

A Clinical Framework to Facilitate Risk Stratification When Considering an Active Surveillance Alternative to Immediate Biopsy and Surgery in Papillary Microcarcinoma

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Background: The 2015 American Thyroid Association thyroid cancer management guidelines endorse an active surveillance management approach as an alternative to immediate biopsy and surgery in subcentimeter thyroid nodules with highly suspicious ultrasonographic characteristics and in cytologically confirmed very low risk papillary thyroid cancer (PTC). However, the guidelines provide no specific recommendations with regard to the optimal selection of patients for an active surveillance management approach. This article describes a risk-stratified clinical decision-making framework that was developed by the thyroid cancer disease management team at Memorial Sloan Kettering Cancer Center as the lessons learned from Kuma Hospital in Japan were applied to a cohort of patients with probable or proven papillary microcarcinoma (PMC) who were being evaluated for an active surveillance management approach in the United States.

Summary: A risk-stratified approach to the evaluation of patients with probable or proven PMC being considered for an active surveillance management approach requires an evaluation of three interrelated but distinct domains: (i) tumor/neck ultrasound characteristics (e.g., size of the primary tumor, the location of the tumor within the thyroid gland); (ii) patient characteristics (e.g., age, comorbidities, willingness to accept observation); and (iii) medical team characteristics (e.g., availability and experience of the multidisciplinary team). Based on an analysis of the critical factors within each of these domains, patients with probable or proven PTC can then be classified as ideal, appropriate, or inappropriate candidates for active surveillance.

Conclusion: Risk stratification utilizing the proposed decision-making framework will improve the ability of clinicians to recognize individual patients with proven or probable PMC who are most likely to benefit from an active surveillance management option while at the same time identifying patients with proven or probable PMC that would be better served with an upfront biopsy and surgical management approach.

Introduction

SCREENING AND AUTOPSY STUDIES indicate that asymptomatic papillary microcarcinomas (PMCs) are present in at least 5–10% of the U.S. adult population (1), representing nearly 16 million people with undiagnosed thyroid cancer. Despite this huge pool of subclinical cases, the prevalence of thyroid cancer in the United States is only 0.5 million patients (2), indicating that <3% of this subclinical reservoir has been detected and diagnosed. Unless the aggressive evaluation of subcentimeter thyroid nodules with high-resolution ultrasound (US) and US-guided fine-needle aspiration (FNA) is curtailed, the incidence of thyroid cancer will continue to increase dramatically as more and more cases of subclinical, low-risk papillary thyroid cancer (PTC) are identified (3,4).

Since the vast majority of these subclinical thyroid cancer foci progress either slowly or not at all (5,6), it is critical to reevaluate the traditional management approach, which rou-

tinely recommends immediate thyroid surgery for all biopsy-proven PTCs. This is particularly important, since thyroid surgery can result in clinically significant morbidity (alterations in voice associated with damage to recurrent and superior laryngeal nerves, hypoparathyroidism, and rarely airway obstruction associated with bilateral vocal cord dysfunction, hematoma formation, or infection), particularly when the surgery is performed by low-volume surgeons (7,8). Furthermore, after total thyroidectomy, many patients have persistent fatigue (9), weight gain (10), and cognitive complaints (11), even when optimized on thyroid hormone therapy. In light of the very low disease-specific mortality associated with PMCs, the lack of proven benefit of thyroid surgery, and the potential for side effects and complications from thyroidectomy, there is an obligation to consider alternative management strategies carefully.

Active surveillance is a conservative observational management strategy that is currently being offered to properly

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selected patients with prostate cancer, urethral cancer, and some non-Hodgkin lymphomas. It is important to note that biopsy-proven disease is not a requirement for an active surveillance management program. This term can also be applied to clinical scenarios where the clinical, imaging, or cytological findings are highly suggestive of malignant disease (e.g., thyroid nodules with ultrasonographic features that are very suspicious for thyroid cancer, or cytology classified as suspicious for PTC [Bethesda V cytology]). In patients being followed with active surveillance, definitive therapy (usually preceded by definitive diagnostic procedure) is not recommended until there is evidence of disease progression. Because of the relatively indolent nature of these malignancies, deferring definitive diagnosis and therapy until documented disease progression has no impact on disease-specific survival.

Recognizing that immediate biopsy and surgical intervention may not be in the best interest of every low-risk thyroid cancer patient, the Kuma Hospital physicians developed and validated an active surveillance management approach as an alternative to immediate surgical resection in cytologically confirmed PTC (5,12). When followed with active surveillance, the vast majority of PMCs do not progress (or progress very slowly) when observed for many years (5,6,13). In fact, patients being followed with active surveillance demonstrate the same risk of locoregional spread, distant metastasis, and disease-specific mortality as patients undergoing immediate surgery: none of the patients with active surveillance in Kuma Hospital developed distant metastasis or died of the disease (5,6). Importantly, even patients who demonstrated disease progression while under active surveillance were effectively treated with thyroid surgery, indicating that a delayed surgical management approach in properly selected patients had no impact on disease-specific survival (5,6).

Interestingly, the only clinical factors that predicted tumor progression were age at the time of diagnosis and pregnancy during observation (14). Young patients (<40 years) were more likely to experience thyroid tumor enlargement and novel lymph node appearance compared with middle-age (40–59 years) and older patients (>60 years) (15,16). An increase in the size of the PMC was seen in four of the nine women who became pregnant while being followed with active surveillance (14). However, further studies with larger sample sizes are needed to define the impact of pregnancy accurately in very low-risk PTC. While there is much interest in potential molecular predictors of disease progression, there is currently no validated molecular profile that can be used to exclude very low-risk patients definitively from an initial active surveillance management approach.

It is important to emphasize that patient selection and careful follow-up will be the key to a successful active surveillance approach, as a very small number of patients with apparently low-risk thyroid cancer die from their disease, even after presenting with what appeared to be intrathyroidal PMCs treated with surgery (17). There is little doubt that the excellent outcomes associated with the observation approach at the Kuma Hospital are the result of careful patient selection by an experienced thyroid cancer management team with access to state-of-the-art cytology and US facilities (12).

The 2015 American Thyroid Association (ATA) thyroid cancer management guidelines state that while surgery is generally recommended for biopsy-proven thyroid cancer, an active surveillance management approach “can be consid-

ered” as an alternative to immediate surgery in patients with very low-risk tumors (e.g., PMCs without clinically evident metastases or local invasion and no convincing cytology or molecular evidence of aggressive disease) (18). Furthermore, the 2015 ATA guidelines strongly discourage FNA of asymptomatic subcentimeter thyroid nodules, even if ultrasonographically suspicious, endorsing serial ultrasonographic follow-up, with cytology evaluation recommended only if there is evidence of disease progression (18). Taken together, it is clear that the intent of the guidelines is to avoid an immediate rush to definitive cytologic diagnosis and surgical treatment of most intrathyroidal subcentimeter PTCs, while at the same time recognizing that until the guidelines are uniformly implemented, some recommendations need to be made for patients who do have cytologically confirmed PMCs. While this conservative management approach is endorsed, the guidelines do not discuss in any detail the wide variety of clinical factors that need to be taken into account when considering active surveillance as an alternative to immediate biopsy and surgery in an individual patient with proven or suspected PMC. This manuscript describes the clinical decision-making framework that was developed at Memorial Sloan Kettering (MSK) Cancer Center as the lessons learned from Kuma Hospital were applied to the evaluation of the more than 200 patients with probable or proven PMC being considered for an active surveillance approach in the United States.

A Framework for Clinical Decision Making

A risk-stratified approach to the evaluation of patients being considered for active surveillance requires an evaluation of three interrelated but distinct domains (see Table 1):

- *Tumor/neck US characteristics:* factors considered here include the size of the primary tumor, the location of the tumor within the thyroid gland, molecular profile, and the status of the cervical lymph nodes.
- *Patient characteristics:* factors considered here include the age of the patient, child-bearing potential, family history of thyroid cancer, the willingness of the patient to defer immediate surgery, and compliance with follow-up.
- *Medical team characteristics:* factors considered here include the availability and experience of the multidisciplinary team, the quality of neck ultrasonography, and the experience of the clinician treating thyroid cancer.

The findings within each of these three domains allow the patient to be classified into one of three categories that express the suitability of an active surveillance management approach (see Table 1):

- *Ideal candidate:* the classic ideal patient would be an older patient with a probable or proven solitary PMC with well-defined nodule margins, not adjacent to the thyroid capsule and confined to the thyroid parenchyma.
- *Appropriate candidate:* these patients may be younger, have multifocal disease, disease that is adjacent to the thyroid capsule at noncritical locations, a potentially more aggressive molecular phenotype, or have other ultrasonographic findings that are likely to make follow-up more difficult (thyroiditis, nonspecific lymphadenopathy, or other benign-appearing nodules).
- *Inappropriate candidate:* these patients have tumors in critical subcapsular locations (adjacent to the recurrent

TABLE 1. A RISK-STRATIFIED APPROACH TO DECISION MAKING IN PROBABLE OR PROVEN PAPILLARY MICROCARCINOMA

<i>Candidates for observation</i>	<i>Tumor/neck US characteristics</i>	<i>Patient characteristics</i>	<i>Medical team characteristics</i>
Ideal	<ul style="list-style-type: none"> • Solitary thyroid nodule • Well-defined margins • Surrounded by ≥ 2 mm normal thyroid parenchyma • No evidence of extrathyroidal extension • Previous US documenting stability • cN0 • cM0 	<ul style="list-style-type: none"> • Older patients (>60 years) • Willing to accept an active surveillance approach • Understands that a surgical intervention may be necessary in the future • Expected to be compliant with follow-up plans • Supportive significant others (including other members of their healthcare team) • Life-threatening comorbidities 	<ul style="list-style-type: none"> • Experienced multidisciplinary management team • High-quality neck ultrasonography • Prospective data collection • Tracking/reminder program to ensure proper follow-up
Appropriate	<ul style="list-style-type: none"> • Multifocal papillary microcarcinomas • Subcapsular locations not adjacent to RLN without evidence of extrathyroidal extension • Ill-defined margins • Background ultrasonographic findings that will make follow-up difficult (thyroiditis, nonspecific lymphadenopathy, multiple other benign-appearing thyroid nodules) • FDG-avid papillary microcarcinomas 	<ul style="list-style-type: none"> • Middle-aged patients (18–59 years) • Strong family history of papillary thyroid cancer • Child bearing potential 	<ul style="list-style-type: none"> • Experienced endocrinologist or thyroid surgeon • Neck ultrasonography routinely available
Inappropriate	<ul style="list-style-type: none"> • Evidence of aggressive cytology on FNA (rare) • Subcapsular locations adjacent to RLN • Evidence of extrathyroidal extension • Clinical evidence of invasion of RLN or trachea (rare) • N1 disease at initial evaluation or identified during follow-up • M1 disease (rare) • Documented increase in size of ≥ 3 mm in a confirmed papillary thyroid cancer tumor 	<ul style="list-style-type: none"> • Young patients (<18 years) • Unlikely to be compliant with follow-up plans • Not willing to accept an observation approach 	<ul style="list-style-type: none"> • Reliable neck ultrasonography not available • Little experience with thyroid cancer management

US, ultrasound; RLN, recurrent laryngeal nerve; FDG, fluorodeoxyglucose; FNA, fine-needle aspiration.

laryngeal nerve or trachea), have evidence of spread outside the thyroid by either direct extension or metastases, or have evidence of disease progression on serial examinations.

Rationale for Classification as an Ideal Candidate for Active Surveillance

Data from Kuma Hospital convincingly show that patients who are ideal candidates for active surveillance will demonstrate a <1–2% rate of disease progression (5). Furthermore, salvage therapy is very effective at the time of disease progression, with no significant morbidity or mortality associated with a delayed management approach (5,6).

The ideal patient is usually older than 60 years of age with a thyroid nodule with well-defined borders and surrounding normal thyroid parenchyma who is willing to accept an observational management program under the guidance of an experienced thyroid cancer management team that uses high-quality neck ultrasonography. Since thyrotropin (TSH) is a growth stimulant to thyroid cancer (19,20), levothyroxine is used as necessary to achieve a normal TSH at MSK. At Kuma Hospital, patients are given the option of levothyroxine therapy to achieve mild suppression in an effort to decrease further the likelihood of disease progression (15).

In many cases, a stable, small thyroid nodule has been observed for many years but then is evaluated with FNA for a variety of reasons. In these cases, long-term stability of the biopsy-proven thyroid nodule makes it unlikely that the nodule will rapidly progress.

In addition to the size of the primary nodule being <1 cm in maximal dimension, the ideal candidate also demonstrates a nodule with well-defined margins. Since the follow-up of thyroid nodules is based almost exclusively on serial US measurements, nodules that have indistinct margins are more difficult to follow, as there is likely to be more variation in size determinations.

Also included in this group are patients with life-threatening comorbidities that are likely to be the cause of demise long before clinically significant progression of the thyroid cancer.

Successful active surveillance also requires the support of relevant family members, friends, and healthcare providers. It is important to provide information and support to other members of the patient's healthcare team and even family and friends with the permission of the patient.

Finally, the ideal candidate also participates in a prospective data collection protocol with data collected in a uniform manner so that the outcomes can be reported and compared.

Rationale for Classification as an Appropriate Candidate for Active Surveillance

Compared with ideal patients, patients classified as being appropriate candidates have a higher risk of disease progression (e.g., middle-aged patients) (15), child-bearing potential with or without immediate plans for pregnancy (14), or have specific characteristics that will make it more difficult to follow with observation (e.g., less than high-quality neck ultrasonography, potential of tumor multifocally in patients with a strong family history of thyroid cancer) (21), subcapsular location not adjacent to critical structures (e.g., trachea or recurrent laryngeal nerve), a potentially more aggressive molecular phenotype, or ill-defined nodule margins (22). While a disease progression rate of approximately 10% is

expected in this cohort, treatment offered at the time of disease progression will still be very effective and associated with excellent clinical outcomes when these patients are followed carefully by an experienced management team. At both Kuma Hospital and MSK Cancer Center, observation is routinely recommended for patients in this category, as ongoing studies demonstrate that even in a very experienced thyroid cancer center, immediate surgery is more likely to cause unfavorable outcomes (such as vocal cord paralysis and hypoparathyroidism) than an active surveillance management approach (23).

Because the precise risk for disease progression is not well established in BRAF^{V600E}-positive (24), fluorodeoxyglucose (FDG)-positive PMCs (25,26), or patients with other potentially aggressive molecular phenotypes (27), they were included in the appropriate candidate category until further studies provide a basis for making them either ideal or inappropriate candidates. At this time, molecular characterization of the tumors is not required prior to an active surveillance management approach. Despite the possibility that each of these situations could be associated with slightly more aggressive disease, serial US is expected to identify disease progression readily in each of these scenarios (potentially aggressive molecular profile or FDG-avid primary tumors) in time for salvage therapy still to be very effective.

The presence of ultrasonographic findings of Hashimoto's thyroiditis (HT) complicates an active surveillance management approach. The nonspecific ultrasonographic findings seen in HT complicate follow-up by making it more difficult to assess tumor size or identify other areas of concern within the thyroid both at presentation and during follow-up (28,29). Furthermore, HT often leads to atypical cervical lymphadenopathy (30), which makes it more difficult to exclude locoregional metastasis confidently. Unless the cervical lymph nodes are >1 cm and very suspicious, patients with HT are followed with active surveillance, even in the setting of small atypical perithyroidal lymph nodes. Biopsy of cervical lymph nodes is reserved for very suspicious lymph nodes >1 cm or atypical lymph nodes demonstrating structural progression during active surveillance.

Rationale for Classification as an Inappropriate Candidate for Active Surveillance

An observation approach in these patients is contraindicated because thyroid surgery (with or without radioactive iodine ablation) has been demonstrated to be beneficial, because minor disease progression could lead to significant morbidity, or because a high rate of disease progression is expected. Patients with suspected or confirmed PMC are classified as inappropriate candidates for observation because locoregional or distant metastases are identified at the initial presentation; significant morbidity could be associated with even minor disease progression (e.g., extrathyroidal extension, subcapsular location near recurrent laryngeal nerve) (5,6); a very high rate of disease progression is expected (e.g., aggressive cytology (31), or previously documented increase in size of ≥ 3 mm in a confirmed PTC); the patients are children (<18 years old); or there are concerns regarding compliance or quality of follow-up.

A Practical Approach to Active Surveillance

It is important to emphasize that an active surveillance management approach does not mean that thyroid biopsy or

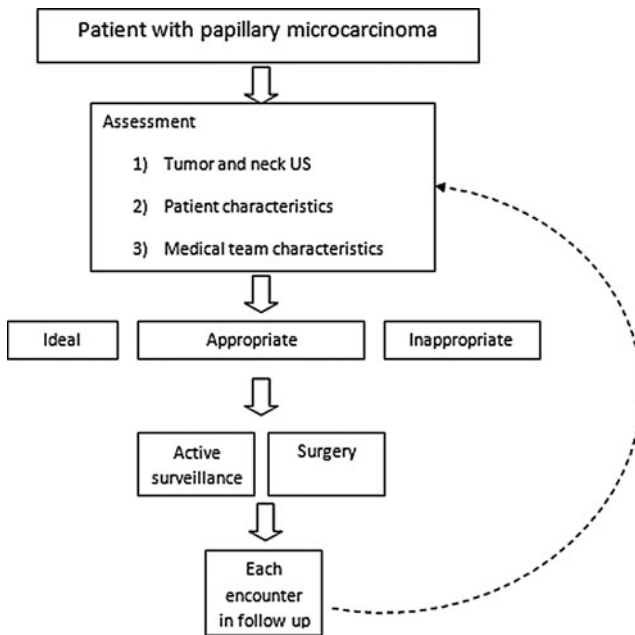


FIG. 1. Ongoing risk stratification for the management of patients with papillary microcarcinoma.

surgery will never be necessary. Therefore, the options for initial management are presented as either immediate surgery or active surveillance with the possibility of delayed biopsy or surgery, although this possibility is low.

As noted above, the primary focus of the initial evaluation is to obtain the information necessary to classify the patient as an ideal, appropriate, or inappropriate candidate for observation. In addition to an assessment of the patient and medical team characteristics, this initial evaluation requires a high-quality neck ultrasonography that carefully evaluates the size and location of the thyroid cancer and the status of the cervical lymph nodes. Thyroid function tests are also obtained to ensure the patient is euthyroid. Evaluation of the images of previous ultrasonographic examinations are often helpful in establishing the stability (or lack thereof) of the index thyroid cancer and other nodules.

Using the approach developed at Kuma Hospital, patients are excluded from observation if they have high-risk features such as locoregional or distal metastasis (very rare), signs of recurrent laryngeal nerve or tracheal invasion, aggressive histologies (very rare in PMC), or evidence of disease progression. Patients are also excluded if a thyroid nodule is in a subcapsular location adjacent to the expected course of the recurrent laryngeal nerve. Tumor multifocality, family history of thyroid cancer, sex, and age did not exclude patients from an observation approach.

When evaluating subcentimeter thyroid nodules with “high suspicion sonographic pattern for papillary thyroid cancer,” as defined by the ATA guidelines (18), FNA cytology is not necessary in patients who appear to be either ideal or appropriate candidates for an active surveillance management approach. Avoiding cytologic confirmation of thyroid cancer has important management implications, as many patients in the United States appear to find it difficult to accept active surveillance once a suspicious nodule has been confirmed to be thyroid cancer. Conversely, establishing a

definitive diagnosis in a subcentimeter thyroid cancer with a high suspicion sonographic pattern may be appropriate if the tumor/neck US characteristics suggest that the patient would be an inappropriate candidate for active surveillance if the suspicious thyroid nodule was cytologically confirmed to be thyroid cancer (e.g., evidence of extrathyroidal extension, N1 or M1 disease, a 5–9 mm nodule in a subcapsular location adjacent to a recurrent laryngeal nerve, or >5 mm increase in size over 6–12 months of observation).

In most cases, the active surveillance approach requires neck ultrasonography approximately every six months until stability is documented (usually two years). Once disease stability is documented, neck ultrasonography is then done every one to two years or less frequently. Thyroid function tests are done annually. The role of serum thyroglobulin determinations is unknown and not routinely done.

Just as the response to therapy evaluations of PTC (32) and medullary thyroid cancer (33) have been described, it is important to re-evaluate patients under observation continually in order to determine if their suitability for continued observation has changed over time (see Fig. 1).

Conclusion

Given the high prevalence of subclinical PMC in the general population, the relative indolent nature of the disease, the effectiveness of an observational management approach, and the risks associated with aggressive up-front diagnosis and therapy, an active surveillance management approach appears to be a viable management option in properly selected patients with probable or proven PMC followed in specialized centers. This approach should decrease the perceived need for immediate FNA in the majority of subcentimeter thyroid nodules. In order for active surveillance to be successful, clinicians will be required to assess critically the tumor/ultrasonographic characteristics, the experience of the medical team, and the patient/family attributes in order to determine the appropriateness of an observational management approach for each patient.

Author Disclosure Statement

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