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Observation versus surgery?: A treatment paradigm shift for the fastest rising cancer diagnosis in the world: papillary thyroid cancer

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Observation versus surgery?

A treatment paradigm shift for the fastest rising cancer diagnosis in the world:

papillary thyroid cancer

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Abstract

Papillary thyroid cancer has increased in incidence dramatically over the past three decades making it the fastest rising cancer diagnosis in the world. The prognosis of this disease remains excellent despite this dramatic rise which has called into question the risk of overdiagnosis and overtreatment of this disease. The American Thyroid Associated (ATA) currently recommends surgical treatment for all confirmed malignant thyroid nodules over 1 cm in diameter. However, some research suggests that tumors under 1 cm have a greater prevalence of lymph node metastases while other research suggests that observation is an appropriate option for tumors greater than 1 cm without other unfavorable features. In order to provide the best management for this disease, clinicians should be monitoring emerging studies on this topic while researchers need to explore the outcomes from the various treatment modalities. In the meantime, treatment for papillary thyroid cancer should be evaluated and treated on an individualized basis.

Introduction

When patients learn that they have cancer, they experience heightened anxiety and expect to be comforted with a clear treatment plan outlined by their clinicians. In the case of papillary thyroid cancer, the guidelines are changing and providers and patients alike are confused about how to proceed. This lack of consensus is particularly relevant because a significant increase in the incidence of papillary thyroid cancer has occurred in the last three decades, making it the fastest rising cancer in the US, the 6th leading cancer diagnosis in the world and the most common endocrine malignancy.[1] Nonetheless, the prognosis of papillary thyroid cancer has remained extremely favorable and its mortality rate has remained unchanged despite the significant increased incidence rate.[2] The reason for the increased incidence is not fully understood at this time; however, the hypothesis most recognized is

that advancements and increasing availability of imaging techniques such as neck ultrasound, have improved the ability to diagnose small thyroid nodules, thus increasing the frequency of diagnosis.

This increased frequency of diagnosis has created controversy among providers and researchers regarding the treatment of this cancer especially because of concerns about potential overtreatment of cancer that has such an excellent prognosis if left untreated. Currently, many sources provide suggestions on how to proceed with treatment but few well-funded, peer-reviewed controlled trials are available to help providers make evidence-based decisions.[3] The standard of treatment for papillary thyroid cancer as defined by the American Thyroid Association is to achieve disease-free status through surgical treatment of malignant thyroid nodules > 1 cm followed by radioactive iodine ablation and lifelong thyroid hormone replacement.[3] Additionally, to eliminate risk for overtreatment, the recommendations state that thyroid nodules found on imaging should not be biopsied until they are > 1 cm. Despite these guidelines, the lack of consensus about treatment options in clinical practice causes confusion for providers and their patients. Furthermore, active surveillance of papillary thyroid cancer given its indolent nature and excellent prognosis has become a more popular option in recent years. The different therapeutic options available to patients with papillary thyroid cancer will be explored, with the focus on whether observation or standard surgical treatment provides the best overall outcome for patients.

Discussion

Despite the increased incidence of thyroid cancer over the past several decades, mortality rates have not changed and survival rates have remained stable at over 98% at five-year follow up.[4] This excellent prognosis challenges current recommendations of surgical excision of thyroid nodules. As a result, researchers have suggested the possibility of observation instead of surgery in cases of papillary thyroid cancer. One such study from Kuma Hospital in Japan planned to prove this hypothesis and

conducted an observational trial for >700 patients diagnosed with papillary thyroid cancer from the years of 1993 to 2001. In this study, patients with papillary thyroid cancer but without unfavorable characteristics (such as tumors located adjacent to the trachea, tumors invading the recurrent laryngeal nerve, or lymph nodes highly suspicious of metastasis) were given the option to choose observation or the standard surgical treatment. The observation group was followed annually; tumor size as well as evaluation for lymph node metastases were recorded each year. At one year follow up, 70% of patients did not have any change in tumor size. Furthermore, at five-year follow up, 72.3% of the previously unchanged group did not have any change.[5] These findings were significant in that they provided strong evidence supporting the hypothesis that observation of thyroid cancer is a valid therapeutic approach. However, in this same study, it was determined that microcarcinomas, which are defined as less than 1 cm, were found to have a higher rate of lymph node metastases than the larger tumors. This is important because it challenges the original guidelines from the American Thyroid Association that recommend observation rather than biopsy of thyroid nodules under 1 cm. The strength of this study comes from its large sample size; however, limitations included the retrospective and observational study design and the duration of follow up being limited to 5 years.

Another study published in 2017 examined whether immediate surgery versus delayed surgery and observation had any effect on clinical outcomes. The study separated patients into three groups, one with immediate surgery, one with surgery between 6-12 months of diagnosis, and surgery 12 months after diagnosis. No significant differences in thyroid cancer, either recurrence or persistent disease were found among the patients in the three groups. This evidence reinforced the idea that a period of observation of thyroid cancer could be offered to patients without adversely affecting their long-term prognosis.[6] Like the prior study, the strength of this research comes from its large sample size of 2863 patients. However, the patients are from a single hospital which may have led to bias in

determining which treatment option to choose. Furthermore, it is a retrospective observational study, limiting its quality of evidence.

The slow growing nature of thyroid cancer along with its behavior of remaining latent for many years without harmful effects has also led researchers to evaluate the potential complications of traditional surgical treatment of thyroid cancer. The risks of thyroid surgery include transient hypoparathyroidism, permanent hypoparathyroidism, potential laryngeal nerve damage, and permanent vocal cord paralysis; nonetheless, the risks of long term damage are relatively low at 0.2% for permanent vocal cord paralysis and 1.6% for permanent hypoparathyroidism.[7] One of the most significant negative outcomes of thyroid surgery is a decrease in the quality of life due to the need for lifelong hormone replacement with levothyroxine. The potential adverse effects reported with levothyroxine treatment can include thyrotoxic symptoms that lead to reduced exercise tolerance, anxiety, and cardiovascular effects like increased resting heart rate, tachyarrhythmias, and atrial fibrillation.[8] Lifelong levothyroxine treatment with TSH-suppressing doses necessary for preventing papillary thyroid cancer recurrence can also lead to decreased bone mineral density with consequent increased risk of osteoporosis and fragility fractures.[8] These latter effects are more likely to occur when TSH levels are suppressed to 0-0.3 mU/L which is the recommendation for TSH-dependent tumors. Furthermore, appropriate TSH levels can be difficult to manage and require close follow up which include several appointments a year for these patients and multiple trips to the laboratory for monitoring, all of which are expensive and can affect the quality of life.

Other risks from traditional therapy include toxicities and complications due to radioactive iodine (RAI) treatment for remnant thyroid cancer ablation. The use of RAI has been routine after total thyroidectomy given the high percentage of lymph node metastases with papillary thyroid cancer but few studies have outlined the risks of RAI. A study in 2015 examined these risks and found that the use of RAI increased from 4% in 1972 to 40% in 2008. Patients who received RAI had significantly elevated

risk of developing secondary malignancy later in life at a rate of 1 in every 227 individuals compared to individuals who did not receive RAI.[9] The most prevalent secondary malignancies include leukemia and salivary gland cancer. Other studies revealed chronic toxicities from RAI including sialadenitis, oligospermia, and ovarian failure.[9] These results came from a large sample size of 3850 patients which is a strength of this study; however, few studies examining RAI in this setting are available for comparison, thus limiting this study. Nonetheless, given the excellent prognosis of thyroid cancer and long-life expectancy in general, it is essential that clinicians and patients understand the risks of developing secondary cancers from RAI therapy when evaluating treatment options.

Despite the alternative management options and despite studies revealing negative effects as described above, total thyroidectomy with radioactive iodine remnant ablation is still the number one treatment option for papillary thyroid cancer.[10] The goal of papillary thyroid cancer treatment as defined by the American Thyroid Association is to eradicate any signs of disease. Disease-free is defined by negative tumor markers and a negative whole-body scan after treatment which is only achieved by thyroidectomy, radioactive iodine ablation with iodine-131, and lifelong TSH suppression with levothyroxine treatment.[11] With this combination of treatments, the rate of recurrence is lower when compared to more conservative management options. A retrospective observational study of over 50,000 patients supported this treatment because it showed that less aggressive surgery, like a lobectomy, resulted in a higher rate of cancer recurrence and death compared to total thyroidectomy.[12] The data for this study were taken from databases and cancer registries which limited the amount of information that could be studied about each individual patient case but did provide a very large sample size. Another study published in 2019 focusing on surgical options for papillary thyroid (removing only the tumor and its margins) reduced surgical risks; however, 5% of these patients had recurrent disease and required further thyroid surgery.[13] This study had a small sample size of only 79 patients and a

limited follow up period but is one of the only studies that showed clinical outcomes of conservative thyroidectomy compared to total thyroidectomy for papillary thyroid cancer.

Although total thyroidectomy has several disadvantages, it not only permits, but is required before remnant ablation with RAI. This option allows for accurate evaluation of recurrence with thyroglobulin tumor markers which is more useful after the thyroid tissue has been removed.[14] Reasons for resistance to adoption of observation over the traditional treatment pathway have also been described in another study and included patient fear of a cancer diagnosis, clinician unwillingness to discuss more conservative options, and lack of observational studies showing the efficacy of different surgical options.[14]

With the various options available for treatment of papillary thyroid cancer and the controversy surrounding them, it appears the best way to manage treatment is to focus on the features of papillary thyroid cancer that determine its aggressiveness and likelihood of metastases. Despite its excellent prognosis, significant morbidities are associated with papillary thyroid cancer that can be detrimental if left untreated and must be evaluated prior to choosing a treatment path. The first and most well-studied feature of papillary thyroid cancer that increases its mortality rate and risk of recurrence is tumor size.[15] A threshold of 1 cm has consistently been referenced as a determining factor in in choosing the next steps in therapy; however, a study published in 2014 with a large sample size of 60,000 patients showed no survival benefit with lobectomy versus thyroidectomy for tumor sizes between 1-4 cm.[16] These data were also collected from databases which have similar limitations as noted above regarding potential for missing information on individual patients and for coding errors (which were less likely). Alternatively, a study published in 2018 showed that in cases that were initially considered low risk based on tumor size of < 1cm, 18% of these “low-risk” cases were required to have total thyroidectomy after initial conservative management (including observation or minimal excision with lobectomy) based on recurrence or presence of non-low risk lymph node metastases found during surgery.[15] An important

limitation of this study was that the patient population was entirely of Asian ethnicity, individuals who are known to have the highest percentage of lymph node metastasis. The study design was strong because it was conducted at a single institution, allowing for consistency in analysis. The evidence from this study challenges the current recommendations of size being the decision-making factor for surgical management. Furthermore, it questions which factors, if any, are reliable for deciding optimal management of this cancer.

The answer to the question of whether observation or surgery with RAI is better may include assessing the patient for clinical symptoms and signs of extrathyroidal or lymph node involvement. Presence of factors concerning for lymph node involvement or extrathyroidal extension provide strong indication for radioactive remnant iodine ablation which requires total thyroidectomy to complete. The issue with this approach is that lymph node metastases are not always readily apparent on ultrasound and are often not discovered until the patient is already in surgery. Lymph node metastases is determined by sampling lymph nodes after dissection for presence of cancer cells. At this point, the patient has already been exposed to the risks of surgery and observation is no longer an option. The above argument also applies to multifocal disease, defined as tumors located in both lobes or more than one tumor present in the same lobe.[16] For those individuals, total thyroidectomy is the most efficient and practical option.

Another factor that can help predict optimal treatment is patient age. Compared to adults, pediatric papillary thyroid cancer presents differently. Ninety percent of pediatric patients have lymph node metastases at initial diagnosis.[17] In addition, higher rates of cervical lymph node metastases, extra-thyroidal extension, and distant metastases are found on initial evaluation. Paradoxically, pediatric patients also have a better prognosis than adults, possibly due to their improved immune systems and biologic environments. These findings challenge the traditional treatment approach. However, in a study in 2004 from the *Journal of Pediatric Surgery,* 33% of pediatric patients who had conservative treatment

with hemi-thyroidectomy had tumor recurrence that required a completion thyroidectomy. In pediatric patients, the high disease recurrence rate and consequent need for surgery completion resulted in reverting to the standard of treatment of total thyroidectomy, RAI, and levothyroxine supplementation[17]. The study has a small sample size of only 56 patients. Nonetheless, individual patient factors including history of prior radiation and genetic testing results, were available due to the small sample provided, adding to the study's strength.

Lastly, the location of the thyroid tumor is important to consider when determining the risk of papillary thyroid cancer progression. Tumors that are located near the trachea or near the recurrent laryngeal nerve are considered higher risk given their predisposition to invade these important structures. In these cases, surgical treatment is recommended.[5]

Conclusion

With the options available to providers and patients for treatment of papillary thyroid cancer, it is important to develop guidelines that help providers and patients make well-informed and prudent decisions. The evidence available on this topic helps provide clarity to patients and clinicians when making this treatment decision. Based on the risks and benefits of observation versus surgery, and on the data about features of papillary thyroid cancer that predict its behavior, a relatively non-biased approach to selecting treatment can be made. According to current evidence, some of the disease features that qualify for the standard treatment pathway automatically include tumors > 4 cm, multi-focal tumors in one or both lobes, pre-operative evidence on ultrasound imaging of tumors extending outside of the thyroid, lymph node metastases, or distant metastases.[14] In addition, patient age appears to play a major role in disease progression making surgery the preferred treatment option for patients under the age of 16. Outside of these definitive factors, an informed decision should be made based on the features of the tumors themselves. Tumors between 1 – 4 cm should be evaluated for other

aggressive features as listed above (location, metastases) and surgery is likely the best option here as well; however, patients should be educated that these tumors are typically slow-growing and active surveillance for up to 5 years can be considered prior to opting for immediate surgery.

Contrary to the guidelines from the ATA, evidence suggests that tumors < 1 cm should be evaluated for lymph node metastases as they have been found to have a higher than expected percentage of lymph node invasion. More research is needed to determine lymph node metastases pre-operatively which may include assessment of thyroglobulin levels, more advanced imaging techniques, or fine needle aspiration sampling. If no evidence of lymph node or extra thyroidal metastases is found, then observation of these tumors should be considered first-line for all patients with tumors < 1cm with ultrasound follow up every six months to monitor for changing features of the disease.

Although studies on papillary thyroid cancer have traditionally been scarce, the changing landscape and increasing incidence will likely encourage more research in the coming years that could help refine optimal treatment guidelines. For example, promising research is on the horizon that uses molecular markers from the fine needle biopsy aspiration used for diagnosis to determine high versus low risk phenotypes to further guide treatment[18].

Given the rapidly increased incidence of this disease, it is extremely likely that clinicians will be faced with individuals affected by this disease at some point in their careers. Thus, it is imperative that clinicians are aware of the new literature on this topic and consult peer-reviewed research studies when determining treatment plans for their patients with papillary thyroid cancer. If more clinicians and patients are educated on observation of papillary thyroid cancer as a legitimate treatment option, surgery can be avoided in many cases, ultimately leading to eliminating risks associated with surgery and radioactive iodine treatment. Alternatively, knowing what features lead to more aggressive cancers can help providers make a quick decision for surgery which will avoid any delays in treatment and ideally, provide better outcomes for patients.

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