MANAGEMENT OF ENDOCRINE DISEASE

Papillary thyroid microcarcinoma: toward an active surveillance strategy

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Abstract

In the last decades, the incidence of thyroid cancer (TC) has more than doubled, but the disease-specific mortality rate was stable. To date, 30–40% of all TC is represented by papillary microcarcinomas (mPTC), an indolent tumor, that probably remained undiagnosed before routine ultrasound use. In 1993, Miyauchi was the first who hypothesized a conservative approach for low-risk mPTC and introduced the concept of active surveillance (AS) in its clinical management. The progression rate of mPTC during AS was low and delaying surgery did not impact the efficacy of treatment or outcome. Since then, several authors from all over the world have reported their experience of AS in mPTCs. As suggested by current guidelines, AS can be considered as an alternative to immediate surgery to avoid overtreatment in low-risk mPTC and may be the strategy to avoid complications from unnecessary surgery. In the last years, AS inclusion criteria have been extended to both bigger tumors and to younger/healthier patients. The adoption of AS should take into consideration not only tumor characteristics but also patient psychological profiles and medical team expertise. Its safety and efficacy have been demonstrated in long-term outcome studies and in other types of tumors; however, skepticism in patients, families and physicians should be overcome by strong recommendations coming from scientific guidelines. This review analyses the several and different experiences of AS and the potential obstacles in implementing it as a routine approach in mPTC patients.

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Introduction

Papillary thyroid microcarcinoma (mPTC) is defined as a small papillary thyroid tumor measuring less than 1 cm (1). This description does not take into account well established

prognostic factors of thyroid cancer and mPTCs include a wide spectrum of thyroid tumors that ranges between clinical irrelevant to, although rare, metastatic disease. In this spectrum of risk, metastatic mPTC requires active and

Invited Author's profile

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immediate treatment, with total thyroidectomy, lymph node dissection, radioiodine treatment, when indicated. On the opposite side of the spectrum, the management of mPTC without these aggressive features remains a matter of debate, especially nowadays that they represent more than 30% of differentiated thyroid cancer (DTC) cases (2, 3, 4, 5). Almost all mPTCs are incidental findings at neck imaging or during thyroid surgery for benign conditions. These incidental findings have caused a high number of surgical procedures for an indolent disease that would likely remain stable and would not have been diagnosed otherwise (6).

The oncology community has widely discussed the potential harms of such high-intensity screening strategies and their downstream costs. Up to a certain threshold, screening detects minor forms of disease and reduces the expectation that earlier detection leads to lower morbidity and mortality (7). For this reason, some experts advocated a conservative management approach in selected patients with intrathyroidal mPTC (8, 9, 10) and current guidelines do not recommend for thyroid cancer screening in asymptomatic adults (11).

The mPTC model requires a shift to precision medicine. Closely tailoring medical decisions, treatments, and procedures should be based on individualized risk estimates. In this line of thinking, the American Thyroid Association guidelines (12), Italian Expert Consensus (13), and the Consensus Statements from the Japan Association of Endocrine Surgery (14) reviewed the traditional *one-size-fits-all* approach and suggested an observational management in selected mPTC patients. In addition, they underline the importance of patients' choice in decision-making. In a tailored approach to cancer disease management, active surveillance (AS) is entering the clinical practice as a possible solution to mitigate overtreatment and as an alternative to aggressive and immediate treatment.

It has been suggested that there will be from 212 215 to 259 785 new thyroid cancer diagnoses in United States with at least 67 344 patients having tumors of 1.5 cm or smaller, and at least 50 578 having tumors smaller than 1 cm over the next 5 years who will be potential candidates for AS as a management strategy (15). These projection numbers refer to the United States, but the expected increase is worldwide and the numbers of new thyroid cancer cases all over the world would be much bigger (16). In this review, we will discuss the benefit of AS strategy in mPTC patients. Our objective is to enhance the relevance of AS in clinical practice, underlining its safety and effectiveness in patients with low-risk thyroid cancer.

The premises to support AS arise from: (1) the clinical and scientific experience that showed that the mortality rate of DTC is low and did not increase over time (17) and (2) the risk of recurrence of intrathyroidal mPTC is almost negligible (18,19).

Epidemiology

The worldwide increase of DTC incidence is mostly attributable to the improvement in the detection and diagnosis of intrathyroidal mPTC (2, 16, 17). Despite this increase, the mortality rate is low and stable (17). Moreover, the autopsy findings prevalence remains unchanged in the last years, and it is 100–1000 times higher than DTC prevalence. On these bases, the actual incidence appears lower than expected, too (20). Such an increase is likely attributable to the widespread use of ultrasound (US), MRI, or PET used for unrelated neck conditions and to the improvement in detection and diagnosis of subclinical disease, particularly mPTC. Consequently, the size threshold to perform fine-needle aspiration cytology (FNAC) has decreased over the last 20 years. Years ago, only palpable nodules were biopsied; following the widespread ultrasound use induced the small nodules to be subjected to FNAC (21). In the United States, this phenomenon is recognized as the 'epidemic of diagnosis' (2). Current guidelines do not recommend screening for thyroid cancer in asymptomatic adults (11) and do not require FNAC of small, high suspicious thyroid nodules (12). Previous guidelines (22) had been given on the basis for this change, discouraging the FNAC of smaller and less suspicious nodules. The data reported by Morris *et al.* (23) had already suggested a shift in clinical practice: the incidence of thyroid cancer in the United States increased until 2010, then a stabilization in incidence rate was recorded. Likely in the following years, we will observe a decline in the incidence trend and overdiagnosis. As a consequence, this attitude will reduce not only subsequent surgery but also AS, patient anxiety, inappropriate resources allocation, and costs.

Active surveillance in mPTC the Japanese experience

Many retrospective studies had shown the excellent outcome of low-risk mPTC that seems to be likely related to the indolent nature of mPTC rather than to the effectiveness of therapy (24, 25, 26). Based on these findings, Miyauchi and colleagues were the first

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who hypothesized a conservative approach for low-risk mPTC. They postulated that most mPTC remain small for a long time, or even indefinitely as supposed on the basis of the autopsy findings (20), and that AS could identify the subgroup of mPTC that will be growing or developing lymph nodes metastases, thus necessarily requiring surgical treatment. With this aim, in 1993 they introduced AS in the clinical management of selected mPTC patients of Kuma Hospital in Japan, excluding those with trachea or recurrent laryngeal nerve proximity, high-grade malignancy findings at the cytological examination, suspicious lymph nodes metastasis at neck US or cytologically proven metastasis. After a 10-year observation, only 8 and 3.8% of 1235 mPTC showed disease progression, in terms of nodule enlargement or appearance of lymph node metastases, respectively (10). Neither clinical nor pathological features were related to mPTC progression in this cohort, excluding a younger age at diagnosis (10). None of the patients who underwent delayed surgery showed life-threatening metastases, disease recurrence, or died of thyroid carcinoma during AS or after surgery. These results clearly demonstrated that only a small percentage of mPTC really require surgery and that a surgical treatment performed after mPTC progression would be as effective as immediate surgery, with no impact on patient survival.

In the same years, at the Cancer Institute Hospital in Tokyo, 269/300 asymptomatic mPTC (90%) remained unchanged, 9 (3%) decreased, whereas the remaining 22 (7%) increased in size, during a mean of 5 years (range 1–17) of observation. Three patients (1%) with lymph node metastases and nine (4%) with mPTC increase underwent surgery. Nobody had an extrathyroidal extension or developed distant metastases, as well as no postoperative recurrences (27). They also stated that changes in ultrasonographic pattern could predict the mPTC outcome during AS. Particularly, the appearance of macrocalcification and the loss of vascularization seem to be associated to mPTC stability during AS (28).

Active surveillance in mPTC, outside Japan

Having promising results, AS was shyly introduced in mPTC management also in other countries, confirming the effectiveness and the safety of this approach (29, 30, 31). In 2017 Tuttle *et al.* (29) conducted the first prospective study of AS in the United States on 291 cases of low-risk DTC with a cutoff set at 1.5 cm. They showed that only 3.8% of tumors increased in size by ≥ 3 mm in

a mean period of 29 months. Moreover, they found that younger age was a risk factor for progression, in keeping with Japanese results (10).

In Korea, 192 patients who either refused or were at high risk for surgery were followed up to 1 year or more. The study confirmed that only 2% of them showed disease progression in a mean period of 30 months (30).

The recently published research letter by Sanabria *et al.* (32) evaluated tumor growth of DTC up to 1.5 cm, based on increasing of 3 mm in the maximal diameter, and showed that the overall progression rate at 13 months was 3.5%.

Recently, a single-center Italian study by Molinaro *et al.* (31) confirmed the low rate of progression of DTC (measuring up to 1.3 cm) during a median follow-up of 19 months, and concluded that AS is a safe and feasible approach also for mPTC Italian patients.

As shown in Table 1, several of these studies (29,31, 32, 33) also included DTC >1 cm for AS without any impact on outcome, at least in a short period of follow-up time. Sakai and Sugitani (34) moved further proposing an AS strategy in low-risk PTC between 1 and 2 cm and this cohort showed no difference in outcome when compared with the group ≤ 1 cm. These encouraging findings may extend the inclusion criteria of AS by enrolling patients with larger DTC, up to 2 cm in the largest diameter, still intrathyroidal and with no evidence of lymph node metastases.

Clinical indications for active surveillance in mPTC

Based on these encouraging results, American Thyroid Association guidelines (12), Italian Expert Consensus (13) and the Consensus Statements from the Japan Association of Endocrine Surgery (14) suggest AS as an alternative to immediate surgery to avoid overtreatment in unifocal intrathyroidal mPTC, without metastatic lymph nodes or aggressive cytological features. They recommend AS, especially in patients at high surgical risk because of comorbidities, patients with short life expectancy or patients with concurrent medical or surgical issues that need to be addressed before thyroid surgery.

The multifocality or the subcapsular location of mPTC (<3 mm abutting the thyroid capsule) are regarded as potential contraindications for AS, as well as the previous external radiotherapy, or family history of differentiated thyroid carcinoma (12, 13). However, these are only weak risk factors for thyroid cancer progression and surgery

Table 1 Summary of active surveillance trial on mPTC: the worldwide results.

Reference	Country	Patients, n	Age (years) at diagnosis, mean ± S.D. (range)	Maximum diameter (mm) at baseline, mean ± S.D. (range)	Months of observation, mean ± S.D. (range)	Surgeries, n (%)	mPTC enlargement ^a , n (%)		LNF MTS, n (%)	Distant MTS, n (%)	Mortality, n (%)
							Diameter	Volume			
(10)	Japan	1235	Mean: NA; ≥60: 40%; 40–59: 46%; <40: 14%	Mean: NA; ≤5: (26%); 5–8: (56%); 8–10: (18%)	60 (18–227)	120 (9.7%)*	58 (4.6%)		19 (1.5%)	0	0
(27)	Japan	230 (300 mPTC)	54 (23–84)	8 ± 2.4	60 (12–204)	16/230 (7.0%)	22/300 (7.3%)		3 (1.3%)	0	0
(28)	Japan	384	54 ± 11.9 (23–84)	ND	82 ± 52 (12–276)	19 (5%)	29 (6%)		4 (1%)	0	0
(29)	USA	291	52 ± 15 (20–86)	≤10: (80%); 11–15: 20%	29 ± 19 (6–166)	11 (3.8%)	11 (3.8%)	36 (12%)	0	0	0
(30)	Korea	192	51.3 (42.9–59.5)†	5.5 mm	30	9 (4.5%)	4 (2%)	24 (12%)	1 (0.5%)	0	0
(52)	Korea	370	51 ± 11.7	5.9 ± 1.7	32 (21–8)	24 (6.5%)	13 (3.5%)	86 (23%)	5 (1.3%)	0	0
(45)	Korea	126 (127 mPTC)	51.0 (44.0–8.0)†	5.7 (4.7–6.7)†	25 (17–37)	4 (3%)	7 (5.6%)	25 (20%)	1 (0.8%)	0	0
(32)	Colombia	57	51.9 ± 14.5 (24–85)	9.7 ± 4.3 (3–26)	13.3 (0–54)	3 (5%)	2 (3.5%)		0	0	0
(34)	Japan	61	54.4 ± 10.7	11.7 ± 1.1 (11–16)	95 (12–204)	5 (8%)	4 (7%)	7 (11%)	2 (3%)	0	0
(34)	Japan	360	53.9 ± 12 (23–84)	7.6 ± 1.8 (2–10)	87 (6–300)	ND	29 (8%)	74 (21%)	3 (1%)	0	0
(33)	Argentina	34 (ST: 28; PR: 6)	‡ST: 41 (15–79); ‡PR: 42 (26–79)	9.2 ± 2.95	48.8 ± 29.6 (7–12)	2 (0.6%)	6 (17%)		0	0	0
(31)	Italy	93	44 ± 15 (18–82)	9 ± 2.5 (3–13)	19 (6–54)	3 (3%)	2 (2%)	15 (16%)	1 (1%)	0	0

Sn (%) of patients who underwent thyroid surgery because of mPTC enlargement and/or lymph nodes metastases appearance; *43/1235 (3.5%) of patients underwent to thyroid surgery because of developing of clinical disease (such as palpable lymph node and/or mPTC diameter >12 mm); ^an (%) increase in diameter (≥3mm) or in volume (≥50% than baseline); †values presented as median (IQR); ‡ values presented as median (range).

LNF, lymph node; mPTC, papillary thyroid microcarcinoma; MTS, metastases; NA, not available; PR, progressive mPTCst, stable mPTC.

could be considered overtreatment in most of these cases (8, 9, 10).

According to our experience (31), we are confident in recommending AS to every intrathyroidal mPTC patient, regardless of age or comorbidity. There is no evidence that a delayed surgery of 6–12 months can impair the outcome of the disease in any type of patients, thus all patients can start with AS and then interrupt it upon any evidence of disease progression. As matter of fact, mPTC, but even bigger DTC, diagnosed during pregnancy are commonly and safely treated at the end of the pregnancy or even after a few months of lactation (35). Thus, the most intriguing question today is: what stands in the way of practicing the same procedure in all other cases?

An experience, that can be useful to be recall in this regard, is the recent unavoidable choice to perform AS of thyroid cancer diagnosed during 2020, due to the pandemic of Covid-19. Interestingly, the lesson learned from this delay in treatment confirms that AS is a safe and effective strategy and can be viewed as a possibility of care making patients and clinicians more receptive to accept and propose AS, respectively (36).

The right patient and the right team for an active surveillance strategy

The patients, who accepted AS as first-line management approach, should accept to perform regular evaluations, which consist of clinical evaluation, neck US and blood samples, every 6 months for the first 2 years and then yearly. They must be aware that the appearance of metastatic lymph nodes, confirmed by cytology and thyroglobulin (Tg) measurement on the wash-out of the needle used for FNAC, or an increase in size more than 3 mm for each nUS diameter of mPTC, confirmed in two consecutive exams, are indications to transition from AS to surgical intervention. It is also worth highlighting the importance of patients' preferences in decision-making and the possibility that they can opt out for surgery also in the absence of disease progression at any time during observation (Fig. 1).

The physicians' team should have definite features: they must be fully aware of what is an AS strategy, and be skilled in performing thyroid and cervical lymph nodes US. Chung *et al.* (37), reported a difference of

We set the size cut-off at 1.3 cm, because of the wide echographic inter- and intra-observer variability and the shrinkage of paraffin-fixed tissue that usually cause an underestimation of histological measures
* every 6 months for two years, then yearly; § preferred; ^ in selected cases with or without therapeutic lymph nodes dissection

Figure 1

Algorithm for low-risk mPTC management. Solid lines are the preferred first-line approach, dashed lines the second-line alternatives. Green boxes and lines include the factors that argue in favor of surveillance, pink ones the events that require closer surveillance or further investigations, red ones the indications for surgery.

Figure 2

Ultrasound images of a stable mPTC during active surveillance. (A) Transversal (left side) and longitudinal (right side) baseline mPTC images. (B) Transversal (left side) and longitudinal (right side) mPTC ultrasound images confirming the stability of the nodule after 1 year of observation.

up to 24% in the maximum diameter and 72% in the volume within measurement error on US. Inter and intra-observer variability should be reduced by having a group of operators who should be aware to compare images, not

Figure 3

Ultrasound images of progressing mPTC during active surveillance. (A) Transversal (left side) and longitudinal (right side) baseline mPTC images. (B) Transversal (left side) and longitudinal (right side) mPTC ultrasound images showing the increasing of mPTC diameters after almost 1 year of observation.

Figure 4

Ultrasound images of progressing mPTC for the appearance of metastatic laterocervical lymph node, suspected at neck ultrasound, confirmed at cytology, and thyroglobulin measurement in the wash out fluid, after 2 years of active surveillance. (A) Transversal (left side) and longitudinal (right side) ultrasound images showing the stability of mPTC diameters. (B) Transversal (left side) and longitudinal (right side) images showing the appearance of a suspicious laterocervical lymph node.

only the last one but also the previous to better follow the growth of the nodule. They must well establish the stability of the nodule (Fig. 2) or its size progression (Fig. 3) and the appearance of lymph nodes (Fig. 4) with an US procedure that should look at the entire neck and not only at the thyroid.

The accurate communication between patients and physicians is the *conditio sine qua non* for a successful AS. In this view, a risk stratification of mPTC patients (38) has been proposed: not only clinical features, but sociocultural and psychological evaluation (i.e. willing to accept this approach, awareness of possible surgical treatment in the future, compliance to follow-up) are certainly critical to identify the ideal candidate for AS.

Clinical subsets

Age

With the exception of children and adolescents, adult patients at any age were enrolled in the studies (Table 1). Ito and colleagues found an inverse correlation between age and disease progression: younger age (≤ 40 years old) was a significant prognostic factor for progression

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(10). However, the age influence in the decision-making to submit the patients to AS or perform an immediate surgery is still a controversial issue since some studies reported a higher rate of progression in this subgroup (10,29), but others did not find any difference (31). A recent meta-analysis of five studies on more than 2300 mPTC patients confirmed a lower risk of progression during AS in patients older than 40 years (39). However, it should be taken into consideration that the higher risk of progression in younger patients is related to the estimated lifetime probability of mPTC progression that is higher in younger (48.6, 25.3, and 20.9% for patients in their 20s, 30s, and 40s at presentation, respectively) and lower in older patients (3.5% in their 70s) (40). Therefore, according to these findings and considerations, older mPTC patients represent the best candidates for AS. Nonetheless, about 40% of younger patients could be safely followed up without requiring surgical treatments during their lifetime (40) or at least could significantly delay the time of surgery without impairing the final outcome of the disease. According to these evidences, young age (<40) should not be considered an exclusion criterion *per se*. In fact, PTC patients younger than 55 years at presentation had an excellent outcome and also the appearance of lymph nodes metastasis does not have any impact on outcome (41). However, young patients should be made aware that the surgical shift is highly likely during their long lifetime. Nevertheless, delaying surgery in younger patients would reduce the negative long-term side effects of lifetime thyroxine replacement therapy.

Pregnancy

AS is a likely safe and effective strategy during pregnancy as demonstrated by a study reporting that only 8% of pregnant women showed mPTC progression, and the after-delivery thyroidectomy was curative (35). The stimulatory effect on mPTC, attributable to human chorionic gonadotropin during pregnancy, is not backed by solid evidence. Moreover, a surgical treatment during the first and third trimesters is affected by a high risk of abortion or premature delivery (42), thus AS is strongly suggested for this category of patients, at least until the end of the pregnancy. The question of whether to continue AS or not after-delivery would not be different to any other patient choosing this strategy. The choice will be highly dependent on the nodule growth during the pregnancy and the personal choice of the patient.

TSH suppression

Another controversial point is the relationship between TSH suppression and mPTC, as higher TSH level has been correlated to malignancy (43). Sugitani *et al.* (44) proved that TSH levels are not associated with mPTC progression during AS, while Kim *et al.* (45) argued otherwise. Therefore, further comparative studies are necessary to draw more definitive conclusions and now TSH suppression in mPTC during AS is not generally recommended. At variance, the correction of a concomitant subclinical hypothyroidism is indicated.

Surgical adverse event

Comparing mPTC patients who underwent immediate surgery and those who chose AS, Oda *et al.* (46) found that the incidence of adverse events was significantly higher in the immediate surgery group even if performed by highly skilled endocrine surgeons. The immediate surgery group had a significantly higher incidence of transient vocal cord paralysis (4.1% vs 0.6%, $P < 0.0001$), transient hypoparathyroidism (16.7% vs 2.8%, $P < 0.0001$), and permanent hypoparathyroidism (1.6% vs 0.08%, $P < 0.0001$). Two patients (0.2%) in the immediate surgery group developed permanent vocal cord paralysis, while none in the AS group had this complication. One could argue that these findings are obvious because the adverse events reported in the first group are strictly correlated with the surgery and cannot be present in the second group of non-operated patients. Truthfully, one of the objectives of AS is to avoid or delay as much as possible the potential risks of thyroid surgery, without compromising the outcome of the disease.

Cost-effectiveness

In some contexts, economic aspects are as important as medical or psychological issues and may influence the management choice in mPTC patients. The analysis of medical cost confirmed that the total cost of immediate surgery was more than four times greater than AS both in Japan (47) and China (48), and the costs of delayed surgery were included in the AS group. In Hong Kong, AS seems to be more cost-effective than immediate surgery during the first 16 years after mPTC diagnosis, and thereafter, regardless of patient age, complications, and progression rates (48). However, not all studies on cost-effectiveness are consistent and some have shown that surgery is more cost-effective than AS (49, 50). In some

cases, insurance status also exerts an impact on the extent of treatment applied. Patients with private or public health insurance (73% of the cohort) were more likely to have mPTC compared with uninsured ones. Regardless of less aggressive carcinomas, privately insured patients were more likely to be treated more extensively, than uninsured ones. Private insurance independently increased the probability of total thyroidectomy, lymphadenectomy, and postoperative radioiodine therapy (51). The medical costs are a relevant issue and vary from country to country and this issue should be locally evaluated. However, management disparities based only on economic issues should be avoided.

Regarding the cost of AS and the need to perform periodic evaluations, we must consider that patients submitted to thyroidectomy must be periodically evaluated to verify the adequacy of therapy and to control the risk of relapse by measuring serum Tg and performing neck US. No major differences in the timing and type of evaluations are ultimately present in the two types of follow-ups.

Evaluation of mPTC growth

Tuttle *et al.* (29) evaluated not only diameter but also changes in tumor volume during AS and found that 12.7% of tumors increased in volume by >50%. Moreover, these authors speculated that the increase in mPTC volume allowed earlier identification of tumor growth. Similar results were obtained by Korean (52) and Italian groups (31). Moreover, Miyauchi *et al.* (53), consistent with other authors (27, 29), showed that spontaneous decrease in tumor volume may be a common occurrence, showing the lack of aggressiveness in the natural course of the disease. However, it is important to consider not only the growth but also the time-lag of growth, enabling an earlier identification of lesions that will progress to significant disease. Advances in knowledge on tumor growth could help in understanding which patients could benefit from stricter monitoring or surgical treatment. Further studies need to be designed to determine the cut-off for defining meaningful change in the maximum diameter and volume for mPTC during AS.

Molecular markers

To date, the role of genetic mutations (e.g. *BRAF*, *RAS*, *TERT*, etc.) and/or rearrangements (such as *RET/PTC*) are

not completely clarified in mPTC during AS, albeit they strongly predict a poor prognosis in operated DTC(54). Yabuta *et al.* (55) described the same prevalence of *BRAF* mutation in surgical specimens of mPTC. They found *BRAF* mutation in 80, 70, and 64% of mPTC surgically removed for the appearance of lymph nodes metastases, tumor growth, and reasons not related to disease progression, respectively. Regarding *TERT* promoter, they did not find any mutations in analyzed groups. Based on available data, the *BRAF* or *TERT* promoter mutation alone is not sufficient to predict an aggressive behavior of mPTC during AS. Other gene mutations are likely to give cancer cells a selective advantage in growth and invasiveness. A recent research analyzed mutations of genes coding for cell adhesion molecules or proteins used in cell migration, which seem to discriminate low-risk mPTCs from those with greater aggressiveness (56).

Anxiety

Currently, this conservative approach in clinical practice is mainly limited by the burden of cancer diagnosis, its impact on patients' everyday life, and the wide skepticism also shown by general practitioners, different specialists, and institutions. The assessment of the quality of life and the long-term results of AS, also outside Japan, might improve the patients' acceptability and compliance in the future. As Davies described in a questionnaire survey about Kuma Hospital patients (57), 37% replied they had cancer worries sometimes, 60% replied their worry decreased over time and 83% considered AS the best choice for themselves. In addition, the rate of mPTC patients who prefer AS as a management option increased over time in both Japanese and Italian experiences (31, 58). Such behaviors seem to reflect a change in mind mainly correlated to the confirmed effectiveness and safety of AS during time.

Moreover, an *ad interim* analysis of MAeSTro study (59) showed the results of the comparison of quality of life (QoL) at diagnosis and during observation (median 8 months) of mPTC patients based on their choice of management. Better psychological health at baseline and physical and psychological health at follow-up were observed in the AS group ($n=203$) than in the immediate surgery group ($n=192$). The last one experienced more fatigue, changes in voice and appearance for the presence of the scar, less satisfaction, but low fear of recurrence/progression.

In a cross-sectional study by Jeon *et al.* (60), 12-item short-form health survey, thyroid cancer-specific QoL, and fear of progression were evaluated in 191 mPTC patients.

mPTC patients subjected to lobectomy ($n = 148$) reported more health-related problems compared to patients who decided not to operate ($n = 43$), even if the fear of progression was similar in the groups. Similar results were reported by Nakamura *et al.* (61).

Open issues

AS is a work in progress and several issues remain open and in particular, the ideal frequency of follow-up evaluations and the optimal timing for surgery in progressive cases. The criteria of mPTC growth >3 mm in each diameter and/or metastatic lymph node development may not practically reflect the real aggressiveness of the tumor. More precise radiologic tools to improve the detection of minimal extrathyroidal extension and the identification of molecular biomarkers that can predict progression are needed.

The evidence that a delayed surgery does not compromise the outcome of these patients should be the real rationale to choose an AS strategy. Scanty data on the QoL of patients in AS is available, while it might improve the patients' compliance and self-awareness in the future. It is relevant that awareness that surgery is not the conditioned reflex in case of a diagnosis of cancer and that the outcome of the disease would not change is increasing over time.

Building evidence that will modify the next thyroid cancer guidelines should be the priority of the endocrinology scientific community developing high-quality data on several treatment options (from AS to local ablative therapies) and treatment support interventions on patient-centered outcomes (62). However, the ultimate goal of AS in mPTC is to mitigate overtreatment due to its indolent nature and identify only clinically relevant cancers. In this view, local ablative therapies may be a less invasive step to overtreatment whereas our view is to avoid useless, costly, and potentially harmful treatments. Local ablative therapies should not replace surgery as a less invasive means to treat thyroid cancer. They remain an alternative option, especially for those patients unable to withstand the burden of having non-treated cancer. AS should be the first choice in mPTC patients. A powerful network should be built around patients so that they are followed up regularly and are able to discuss their health status without receiving contradictory opinions. The patient's data should be available to the network of national hospitals treating thyroid cancer to avoid any

loss in follow-up or changing strategy just on the basis of clinician's opinion not keen in accepting AS.

Conclusions

AS in mPTC shows similar excellent outcomes of surgery groups. Even more, delayed surgery in mPTC is not related to a higher risk of distant metastases or cancer-related mortality. Both surgery and AS are associated with emotional stress and anxiety and the timing and types of periodical evaluations will be very similar. Besides, surgery, particularly total thyroidectomy, may lead to permanent complications in a relatively large number of patients, and this risk is disproportionate to the real risk of morbidity and mortality of mPTC. The majority of cases are characterized by a normal thyroid function and patients in AS would not require any medical treatment, conversely to the operated, since also patients treated with lobectomy may require a thyroxine therapy at least in half of cases (63). Only the QoL of patients and doctors' experiences may play a crucial role in this decision-making process. The cornerstone of this decision is the consciousness that delaying surgery in low-risk DTC does not affect the outcome of these patients.

Declaration of interest

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