factors for poor prognosis even in patients with PTMC, accurate evaluation of these factors is recommended. US is recommended for detecting clinical LNM and ETE. If evaluation with US is insufficient, additional evaluation with contrast-enhanced CT is appropriate.

Small LNM or minimal ETE can be found during surgery or by histopathological examination in PTC patients without clinical LNM or ETE. However, these findings have not been shown to be risk factors for cancer mortality.

Comments

Clinical LNM and ETE as found on imaging tests are risk factors for mortality even in patients with PTMC [71]. Sugitani et al. reported that development of clinical LNMs was found in 1% among 230 patients who

| Author          | Suspicious findings                  | Ratio (95%CI) | Benign findings | Ratio (95%CI) |
|-----------------|--------------------------------------|---------------|-----------------|---------------|
| Brito (2014)    | Taller than wide                     | 11.14 (6.6–18.9) | Spongiform     | 12 (0.61–234.3) |
| Brito (2014)    | Infiltrative margins                 | 6.89 (3.35–14.1) | Cystic nodule   | 6.78 (2.26–20.3) |
| Brito (2014)    | Internal calcification               | 6.78 (4.48–10.24) | Isoechoic       | 3.6 (2–6.3) |
| Brito (2014)    | Hypoechoic                           | 4.5 (3.2–6.4) |                  |               |
| Brito (2014)    | Solid nodule                         | 4.45 (2.63–7.5) |                 |               |
| Brito (2014)    | Increased blood flow (centrally)     | 1.8 (1.48–2.2) |                 |               |
| Campanella (2014) | Nodule height greater than width   | 10.15 (6.72–15.33) |                |               |
| Campanella (2014) | Absent halo sign                   | 7.14 (3.71–13.71) |                |               |
| Campanella (2014) | Microcalcifications                | 6.76 (4.72–9.69) |                |               |
| Campanella (2014) | Irregular margins                  | 6.12 (3.12–12.02) |                |               |
| Campanella (2014) | Hypoechoogenicity                  | 5.07 (3.47–7.43) |                |               |
| Campanella (2014) | Solid nodule structure             | 4.69 (2.63–8.36) |                |               |
| Campanella (2014) | Intranodular vascularization       | 3.76 (2.04–6.95) |                |               |
| Campanella (2014) | Nodule size ≥4 cm                   | 1.63 (1.04–2.55) |                |               |
| Campanella (2014) | Single nodule                      | 1.43 (1.09–1.88) |                |               |

Table 3 Meta-analysis of sonographic findings contributing to diagnosis of benign and malignant thyroid nodules
underwent active surveillance for low-risk PTMC for an average of 5 years, although ETE and distant metastasis did not appear. In that report, no recurrence of PTC was observed in 12 patients who underwent conversion surgery for any reason after active surveillance [72]. However, the 10-year disease-specific survival rate for 56 cases of PTMC with clinical LNM was 80%, and prognosis was particularly poor for cases with ETE, extra-lymph node extension, or LNM with a size of ≥20 mm.

Yu et al. reported that the postoperative disease-specific survival rate was 99.5% for 10 years and 99.3% for 15 years in a retrospective observational study of 18,445 cases of PTMC using the SEER database in the United States [54]. They also reported that LNM and ETE in addition to age ≥45 years, male sex, African-American ethnicity, or minority race were risk factors for decreased overall survival. Park et al. from Korea examined 3,174 surgical cases of thyroid carcinoma (3,073 cases were PTC, including 1,518 cases with tumor size ≤10 mm and 1,022 cases with a tumor size 10–20 mm). They reported that the 10-year disease-specific survival rate showed no significant difference among cases with no ETE, microscopic ETE, and extension only to the strap muscles, but was significantly poorer in cases with extension to the subcutaneous tissue, larynx, trachea, and esophagus compared to other cases [73].

On the other hand, small LNM or minimal ETE is often confirmed at the time of surgery or histopathological examination even in patients with PTC diagnosed as having no clinical LNM or ETE. In particular, the detection of LNM in the central compartment by US has been reported as difficult [74]. Wang et al. reported that 395 cases (33%) had LNM in the central compartment in the histopathological examination of 1,204 cases of PTMC [75]. Zhao et al. reported that 218 of 521 cases with PTMC had LNM in the central compartment, among which 149 cases (68%) were undetectable with US before surgery [76]. The frequency of minimal ETE was reported to range from 6.3% to 48% [54, 77-81].

Regarding the significance as a prognostic factor of LNM and ETE that were only diagnosed histopathologically, not clinically, Xu et al. reported that the recurrence-free survival rate in 3,607 cases with PTMC was 87.5% (26 cases of cervical lymph node recurrence, 13 cases of remnant thyroid recurrence) and histopathological LNM was not a prognostic factor [82]. Diker-Cohen et al. reported that minimal ETE did not affect cause-specific survival in a meta-analysis of 2,580 cases in 5 studies of PTMC [83]. Moreover, minimal ETE that can be diagnosed only by microscopic examination and ETE only to the strap muscles have been reported as not representing independent risk factors for cancer mortality [84-86].

As for the imaging modality to detect clinical LNM and ETE, US was recommended in the guidelines of ATA and JAES [4, 71]. If the evaluation with US is insufficient, additional evaluation with contrast-enhanced CT is appropriate.

**CQ3-3: Is evaluation of distant metastasis for PTMC recommended?**

**Summary**

The frequency of distant metastases to the lung, bone, and brain in PTMC was reported to be 0.14–0.50%. Distant metastasis is extremely rare in PTMC without LNM or ETE, which are indicated for active surveillance. No reports found new distant metastases during active surveillance. Evaluation of distant metastases in low-risk PTMC is therefore not mandatory.

**Comments**

Distant metastasis has been reported as one of the poor prognostic factors for PTMC [54]. The frequency of distant metastasis at the time of PTMC diagnosis has been reported in several retrospective observational studies. Roti et al. reported that distant metastases at the time of diagnosis of PTMC were found in 35 of 9,313 cases (0.37%) in a meta-analysis of 17 studies from 1966 to 2008 [87]. Analysis using the SEER database revealed that ETE was 6.3%, pathological LNM was 12.4%, and distant metastasis was 0.5% in 18,445 patients with PTMC who underwent surgery between 1988 and 2007 [54]. Jeon et al. retrospectively analyzed 8,808 cases of PTMC who underwent initial surgery at the Asan Medical Center in Korea from 1999 to 2012, and found distant metastasis in 12 cases (0.14%), among which ten of these were associated with clinically apparent LNM [88].

Indeed, Kawano et al. reported that no distant metastasis was detected by preoperative chest CT performed for 1,000 patients with low-risk PTMC at Kuma Hospital from January 2006 to August 2011 [89].

Sugitani et al. reported that no new distant metastases were observed during 1–17 years of active surveillance for 230 patients with low-risk PTMC at the Cancer Institute Hospital in Japan [72]. Ito et al. reported that no appearance of distant metastases was seen among 1,235 cases of PTMC under active surveillance during a 10-year follow-up period at Kuma Hospital [90]. Tuttle et al. also reported no new distant metastases in 291 cases of PTMC with tumor size <15 mm during the median 25 months of follow-up at Memorial Sloan Kettering Cancer Center in the United States [91].

In summary, as distant metastases are extremely rare in cases of low-risk PTMC without clinical LNM or ETE, evaluating distant metastases is not mandatory in these cases.
CQ4: Is active surveillance recommended over immediate surgery for low-risk PTMC?

Summary

Active surveillance of low-risk PTMC has been reported with a low incidence of disease progression. When conversion surgery was performed at a slightly advanced stage, no subsequent recurrence or adverse event on survival was reported.

Younger age has been reported as a risk factor for progression (increasing tumor size, clinical LNM) during active surveillance for low-risk PTMC.

Surgery performed for low-risk PTMC carries little concern regarding recurrence, but surgical complications such as permanent hypoparathyroidism and permanent recurrent nerve palsy still occur, albeit rarely, even when surgery is performed by well-trained thyroid surgeons.

The 10-year-medical cost of immediate surgery is reported to be higher than that of active surveillance under the Japanese Health Care Insurance System.

Few studies of quality of life (QOL) or patient-reported outcomes (PRO) have compared active surveillance and immediate surgery. Active surveillance is associated with better physical QOL because surgical complications such as permanent hypoparathyroidism and permanent recurrent nerve palsy still occur, albeit rarely, even when surgery is performed by well-trained thyroid surgeons. On the other hand, active surveillance may cause more anxiety than immediate surgery, but this anxiety has been shown to decrease over time.

In conclusion, active surveillance is considered a safe and valid strategy for PTMC if appropriately indicated. In particular, the elderly have a low probability of progression and are considered good candidates for active surveillance.

Comments

Disease progression under active surveillance (Table 4)

The definition of disease progression during active surveillance is as follows: tumor growth, clinically evident ETE, and novel lymph node or distant metastases. The definition of tumor growth was reported by two measurement methods: an increase in maximum tumor diameter by ≥3 mm, or enlargement as a 50% increase in tumor volume.

During active surveillance, 2–26% of patients with PTMC showed tumor growth, while >70% had no disease progression [72, 90-103]. In a report from Kuma Hospital, which had the longest observation of the largest cohort in the world, 1,235 patients with an average of 60 months of active surveillance displayed a cumulative tumor growth (increase in maximum tumor diameter by ≥3 mm) rate of 8.0%, and a cumulative increase of novel LNM of 3.8% at 10 years, respectively [90]. In addition, a report from the Cancer Institute Hospital found that 409 patients with active surveillance for a median observation period of 6.8 years showed an increase of ≥3 mm in maximum tumor diameter for 6.0% and LNM for 1.0% [92].

Reports on active surveillance from overseas have been increasing in recent years. Reports from the United States [91], Korea [99], Italy [101], and Colombia [103] have shown that the incidence of a ≥3-mm increase in maximum tumor diameter was 3.8%, 3.5%, 2.1%, and 10.8%, respectively. Although the observation period was shorter than that reported from Japan, no significant difference in the frequency of disease progression was identified, and active surveillance of PTMC seems to be an acceptable strategy in various countries.

Reports from the United States [91] and Colombia [103] have included patients with tumor diameters of 10–15 mm (reports from Colombia also include tumors >15 mm that were inoperable due to comorbidities). In Japan, active surveillance of T1bN0M0 PTCs has been reported by Cancer Institute Hospital [96] and Nagoya University [102]. Sixty-one T1b patients were observed for an average of 7.9 years at the Cancer Institute Hospital. In 7% of cases, tumor diameter increased by ≥3 mm, and LNM appeared in 3% of cases [96]. The incidence of progression did not differ between T1a cases and T1b cases. Active surveillance of T1b cases is not the recommended management in the guidelines, but may be adapted as evidence accumulates.

Risk factors for tumor growth have been reported to be young age, lack of calcification on US (presence of calcification in some reports), and rich vascularity [90, 92, 95, 100, 104]. On multivariate analysis at Kuma Hospital, young age (<40 years) was an independent predictor of PTMC progression, but family history and multiplicity were not [90]. Furthermore, they estimated that the lifetime probability of disease progression was 48.6% for patients in their 20s at presentation, 25.3% in the 30s, 20.9% in the 40s, 10.3% in the 50s, 8.2% in the 60s, and 3.5% in the 70s [94]. Young age is a risk factor for progression of PTMC, which has also been reported in the United States, Korea, and Colombia [91, 99, 103]. Koshkina et al. conducted a systematic review and meta-analysis of active surveillance and reported that risk ratio for a ≥3-mm increase in tumor diameter for patients ≥40 and <40 was 0.55 (95%CI, 0.36-0.82). They concluded that the risk of tumor growth decreased with age [105]. Younger patients should be recommended for surgery, as this population is more likely to experience disease progression. However, more than half of patients in their 20s and about three-quarters in their 30s do not need surgery over the course of their life. There is no evidence for active surveillance in patients <20 years old.
Prognosis and recurrence after conversion surgery during active surveillance

According to reports from Kuma Hospital and Cancer Institute Hospital, no patients had distant metastases, life-threatening recurrence, or thyroid cancer-associated death during active surveillance, including cases of conversion surgery [90, 92]. Oda et al. reported that regarding recurrence after conversion surgery, lymph node recurrence appeared in 1.1% within 3 years, but curative resection was possible by reoperation [93]. Prognosis and recurrence after conversion surgery during active surveillance from overseas have been reported from Korea and the United States. Oh et al. reported that 58 patients who underwent conversion surgery had no lymph node recurrence, distant metastases, or thyroid cancer-associated death in the mean postoperative period of 18.7 months [99]. Tuttle et al. reported that 10 patients who underwent conversion surgery experienced no recurrence during the mean postoperative period of 7.3 months [91]. Active surveillance can be considered as a way to identify patients who need surgery, since no difference in prognosis exists between conversion surgery during active surveillance and immediate surgery.

PTC is widely known to frequently show histopathological LNM. Similarly, PTMC also has about a 10–30% risk of pathological metastases when lymph node dissection is performed, even in patients without clinical LNM (see CQ3-2). However, from the results of active surveillance in Japan, progression of these potential LNM into clinical problems appears rare, and if surgery is performed when these metastases become detectable on imaging, prognostic problems are not expected [72, 90, 92-96].

### Table 4  Disease progression under active surveillance

| Country, Year, Institution | Study design | Number of patients | Follow-up time mean, median* (range) | Tumor growth rate (maximum diameter ≥3 mm) (4.6% 4.9%/5 years 8.0%/10 years) | Tumor growth rate (tumor volume ≥50%) | Lymph node metastasis rate | Extrathyroidal extension rate | Distant metastasis rate |
|----------------------------|--------------|--------------------|-------------------------------------|-----------------------------------------------------------------|-------------------------------------|--------------------------|--------------------------|-------------------------|
| Japan 2014(b) Kuma Hospital | Prospective cohort | 1,235 | 60 months (range 18–227) | ND | 1.5% | 1.7%/5 years 3.8%/10 years | 0.16% | 0% |
| Japan 2016(b) Cancer Institute Hospital | Prospective cohort | 409 | 6.8 years* (range 1–23) | 6.0% | 6.3%/5 years 7.3%/10 years | ND | 1.0% | 0% | 0% |
| United States 2017(c) Memorial Sloan Kettering Cancer Center | Prospective and retrospective cohort | 291 | 25 months (range 6–166) | 3.8% | 2.5%/2 years 12.1%/5 years | 12.4% | 11.5%/2 years 24.8%/5 years | 0% | 0% | 0% |
| Korea 2018(b) Asan Medical Center, Samsung Medical Center, Seoul St. Mary’s Hospital | Retrospective study | 370 | 32.5* (IQR 21.5–47.6) | 3.5% | 23.2% | 1.4% | ND | 0% |
| Japan 2019(b) Cancer Institute Hospital | Prospective and retrospective cohort | T1a:360 T1b:61 | 7.3 years (range 0.5–25) 7.9 years (range 1–17) | 8% | 7% | 21% | 11% | 1% | 3% | 1.6% | ND | 0% |
| Italy 2019(b) University Hospital of Pisa | Prospective study | 93 | 19 months* (range 6–54) | 2.1% | 16% | 1.1% | ND | 0% |
| Japan 2019(b) Nagoya University | Retrospective study | 41 (T1b:7) | 62 months (range 7–180) | 4.8% | ND | 0% | ND | 0% |
| Colombia 2020(b) Neck Cancer Center in Medellin | Prospective study | 102 | 13.9 months* (range 0.2–112) | 10.8% | 25.5% | ND | ND | ND |

ND, no data; IQR, interquartile range
Adverse events related to surgery (Table 5)

Surgical outcomes for PTMC are excellent and the recurrence rate is very low (see CQ2). However, only a few reports have focused on the surgical complications of immediate surgery and conversion surgery [72, 93, 106, 107].

Oda et al. at Kuma Hospital compared the frequency of unfavorable events including surgical complications for PTMC between active surveillance and immediate surgery [93]. Patients who chose active surveillance had less incidence of transient vocal cord paralysis (0.6% vs. 4.1%, \( p < 0.0001 \)), transient hypoparathyroidism (2.8% vs. 16.7%, \( p < 0.0001 \)), and permanent hypoparathyroidism (0.08% vs. 1.6%, \( p < 0.0001 \)) than those who underwent immediate surgery. Permanent vocal cord paralysis was observed in 0.2% of patients who underwent immediate surgery. Even if a well-trained thyroid surgeon performs surgery for PTMC, concerns remain regarding surgical complications, and if active surveillance is adopted, adverse events due to surgery can be avoided. However, in this report, the frequency of transient hypoparathyroidism and transient vocal cord paralysis in patients who converted from active surveillance to surgery was 35.1% and 7.4%, respectively, which was higher than in cases of immediate surgery. Reports have also been made from the Cancer Institute Hospital about cases of conversion surgery during active surveillance; while no complications were observed, reported cases were limited to only 16 cases [72]. Evidence remains insufficient regarding the frequency of complications between conversion surgery and immediate surgery, because the number of conversion surgery cases was low.

Medical cost

Lang et al. in Hong Kong first reported the cost-effectiveness of active surveillance for PTMC. They reported that active surveillance could reduce medical costs for the first 16 years compared to immediate surgery [108]. A report from Lin et al. in Australia indicated that active surveillance had lower medical costs than immediate surgery during the first 16.2 years, but immediate surgery offered economic advantages for young people who need long-term follow-up [109]. Venkatesh et al. had shown that lobectomy is more cost-effective than active surveillance for patients in whom nonoperative management would be associated with at least a modest decrement in QOL [110]. However, care is needed when interpreting these reports, which originate from overseas under different medical insurance systems from that in Japan.

Oda et al. reported the medical costs for active surveillance under the Japanese Health Care Insurance System. From follow-up at Kuma Hospital in Japan, the 10-year total cost of immediate surgery was 4.1-times the cost of active surveillance (928,094 yen/patient vs. 225,695 yen/patient) [111]. However, the interval and duration of postoperative follow-up vary in actual clinical practice depending on the patients and facilities. Furthermore, it is important to note that young people often undergo conversion from active surveillance to surgery and require long-term follow-up.

QOL/PRO

When deciding the management strategy for patients with PTMC, it is important to know the PRO such as health problems and anxiety that would be experienced by patients who actually experience medical care.

| Adverse event                      | AS: 1,179 patients (including 94 patients who underwent conversion surgery) | Immediate surgery | Conversion surgery after AS: 94 | Conversion surgery after AS: 16 | Total thyroidectomy: 97 (include 8 patients who underwent central lymph node dissection) | Total thyroidectomy: 52 (lymph node dissection unknown) |
|------------------------------------|---------------------------------------------------------------------|-------------------|---------------------------------|---------------------------------|-------------------------------------------------|-------------------------------------------------|
| Transient hypoparathyroidism       | 33 (2.8%)                                                          | 163 (16.7%)       | 33 (35.1%)                      | ND                              | 16 (17%)                                        | ND                                              |
| Permanent hypoparathyroidism       | 1 (0.08%)                                                          | 16 (1.6%)         | 1 (1.1%)                        | 0 (0%)                          | 5 (5%)                                          | 2 (3.8%)                                        |
| Transient vocal cord paralysis     | 7 (0.6%)                                                           | 40 (4.1%)         | 7 (7.4%)                        | 0 (0%)                          | 3 (3%)                                          | ND                                              |
| Permanent vocal cord paralysis     | 0 (0%)                                                             | 2 (0.2%)          | 0 (0%)                          | 0 (0%)                          | 0%                                              | ND                                              |

ND, no data
However, patient views on the management of active surveillance or surgery have rarely been reported, and evidence of preference between active surveillance and surgery from the perspective of patients remains limited.

Smulever et al. reported that only 26 (19%) of the 136 PTMC patients with tumor size <15 mm selected active surveillance, and the reason for most patients to select surgery was anxiety [112].

In addition, in many active surveillance reports, many reasons beyond cancer progression support patient decisions to select conversion surgery. Oh et al. reported that 48.3% of the reasons for conversion surgery involved patient anxiety [99], and Oda et al. at Kuma Hospital also reported that 54% of the reasons for conversion surgery involved “patient preference” [93].

As a report from the perspective of patients who underwent active surveillance for PTMC, Davies et al. recently reported a qualitative study that addressed the experiences of 243 PTMC patients. Thirty-seven percent of respondents reported worrying about cancer sometimes or more frequently, but 60% said their worries decreased over time. Moreover, 80% of respondents agreed that their decision to choose active surveillance matched their personal values, and 83% of respondents agreed that undergoing active surveillance was the best decision [113].

Table 6 shows PRO studies comparing patients who underwent immediate surgery and those who received active surveillance for PTMC. Joen et al. compared QOL between 43 patients who underwent active surveillance and 148 patients who underwent lobectomy by the 12-item short-form health survey version 2.0 (SF-12v2) questionnaire in a cross-sectional survey, and reported that psychological problems in daily life were less frequent in the active surveillance group than in the lobectomy group. In addition, in an evaluation using Thyroid Cancer Quality of Life (THYCA-QoL), the active surveillance group was found to experience fewer problems involving the nerves, muscles, pharynx, oral symptoms and wounds than the lobectomy group. However, in an evaluation using fear of progression, no differences about fear of cancer progression were identified between groups [114]. In Japan, Yoshida et al. compared anxiety, symptoms and concerns related to PTMC between 20 active surveillance patients and 30 surgery patients in a cross-sectional survey using the State-Trait Anxiety Inventory and a visual analog scale to measure symptoms and concerns. Compared with the surgery group, the active surveillance group showed deeper anxiety, but according to multiple regression analysis, the degree of anxiety correlated with the trait anxiety of each patient, and not with the choice of active surveillance or surgery. In addition, anxiety correlated inversely with the observation time. In addition, symptoms of “discomfort in the neck”, “weak voice” and “nervousness about neck appearance” were favorable in the active surveillance group, and “satisfied with the clinical management”, “anxious about the disease” and “troubles with swallowing” differed little between groups [115]. Kong et al. conducted a multicenter, longitudinal study in Korea comparing 192 active surveillance patients and 203 surgery patients using a THYCA-QoL. The active surveillance group was superior to the immediate surgery group in psychological health at baseline, and in physical and psychological health at after a mean follow-up of 8.2 months [116].

While active surveillance is superior to immediate surgery in terms of physical QOL, psychological QOL such as anxiety may be stronger than for surgery. However, patient anxiety is considered to gradually decrease over time. Previous studies of PRO on PTMC management have been hampered by limitations such as a biased period from diagnosis to investigation, small numbers of cases, and a short observation period. The evidence of PRO on PTMC remains insufficient, and long-term comparative studies regarding PROs are required.

Conclusions

A new management policy of active surveillance for patients with low-risk PTMC has been introduced from Japan, and has gradually been adopted worldwide to avoid overtreatment of this mostly harmless disease. Reports from Japan are limited to the two institutions that started prospective clinical trials in the 1990s, and reports from overseas have short observation periods. However, active surveillance can be recommended as providing appropriate management from the viewpoint of safety (oncological outcome and adverse event), QOL/PRO and medical cost. In fact, according to a questionnaire survey by the Japan Association of Endocrine Surgeons and the Japanese Society of Thyroid Surgery, active surveillance is applied to 54% of T1aN0M0 PTC in Japan, and is considered to still be spreading [117]. However, some points must be noted when performing active surveillance.

First, not all PTMCs (maximum tumor size ≤1 cm) are suitable for active surveillance. Some PTMCs show high-risk features such as clinical LNM, distant metastasis, and ETE, and have a poor prognosis. Making management decisions after reaching an accurate diagnosis is important. Considering that all thyroid nodules ≤1 cm in diameter can be left alone represents a serious error.

Second, for active surveillance, an “appropriate medical care team” is mandatory. Experienced physicians or sonographers should examine the US findings of primary
lesions and lymph nodes over time.

Third, old patients with low-risk PTMC are good candidates for active surveillance, because the incidence of disease progression is low, whereas PTC in elderly patients is known to show poorer prognosis than that in younger patients. If PTMC in the elderly develops to clinical disease, prognosis might be poor, and active surveillance needs to be continued for life.

Fourth, evidence concerning QOL/PRO for the management of PTMC remains limited. It is important for physicians to understand the perspectives of patients and to provide appropriate information with an appropriate attitude, in a process of shared-decision making.

For more specific and practical indications and strategies to implement active surveillance for patients with PTMC, we refer readers to “Indications and strategy for active surveillance of adult low-risk papillary thyroid microcarcinoma: consensus statements from the Japan Association of Endocrine Surgery task force on management for papillary thyroid microcarcinoma” [118].

Table 6  Patient-reported outcomes. Study reports comparing immediate surgery and active surveillance

| Country, Year, Institution | Study design | Number of patients | Period from diagnosis or treatment to investigation | Instrument of measurement |
|---------------------------|--------------|--------------------|----------------------------------------------------|---------------------------|
| Korea 2019 (14) Anan Medical Center | Cross-sectional study | Surgery: 148 AS: 43 | Median 38.0 months (range 25.4–53.0) | SF-12v2, THYCA-QoL questionnaire, FoP questionnaire |
| Japan 2020 (15) Tokyo Women’s Medical University | Cross-sectional study | Surgery: 30 AS: 20 | Median 4.25 years (range 2.8–6.2) | STAI From JYZ, VAS developed to measure symptoms and concerns |

SF-12, 12-item short-form health survey version 2.0; THYCA-QoL, thyroid cancer quality of life questionnaire; STAI, State-Trait Anxiety Inventory; FoP, fear of progression questionnaire; VAS, visual analog scale

| Country, Year, Institution | Study design | Number of patients | Observation period | Instrument of measurement |
|---------------------------|--------------|--------------------|-------------------|---------------------------|
| Korea 2019 (16) Seoul National University Hospital, Seoul National University Bundang Hospital, National Cancer Center | Longitudinal study | Immediate surgery: 203 AS: 192 | Mean 7.1 ± 4.2 months | Thyroid-specific QoL questionnaire |

SF-12, 12-item short-form health survey version 2.0; THYCA-QoL, thyroid cancer quality of life questionnaire; STAI, State-Trait Anxiety Inventory; FoP, fear of progression questionnaire; VAS, visual analog scale

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