



# European perspective on active surveillance for papillary thyroid microcarcinoma – are we ready?

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*Contributions:* (I) Conception and design: A Czarniecka; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Abstract:** Due to the growing population of patients with low-risk papillary thyroid cancer, active surveillance is increasingly considered worldwide instead of immediate surgical intervention. The study is a short summary of the current knowledge on this subject from the European perspective. So far in Europe, the results of one Italian non-randomized prospective observational study with a relatively short follow-up (19 months) have been published. The study assessed a group of 93 patients with low advanced papillary thyroid cancer or with the suspicion of cancer (Bethesda V). The current study results are not different from those obtained in other parts of the world and confirm the possibility of safe active surveillance in a properly selected group of patients. The results also should prompt other experienced European centers to initiate such management. For example, the Danish researchers have recently conducted a retrospective analysis of a group of 803 patients whose aim was to assess the prevalence and course of papillary thyroid microcarcinoma depending on the method of cancer detection and the possibility of identification of patients who are eligible for active surveillance. When the possibility of introducing active surveillance to the therapeutic management of thyroid microcarcinoma in Europe is considered, several important aspects must be taken into account. These aspects include a higher prevalence of multinodular goiter and thyroiditis in the European population compared to American and Asian populations, differences in the organization and financing of healthcare systems in different countries, various aspects of legal regulations and a more conservative approach to the methods of treatment of malignancies among both patients and medical teams. It seems that currently in Europe active surveillance as a management option for low-risk papillary thyroid cancer should be considered. However, it ought to be conducted only by experienced centers as part of clinical programs.

**Keywords:** Thyroid cancer; active surveillance

Received: 27 April 2020. Accepted: 03 July 2020; Published: 30 September 2020.

doi: 10.21037/aot-20-37

**View this article at:** <http://dx.doi.org/10.21037/aot-20-37>

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## Introduction

Over the last decade much has changed in the diagnostic and therapeutic approaches to patients with differentiated thyroid cancers, and particularly to patients with papillary thyroid carcinoma (PTC). The change was noted in respect to the recommended extent of surgical treatment and to the indications for adjuvant radioiodine therapy in a low-risk patient group (1,2).

According to the 2009 guidelines of the American Thyroid Association (ATA), lobectomy should be performed in patients with papillary thyroid microcarcinoma (PTMC) (unifocal cancer  $\leq 1$  cm in diameter) with no lymph node involvement (3).

In 2015, indications for lobectomy were extended to cT2N0M0 (intrathyroidal tumor  $\leq 4$  cm in diameter) (1). At that time, indications for prophylactic central lymph node dissection were practically limited to T3–T4 cancers (1). In addition, in 2015, ATA recommendations considered active surveillance (AS) a possible management option in a selected group of patients with low-risk PTC (1), which initiated a broader and novel new therapeutic approach to this group of patients outside of Japan.

The ATA guidelines have a significant influence on the recommendations on the diagnosis and treatment of patients with thyroid cancer in other countries, including those in Europe where tendency to treatment de-escalation in patients with PTC is also observed.

However, a change in the therapeutic approach is not an easy process. In some countries, e.g., in Poland, abandonment of radical management in PTMC met with considerable resistance in the case of patients and the medical community. After several years of fierce debate (4,5), lobectomy in patients with PTMC (cT1aN0M0) finally became a possible, common and recommended treatment modality as late as in 2015 (2). Since that time, it has been performed successfully.

A very good or even excellent prognosis in PTMC has been observed and reported for many years (2,6). Some PTMCs are not clinically significant, which is confirmed by post-mortem studies. Frequent and incidental findings of PTMC in patients who died due to other causes [in over 30%, e.g., in the Finnish study (7,8)] indicated that this type of cancer was not characterized by an aggressive growth, nor did it affect the clinical condition of those patients. The insignificant percentage of small, clinically silent cancers detected incidentally after surgery for nodular goiter (from 3.6–10%) also confirms the low malignancy of PTMC

(9,10).

On the other hand, the development of diagnostic techniques, the wide availability of modern ultrasound devices and the use of fine needle aspiration biopsy (FNAB) have had an influence on the increased worldwide incidence and diagnosis of low-risk PTC, particularly in high-income countries (6). As a result, thyroid cancer has not been a rare malignancy as it was observed in the 1980s and the 1990s. Therefore, both physicians and patients are forced to face the “worldwide thyroid cancer epidemic” (11).

The increase in the incidence of PTC has not resulted in an increase in mortality rates, which suggests overdiagnosis that could lead to overtreatment (6,11). More than 50% of PTCs have a diameter  $< 1$  cm (12), which again opened the discussion on the optimal therapeutic management in patients with an excellent clinical course and prognosis.

In addition, recently more attention has been paid to the need for personalized treatment, reduction of complications and adverse events, improvement in the quality of life of patients and also to the need for considering the benefit-risk ratio resulting from diagnostic and therapeutic management (1,2). The above factors contributed to the development of a strategy of AS in patients with low-risk PTC as opposed to immediate surgical intervention even of limited extent (lobectomy).

## Active surveillance as a novel therapeutic option

Active surveillance is currently a novel option in the therapeutic algorithm for PTC. The first reports on the possibility for safe use of this strategy came from Japan (13–17). Currently, there are robust data from the Far East, i.e., Japan and Korea (18–20) and the United States (21,22), which show excellent oncologic outcomes in patients undergoing AS for PTC (6).

Based on the above reports, Brito *et al.* (23) developed the proposal of the algorithm for the enrollment in AS based on clinical patient characteristics, tumor/neck ultrasound characteristics and the medical team characteristics (*Table 1*) to standardize the indications for this treatment modality and to make it more common.

Even in Japan which pioneered this novel management strategy at Kuma Hospital in 1993, the indications and recommendations for AS vary significantly between institutions. Hence, to improve further implementation of this management modality, physicians and patients (even in Japan) should be further educated, and the sociomedical environment needs to be improved (18).

**Table 1** A risk-stratified approach to decision making in probable or proven PMTC based on the analysis conducted by Brito *et al.* (6,23)

AS candidate	Approach
AS ideal candidate	
Patient features	Older patients (>60 years) Acceptance of AS approach and future surgery if needed Reliable and compliant with follow-up Significant comorbid conditions or limited life expectancy
US characteristics	Solitary thyroid nodule with well-defined margins Nodule surrounded by >2 mm of normal gland parenchyma No evidence of ETE Imaging documenting stable size of nodule over time No evidence of nodal metastases No evidence of distant metastases
Others tumor features	No high-risk features on cytological or molecular studies
Medical team features	Experienced multidisciplinary management team High-quality neck ultrasonography available Prospective data collection Tracking/reminder program to ensure proper follow-up
AS appropriate candidate	
Patient features	Younger patients (18–59 years) Acceptance of AS approach and future surgery if needed Reliable and compliant with follow-up Strong family history of papillary thyroid cancer Child bearing potential
US characteristics	Multifocal PTMC Nodule with subcapsular location away from critical structures (i.e., RLN) No evidence of ETE Ill-defined margins Background US findings making follow-up assessment difficult (multiple benign, thyroid nodules, thyroiditis, nonspecific enlarged LNs)
Others tumor features	FDG avid PTMC
Medical team features	Experienced endocrinologist or thyroid surgeon Neck ultrasonography routinely available

**Table 1** (continued)

Table 1 (continued)

AS candidate	Approach
AS inappropriate candidate	
Patient features	Young patients (<18 years)
	Non-compliance with the follow-up
	Non-acceptance of surgical approach
US characteristics	Subcapsular location near RLN
	Evidence of ETE
	Evidence of invasion into the trachea or esophagus
	Clinically evident nodal metastases
	Clinically evident distant metastases
	Increase in size on imaging
Others tumor features	Aggressive features on cytological studies
Medical team features	Reliable neck ultrasonography not available
	Little experience with thyroid cancer management

AS, active surveillance; ETE, extrathyroidal extension; LNs, lymph nodes; PTMC, papillary thyroid microcarcinoma; RLN, recurrent laryngeal nerve US, ultrasound.

Of note, however, the research on AS has only come from a few worldwide centers. Of all European countries, AS has been conducted in only one center in Italy as part of a prospective non-randomized observational study with a relatively short medial follow-up of 19 months (24). The results of the Italian study are in line with the Japanese outcomes.

Disease progression and delayed surgery were observed in a similar percentage of cases, which did not influence the treatment results. The study confirmed the possibility of safe AS in a selected group of patients with the cytological diagnosis of PTC or suspected PTC (Bethesda V and VI) (25). Interestingly, of all the eligible patients, 50% of subjects (93/185) initially gave consent for enrollment in the proposed observational management and another 20% of patients (19/93) decided to transition to surgical intervention even though there was no evidence of disease progression. Therefore, the follow-up was continued in 74 patients as planned, i.e., in 40% of patients who were initially recommended such management. Additionally, 3 patients showed clinical progression and required surgical intervention. Currently, 71 of enrolled patients are still on AS (24). The study is conducted in a tertiary referral center with extensive experience in the diagnosis and treatment of thyroid cancer. Therefore, this method cannot yet be

commonly used, which was emphasized by the authors of the study (24).

However, there has also been a recent increase in interest in this therapeutic option in patients with low-risk PTC also in other European countries. A Danish team conducted a retrospective study on a group of 803 patients. Their aims of the analysis were to assess the incidence and the outcome of PTMC depending on the method of tumor detection and to identify patients that may be suitable for AS. The authors stressed that PTMC patients without suspicion of metastasis had the same low risk of recurrence as incidental cases and could be candidates for AS (25).

### Are we ready for active surveillance in Europe?

Considering the possibility of introducing AS into the therapeutic management of PTMC in Europe, several important aspects should be taken into account. Firstly, in the European population, multinodular goiter is more prevalent compared to a single lesion in the thyroid gland, which makes it difficult to follow up the lesion. In addition, a significant percentage of autoimmune thyroiditis is currently reported in Europe. In these cases, a characteristic ultrasound image may also hinder AS (2).

It seems that European patients and their attending

physicians are characterized by considerably greater fear of the consequences of cancer disease and by aiming at a rapid and radical solution to the problem.

This attitude was observed when a Polish prospective clinical trial on thyroid cancer staged T1N0M0 was initiated. The aims of study were to make lobectomy more commonly applied in Poland and to reduce prophylactic central lymph node dissection in low-risk PTC (4,5). The implementation of lobectomy as a therapeutic option in PTMC required many years of effort to convince the medical community, particularly endocrinologists (2).

Active surveillance requires an experienced medical team and patients' complete acceptance of such management, strong motivation and determination, which was stressed by the Italian team (24).

Ito *et al.* paid attention to the problem of implementation of AS (26). The number of patients whose therapeutic strategies were determined by endocrinologists increased compared to the situation when the treatment method was determined by surgeons (26). Therefore, next to motivation of patients, the treatment team must also be convinced about the relevance of such management.

Currently, it seems that in European countries, including Poland, the community of endocrinologists is not yet ready for the introduction of AS. Endocrinologists working in oncology centers are more likely to implement this strategy as they are more experienced in the treatment and management of thyroid cancer patients.

In addition, there is no clear evidence of cost reduction of such management for the healthcare system in different countries. On the one hand, the Japanese study showed more than a 4-fold decrease in costs of AS compared to immediate surgical intervention in a 10-year follow-up (27). On the other hand, the Australian cohort showed that surgery may have a long-term economic advantage for younger Australian patients with PTMC who are likely to require more than 16 years of follow-up in an AS surveillance scheme (28). Therefore, in young patients at higher risk of recurrence, immediate surgery seems to be more beneficial from the economic perspective (28).

Standardized recommendations for AS have not been established yet. A uniform schedule of follow-ups for patients undergoing AS has not been developed either. The psychological aspect of life in cancer patients cannot be neglected when the possibility of the implementation of AS is considered on a larger scale.

Therefore, it is important to assess their quality of life during AS, as well as to evaluate and compare the quality of

life of patients after immediate surgery (29-31). Such initial reports have already been published (29-32).

Elderly patients with comorbidities seem to be better candidates for AS (23). However, if progression is observed in this group of patients, postponement of surgery may be associated with a higher perioperative risk due to comorbidities and general anesthesia.

It is also confirmed that cancer progression or dissemination is also found in some patients despite the generally good prognosis of patients with PTC and mostly excellent prognosis for PTMC (33,34).

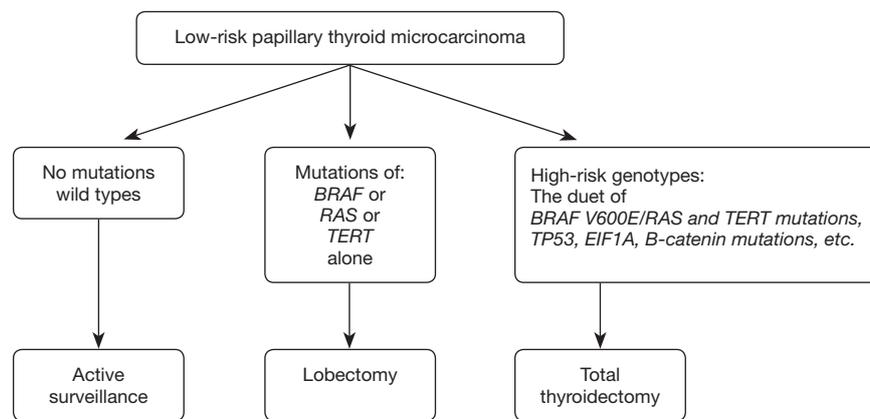
Currently, it seems crucial to identify patients at high risk of tumor progression in whom AS could practically contribute to worsening the prognosis. Therefore, studies should be continued on the prognostic and predictive molecular classifiers, especially those that could assess the molecular profile of the tumor based on preoperative FNAB.

Such molecular classifiers have not been widely available in Europe yet. They are currently at the clinical trial stage (35). In the USA where molecular tests are the most commonly used, they are not standard in everyday clinical practice (1).

In 2019, Xing published the paper on prognostic genetic marker-guided risk stratification and management of thyroid cancer in which the author proposed the algorithm for therapeutic management depending on the type of tumor mutation. Active surveillance seems to be reasonable only for clinically low-risk wild-type *BRAF* PTMC (*Figure 1*) (34).

However, other authors questioned the role of the *BRAF* mutation as a single, independent factor on which therapeutic decisions related to PTC should be based. Although its significance for a poor prognosis has been confirmed (34,36,37), the mutation was found in more than 50% of PTMCs (38,39). Also, most of them are still characterized by excellent prognosis and an indolent clinical course. The role of the *TERT* mutation for the unfavorable clinical course of PTMCs is not clearly confirmed either (34,40). It seems that at the time of enrollment of patients with PTMCs for AS, the co-occurrence of various mutations associated with tumor progression should be considered, e.g., *BRAF*, *TERT*, *p53*, *CTNNB1* (34,41).

Finding sensitive and specific molecular markers which allow a better assessment of possible disease progression may contribute to the use of AS on a larger scale as a management option for patients with thyroid cancer. However, further research is warranted and currently it



**Figure 1** Therapeutic management proposal in a low-risk patient group depending on the molecular tumor profile according to Xing (34).

is a matter of the future. Nevertheless, as the example of prostate cancer shows, this is the right direction of further research as indicated by Klein *et al.* using a robust and validated prognostic signature (Decipher<sup>®</sup>). Therefore, molecular profiling of such tumors may better select patients for AS at diagnosis and trigger appropriate intervention during follow-up (42).

Ze *et al.* searched the available databases (until May 2019) and observed that only 4 centers worldwide recruited patients in their registered AS studies. Those trials included Canada, Hong Kong, South Korea and the United States (33). However, no such trial is currently conducted in Europe. Perhaps it would be possible to plan a multicenter European trial based on a uniform protocol. Patients with low-risk PTC account for over 40% of diagnosed PTC, which is a significant population that requires modern and individualized therapeutic management (43-47). In the future, such management could be introduced to the centers other than tertiary referral hospitals, which could be beneficial for patients with a favorable prognosis.

## Summary

Currently, AS can be one of the management options for a selected group of patients with PTC. The choice of the therapeutic modality should be based on the preferences of patients and treatment teams as well as on an objective assessment of risk factors for tumor progression, which is currently neither obvious nor conclusive.

It seems that in Europe, this strategy as a management option for low-risk PTC should be considered. Bearing in mind legal aspects, it should be currently limited to clinical trials and conducted only in experienced centers. For this

moment, however, we are not ready for the common use of AS in clinical practice in Europe.

## Acknowledgments

We acknowledge the linguistic assistance provided by Assistant Professor Arkadiusz Badziński, PhD, a medical translator and interpreter, in the preparation of this manuscript.

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Annals of Thyroid* for series “Recent Challenges in the Management of Thyroid Tumors”. The article has undergone external peer review.

*Peer Review File:* Available at <http://dx.doi.org/10.21037/aot-20-37>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aot-20-37>). The series “Recent Challenges in the Management of Thyroid Tumors” was commissioned by the editorial office without any funding or sponsorship. Marcin Barczynski served as the unpaid Guest Editor of the series and serves as an unpaid editorial board member of *Annals of Thyroid* from Oct 2019 to Sep 2021. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aot-20-37

**Cite this article as:** Czarniecka A, Oczko-Wojciechowska M, Barczynski M. European perspective on active surveillance for papillary thyroid microcarcinoma—are we ready? *Ann Thyroid* 2020;5:15.