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REVIEW – CLINICAL ONCOLOGY

Active surveillance of low-risk papillary thyroid carcinoma: a promising strategy requiring additional evidence

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Abstract

Purpose Papillary thyroid carcinoma (PTC), the most common malignant tumor of the thyroid, has been criticized as overtreated by some researchers in recent years. Active surveillance (AS) was first proposed at Kuma Hospital in 1993, and popularized in other institutes ever since. We provide a brief review of low-risk PTC active monitoring studies to date, and discuss the advantages of AS and limitations of existing studies.

Results Most papillary thyroid microcarcinomas do not show significant growth or new lymph node metastasis in a 10-year AS period. Patients who undergo delayed surgery during AS generally have a good prognosis. Tumor progression correlates with age, calcification pattern, and Ki-67 positivity. Serum thyroid stimulating hormone concentration and pregnancy might also influence tumor progression in some studies.

Conclusion Active surveillance for low-risk PTC has shown its safety and feasibility in certain populations. In the future, it is warranted to determine valuable tumor progression predictors and most suitable PTC patients for AS.

Keywords Active surveillance · Thyroid · Papillary carcinoma · Low-risk · Observation

Introduction

Papillary thyroid carcinoma (PTC) is an inert malignancy and has a preferred ideal prognosis. The incidence of PTC has increased remarkably in recent years (Davies and Welch 2014; Ahn et al. 2014). Once diagnosed, PTC patients receive active treatment, as with patients with other malignant tumors. Changes of PTC epidemiological characteristics in recent years drive researchers to rethink whether PTC is overtreated. Thereafter, a strategy of active surveillance (AS) instead of immediate surgery was proposed in confirmed low-risk PTC patients (Ito et al. 2003).

Epidemiology of PTC

The incidence of thyroid cancer has increased since the past 2 decades. Thyroid cancer was diagnosed 15 times more often in 2011 than in 1993 in South Korea. Likewise, the incidence of thyroid cancer in the United States increased from 49 per 10,000 persons in 1975 to 143 per 10,000 persons in 2009, making it one of the fastest-growing cancers (Davies and Welch 2014; Ahn et al. 2014). The popularity of thyroid disease screening and advances in detection technology are generally believed to underlie this phenomenon. In fact, a large proportion of autopsy-confirmed patients with thyroid cancer are unaware of their disease throughout their lives. PTC is the most common endocrine malignancy usually with an indolent nature. Approximately 90% of PTCs patients had a satisfactory long-term prognosis after surgery. With the emergence and development of high-resolution ultrasound along with ultrasound-guided fine needle aspiration biopsy (FNAB) (Yokozawa et al. 1995), the incidence

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of papillary thyroid microcarcinoma (PTMC), a papillary thyroid carcinoma measuring 10 mm or less according to the World Health Organization histologic classification (Sobin 1990), has also significantly increased (Davies et al. 2010).

Current treatment strategies for PTC

Because of the indolent nature of PTC, most PTC patients are not endangered if diagnosed at an early stage. Several new technologies, such as video-assisted and robot-assisted minimally invasive techniques via the axillobreast/oral approach, have been developed as reliable therapies for PTC patients (Lee et al. 2011; Nakajo et al. 2013; Anuwong et al. 2018; Dionigi et al. 2018; Park et al. 2016) in addition to traditional open surgery. A number of non-surgical treatments have also been applied to clinical practice (Papini et al. 2011; Zhou et al. 2017; Zhang et al. 2016; Yue et al. 2014; Li et al. 2018; Teng et al. 2018), which include ultrasound-guided laser/radiofrequency/microwave ablation and percutaneous ethanol injection therapy. The ultimate goal of these treating strategies is to minimize damage while ensuring safety and effectiveness. Individualized therapy has been advocated, along with the emerging of various molecular biomarkers. They may provide numbers of targets for disease treatment. In PTC, biomarkers such as *BRAF*, *TERT* and *RAS* mutations, and *RET/PCT* and *PAX8/PPARγ* rearrangements might help classify PTC patients for more precise treatment, based on their predictive effect on tumor diagnosis and prognosis. These genetic variants could be determined with tissue specimens from FNAB (Armstrong et al. 2014; Cohen et al. 2003; Liu et al. 2013, 2016; Tallini et al. 1998; Xing et al. 2004, 2013, 2014; Zou et al. 2014).

Brief introduction of AS

During AS, patients regularly followed up will have their tumors assessed mainly through imaging examinations, instead of receiving immediate surgery. AS was first applied in managing prostate cancer, a type of carcinoma with a relatively good prognosis (Parker 2004). The safety of AS has been generally confirmed in PTC. In 1993, Akira Miyauchi and colleagues conducted the first AS trial in low-risk PTMC patients in Japan (Ito et al. 2003). In their study, PTMC patients with AS were regularly followed up every 6 months or 12 months and underwent ultrasonography. If any unfavorable physical symptoms or imaging signals meeting the indications for surgery emerged, patients were recommended to receive surgery. A series of studies comparing AS with immediate surgery are presented in this review. In the 2015 American Thyroid Association (ATA) management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer, AS was presented as a possible alternative to immediate surgery for low-risk PTMC patients (Haugen et al. 2016). Ever since, an increasing number of AS trials has been performed around the world and sparked a heated debate.

Active surveillance in papillary thyroid carcinoma

Status quo for AS in PTC

Because of the difficulty to obtain strong evidence supporting AS, AS was not performed until 2003, when Ito and colleagues published the first trial of AS (Ito et al. 2003). Thereafter, a number of institutions began to evaluate the safety and feasibility of AS. We systematically searched Medline, Embase, and the Cochrane Library, and found seven published AS trials in PTC patients worldwide (as of January 2019). Selected basic characteristics of these clinical trials were listed in Table 1. Oh et al. (2018) reported the results from three medical centers in South Korea, two of which have published their findings previously (Kim et al. 2018; Kwon et al. 2017).

Inclusion and exclusion criteria

Kuma Hospital, the first hospital to carry out AS in low-risk PTC in 1993, has obtained a substantial volume of findings. Low-risk PTMC patients were selected as candidates for the AS trial in Kuma Hospital. All the patients enrolled were diagnosed through FNAB. Those who displayed bigger tumors (> 1 cm) were excluded in the trial. Other exclusion criteria were (Ito et al. 2003; Miyauchi et al. 2018a, b): (1) FNAB findings suggesting high-grade malignancy such as tall-cell variant; (2) regional lymph-node metastasis or distant metastasis; (3) signs or symptoms of invasion to the recurrent laryngeal nerve or trachea; (4) tumors located adjacent to the recurrent laryngeal nerve or trachea. These characteristics were checked during initial candidate selection, and also throughout the follow-up period. The presence of any of these characteristics suggested recommendations for immediate surgery but not observation should be made. Ultrasound showing signs of tumor progression was also an indication for surgery.

The inclusion criteria of other institutions were not exactly the same as those in Kuma Hospital. Most institutions chose PTMC as the target population. Tuttle et al. (2017) from Memorial Sloan Kettering Cancer Center in the United States and Sanabria (2018) from the School of Medicine, Universidad de Antioquia in Colombia selected intrathyroidal tumors ≤ 1.5 cm as the observation object. Of interest, the maximum diameter of tumors in the study of Tuttle and colleagues increased more rapidly over time than that from other studies (Fig. 1a). Such difference may be

Table 1 Characteristics of currently published thyroid carcinoma AS trials

Countries or regions	Start time (year)	Subjects (*n*)	Hospitals or institutions	Follow-up time	Tumor size enlargement (*n*)[a]	Lymph node metastasis (*n*)	Distant metastasis (*n*)	Patients converted to surgery during AS (*n*, %)	Cancer-specific death (*n*)	References
Japan	1993	1235	Kuma Hospital	Mean 75 months	58	19	0	191 (15.5%)	0	Ito et al. (2014)
Japan	1995	384/421[b]	Cancer Institute Hospital	Median 81.6 months	29[c]	8	0	15 (3.9%)	0	Fukuoka et al. (2016), Sakai et al. (2019)
South Korea	2002	370	Asan Medical Center; Samsung Medical Center; Seoul St. Mary's Hospital	Median 32.5 months	13 (86 in volume)	17	0	58 (15.7%)	0	Kim et al. (2018), Kwon et al. (2017), Oh et al. (2018)
United States	NA	291	Memorial Sloan Kettering Cancer Center	Median 25 months	11 (36 in volume)	NA	0	10 (3.4%)	0	Tuttle et al. (2017)
Colombia	2013	57	School of Medicine, Universidad de Antioquia	Median 13.3 months	2	0	0	5 (8.8%)	0	Sanabria (2018)
In total	1993	2374	–	–	113	NA	0	279 (11.9%)	0	–

NA not available

[a]Tumor size enlargement means a maximal diameter enlargement of more than 3 mm compared with baseline size

[b]One article (Fukuoka et al. 2016) reported 384 PTMC patients; the other (Sakai et al. 2019) reported 360 $T_{1a}N_0M_0$ plus 61 $T_{1b}N_0M_0$ PTC patients, a total of 421 patients

[c]The '29' here is the number of lesions, while the others are numbers of patients

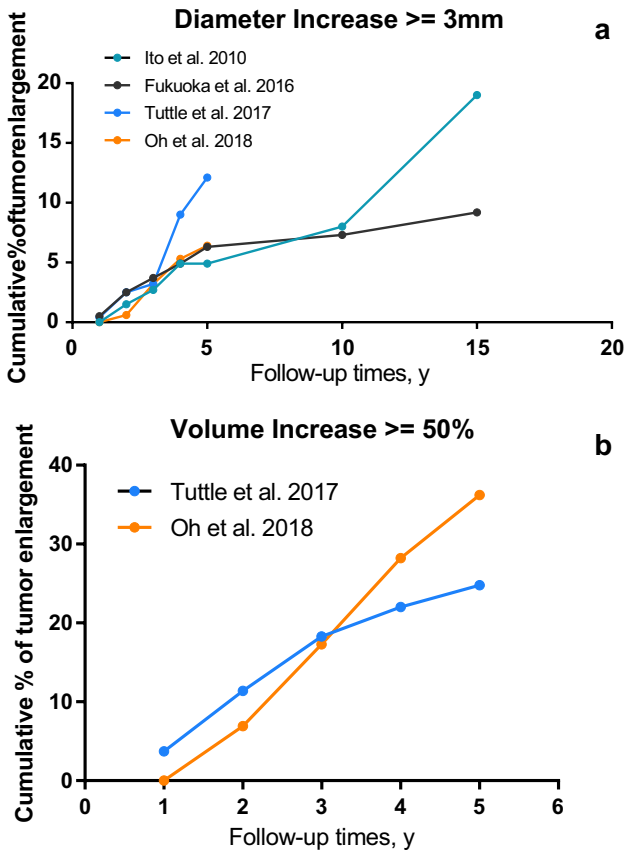

Fig. 1 Progression of tumors during active surveillance. It shows the cumulative rate of tumor progression during AS at different follow-up points in several studies. All patients were followed up by ultrasound. The maximum tumor diameter increased ≥ 3 mm (**a**) and tumor volume increased ≥ 50% (**b**) during the follow-up period were used as the indicators of tumor enlargement

attributable to tumors diameter cutoff difference in the inclusion criteria. Sakai et al. (2019) recently reported data relating to 61 PTC patients undergoing AS at $T_{1b}N_0M_0$ stage at the Cancer Institute Hospital, Japan, in which the maximum tumor diameter was relaxed to 2 cm. In fact, the maximum diameter of most lesions ranged from 1.0 to 1.5 cm, and only two lesions were > 1.5 cm. Patients in three Korean medical centers (Oh et al. 2018) chose AS because of unavoidable reasons such as at high risk for anesthesia caused by cardiopulmonary disease, concomitant with other potential malignant tumors, uncontrolled systemic comorbidities, and pregnancy. Patients demonstrating metastasis, invasion or invasive biopsy cytology were excluded in this study.

Findings from AS studies

Tumor growth during follow-up

Almost all studies reported data on tumor progression during follow-up. The most commonly used indicator from ultrasound test to determine the progression of a tumor was a maximum diameter increase of ≥ 3 mm compared with the baseline size. This protocol was initially proposed by the Kuma Hospital team because it is the smallest difference that can be reliably measured through ultrasonography (Ito et al. 2003). We obtained the cumulative rate of tumor enlargement at different time points from the published survival curves and assembled a combined graph (Fig. 1a). No obvious heterogeneity was detected across all studies on PTMC except that of Tuttle and colleagues during 10-year follow-up. The mean cumulative rate was < 10%. Two studies performed in Japan were followed up much longer than others. In these Japanese studies, data from very long-term follow-up of > 15 years were reported, but with inadequate power [27 patients were followed in Kuma Hospital (Ito et al. 2014) and 26 in Cancer Institute Hospital (Fukuoka et al. 2016), according to their latest articles]. The Colombian study (Sanabria 2018) did not provide much information because of limited number of patients and follow-up, and it is presented as a letter. In this study, 16 out of 57 patients had a tumor diameter increase of 2 mm on average, and two cases showed an increase of > 3 mm.

To determine the kinetics of PTC tumor growth during follow-up, Tuttle and colleagues, followed by Oh et al., measured and calculated tumor volumes with ultrasonography (Tuttle et al. 2017; Oh et al. 2018) (Fig. 1b). Of interest, more patients showed volume enlargement than maximum diameter enlargement. As such, Tuttle (2017) and colleagues proposed that tumor volume change might be a better indicator of thyroid tumor progression than maximum diameter. However, the clinical significance of tumor volume might be inferior to that of the maximum diameter, although the former is more sensitive (Oh et al. 2018). Evidence is limited and which indicator is better for monitoring tumor progression remains an open question.

Novel signs of lymph node metastasis and distant metastasis during follow-up

Seven studies reported data on lymph node metastasis, distant metastasis and disease-specific mortality, as shown in Table 1. Of the 2374 patients with AS, no distant metastasis or disease-specific death was observed. Lymph node metastasis was evaluated with different approaches. Ultrasound tests were applied in the Kuma Hospital (Ito et al. 2014) and the Cancer Institute Hospital (Sakai et al. 2019; Ito et al. 2014; Fukuoka et al. 2016), while a protocol based on FNAB and washout thyroglobulin measurements was carried out by Oh et al. (2018) and colleagues. It is interesting that the study with the latter approach did not show more lymph node metastasis.

Factors associated with tumor progression

In a study of 322 asymptomatic PTMC patients with AS, Sugitani and colleagues did not show a significant correlation between thyroid stimulating hormone (TSH) levels and tumor progression during a mean follow-up of 6.5 years (Sugitani et al. 2014). Similar findings were detected in the study of Ito et al. (2010). In disagreement, A Korean study (Kim et al. 2018) with 127 AS patients demonstrated that sustained elevation of serum TSH concentrations during AS was associated with PTMC progression. These discrepancies might be attributable to difference of tumor progression indicators used in their studies.

In terms of the role of age, there are conflicting results. Ito et al. (2014) revealed that patient age is significantly related to the progression of PTMC under observation. They divided 1235 patients into three subsets based on age and found significant differences in tumor progression parameters such as PTMC enlargement, new lymph node metastasis, and progression to clinical disease between patients < 40 years of age and older patients, contending that older PTMC patients were more suitable for AS. A recent study (Miyauchi et al. 2018a, b) from the same team estimated the lifetime probability of PTMC progression. Age-related tumor progression rates assessed every 10 years during AS increased with age, along with respective lifetime disease progression probabilities (Miyauchi et al. 2018a, b). Oh et al. (2018) also found that relative risk of a tumor size increase in younger patients < 45 years of age almost doubled that in older patients (hazard ratio: 2.2). However, there was no significant difference in maximum diameter across age subgroups, which is contrary to Ito's observation (Ito et al. 2014).

Fukuoka et al. (2016) explored the correlation between the vascularity and calcification of 480 lesions in 384 stage T_{1a} PTMC patients using ultrasound and tumor progression assessments. They divided the calcification patterns into none, micro, macro, and rim, and found that poor vascularity and macro or rim rather than micro calcification were associated with tumor progression. This observation was generalized to patients with stage T_{1b} cancer, confirming a better prognosis in patients with non-calcification or rich vascularity (Sakai et al. 2019).

The prevalence of thyroid cancer in females is approximately three times that in males (Bray et al. 2018). Researchers investigated whether pregnancy would affect tumor progression. Ito and colleagues (Ito et al. 2016) monitored tumor size change from before pregnancy to after delivery in women, and enrolled 50 low-risk PTMC patients to AS. Only four out of 50 patients (8.0%) had PTMC growth during pregnancy and delivery, which did not support a relationship between pregnancy/delivery and PTMC progression. This finding was different from that of a previous study (Shindo et al. 2014), with a smaller number of patients. Difference in patient selection might partly account for these discrepancies, as the study of Ito et al. also included women after delivery.

Hirokawa et al. (2016) performed the only pathological study of PTMC patients under AS. A total of 188 PTMC patients subjected to surgery after > 1 year AS were analyzed. 50.0% and 22.2% of enlarged cases showed a Ki-67 labeling indices of > 5% and > 10%, respectively, much higher than that of non-enlarged cases. Therefore, Ki-67 might be an indicator of tumor enlargement. Tumor enlargement was not associated with chronic thyroiditis or histologic type in this study. In addition, intraglandular dissemination and psammoma bodies, both detectable with ultrasonography, in normal thyroid tissue were reported to be associated with new occurrence of nodal metastasis. All these potential indicators might help guide the choice of AS patients.

Delayed thyroid surgery during follow-up

In most studies, delayed surgery may be recommended when nodules are significantly enlarged (maximum diameter enlarged ≥ 3 mm compared with baseline size), or if signs of lymph node metastasis or distant metastasis are detected, or if patient preference changes. In some cases, patients with concurrent benign thyroid disease progression (Ito et al. 2014), or those with PTMC tumors that tended to grow towards or even invade important organs or structures were included, such as the recurrent laryngeal nerve, trachea, and esophagus (Oh et al. 2018; Fukuoka et al. 2016). The ratio of patients receiving delayed surgery varied from 3.4 to 15.7% among AS studies, with an average of 11.9%. Oh et al. (2018) investigated the reasons why patients accepted surgery in three Korean medical centers. Among the 58 subjects subjected to surgery, 37.9% were because of preference change due to anxiety, 32.8% because of enlarged tumors, and 8.6% because of cervical lymph node metastasis. Therefore, psychological status change might be as important as pathological changes, both of which require attention. No patient reported recurrence after initial thyroid surgery.

Comparison of AS with immediate surgery

It is difficult to perform head-to-head comparison of AS with immediate surgery in PTC patients due to the lack of appropriate and effective outcome of interest. Recurrence rate, an indicator commonly used, is not suitable for AS as no active intervention was performed during AS. Evaluating the outcome of AS patients who turn to surgery because of tumor progression or other causes could be an alternative. Notably, no recurrence was reported among patients who underwent delayed surgery during postoperative follow-up (Ito et al. 2014; Oh et al. 2018;

Sakai et al. 2019; Tuttle et al. 2017), which provided reassurance safety for AS.

Other findings

Other factors should be taken into account if AS is to be promoted as a management strategy in the future. By building a 10-year model, Oda and colleagues estimated that the total cost of immediate surgery was ~ fourfold that of AS for 10-year management after accounting for various factors (Oda et al. 2017). Research from the same group (Oda et al. 2016) showed a significantly higher incidence of unfavorable events, including transient vocal cord paralysis, transient hypoparathyroidism, permanent hypoparathyroidism, postsurgical hematoma, and surgical scars, in patients receiving immediate surgery than AS. The prognosis of the two groups was similar. Surgeons' experience and skills, which vary across different hospitals, should not also be ignored. Centers with excellent treatment of AS can only be compared with centers with excellent surgery. Hospitals leading AS trials might have better surgical centers. The unfavorable events of surgery in these centers, which rarely happens, may be lower than most primary hospitals. The incidence of surgery-related complications would increase if data from primary hospitals are included.

A recent cross-sectional study (Jeon et al. 2019) investigated health-related quality of life (HRQoL) in PTMC patients under AS or lobectomy using three key questionnaires (SF-12 questionnaire scores, THYCA-QOL questionnaire scores, and FoP questionnaire scores). In this study, patients undergoing surgery experienced more health-related problems than AS patients.

Influencing factors in AS decision-making

Brito and colleagues recently developed and tested a tool to support conversations between clinicians and PTMC patients to guide treatment (Brito et al. 2018). Patients using the conversation aid were more likely to choose AS than patients receiving typical health care. Ito et al. reported a trend towards AS for low-risk PTMCs at their hospital (Ito et al. 2018) in 2018. According to their observation, patients whose therapeutic strategy was determined by endocrinologists rather than surgeons were more likely to choose AS. With more studies confirming the safety of AS, it could be anticipated that more patients will choose this conservative therapy.

Discussion

From the initial diagnosis to later follow-up, AS are mainly based on ultrasound and FNAB, which suffers from accuracy limitations when compared with histopathology, the gold standard in tumor diagnosis. Therefore, AS lies beyond the current principles of tumor management, which are always based on the histopathology of malignancy. Because histopathology is not often readily available and sometimes unnecessary, FNAB and ultrasound might be a good choice to screen patients in the absence of histopathology.

Current evidences are very friendly to the development and promotion of AS, but several limitations should be acknowledged in these studies. First, most studies were performed in east Asia, especially Japan and South Korea. No such data have been reported from the other populations. As such, whether this conclusion could be generalized other populations remains unknown. Second, subjective bias cannot be excluded. Almost all related articles showed similar favorability for AS, bias from authors' preference could affect. Third, selection bias could also not be excluded, as patients enrolled in AS trials might prefer AS and thus could influence some outcomes assessment, such as health quality. To support this, only one study analyzed the postoperative pathological characteristics of patients who switched to receiving surgery during AS (Hirokawa et al. 2016). Therefore, expanding AS to all low-risk PTC patients at this stage might not be appropriate, and more evidences are needed.

It is crucial to identify good predictors of tumor progression, if AS is to be recommended as a routine management approach for PTC. Unfortunately, no such predicator has been revealed to date. The psychological impact of persistent survival with tumor cannot be neglected in AS patients. It may be necessary to evaluate patient health-related quality of life during different life periods. Intervention for PTC patients' mental health might be developed in future AS studies.

It is difficult to perform AS in patients with malignant tumors. We searched the clinicaltrials.gov database through May 2019 to identify ongoing AS studies, and found that four institutions are recruiting or preparing to recruit patients in their registered AS studies (Table 2). Among them, the Canadian trial (Sawka 2017) broadened the inclusion criteria of patients to those with tumors with a maximum diameter of < 2 cm, identical with that of Sakai study (Sakai et al. 2019) but twice that of Kuma Hospital. It is notable that a study directly compares another non-surgical treatment, i.e., ultrasound-guided high intensity focused ultrasound (HIFU) ablation with an AS (Lang 2018). We expect results of these studies in near future.

Conclusion

In this review, we discussed the advantages of AS in the management of low-risk PTC. First and most important, AS for low-risk PTC has shown its safety and feasibility. Tumor progression is relatively rare, and distant metastasis

Table 2 Characteristics of ongoing AS trials

Countries or regions	Hospitals or institutions	Title	Estimated duration	Inclusion, maximal diameter	Status	References
Canada	University Health Network, Toronto, Ontario	Deciding on active surveillance or surgery for primary management of low-risk papillary thyroid cancer (AS-PTC)	2016–2026	≤ 2 cm	Recruiting	Sawka (2017)
Hong Kong, China	University of Hong Kong	A prospective randomized trial comparing ultrasound-guided high-intensity focused ultrasound (HIFU) ablation with active surveillance (AS) in the management of low-risk papillary thyroid microcarcinoma (PTMC)	2019–2021	≤ 1 cm	Not yet recruiting	Lang (2018)
Korea	Seoul National University Hospital, Seoul	Active surveillance on papillary thyroid microcarcinoma	2016–2026	≤ 1 cm	Recruiting	Park (2016)
United States	Cedars-Sinai Medical Center, Los Angeles, California	Active surveillance of papillary thyroid microcarcinoma (PMCAS)	2016–2030	≤ 1 cm	Recruiting	Ho (2017)

or disease-specific death was absent during long-term follow-up. Patients who undergo delayed surgery during AS generally have a good prognosis. Second, AS reduces the potential overtreatment of PTC, which would remarkably reduce the economic burden of patients and society. Third, choosing AS avoids surgery-related complications, such as hypoparathyroidism, hoarseness and vocal cord paralysis caused by recurrent laryngeal nerve injury, tracheal intubation failure, and anesthesia accidents. These evidences support that AS could be a promising alternative strategy in certain populations with PTC. In the future, it is warranted to determine valuable tumor progression predictors and the most suitable PTC patients for AS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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