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Active Surveillance for Low-Risk Thyroid Cancers: A Review of Current Practice Guidelines

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The indolent nature and favorable outcomes associated with papillary thyroid microcarcinoma have prompted numerous prospective studies on active surveillance (AS) and its adoption as an alternative to immediate surgery in managing low-risk thyroid cancer. This article reviews the current status of AS, as outlined in various international practice guidelines. AS is typically recommended for tumors that measure 1 cm or less in diameter and do not exhibit aggressive subtypes on cytology, extrathyroidal extension, lymph node metastasis, or distant metastasis. To determine the most appropriate candidates for AS, factors such as tumor size, location, multiplicity, and ultrasound findings are considered, along with patient characteristics like medical condition, age, and family history. Moreover, shared decision-making, which includes patient-reported outcomes such as quality of life and cost-effectiveness, is essential. During AS, patients undergo regular ultrasound examinations to monitor for signs of disease progression, including tumor growth, extrathyroidal extension, or lymph node metastasis. In conclusion, while AS is a feasible and reliable approach for managing low-risk thyroid cancer, it requires careful patient selection, effective communication for shared decision-making, standardized follow-up protocols, and a clear definition of disease progression.

Keywords: Active surveillance; Guideline; Papillary thyroid cancer; Practice guideline; Thyroid neoplasms; Watchful waiting

INTRODUCTION

Thyroid cancer is very common, with its global incidence rate reported as 10.1 per 100,000 in women and 3.1 per 100,000 in men [1]. However, thyroid cancer has a favorable prognosis, with a mortality rate of just 0.5 per 100,000 in women and 0.3 per 100,000 in men [1]. The incidence of thyroid cancer increased dramatically in the 1990s and early 2000s [2]. This dramatic increase has been attributed mainly to the detection of indolent small thyroid cancers, particularly due to the widespread

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use of medical imaging, especially ultrasonography (US) [3,4]. Autopsy studies have also supported this finding, revealing that occult thyroid cancers were present in up to 35.6% of individuals who died from other causes [5]. Consequently, thyroid cancer has become a focal point in the debates surrounding overdiagnosis and overtreatment [6].

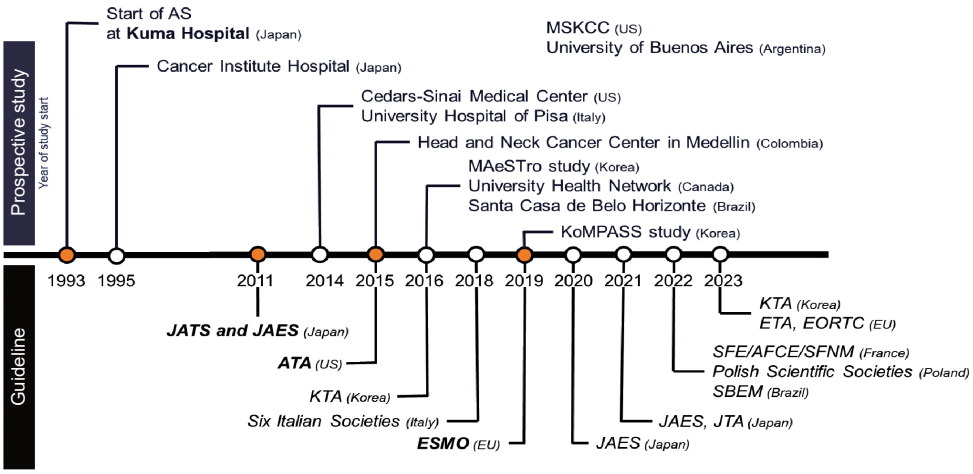
Papillary thyroid microcarcinoma (PTMC), defined as a tumor 1 cm or less in size, has an excellent prognosis [7,8]. The disease-specific mortality of PTMC has been reported to be less than 0.1%, and the recurrence rate is 3% [9]. One reason for these favorable outcomes is the indolent nature of PTMC. When PTMC is monitored without immediate surgery, most cases (>80%) remain stable, with no change in size [10]. Based on PTMC's indolent nature, a treatment strategy known as active surveillance (AS), which involves watchful waiting rather than immediate surgery, has emerged. Kuma Hospital in Japan pioneered a study in 1993 that observed patients with PTMC without surgery, revealing that only 8% and 3.8% of patients experienced tumor enlargement and lymph node (LN) metastasis, respectively, at a 10-year follow-up [11]. Following the publication of the initial results from Kuma Hospital in 2003 [12], the 2011 Japanese guidelines adopted AS [13]. The Japanese Society of Thyroid Surgeons and the Japanese Association of Endocrine Surgeons (JAES) guidelines (2011) state that PTMC measuring 1 cm or less without clinical LN metastasis, distant metastasis, or significant extrathyroidal extension (ETE) can be considered for AS, although the evidence level is low [13].

Due to concerns about overdiagnosis in thyroid cancer and

Table 1. Prospective Studies on AS

Institution (trial no.)	Country	Year	No. of participants	Tumor size Included, cm	Primary outcome	Reference (protocol)
Asia						
Kuma Hospital	Japan	1993–2019 (ongoing)	3,222 AS 2,424 IS	≤1		[11,12,14-24]
Cancer Institute Hospital	Japan	1995–2016 (ongoing)	421 AS 377 IS	≤2		[25]
Seoul National University Hospital, Seoul National University Bundang Hospital, National Cancer Center (MAeSTro) (NCT02938702)	Korea	2016–2019	755 AS 422 IS	≤1	Tumor size change LN or distant metastasis	[27-33] (Protocol [26])
Asan Medical Center, Seoul National University Bundang Hospital, Seoul St. Mary's Hospital, and eight other hospitals (KoMPASS) (KCT0004935)	Korea	2019–ongoing	Recruiting	≤1	Progression-free survival	(Protocol [34])
North America						
Memorial Sloan Kettering Cancer Center	US	NA	291 AS (no IS)	≤1.5	Tumor diameter or volume change	[10]
Cedars-Sinai Medical Center (NCT02609685)	US	2014–2021	112 AS 110 IS	≤2.0	Disease progression (tumor growth, LN, or distant metastasis)	[35]
University Health Network (NCT03271892) → Pan-Canadian (Canadian Thyroid Cancer Active Surveillance Study Group) (NCT04624477)	Canada	2016–ongoing	155 AS 45 IS→ Recruiting	<2.0	Freqeuncy of patients choosing AS or surgery	[38] (Protocol [36,37])
South America						
Head and Neck Cancer Center in Medellin	Colombia	2015–	102 AS (no IS)	<1.5		[39]
Santa Casa de Belo Horizonte	Brazil	2016–2019	77 AS 18 IS	≤1.2		[40]
University of Buenos Aires	Argentina		34 AS (no IS)	≤1.5		[41]
Europe						
University Hospital of Pisa (NCT04129281)	Italy	2014–2020	127 AS (no IS)	≤1.3		[42,43]

AS, active surveillance; IS, immediate surgery; MAeSTro, Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma; LN, lymph node; KoMPASS, Korean Multicenter Prospective Cohort Study of Active Surveillance or Surgery.



Year	Society	Level of evidence/ Grade of recommendation	Recommendation
2011	JSTS and JAES (Japan)	C1, recommended although the evidence level is low	Surgical treatment is mandatory for PTMC patients with clinical lymph node metastasis on palpation or imaging studies, distant metastasis, or significant extrathyroid extension. Patients without these features can be candidates for observation after extensive explanation of the situation and giving informed consent.
2015	ATA (US)	NA	A cytology diagnostic for a primary thyroid malignancy will almost always lead to thyroid surgery. However, an active surveillance management approach can be considered as an alternative to immediate surgery in ~~~.
2016	KTA (Korea)	NA	When the cytopathologic result is malignant, surgical treatment is typically recommended. However, in the following cases, active surveillance can be considered.
2018	Six Italian Societies (Italy)	NA	Even if surgery is the treatment of choice, "no immediate intervention" and active surveillance may be considered for very low-risk PTMC in the following setting: 1. patients at high surgical risk; 2. patients who refuse surgical treatment; 3. patients willing to enter into controlled clinical trials.
2019	ESMO (EU)	Level of evidence III Grade B	Active US surveillance of the thyroid and neck lymph nodes (every 6–12 months) can be proposed for unifocal PTMC (<10 mm) with no evidence of extracapsular extension or lymph node metastases.
2020	JAES (Japan)	Good evidence Weakly recommended	Active surveillance is recommended for patients with very low-risk PTC having no evidence of metastasis or extension, under an appropriate medical care system given a patient's consent, after an adequate explanation of the disease condition and the benefits/risks of the management.
2021	JAES (Japan)	NA	Candidates for AS are adult patients with low-risk PTMC. Table 2 shows those PTMCs indicated for surgery.
2021	JTA (Japan)	NA	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.
2022	SFE/AFCE/SFNM (France)	Level of evidence ++ Grade A	Cytologically proven carcinomas and EU-TIRADS 5 nodules of ≤10 mm, without ultrasound evidence of lymph node metastasis or gross extra- thyroidal extension, distant from the recurrent nerve and trachea can be actively monitored in consultation. Patients aged ≥45 years are better candidates for active surveillance than younger patients.
2022	Polish Scientific Societies (Poland)	High QoE (quality of evidence) SoR1 (strong recommendation)	For the preoperative diagnosis of stage cT1aN0M0 papillary carcinoma in a single focal lesion <1 cm in the largest dimension, surgery may be waived if it is a low-risk lesion, and the patient agrees to such a management.
2022	SBEM (Brazil)	NA	Active surveillance may be an appropriate initial choice in selected patients, and the criteria to recommend this approach are detailed (abstract).
2023	EORTC (EU)	NA	Presently, several treatment modalities with similar oncologic outcomes are available for patients with PTMC (1) thyroid lobectomy, (2) total thyroidectomy, (3) minimally invasive treatment therapy, and (4) active surveillance. Specific patient and tumour characteristics and potential risks of overtreatment have to be considered with the multidisciplinary team before making a treatment choice.
2023	KTA (Korea)	Conditional for recommended	In adult patients diagnosed with PTMC through pathological and imaging studies such as ultrasound, active surveillance can be considered if careful assessment confirms the absence of high-risk histological features (aggressive cell types), invasion into surrounding tissues like trachea or nerves, cervical lymph node metastasis, or distant metastasis, thereby establishing them as low-risk.
2023	ETA (EU)	NA	In the case of 5–10 mm EU-TIRADS 3, 4, and 5 nodules undergoing FNA and classified as Bethesda class V or VI, surveillance or minimally invasive treatment may be offered as alternative options in the absence of suspected lymph node involvement or extra-thyroidal extension (footnote of Fig. 2).

Fig. 1. Guidelines on active surveillance (AS) for thyroid cancer. The guidelines were written in English, other than the Korean Thyroid Association (KTA) guidelines, which were first written in Korean and then translated into English. MSKCC, Memorial Sloan Kettering Cancer Center; MAeSTro, Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma; KoMPASS, Korean Multicenter Prospective Cohort Study of Active Surveillance or Surgery; JATS, Japan Society of Thyroid Surgeons; JAES, Japanese Association of Endocrine Surgeons; ATA, American Thyroid Association; ESMO, European Society for Medical Oncology; ETA, European Thyroid Association; EORTC, European Organization for Research and Treatment of Cancer; SFE, French Society of Endocrinology; AFCE, French Association of Endocrine Surgery; SFNM, French Society of Nuclear Medicine; SBEM, Brazilian Society of Endocrinology and Metabolism; JTA, Japan Thyroid Association; JSTS, Japanese Society of Thyroid Surgeons; NA, not available; PTMC, papillary thyroid microcarcinoma; US, ultrasonography; PTC, papillary thyroid carcinoma; EU-TIRADS, European Union Thyroid Imaging Reporting and Data System; FNA, fine-needle aspiration.

the favorable outcomes of PTMC as demonstrated in Japanese studies on AS, several prospective studies on AS have been conducted in various countries (Table 1) [10-12,14-43]. These studies have had a significant impact on thyroid cancer management guidelines around the world. The American Thyroid Association (ATA) guidelines published in 2015 recognize AS as an alternative to immediate surgery for PTMC [44]. Currently, various international guidelines offer recommendations on the consideration of AS for thyroid cancer, as detailed in Fig. 1 [13,44-56]. In this review, we discuss the current practice guidelines, with a focus on the indications for AS, the follow-up protocol, and the definition of disease progression.

INDICATIONS OR CANDIDATES FOR AS

The initial criteria for AS were derived from studies conducted in Japan. Kuma Hospital in Japan implemented AS for PTMC measuring less than 1 cm, excluding cases where the tumor was located adjacent to the trachea or on the dorsal surface of the thyroid lobe, which could potentially invade the recurrent laryngeal nerve (RLN), or if there was evidence of LN metastasis [15]. With increasing experience and research findings on AS in Japan, Brito et al. [57] proposed a comprehensive framework for categorizing tumors, patients, and medical team characteristics as ideal, appropriate, or inappropriate for AS consideration and decision-making (Table 2). Subsequently, numerous studies and guidelines have adopted this approach. Most guidelines recommend considering AS for tumors that measure 1 cm or less, show no aggressive subtypes on cytology, do not exhibit ETE, and do not have clinical LN or distant metastasis. However, debate continues over the indications for AS. Initially, Japanese groups selected the safest candidates for AS. However, subse-

Table 2. A Risk-Stratified Approach to Decision-Making in Probable or Proven Papillary Microcarcinoma

Candidates for observation	Tumor/neck US characteristics	Patient characteristics	Medical team characteristics
Ideal	Solitary thyroid nodule Well-defined margins Surrounded by ≥2 mm normal thyroid parenchyma No evidence of extrathyroidal extension Previous US documenting stability cN0 cM0	Older patients (>60 years) Willing to accept an active surveillance approach Understands that a surgical intervention may be necessary in the future Expected to be compliant with follow-up plans Supportive significant others (including other members of their healthcare team) Life-threatening comorbidities	Experienced multidisciplinary management team High-quality neck ultrasonography Prospective data collection Tracking/reminder program to ensure proper follow-up
Appropriate	Multifocal papillary microcarcinomas Subcapsular locations not adjacent to RLN without evidence of extrathyroidal extension Ill-defined margins Background ultrasonographic findings that will make follow-up difficult (thyroiditis, nonspecific lymphadenopathy, multiple other benign-appearing thyroid nodules) FDG-avid papillary microcarcinomas	Middle-aged patients (18–59 years) Strong family history of papillary thyroid cancer Child bearing potential	Experienced endocrinologist or thyroid surgeon Neck ultrasonography routinely available
Inappropriate	Evidence of aggressive cytology on FNA (rare) Subcapsular locations adjacent to RLN Evidence of extrathyroidal extension Clinical evidence of invasion of RLN or trachea (rare) N1 disease at initial evaluation or identified during follow-up M1 disease (rare) Documented increase in size of ≥3 mm in a confirmed papillary thyroid cancer tumor	Young patients (<18 years) Unlikely to be compliant with follow-up plans Not willing to accept an observation approach	Reliable neck ultrasonography not available Little experience with thyroid cancer management

Adapted from Brito et al. [57], with permission from Mary Ann Libert, Inc.
US, ultrasonography; RLN, recurrent laryngeal nerve; FDG, fluorodeoxyglucose; FNA, fine-needle aspiration.

quent observations indicated that even with tumor growth or LN metastasis, delayed surgery did not worsen overall survival compared to immediate surgery [20,58]. Consequently, there have been suggestions to expand the criteria for AS. Conversely, some have advocated stricter criteria to exclude tumors with a higher likelihood of progression. These differing viewpoints drive the ongoing debate regarding the selection of candidates for AS. The criteria proposed in guidelines and prospective studies are summarized below.

Tumor characteristics

Tumor size

AS is typically recommended for PTMC measuring 1 cm or less, according to most guidelines. The inclusion criteria of most prospective studies are also aligned with this size limitation. However, some studies have broadened this criterion. For instance, an Italian prospective study proposed that a threshold of 1.3 cm might be a safe alternative to the standard 1.0 cm [42]. This suggestion accounts for the variability in US measurements and the shrinkage that occurs in paraffin-embedded tissue specimens. The precision of US in measuring thyroid nodules can be compromised by factors such as significant inter- and intra-observer variability, heterogeneous background parenchyma due to thyroiditis, and acoustic shadowing caused by calcifications. Moreover, prospective studies that have applied expanded size criteria of 1.5 and 2 cm have reported low rates of tumor progression and an absence of distal metastasis [35,59]. Discussions are ongoing about expanding the size criterion for AS from 1 to 1.5 cm or 2 cm clinical practice, but further research is needed for validation.

Tumor location

There are still many uncertainties regarding the appropriate locations of tumors that are suitable for AS. Fig. 2 depicts the tumor locations recommended for AS in various guidelines. Most guidelines and prospective studies typically do not consider PTMC with ETE to the strap muscles as a candidate for AS. However, the JAES consensus statements (2021) suggest that tumors located on the ventral side of the thyroid, even those with US features indicating invasion into the strap muscles, may not necessarily require immediate surgery. This recommendation is based on the minimal impact of these features on the patient's quality of life (QOL) and prognosis [50]. ETE exhibits a spectrum, ranging from minor ETE, which is characterized by mere contact or bulging of the thyroid capsule or strap muscles, to gross ETE, which involves significant invasion or replacement of strap muscles (Fig. 2B). The applicability of AS in cases with varying degrees of ETE remains unclear and warrants further research.

In the observational study conducted at Japan's Kuma Hospital, PTMCs located adjacent to the trachea or on the dorsal surface of the thyroid were excluded from AS due to their high risk of tracheal or RLN invasion [15]. Following these criteria, some guidelines recommend against selecting such cases for AS, even in the absence of clear evidence of invasion into the trachea or RLN, if the tumor is in close proximity [47,53,60]. However,

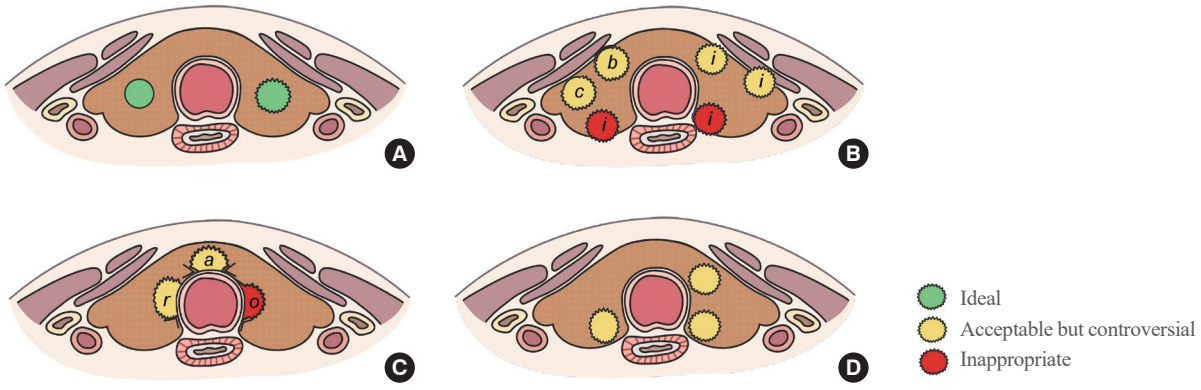


Fig. 2. Ideal or appropriate tumor location for active surveillance (AS). (A) Ideal tumor location. (B) While tumors on the dorsal side of thyroid are excluded from AS, tumors on the ventral side can be considered for AS even if they exhibit contact with (*c*) or bulging of (*b*) the thyroid capsule, or if there is suspected invasion (*i*) into the strap muscle. (C) While tumors contacting the trachea at an obtuse angle (*o*) are excluded from AS, tumors contacting the trachea at an acute or right angle (*a, r*) can be considered for AS. (D) Some guidelines recommend against AS for tumors located close to the trachea or the recurrent laryngeal nerve, and they suggest that AS is appropriate for tumors surrounded by more than 2 mm of normal thyroid parenchyma.

JAES consensus statements (2021) suggests that tumors smaller than 0.7 cm, those merely touching the trachea, or those located away from the RLN's course may be eligible for AS [50]. This recommendation is based on evidence that significant tracheal invasion necessitating tracheal cartilage resection only occurred in PTMCs ≥0.7 cm that formed an obtuse angle with the trachea [61]. Similarly, significant invasion requiring dissection of the RLN only occurred in PTMCs ≥0.7 cm without a normal rim between the tumor and the course of the RLN [61]. However, Newman et al. [62] reported that PTMCs >0.9 cm were unsuitable for AS, even if US or computed tomography did not show signs of RLN invasion, as subcapsular tumors located at the paratracheal area and right lateral posterior lobe area may exhibit gross RLN invasion. In summary, the appropriate tumor location for AS is not yet clearly established, indicating the need for additional research on this topic.

Multiplicity

Some guidelines, including those from the European Society for Medical Oncology (ESMO) in 2019, suggest AS only for patients with single or unifocal PTMC, and recommend immediate surgery for those with multifocal or bilateral PTMC [47,56,60]. However, prospective studies that included patients with multiple lesions have reported that the multiplicity is not a risk factor for disease progression [11,15]. Therefore, JAES (2021) and the Brazilian Society of Endocrinology and Metabolism (SBEM) (2022) guidelines state that patients with multiple PTMC can be candidates for AS [50,53].

US characteristics

The Japan Cancer Institute Hospital reported a significant correlation between strong calcification (either macrocalcification or rim calcification) and poor vascularity of the tumor with a non-progressive tumor status [25]. Based on this observation, the JAES guidelines (2020) note that the presence of strong calcification and poor blood flow observed on US are indicators that tumors are unlikely to grow [48]. However, the role of calcification is debatable, as Oh et al. [63] found that macrocalcification was significantly associated with tumor growth. Recently, Lee et al. [33] reported no association between macrocalcification and tumor progression. The JAES consensus statement (2021) state that the current evidence is insufficient to justify excluding patients with PTMCs from AS based on the degree of calcification or vascularity [50]. Additionally, a Korean prospective study indicated that US features of diffuse thyroid disease and the presence of intratumoral vascularity were associated with tumor growth [33]. Further research is needed to identify the US findings that indicate suitability for AS.

Mutational status

The Italian consensus statement (2018) identifies the *BRAF*^{V600E} mutation as a potential risk factor for disease progression [46], although the evidence supporting this claim remains limited. Some prospective studies have investigated the prevalence of the *BRAF*^{V600E} mutation in patients who underwent conversion surgery after AS. At Japan Kuma Hospital, the surgical specimens of 26 patients were analyzed, revealing no significant difference in the frequency of the *BRAF*^{V600E} mutation among the stable group (64%), the tumor enlargement group (70%), and the LN metastasis group (80%) [64]. Similarly, a Korean prospective study analyzing surgical specimens from 128 patients found no significant difference in the frequency of the *BRAF*^{V600E} mutation between the stable group (83%) and the disease progression group (80%) [32]. While the *BRAF*^{V600E} mutation in PTMC has been associated with aggressive clinicopathological characteristics and higher recurrence rates [65,66], its impact is limited unless it coexists with telomerase reverse transcriptase (*TERT*) mutations, which more significantly affect recurrence [67,68]. However, *TERT* mutations are infrequent in PTMC, with a reported prevalence of only 0.3% to 0.5% [69,70], suggesting that the clinical impact of the *BRAF*^{V600E} and *TERT* mutations might be minor. Further studies are needed to ascertain whether the mutational status, including the *BRAF*^{V600E} mutation, can predict disease progression in AS. These studies should involve molecular profiling of fine-needle aspiration (FNA) or core needle biopsy specimens and subsequent observational follow-up. Therefore, the JAES consensus statements (2021) state that no reliable molecular markers have been identified to date [50].

Patients' characteristics

Medical condition

When considering AS for thyroid cancer, a patient's overall medical condition is a crucial factor. The ATA guidelines (2015) suggest that AS can be considered in patients at high surgical risk because of comorbid conditions, patients with a relatively short expected lifespan (e.g., those with serious cardiopulmonary disease, other malignancies, or very advanced age), and patients with concurrent medical or surgical issues that need to be addressed prior to thyroid surgery [44].

The ESMO guidelines (2019) recommend AS for patients who have not been exposed to radiation in childhood or adolescence [46,47]. However, the evidence supporting this recom-

mendation is limited.

Age

Several prospective studies have consistently shown that younger are more likely to experience disease progression [10,11,21,29,59]. Miyauchi et al. [18] reported that the 10-year disease progression rates during AS were 36% for patients in their 20s, 13%–14% for those in their 30s–40s, and 5%–6% for those in their 50s–60s. Therefore, most guidelines recommend AS for older patients and generally advise against it for patients under the age of 18 to 20 [50,53,60]. While most guidelines do not provide specific age recommendations, the French Society of Endocrinology, French Association of Endocrine Surgery, and French Society of Nuclear Medicine (SFE/AFCE/SFMN) guidelines (2022) suggest that patients aged 45 and older are more suitable for AS [51]. The SBEM (2022) and Korean Thyroid Association (KTA) (2023) guidelines state that AS is ideal for patients aged 60 and above and can be considered appropriate for those between 18 and 59 [53,55].

Family history

Familial differentiated thyroid cancer (DTC) has been shown to have a higher rate of multiplicity, LN metastasis, and recurrence than sporadic DTC [71,72]. However, its disease-specific mortality and overall mortality rates did not significantly differ from those in sporadic DTC [71,73]. The ESMO guidelines (2019) recommend AS for patients without a family history of thyroid cancer [47]. However, Ito et al. [11] found that a family history was not a significant risk factor for disease progression during AS. In line with this, the JAES consensus statements (2021) suggest that patients with a family history of DTC can be considered for AS [50]. The SBEM position statements (2022) indicate that while surgery is typically preferred for familial DTC, AS could be a therapeutic alternative [53].

Concomitant thyroid disorder

The JAES (2021) and SBEM (2022) guidelines state that AS is not contraindicated for patients with Graves' disease or Hashimoto's thyroiditis [50,53]. However, in such cases, it is important to note that US evaluation can be challenging due to the heterogeneity of the background thyroid, and high thyroid-stimulating hormone (TSH) levels may potentially stimulate tumor growth.

Childbearing age or pregnancy

Pregnancy and the consequent increase in beta-human chorionic gonadotropin may potentially enlarge thyroid nodules and cancer [74]. However, Kuma Hospital reported that in the majority of cases (92%), AS was possible during pregnancy without any change in tumor size [75]. Therefore, the JAES (2021) and SBEM (2022) guidelines indicate that patients who are planning to conceive, as well as patients who are pregnant, can be candidates for AS [50,53]. Existing guidelines have not addressed the issue of hormone replacement therapy in postmenopausal women because the relationship between hormone replacement therapy and tumor growth of thyroid cancer remains unclear [76].

Sex

Inconsistent results have been reported regarding whether male sex is a prognostic factor in PTMC. Some studies have found higher rates of LN metastasis or recurrence in men, while others have not reported such an association [77,78]. This inconsistency extends to AS studies. A Korean prospective study found a significant correlation between male sex and tumor progression during AS [29,33]. However, other prospective studies on AS have not found any association between them [10,11,35]. As a result, current guidelines do not include sex as a criterion for determining eligibility for AS.

Shared decision-making

Even when tumor characteristics are deemed ideal or appropriate, and the patient's characteristics align with the criteria outlined above, a collaborative discussion between the patient and the physician is essential for deciding between immediate surgery and AS [46,50,54,55]. This shared decision-making process should consider factors such as QOL, patient-reported outcomes (PROs), and cost-effectiveness. The importance of the patient's perspective and PROs has gained increasing recognition. The Japan Thyroid Association (JTA) position statements (2021) note that AS is associated with better physical QOL, but also increased anxiety [49]. In a cross-sectional study, Jeon et al. [79] found that the AS group reported better QOL in areas such as neuromuscular, throat/mouth, and scar problems compared to the surgery group. Longitudinal studies have initially shown better physical QOL in AS groups compared to surgery groups, but after 1 to 2 years, the QOL scores between the two groups tend to be comparable [28,80]. Yoshida et al. [81] reported higher anxiety in the AS group than in the surgery group. Furthermore, prospective studies have revealed that 54% to 70% of patients who switched from AS to surgery did so not due to disease progression, but because of personal preference or anxiety [16,32]. The JAES consensus statements (2021) state that there is

still a lack of evidence regarding PROs in the management of low-risk PTMC and note that long-term comparative studies are needed on this topic [50].

The JTA position statements (2021) note that the 10-year medical costs of AS were found to be lower than those of immediate surgery in Japan [17,49]. Cost-effectiveness analyses in different countries, such as Hong Kong and Austria, showed that AS was less costly for the first 16 years [82,83], and this trend was also seen in Korea for the first 10 years [30]. In the United States, the cost-effectiveness was found to vary depending on the patient's disutility [84]. Although cost-effectiveness varies by country, AS may initially be more economical; however, over time, surgery might emerge as the more cost-effective approach. Thus, it is crucial to consider the patient's financial situation and life expectancy when making the decisions.

FOLLOW-UP PROTOCOL FOR AS

During AS, it is necessary to perform regular US examination by experienced examiners to monitor for any tumor enlargement or LN metastasis. In a prospective study conducted at Kuma Hospital, patients visited the hospital once or twice a year for blood thyroid tests and neck US examinations [21]. In most other prospective studies, patients were scheduled to visit the hospital every 6 months during the first 2 years, followed by annual visits thereafter [10,26,36]. Reflecting these follow-up protocols, various guidelines recommend specific intervals for US examinations, as detailed in Table 3. Currently, there is no definitive evidence regarding when AS can be safely discontinued. Consequently, it is advised to continue AS throughout life [50,51].

The necessity of TSH suppression during AS remains uncertain. Ito et al. [11] suggested that TSH suppression could be beneficial because 50 of 51 patients undergoing TSH suppression during AS showed no disease progression. Korean studies have found a significant association between high TSH levels and tumor progression [33,85]. However, the Japan Cancer Institute Hospital reported no correlation between TSH levels and tumor enlargement during AS [86]. Consequently, the JAES consensus statements (2021) note the lack of evidence for TSH suppression therapy during AS [50]. The SBEM position statements (2022) recommend maintaining TSH levels within the normal range as the safest strategy to prevent nodular growth and the harmful effects of excessive thyroid hormone [53].

The measurement of serum thyroglobulin (Tg) for evaluation of thyroid nodules is not recommended [44]. Although some prospective studies on AS measured Tg levels, no report suggests that serum Tg level is a predictor of tumor progression [15,26,36,42]. This indicates its limited utility in the follow-up of patients on AS.

DEFINITION OF DISEASE PROGRESSION

The definition of disease progression during AS remains a matter of debate. Generally, disease progression is defined based on tumor growth, clinically evident ETE, LN metastasis, or distant metastasis [49]. ETE, LN metastasis, and distant metastasis are universally accepted as indicators of disease progression and indications for surgery in all guidelines and prospective studies. However, the definition of tumor growth or enlargement varies. The most commonly used criterion is an increase in tumor diameter of ≥3 mm, as suggested by Ito et al. [87]. A study at the

Table 3. Intervals for US Examinations during Active Surveillance

Society	US evaluation
Six Italian Societies (2018)	Every 6 months in the first 2 years and once a year thereafter
ESMO (2019)	Every 6–12 months
JAES (2020)	Once or twice a year
JAES (2021)	Every 6 months in the first 1–2 years and one a year thereafter
SFE/AFCE/SFNM (2022)	Every 6 months in the first year and once a year until the end of the 5th year, then at 7 years, then every 2–3 years (level of evidence ++, Grade B)
Polish Scientific Societies (2022)	Every 6 months in the first 2 years and once a year thereafter (low quality of evidence, weak recommendation)
SBEM (2022)	Every 6 months in the first 2 years and once a year thereafter

US, ultrasonography; ESMO, European Society for Medical Oncology; JAES, Japanese Association of Endocrine Surgeons; SFE, French Society of Endocrinology; AFCE, French Association of Endocrine Surgery; SFNM, French Society of Nuclear Medicine; SBEM, Brazilian Society of Endocrinology and Metabolism.

Table 4. Definitions of Tumor Growth and Surgical Indications

Society	Definition of tumor growth	Surgical indication related to tumor size
JTA (2021)	Tumor diameter increase ≥3 mm Tumor volume increase >50%	Same[a]
JAES (2021)	Tumor diameter increase ≥3 mm	Tumor diameter ≥13 mm
Polish Scientific Societies (2022)	Tumor diameter increase ≥3 mm	Same[a]
SBEM (2022)	Tumor diameter increase >3 mm	Tumor diameter increase >3 mm Tumor diameter ≥13 mm

JTA, Japan Thyroid Association; JAES, Japanese Association of Endocrine Surgeons; SBEM, Brazilian Society of Endocrinology and Metabolism.
[a]The surgical indication related to tumor size is the same as the definition of tumor growth.

US Memorial Sloan Kettering Cancer Center defined tumor growth as a tumor size increase of ≥3 mm in the greatest dimension and a tumor volume increase ≥50% compared with baseline [10]. In a Korean multicenter study, tumor growth was defined as a size increase of ≥3 mm in at least one dimension, or ≥2 mm in at least two dimensions [26]. The US Cedars-Sinai Medical Center study defined tumor growth as an increase of ≥ 5 mm in diameter or a volume increase of ≥100% [35]. The definitions of tumor growth also vary across published guidelines, as summarized in Table 4. While some guidelines and studies require meeting the growth criterion only once, the Japan Kuma Hospital and Canadian prospective studies, as well as the SFE/AFCE/SFMN consensus statements (2022), recommend surgery only when the criterion is met twice in consecutive US examinations [20,36]. Two consecutive confirmations are suggested due to the inter- and intra-observer variability in measuring tumor size using US [88], and the possibility that a tumor meeting the growth criterion once may decrease in size subsequently [89]. Moreover, the JAES consensus statements (2021) suggest that a tumor diameter exceeding 1 cm does not always necessitate immediate surgery [50]. The JAES (2021) and SBEM (2022) guidelines suggest that a tumor diameter reaching 13 mm is a surgical indication (Table 4).

During follow-up, new thyroid nodules may be detected and confirmed as PTMC through FNA. Such newly detected cases of PTMC can be considered either intrathyroidal metastases or new, separate cancers. Currently, no consensus exists in guidelines or prospective studies on whether newly developed PTMC within the thyroid gland indicates disease progression or warrants surgery. Only one ongoing Korean prospective study has categorized the cytopathological diagnosis of a new thyroid cancer lesion as disease progression, but its results are yet to be published [34].

AS WITHOUT FINE-NEEDLE ASPIRATION

With the increasing adoption of AS for pathologically proven low-risk PTMC, there has been growing debate about the necessity of performing FNA on sonographically suspicious subcentimeter thyroid nodules that do not exhibit ETE or LN metastasis. The ATA (2015) and European Thyroid Association (ETA) (2017) guidelines recommend FNA only for thyroid nodules that are 1 cm or larger even if thyroid nodules exhibit a high suspicion US pattern [44,90]. The ETA guidelines (2017) also state that subcentimeter nodules exhibiting highly suspicious US features can be managed either through AS or FNA [90]. Therefore, in countries that strictly follow thyroid nodule evaluation guidelines, the number of pathologically proven low-risk PTMCs may be low. The role of AS in these settings may therefore be less relevant [91]. The majority of guidelines lean toward suggesting AS without FNA for subcentimeter thyroid nodules [92]. More recently, prospective studies are being conducted on AS for highly suspicious subcentimeter thyroid nodules, even without prior FNA confirmation [93]. However, the JTA position statements (2021) continue to recommend FNA for nodules measuring 0.5 to 1 cm that are strongly suspected of being malignant based on US findings [49].

AS IN KOREA

The KTA published guidelines on AS in 2016 and updated them in 2023. The 2016 KTA guidelines stated that AS could be considered for low-risk PTMC patients with a tumor size of 1 cm or less, no aggressive subtype on cytology, no ETE, and no clinical LN or distant metastasis [45]. In contrast, the 2023 KTA guidelines generally recommend AS for the same patient group, indicating a more assertive approach towards AS [55]. This shift was influenced by the results of multiple AS studies conducted

in Korea [26,29,30,32,33]. The 2023 guidelines advise considering AS primarily for patients over the age of 60 but do not provide additional criteria. Furthermore, they do not address the follow-up protocol for AS or the definition of disease progression, underscoring the necessity for more comprehensive guidelines on AS.

CONCLUSIONS

Over the past decade, there has been a significant paradigm shift with the introduction of AS as a new treatment option for low-risk thyroid cancer. This article explores the current landscape of AS, drawing on insights from various guidelines and prospective studies. While AS is a feasible and reliable option for managing low-risk thyroid cancer, it carries the risk of cancer progression. Consequently, careful patient selection and proper implementation are crucial. Central to this approach is the identification of ideal or appropriate candidates for AS, considering tumor characteristics such as size, location, number, and US findings, as well as patient factors like medical condition, age, and family history. Additionally, PROs, such as QOL, and cost-effectiveness should be taken into account. It is critical to discuss these factors with patients to facilitate informed, shared decision-making. For patients who opt for AS, the establishment of standardized follow-up protocols and a precise definition of disease progression are essential for effective monitoring. Moreover, ongoing research to discover markers that can predict disease progression is crucial for improving the efficacy and safety of AS in the management of low-risk thyroid cancer.

CONFLICTS OF INTEREST

Young Joo Park is an editor-in-chief of the journal. But she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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