Review Article

Active surveillance for well-differentiated thyroid cancer

Ahmed Elnahla, Abdallah S Attia, Emmanuelle Ruiz, Scott Mayer, Grace Lee, Emad Kandil

Department of Surgery, Tulane University, New Orleans, LA, USA

Contributions: (I) Conception and design: E Kandil, G Lee, A Elnahla; (II) Administrative support: G Lee, A Elnahla; (III) Provision of study materials or patients: E Kandil, A Elnahla, AS Attia, S Mayer, E Ruiz; (IV) Collection and assembly of data: A Elnahla, AS Attia, E Ruiz; (V) Data analysis and interpretation: A Elnahla, AS Attia, E Ruiz; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Emad Kandil, MD, MBA, FACS. Department of Surgery, Tulane School of Medicine, 1430 Tulane Ave, SL-22, New Orleans, LA 70112, USA. Email: ekandil@tulane.edu.

Abstract: The main goal of active surveillance (AS) for thyroid cancer is to avoid overtreatment by choosing the ideal candidate and effectively monitor for disease progression. Definitive treatment offered once indicated. AS is gaining popularity across different institutions; however, to date, there are no definite guidelines or criteria for its implementation, which explains the distinctions in inclusion criteria and follow-up plans. Although ultrasound is the primary modality to stratify and follow-up the patients, it is not the most accurate in determining aggressive behavior besides being highly subjective. The lack of biologic or molecular markers that can distinguish lesions predisposed to progression is another contributing factor. The cost-effectiveness of AS is questionable; to what extent can AS reduce the cost of treatment is still a matter of debate. This review provides a summary of the current literature on AS and offers an overview of the current challenges for its implementation.

Keywords: Thyroid cancer; active surveillance; papillary thyroid microcarcinoma (PTMC)

Received: 25 March 2020; Accepted: 11 September 2020; Published: 30 December 2020.

doi: 10.21037/aot-20-25

View this article at: http://dx.doi.org/10.21037/aot-20-25

Introduction

Thyroid cancer is the most common endocrine gland malignancy (1). Fortunately, it is highly curable with an excellent prognosis in a majority of cases. Over the last few decades, the incidence of thyroid cancer has skyrocketed to an estimated 52,070 new cases per year in the U.S., which represents a three-fold increase between 1984 and 2016 (2). By 2030, thyroid cancer is expected to become the fourth most common cancer in the U.S. (3). The rapid rise in incidence is partially attributed to the frequency of imaging as well as advances in diagnostic modalities, which have allowed the detection of smaller asymptomatic tumors and increased reporting of incidental findings (4). Despite increasing incidence, however, no associated rise in mortality has been seen (2,5).

Papillary thyroid microcarcinoma (PTMC) is defined as a tumor less than 1 cm and comprises a large proportion of papillary thyroid cancer (PTC) (6). Recently, active surveillance of low-risk, well-differentiated PTCs has been debated in attempts to avoid the risk of the surgical complications, diminished qualify of life, and health care cost related to surgical intervention (7). The aim of this review is to provide further insights into the existing consensus and controversies in the management of PTCs.

Clinical presentation

Incidental thyroid nodules with subsequent diagnosis of PTC can be seen in up to 67% of ultrasonography unrelated to thyroid, 25% of CT scans of neck and chest, 18% of MRI, and less than 2% of PET scans (8-12). A comprehensive ultrasound evaluation of thyroid nodule is the gold standard for initial assessment and diagnosis of thyroid nodules. PTC may occasionally present with an enlarging neck mass, palpable lymph node or hoarseness due to involvement of the recurrent laryngeal nerve (13). Recent American Thyroid Association (ATA) guidelines

published in 2015 recommend a fine needle aspiration (FNA) biopsy of nodules ≥1 cm in greatest dimension with intermediate or highly suspicious features on ultrasound (7). The guidelines do not recommend a FNA for sub-centimeter nodules to prevent over diagnosis and over treatment of PTMC (14). The guidelines recommend a comprehensive neck ultrasound, including cervical lymph node survey, for workup of all thyroid nodules to avoid ignoring metastatic lymphadenopathy (7).

In South Korea, implementation of a routine screening for thyroid nodule resulted in 15-fold increase in incidence of thyroid cancer within 10 years of the screening initiation (15). This is an unfortunate example of "over-diagnosis" leading to an increase in cancer incidence. Various professional organizations in the U.S., including the ATA and the American Association of Clinical Endocrinologists (AACE), do not recommend a routine screening for thyroid cancer in general population (7,16).

Natural history

Autopsy studies have shown that thyroid gland harboring foci of PTC may be present in up to 35.6 % of the population, with a higher frequency in population older than 40 years (17,18). This prevalence is significantly higher than clinically diagnosed thyroid cancer prevalence of 1.1% (19). In a meta-analysis of autopsy studies, Lee *et al*. reported that 11.5% of thyroid glands harbored PTC, with no association to the cause of mortality. However, clinically discovered PTMC may behave differently than PTC discovered at autopsy. PTMC in surgical specimen was much more commonly seen in females, with a female to male ratio of 10.9:1, compared to 1:1 in autopsy. Rates of cervical nodal metastasis in patients with PTMC was 33.4% which was compared to 10% in autopsy (20).

Management

Surgery

Surgical resection is the current standard of care for thyroid cancer. In the U.S., more than 90% of patients diagnosed with thyroid cancer undergo surgery as a primary treatment (21). Although the risk of complications increases with the extent of surgery, the prognosis is usually excellent (22,23). The extent of surgery for PTMC is debated as the extent of surgery has not been correlated with increased survival in PTC (24). In their meta-analysis of 11 studies with 13,801 PTMC patients, Zheng *et al*. reported no difference in mortality between total thyroidectomy and lobectomy, although lobectomy was associated with a higher rate of recurrence (25). The current ATA guidelines recommend thyroid lobectomy for PTMC with no extrathyroidal extension or nodal disease (7). However, in a recent study by Al-Qurayshi *et al*. examining the National Cancer Database, he reported that the majority of PTMC patients underwent total thyroidectomy in up to 83% and the remaining 17% underwent hemithyroidectomy. Interestingly, up to 18.65% of PTMC patients had advanced features such as lymph nodes metastasis, lymphovascular invasion and extrathyroidal extension. Although minimal extrathyroidal extension and lymphovascular invasion, may not directly affect the overall survival, it was strongly correlated with distant metastasis, leading to poor overall survival (26). These features were identified on histopathological exam as it may be difficult to obtain on routing preoperative workup, which further adds to the value of surgery in the management of PTMC.

Surgery has several clear benefits over active surveillance. It removes the primary tumor, facilitates follow-up with serial tumor marker levels, may reduce the recurrence risk, and decrease the need for possible additional surgeries in the future. Additionally, up-front resection may relieve patient anxiety associated with a malignancy diagnosis (27,28).

Given the excellent overall prognosis of PTC in the context of a rising incidence of disease, Kuma hospital in Japan pioneered the concept of active surveillance in favor of immediate surgery in patients with low risk PTMC in 1993. Years of longitudinal surveillance revealed that a high percentage of these tumors remained stable and even regressed over time in some cases (13,27). This seminal observation raised questions regarding the need for surgical intervention in PTMC patients.

Active surveillance

Active surveillance is the deference of surgical treatment in favor of serial monitoring of disease. If the disease is found to be progressing, the patient may choose to exit active surveillance and pursue a surgical option. This management approach has been utilized for years in patients with localized low risk prostate cancers, especially in older patients who were likely to die from other unrelated health conditions (13,29). However, it is important to note that prostate cancer tends to occur in older patients with a

median age of 51, unlike thyroid cancer which has much wider age range at diagnosis (21). Active surveillance for thyroid cancer is gaining acceptance due to the results of recent studies on PTMC. However, in his study using semi-structured interviews with 22 clinicians, Nickel *et al.* reported that they were not comfortable recommending active surveillance as a management approach and the patients currently have a higher preference for surgery. They were concerned about the risk of metastasis and the level of evidence supporting this approach. Nevertheless, most of them felt that biopsy for thyroid nodules <1 cm is not necessary, which can minimize the risk of overdiagnosis (30).

Ito *et al.* followed 340 patients with PTMC and found that only 15.9% had tumor size progression of more than 3 mm over a period of 10 years and only 3.45% of the study population showed lymph node metastasis over the same time period. However, a minimal change in one dimension can still add up to a significant increase in total volume of the tumor. Thirty-two percent of the patients in the study ultimately ended up having a surgery for multiple different reasons. In 2014, the same research group followed 1,235 patients and demonstrated a lower percentage for tumor size growth (8%) but slight increase in lymph node metastasis rate (3.8%) (31). It can be argued that early surgical intervention in this small percentage of patients may have prevented the need for an additional neck dissection surgery for metastatic disease. Sugitani *et al.* followed 230 patients and reported that 7% of the patients had tumor size progression and only 1% had lymph node metastasis over 5 years (13). In the U.S., Tuttle *et al.* (32) followed 291 patients and found that 3.8% had tumor size progression over 2 years. Tumor size progression was defined as growth >3 mm. Kwon et al. (33) followed 192 patients for median of 2.5 years and found that up to 14% of patients had tumor size progression, which represents a high percentage of progression over a relatively shorter follow-up period. Similarly, in a recent study by Smulever et al. tumor size progression was noted in 14.6% and nodal metastasis in 4.8% after a median of 3.1 years (34).

The current ATA guidelines endorse active surveillance as a management option of PTMC (7). However, data are currently limited for low risk PTC larger than 1 cm with only a few studies reporting its validity (35). It is also important to consider that until now the number of the enrolled patients in active surveillance cohorts is slightly over 2000, which is considered a relatively very small number (36). Additionally, not all of these patients have an equal period of follow-up.

Selection criteria for patients chosen for active surveillance were almost identical among the studies, all of which considered a low risk PTC to be smaller than 1 cm. Tuttle et al. included tumors up to 1.5 cm as low risk in their study (32). That same cohort included some tumors that were not Bethesda VI tumors. High-risk tumors were excluded from active surveillance across the studies. High-risk features included tumor location adjacent to the trachea or close to the recurrent laryngeal nerve, FNA findings suggestive of aggressive pathology, the presence of regional lymph node metastasis or distant metastasis, and signs of progression during follow-up. Patients who developed tumor progression by more than 3mm increase in size or presence of lymph node metastasis were advised to exit active surveillance and pursue a definitive, surgical treatment (13,27,31,32). Several studies on active surveillance of PTC have been recently completed and more are ongoing. While there are minor differences in inclusion criteria, the primary outcomes are tumor size progression and lymph node metastasis as shown in *Table 1*.

Patient selection

Active surveillance requires a well-coordinated institutional framework to maintain a high standard of care and achieve desired results. Ideal patient characteristics, tumor-specific features, and adequate support by health care system are necessary as well (41). An active surveillance program is suggested to be instituted only after establishing institutional review board (IRB) approved protocols with full disclosure for selected group of patients (42). Sakai et al. recommended inclusion criteria to include patients older than 60 years with access to insured health care for a long-term follow-up (38). The tumor should be solitary and less than 1 cm, with no evidence of extrathyroidal extension, nodal involvement, or metastatic disease. Adequate patient tracking requires a health care system with multidisciplinary teams, high quality ultrasonography, skilled technicians, and an accessible medical record conducive to tracking patients by multiple providers in the team (41). Oh *et al.* reported that young patients less than 50 years old or male patients with upper pole tumors, subcapsular location, or microcalcifications have a higher risk of developing lymph node metastasis (43). Age less than 40 was reported as an independent factor for PTMC progression by Ito *et al.* (31). Surgery, rather than active surveillance, is recommended for male patients younger than 40 years (44).

Table 1 Thyroid cancer active surveillance cohorts

Author	Year	Country	No of patients	Follow up period (years)	Tumor progression ≥3 mm (%)	Lymph node metastasis (%)
Ito (27)	2010	Japan	340	5; 10	6.4; 15.9	1.4; 3.4
Sugitani (13)	2010	Japan	230	5	9.6	1.3
Ito (31)	2014	Japan	1,235	10	8	3.8
Kwon (33)	2017	S. Korea	192	2.5	14	0.5
Tuttle (32)	2017	USA	291	2	3.8	0
Sanabria (37)	2018	Columbia	57	1	3.5	0
Sakai (38)	2019	Japan	360	7.4	8	0.8
Rosario (39)	2019	Brazil	77	2.5	1.3	0
Molinaro (40)	2020	Italy	93	1.6	2.1	1.1
Smulever (34)	2020	Argentina	41	3.1	14.6	4.8

Pregnancy

High levels of serum human chorionic gonadotropin hormone is concerning for the potential to stimulate growth of thyroid cancer in pregnancy (45). Shindo *et al.* reported a higher incidence of tumor progression among pregnant women, but only 9 pregnant patients were included in this study (46). In another study with a greater sample size of 50 pregnant women with 51 pregnancies, Ito *et al.* showed that 8% (4 patients) had tumor progression during pregnancy and 2% (1 patient) had nodal metastasis 20 months after delivery (47). Although the incidence of tumor progression was 8% during pregnancy, the relatively short follow-up period by the nature of pregnancy cannot be overlooked when evaluating disease progression in this patient population. Studies with larger sample size are needed to obtain more reliable conclusions and recommendations.

Diagnostic accuracy of ultrasound

In contrast to prostate cancer, active surveillance for thyroid cancer is centered around reliable detection of tumor progression by imaging studies. It is critical to assess available imaging modalities for accurate evaluation of tumors that are at high likelihood of progression. One of the factors associated with an increased risk of tumor progression and also an indication for surgery is the presence of extrathyroidal extension (7,48). Several studies have assessed the accuracy of ultrasound in detecting minimal and gross extrathyroidal extension. The overall sensitivity of ultrasound in extrathyroidal extension detection varies from 25–100% with variable specificity from 13–93% (49-51). The wide variability reflects that ultrasound may not be a reliable tool in detecting extrathyroidal extension. Variations are attributed to technician skills and different degrees of tumor extension. Addition of CT scan to ultrasound assessment has been reported to decrease both the false positive and the false negative rate, leading to higher positive predictive value up to 83% compared to US or CT alone at 72.2% and 81.8% respectively, in a study on 377 patients by Lee *et al.* (52).

Lymph node metastasis to central neck compartment in PTC is frequently seen, and less commonly to the lateral neck with older patients having higher rates of recurrence and mortality (53). In studies examining the role of prophylactic neck dissection, 30% of the patients with PTC had clinical lymph node metastasis at the time of presentation, and up to 80% had micro-metastasis (54,55). The sensitivity of ultrasound in detecting lymph node metastasis for central and lateral neck is 22.6–55% and 62–100%, respectively (56,57). For higher detection sensitivity of lymph node metastasis, a combination of CT scan and US is recommended for active surveillance, as multi-modal imaging improves the detection sensitivity for nodal disease in central and lateral neck up to 73% and 95.9% (57,58). Clearly, performing CT scans for these patients with PTMC will add significant cost on our healthcare system.

Patient factors

Although old age is typically associated with a poorer

prognosis in thyroid cancer, active surveillance studies reported that an advanced age may correlate with a decreased likelihood of tumor progression and nodal metastasis. Miyauchi *et al.* reported the rate of progression of PTMC over 10 years in different age groups and concluded that older patients are best suited for active surveillance. The estimated probability of lifetime progression of the tumor was 60.3% and 37.1% for patients in their 20s and 30s. The estimated probability of progression decreased to 27.3% and 14.9% in patients in their 40s and 50s, and was significantly lower at 9.9% and 3.5% for 60s and 70s (31,59). The increased risk of lifetime disease progression in younger patients advocates for a definitive treatment rather an active surveillance in younger patients. As they are most likely to need surgery at some point in the future. However, deferring surgical intervention for suitable time to the patient remains a valid option.

The patient preference and willingness to participate in active surveillance may be difficult to predict (47). Despite strong evidence published from Japan and the U.S., active surveillance is still a relatively new management option for PTMC in the U.S. Different socioeconomic, educational, and cultural background may play a role in accepting the surveillance approach (27). Anxiety and stress associated with a cancer diagnosis may greatly impact a patient's quality of life (60). In their study of 395 patients, Kong *et al.* reported a better quality of life in patients who were enrolled in the active surveillance compared to patients who underwent surgery. However, the follow-up period was relatively short with a median duration of 9 months (61). Based on surveys, interview responses and field observations of active surveillance cohort at Kuma Hospital, Davies *et al.* reported that up to 37% of patients were worried sometimes (or more) about their cancer and up to 14% had some form of effect on their daily life activities (62). To our knowledge, studies comparing quality of life in thyroid cancer patients undergoing active surveillance to surgical intervention are lacking. Some patients may prefer active surveillance over surgery due to the fear of complications and the possible need of lifelong hormone replacement. On the other hand, patients who prefer surgery are assured by a definitive early treatment. Most patients rely on their physician as the primary source of medical information, and they are often influenced by the physician's opinion and advice. Patients should be well informed on different treatment options for appropriate shared decision making.

Compliance with follow-up is an integral part of successful active surveillance. In a prospective study of 4,547 patients with low risk prostate cancer, patient compliance dropped over time from 81% the first year to 33% after 10 years (63). However, it is important to highlight that the prostate cancer population is all male, and thyroid cancer patient compliance may be different due to female patient prevalence.

Biologic and molecular markers

In prostate cancer, a tumor marker, serum prostate-specific antigen (PSA), is integral in screening patients at risk for malignancy as well as recurrence. Unfortunately, no such a tumor marker is available for thyroid cancer. Sugitani *et al.* reported no association between thyroid stimulating hormone (TSH) and tumor progression in their active surveillance cohort, using baseline TSH at diagnosis or the mean TSH during follow-up (64). However, a recent study demonstrated that during follow-up, a higher TSH level maybe associated with tumor progression [multivariate analysis, hazard ratio (HR) =3.55 (1.22–10.28), P=0.02] (65). The TSH trend as a prognostic indicator needs to be further evaluated.

Different molecular markers have been studied to identify low-risk PTC such as *BRAF*, *RAS*, *TERT* promoter mutations, RET fusion proteins, and miRNAs (66,67). The detection of $BRAF^{V600E}$ mutation is a widely used prognostic tool (68-70); however, its accuracy in predicting disease progression is debated (68,69). In a study of 182 patients with PTMC, a risk score calculation, which accounted for $BRAF^{V600E}$ mutation, was able to predict the presence of central lymph node involvement with sensitivity of 63.4% specificity of 80.2%, and an area under the ROC (AUC) of 0.755. To our knowledge, $BRAF^{V600E}$ mutation status was not analyzed in active surveillance cohort to validate its prediction power of tumor progression. *TERT* promoter mutation is implicated with very aggressive variant of PTC, but its prognostic value in PTMC is poorly elucidated (71,72). Rusinek *et al.* reported 3 out of 82 PTMC specimens harboring *TERT* promoter mutations. However, these specimens did not present angioinvasion, infiltration of tumor capsule, multifocality, or lymph node metastasis (71). Additionally, in active surveillance cohort of 26 patients Yabuta *et al.* reported that none of the patients who developed tumor progression harbored TERT mutation (73).

RAS mutation and clinical parameters have been studied in a cohort of PTMC (74). No significant association between *RAS* mutation and clinical criteria were found,

leading to the conclusion that *RAS* mutation alone cannot identify low-risk PTC that have the potential to evolve during active surveillance period.

Several miRNAs have been proposed as a diagnostic tumor marker to detect thyroid cancer and to be used as a prognostic marker after surgery (75). Their relevance in identifying patients who are candidates for active surveillance is currently being validated to predict disease progression during active surveillance.

The development of reliable molecular markers that can predict the likelihood of disease progression will improve risk stratification and selection of patients for active surveillance program. Unfortunately, despite the progress that has been made with different markers such as BRAF, RET and microRNA there is currently no specific marker that is able to predict disease progression in PTC (76).

Cost effectiveness

Performing a cost-effective analysis of active surveillance versus immediate surgery is rather challenging. Even in prostate cancer, which has a well-established active surveillance protocol, the findings are mixed and are largely dependent on the location and the specific nuances of the management protocol. Active surveillance for prostate cancer patients between 60–70 years of age is more cost-effective than surgery, but the same is not true in patients between 45–55 of age (61). This finding demonstrates that the cost-effectiveness of surveillance is improved with patients who have a shorter expected life span. A majority of patients with thyroid cancer typically present between 45–54 years of age, which is significantly younger than the average age of presentation for prostate cancer (2). However, in a study of 349 patients in Australia, the cost of surgery was estimated to be equal to the cost of active surveillance for 16.2 years (77). Thus, surgery is a more cost-effective option for young patients who are more likely to require longer follow-up. When determining optimal care of patients, treatment decisions are made on individual basis with many different factors weighing in.

Conclusions

Active surveillance is a recognized management approach for a select group of patients with low-risk PTC, although it is not widely accepted or practiced yet in the U.S. With the propensity of thyroid cancer to affect younger age groups, active surveillance requires decades of monitoring to assess the true potential for disease progression and associated morbidity. Active surveillance may be a more appropriate alternative management option for older patients with low-risk PTC, rather than younger patients.

Currently, we do not have specific criteria or molecular markers to identify PTMC that are at high risk for progression. Molecular studies may provide valuable information regarding the likelihood of tumor progression and aid the selection of ideal patients for active surveillance.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Jonathon Russell and Jeremy Richmon) for the series "The Management of Thyroid Tumors in 2021 and Beyond" published in *Annals of Thyroid*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aot-20-25). The series "The Management of Thyroid Tumors in 2021 and Beyond" was commissioned by the editorial office without any funding or sponsorship. 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-20-25
Cite this article as: Elnahla A, Attia AS, Ruiz E, Mayer S, Lee G, Kandil E. Active surveillance for well-differentiated thyroid cancer. Ann Thyroid 2020;5:22.