Review Article

Active surveillance for micropapillary thyroid carcinoma: a clinical review

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Abstract: With the rapid rise in the incidence of micropapillary carcinoma, there is increasing concern about its overdiagnosis and overtreatment. There is considerable interest in managing patients with micropapillary carcinoma with active surveillance or deferred intervention. Various institutions around the world are practicing active surveillance. The major question remains as to who the ideal candidates are and how best to monitor these patients. This clinical review will discuss the ideal, appropriate, and inappropriate patients for active surveillance. It will also discuss the follow-up strategy for these patients and some of the adverse clinical features that will be used to decide against active surveillance. There are uncertainties as to who should be offered active surveillance. Various studies have shown approximately 10% of the patients switching to surgery primarily related to fear factor rather than increase in the tumor size or lymph node metastasis. The results of immediate surgery do raise issues related to complications of thyroid surgery and quality of life. The most ideal candidate would be patients with a tumor below 1 cm, intrathyroidal. For the patient who is a minimalist, the follow up strategy includes, ultrasound every 6 months for the first 1 or 2 years, and then every year after that. If there is a substantial change in the tumor volume or nodal metastasis, surgery should be considered, which happens in less than 10 percent of patients according to many studies. Based on existing literature and clinical experience, it appears that active surveillance is an appropriate strategy for monitoring micropapillary carcinoma.

Keywords: Micropapillary carcinoma; active surveillance; deferred intervention; conservative treatment; thyroid cancer

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Introduction

Background

The rapid rise in incidence of thyroid cancer is well known worldwide; for example, the incidence of thyroid cancer has risen almost four times in the United States over the last quarter of a century while it has risen approximately 15 times in South Korea (1). This is primarily related to incidentally detected micropapillary carcinomas during routine ultrasound evaluation of the thyroid, which has resulted in overdiagnosis and overtreatment. Likely due to an increasing appreciation of overdiagnosis, the rates of thyroid cancer have fallen in Korea and stabilized in the United States (2). This has generated considerable debate in the recent literature, particularly regarding its impact on patient outcomes and cost. The standard of care in these patients would have been an appropriate thyroidectomy. Generally, the old dictum of using radioactive iodine has

been essentially abandoned in patients with micropapillary carcinoma. The treatment choices for micropapillary carcinoma include lobectomy, total thyroidectomy, total thyroidectomy with central compartment dissection, total thyroidectomy with radioactive iodine, newer ablative techniques (radiofrequency ablation, laser), and active surveillance. Clearly, it would be almost impossible to operate on every micropapillary carcinoma diagnosed as an incidental finding either on clinical examination or imaging studies or routine ultrasound evaluation of the thyroid. Autopsy studies frequently identify incidental, asymptomatic micropapillary carcinoma. People live with it, they grow with it, and most of them will die with it and not of it. There are, of course, concerns about thyroid surgery, including neck scarring, complications and side effects of thyroid surgery, lifetime thyroid medication, and lifetime follow-up. There are also quality-of-life concerns after thyroidectomy, even though most patients do well with thyroid replacement. It is extremely important to manage these incidental microcarcinomas from a scientifically rational approach and maintain the best quality of life for the patient.

Rationale and knowledge gap

There clearly is over diagnosis and over treatment of micropapillary carcinoma. As we know 6–15% of the patients live normal life with micropapillary carcinoma, we need to challenge the issues regarding routine surgery for micropapillary carcinoma. It is quite common that these tumors remain stable for a long period of time. We also need to appreciate the risk of complications of surgery and relative stability of the tumor in 90% of the patients. The biology of the micropapillary carcinoma is much different than other aggressive human cancers.

The concepts behind active surveillance

In 1993, after careful consideration, Miyauchi from Kobe, Japan, suggested active surveillance in patients with microcarcinoma (3,4). While researching non-surgical approaches, he and his unit conducted a study with approximately 2,153 patients with microcarcinoma (55% of whom were on active surveillance while 45% were in the immediate surgery group). This number is probably growing now, as more and more patients are agreeing to active surveillance. They reported the stability of the disease in more than 92% of the patients. Approximately 5% of the patients did go for surgery either primarily because of the increase in the size of the tumor or patient's unwillingness to be monitored. The new appearance of the lymph node metastasis was noted only in less than 1% and the increase in the size of the primary tumor occurred in only 3% of the patients. Although the 2014 *New York Times* report described an epidemic of thyroid cancer, as far as we are concerned it is truly instead a thyroid cancer pandemic, given the extent of its rapid rise around the world.

We are quite familiar with the incidence of micropapillary carcinoma in the autopsy series, which is highest reported in Finland, Japan, and the Philippines, while in the United States it is between 5–10% and approximately 10% in Canada. Looking at this very critically, approximately 15–20 million Americans have micropapillary carcinoma. As technology has advanced to find these microscopic tumors, there is major concern among physicians regarding how to determine the best management plans for these individuals. Most of the time we recognize the stability of the tumor over a period of time. The clinical questions that come up are: What is the natural history of microcarcinomas during observation? What percentage of them grow? What percentage of them metastasize to the lymph nodes?

Objective

From the active surveillance studies, it has been shown that less than 10% will grow and approximately 2–3% will develop nodal metastasis over 5–10 years of observation, none of which has a major impact on the long-term outcome (3). In all of the active surveillance studies, none of the patients under active surveillance died of thyroid cancer or developed major cancer-related problems. So, it is important to appreciate that the decision is more important than the incision. The observational data were also published in 2017 by Tuttle *et al.* from Memorial Sloan Kettering Cancer Center (MSK) with their large series (approximately 291 patients), the first of its kind in the United States (5). The continued surveillance was maintained in 96% of the patients. Approximately 4% of patients underwent surgery due to an increase in size of the tumor or concerns of the patient and family. None of the patients died of thyroid cancer.

Active surveillance—the philosophy of management

With active surveillance, immediate surgery is avoided in favor of continuous monitoring (also referred to as active

monitoring, expectant management, vigilant observation, watchful masterly inactivity, or deferred intervention). Some issues related to papillary microcarcinoma and observation probably revolve around the nomenclature used by the pathologist as cancer. As the "C" word is unsettling for most patients—who become worried about the growth of the tumor or their family responsibilities or even death due to the cancer—some practitioners have proposed changing the name to papillary microtumor or IDLE (Indolent Lesion of Epithelial Origin). We think most patients will understand the philosophy of observation if we use the analogy of the prostate cancer and continuous monitoring. It is important to train primary care physicians, who are the first to meet with patients, and there should be more publicly available information and education about the benefit of active surveillance. It should be recognized that active surveillance is not inappropriate management, but it may be considered as deferred intervention in properly selected patients. Quite often physicians are concerned about medicolegal issues; however, expansion of public knowledge will help, and it would be important to make sure the well-defined selection criteria and standardized follow-up protocols are developed and offered to the patients. Needless to say, patients can change their mind at any time and opt for surgery. The success of an active surveillance program also requires multidisciplinary involvement with the surgeons, endocrinologists, radiologists, and other physicians involved in the micropapillary carcinoma disease management team.

The clinical scenario of active surveillance

The principles behind active surveillance are easy to understand if we consider case studies of patients from different groups. For example, an 85-year-old man undergoes routine carotid ultrasound and the sonographer finds a 5-mm nodule in the right lobe of the thyroid and the family insists he undergo a fine-needle aspiration biopsy of this tiny nodule, which is reported to be papillary carcinoma. What now? We do not think there will be many surgeons or endocrinologists mandating an immediate surgical intervention. It is quite likely this nodule has been there for a while and can be easily monitored. Another example involves a 25-year-old female medical student who during a routine ultrasound of the neck as part of a radiology rotation is found to have a 7-mm nodule on the right side and a 5-mm nodule on the left side; at the insistence of the radiologist, she undergoes a biopsy on both sides and it is papillary carcinoma on both sides. What will we do? Obviously, the optimal treatment with a diagnosis of carcinoma on both sides is total thyroidectomy. However, in a 25-year-old woman who has a long life ahead, credible academic responsibilities, and proposed family responsibilities, active surveillance is a very reasonable option based on the patient's preferences, values, and risk tolerance. Total thyroidectomy may represent excessive therapy in this patient with a lifetime supplementation of thyroid medication and even in the best of hands 2% risk of complications related to nerve injury or temporary or permanent hypoparathyroidism. Adjusting these patients to thyroid medication may be easy in principle but more difficult in practice; there are quite often complaints that "I just don't feel the same." Quality of life in these individuals needs to be better studied.

Who should we refer for active surveillance?

In conjunction with Professor Miyauchi, Tuttle and his group from MSK defined three interrelated domains, such as tumor and ultrasound characteristics, medical team characteristics, and patient characteristics (6-11). Based on these decision-making domains, a clinical framework was developed to facilitate risk stratification to characterize patients as either ideal, appropriate, and inappropriate for an active surveillance initial management approach. Tumor characteristics for ideal patients are a solitary intrathyroidal nodule, well-defined borders, tumors surrounded by normal thyroid tissue, no extrathyroidal extension, or no evidence of metastatic disease to the central compartment or lateral compartment. Ideal patient characteristics include age above 60 years, patient acknowledgment that future surgery may be required, and patient cooperation and compliance with regular follow-up. If present, comorbidities are obviously prioritized in the management plan rather than the cancer itself. Many patients may have another concurrent malignancy, which unlike micropapillary carcinoma is a major decision maker and should be the focus of initial disease management. Medical team characteristics—experienced multidisciplinary team, experienced ultrasonographer, appropriate data collection and departmental support, and appropriate coordination and decision making between the surgeon and the endocrinologist after appropriate imaging studies such as ultrasound and, when necessary, a CT scan—are also important.

Tumors with irregular margins should be carefully

evaluated as there is probably a likelihood of higher incidence of both extrathyroidal extension and nodal metastasis. Patients classified as inappropriate for active surveillance are those with involvement of the surrounding soft tissues adjacent to the recurrent laryngeal nerve, gross extracapsular spread, tumors with metastatic disease either to the central or lateral compartment or needle biopsy suggestive of aggressive variety of tumor. Even though BRAF has been included in some of the fine-needle aspiration biopsies we would not consider that as a major decision-maker unless the tumor itself shows aggressive clinical features. Age has always been brought as a concern and there is good data from Miyauchi's group that even in young patients they can be enrolled into active surveillance with the understanding that approximately 40–50% may require surgery; however, we may be able to defer their surgery until they find an opportune time in their life for surgery or show distinct increase in the size of the tumor (12,13). Interestingly, the older patients do very well with active surveillance with very little tumor growth over a period of time. A large number of publications are noted in the recent literature on active surveillance in different parts of the world, such as Japan, Korea, and the United States. The basic principle is to actively monitor these patients with routine ultrasound at an interval of 6–12 months. It clearly requires a deep understanding on the part of the patient and their family that we are just monitoring their cancer. An analogy of prostate cancer will help the patient understand the philosophy of active surveillance. Recently, several reviews and meta-analyses have been published (12,14,15). The results published are practically identical in various series, with avoidance of surgery in 90% of patients. Obviously if the patient is maximalist, the surgery is quite helpful to alleviate their anxiety and good outcome.

Strategy of observational approach

Quite a few issues go into decision making which we have discussed about the appropriate candidate for observation. Generally, these patients will require serial ultrasounds. Initially, we prefer to obtain ultrasounds of the thyroid and cervical lymph node chains every 6 months to give confidence to the patient about the stability of the thyroid nodule. Thyroid hormone therapy is recommended if needed to keep the thyroid stimulating hormone (TSH) in the normal range and less than about 3 mIU/L. Once we know that the thyroid functions are satisfactory, they are usually repeated every year.

The indications for surgical intervention under observation are:

(I) Increase in the size of the tumor more than 3 mm. Although we use 3 mm as a general consideration, generally any increase in the size of the tumor more than 100% should be a consideration for surgical intervention or more careful follow-up.

(II) Identification of metastatic nodes in the central compartment which happens probably in approximately 2–3% of people.

(III) Direct invasion of the surrounding tissues should be a strong indication for surgery that is best evaluated with a good ultrasound and cross-sectional imaging if needed. The posterior tumors are not the best for observation or the anterior tumors in the isthmic area may invade the surrounding structures. The last but not least is the patient's preference.

(IV) Patient preference is important and can change over time. Sometimes, young individuals switch to the surgical approach for a variety of reasons, including anxiety after discussion with friends or family members, the gravity of the word "cancer", or occasionally listening to other people about their concerns about progression of the thyroid cancer or hearing another patient with medullary carcinoma or anaplastic carcinoma going wild and rushing into surgery.

(V) Uncommonly, one would consider surgical intervention mainly for the insurance issues or other indications for thyroid surgery (concurrent hyperparathyroidism, increase in benign thyroid nodules). Usually, kidney or liver donations are not accepted with a diagnosis of active cancer and the surgery may be considered. Likewise, transplant centers usually consider a known cancer to be a contraindication to receiving an organ transplant, and thus surgery may be required to render the patient disease-free to facilitate organ transplantation.

It should be recognized that active surveillance requires a complete understanding in the triangular fashion with the surgeon, the endocrinologist, and the patient (as well as family members). The strategy of active surveillance will result in approximately 10% migrating from active surveillance to surgery, 5% due to increase in the size of the thyroid nodule or new lymph nodes and 5% mainly because of the patient and the family wishes. However, in all the reported series there were no adverse findings either at the

time of surgery or outcome. The long-term follow-up on these patients has been quite satisfactory with no adverse or deleterious effect in the long-term outcome or mortality.

Medical decision making for active surveillance

Once again, the decision-making rests on the patient, the surgeon, and the endocrinologist who is going to monitor and follow the patient. It is very important to make sure the patient understands the reason behind the active surveillance. The idea of active surveillance is not to defer the treatment or offer inferior treatment but to continuously monitor the tumor, which the patient may live with for a long time. Whether a patient will need surgery in the near or distant future is difficult to determine; however, generally most of these patients can be monitored very well based on the international studies. Several international studies have been performed and meta-analysis has also shown that the overall risk of increasing in the size of the thyroid nodule is about 3–5% and the novel nodal metastasis is noted in less than 2% of the people. The patients who generally switch to surgery are the ones with considerable anxiety or some of the family members pushing them for surgery. In this aspect, it is very important to understand the difference between maximalist and minimalist. Pamela Hartzband and Jerome Groopman have published on the subject of medical decision making, including how to decide what is right for you in terms of a maximalist or minimalist approach (16). Maximalists prefer aggressive surgery (i.e., "wants surgery yesterday"), and these patients are not ideal candidates for observation. On the other hand, minimalists believe that tumors of this type can be observed to monitor whether surgery would be appropriate at an opportune time; these are the right candidates for observation. Patients who remain doubtful are not the best candidates, and the patients who are technologically oriented are also not the best candidates. Again, there has to be a good discussion between the patient and the treating physician.

It is also important that the surgeon works with the endocrinologist who has the same philosophy and the decision about the surgery versus observation will depend upon a dedicated and good ultrasound to make sure there are no adverse imaging features which will push the patient into surgery and continuous monitoring over a period of time. Obviously, there are always cost concerns; however, the whole idea is to try to avoid surgery in these incidentalomas. In principle, a significant number of the general population (approximately 10%) may be harboring microscopic papillary carcinoma and we do not need to push every one of them where the diagnosis of papillary carcinoma is made incidentally. Needless to say, if the tumor is palpable or patient is symptomatic, they will definitely need surgery. The philosophy of the maximalist is generally "Why wait? More is better." While minimalists take a "Less is more" approach and feel that any unintended consequences of surgery outweigh potential benefits. This is where the philosophy of believers and doubters, and the idea of technology orientation versus naturalistic orientation comes in. Patients and their families must understand the philosophy behind observation. The surgeon and the endocrinologist need to explain to the patient that this is what they would also recommend for their own family members and that there is no rush to operate, especially in young people who may have concerns about the complications of surgery. Although surgery for thyroidectomy is generally quite safe, complications do occur in the range of 1–3% including nerve injury and parathyroid problems. However, it is important to note that the rates of complication may be significantly higher when thyroid surgery is done outside of major medical centers. Some of these patients may need thyroid medication and getting adjusted to the thyroid medication and quality of life are important concerns. The old philosophy "let the punishment fit the crime" is so critical in management of these patients.

It is also important to make the patient and their family aware that the thyroid cancer diagnosis was totally incidental, the tumor is a microcarcinoma and it is quite likely it may have been there for many years. Patients need reassurance that this particular cancer is not detrimental to their health and will not lead to major catastrophe in future. The benefit of monitoring to see if there is any change in the future and deferring surgery until then should be emphasized. There are several recent publications from different parts of the world supporting active surveillance for micropapillary carcinoma (17-20).

Adverse features of papillary microcarcinoma

Certain thyroid tumor features are considered adverse—for example, clinical and radiological features such as irregular margins, infiltrating borders, radiological or clinical gross extrathyroidal extension, presence of nodal metastasis, distant metastasis, or the cytology report showing aggressive pathology. Multicentric tumor is always a debatable question; however, generally the combination

of all multicentricity below 1 cm does not have any major adverse features. Location of the tumor is also important; for example, the disease management team needs to assess whether it is against the posterior wall of the trachea, if it is coming out of the thyroid gland, if it is abutting the trachea, or if it is likely to injure the recurrent laryngeal nerve in the future. Patients with isthmic tumors are also not the best candidates, as the isthmus is quite thin, approximately 3 mm, and most tumors in the isthmus generally extend out of the thyroid gland, including involvement in the surrounding soft tissues; the possibility of adherence to the trachea or the soft tissues of the neck is much higher. Additionally, the psyche and anxiety of the patient must be considered carefully. This is where the judgment call comes between the surgeon, endocrinologist, and the patient. Patients who are severely distressed by the diagnosis of cancer, or whose fears about thyroid cancer cannot be managed, are not the best candidates for observation. Immediate curative surgery might be a better approach for these patients instead of the watchful monitoring involved in active surveillance. We do need to realize that active surveillance is not about avoiding surgery but rather deferring the intervention until appropriate timing.

Active surveillance—"out of the box"

Although Miyauchi *et al.* have published their data on microcarcinoma below 1 cm, MSK extends the limit to 1.5 cm with no adverse outcome (3,5). Even in older people, thyroid cancer with nodal metastasis could be observed. Again, these are the patients who are out of the box, whose co-morbidity or age is a deterrent to surgical intervention. It is also a well-known practice in recurrent thyroid cancer to continue to observe the patient. Even though we do not use the classical active surveillance for management for recurrent thyroid cancer essentially the principle remains the same. The recurrent nodal metastasis which is below 1 cm may be hard to find during surgical exploration. It is easy to get a diagnosis on needle biopsy but sometimes difficult to find and sometimes confers higher risk of injury to the parathyroid and recurrent laryngeal nerve, and these patients can be easily monitored and followed (21). Occasionally, these small recurrent nodal metastases may be treated with alcohol injection. So, the active surveillance in clinical practice is applicable to the primary tumor, to the lymph node metastasis and also to the distant metastasis. It is not uncommon in our practice when the distant metastasis is asymptomatic to be monitored especially in the setting of small volume, slowly growing pulmonary metastasis. So, the decision making about active surveillance rests on the tumor volume, tumor location, rate of change of the tumor (doubling time), the follow-up strategy and indications for intervention and the patient philosophies.

Newer technology in the management of micropapillary carcinoma

Although the standard of care for micropapillary carcinoma would be a lobectomy and isthmusectomy with a decision to be made in the operating room based on gross findings of the primary tumor, nodal disease, etc., there have been technological advances in recent years where some other techniques are used (e.g., alcohol ablation, which has been a practice at the Mayo Clinic mainly for the lymph nodes but occasionally for small microcarcinomas). There is a growing interest and experience of radiofrequency ablation mainly from Korea and Brazil and primarily for benign tumors however it has been applied for the malignant pathology also (22). Laser ablation is another technologic advance. Again, one needs to be absolutely sure that the tumor is well inside the thyroid and unlikely to have any deleterious effect on the surrounding structures such as recurrent laryngeal nerve or the carotid artery. Microwave ablation is another technology. Again, the technological advances will depend upon the institutional practice and experience of the surgeon; however, the interventional radiologists are getting very active in this approach in managing microcarcinomas.

Conclusions

Successful application of active surveillance in papillary microcarcinoma relies on appropriate patient selection based on patient characteristics, tumor/imaging characteristics and medical team characteristics to classify patients as either ideal, appropriate, or inappropriate for minimalistic management approaches. Patients who are medical minimalists and compliant with follow-up are the best candidates. It should be performed in a good multidisciplinary institution with a track record of active surveillance with experienced thyroidologists and available radiographic expertise. Active surveillance requires long-term follow-up with a good ultrasound, comparison with the previous ultrasound, and good clinical examination. During follow-up, the role of TSH suppression and indications for surgery will continue to be assessed. Again, we must realize the ultimate effect on the patient's quality of life is

very important. Active surveillance is an alternative to total thyroidectomy or lobectomy for microcarcinomas, but it is not for every low-risk thyroid cancer, or for every patient, or for every clinician. It requires a deep understanding between the surgeon, the endocrinologist, and the patient and the availability for regular follow-up. The philosophy of treatment is individualized, personalized, and precise. There is also a parallel concern about treatment of anxiety. In short, shared decision making between the patient and experienced multidisciplinary medical team members provides the ideal clinical situation to safely and effectively employ active surveillance in properly selected patients with low-risk papillary thyroid cancer.

There is always a concern about monitoring any cancer. What we don't know is which of these micro carcinomas may behave aggressively. Clearly those with irregular border, invading the posterior area, or extrathyroidal extension should undergo surgery. Approximately 1–2% of micropapillary carcinoma do present with nodal or distant metastasis, so a thorough initial evaluation with a dedicated ultrasound of the thyroid and neck is quite critical. Even though we have not used molecular markers such as BRAF in the decision making, it is something that should be studied for future analysis. There may be other molecular markers which may help in future.

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