Chapter 11
Papillary Thyroid Cancer

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Objectives

1. To understand the presentation and diagnosis of papillary thyroid cancer (PTC)
2. To review the risk factors for recurrence and mortality in PTC
3. To discuss the initial surgical recommendations for PTC
4. To examine the clinical indications for radioactive iodine for PTC
5. To review the appropriate long-term management, surveillance, and follow-up for patients with PTC

Case Presentation

A 44-year-old woman with chronic neck pain was incidentally found to have a left thyroid nodule on magnetic resonance imaging (MRI) of the neck. Her medical history was otherwise unremarkable. Thyroid ultrasound revealed a lone 1.1-cm left thyroid nodule with prominent intranodular vasculature flow, irregular borders, and microcalcifications. Endocrinology was then consulted. Free thyroxine (FT_4) and thyroid-stimulating hormone (TSH) were in the normal range. No family history of thyroid disease or cancer was noted, and the patient had no radiation exposure history.

The physical examination was unremarkable, including no palpable thyroid nodules or lymph nodes in the neck. Ultrasound-guided fine-needle aspiration of the nodule was performed, and the cytology report noted scant colloid, crowded groups of follicular cells with distinct nuclear grooving, and overall consistent with papillary thyroid cancer. Recommendation was for total thyroidectomy, and pathology confirmed a 1.1-cm well-encapsulated papillary thyroid cancer (PTC) with no evidence of local invasion or disease metastatic to lymph nodes. However, an incidental

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3-mm focus of papillary thyroid cancer was noted in the right thyroid lobe as well. The patient proceeded to receive ablation therapy with 100 mCi radioactive iodine, with posttreatment whole-body scan revealing only focal, intense uptake in the thyroid bed. Levothyroxine therapy was started and dose titrated to achieve a goal TSH of 0.1 to 0.3 μIU/mL. One year after initial surgery, the patient underwent a withdrawal whole-body scan, which revealed no evidence of local or metastatic disease. At the time, TSH was 100 μIU/mL and thyroglobulin plus antithyroglobulin antibody levels were undetectable. Neck ultrasound was also unremarkable at 1 year.

Risk Factors for Thyroid Cancer

Both the prevalence of thyroid nodules and thyroid cancer are increasing [1]. In areas that are iodine sufficient, the prevalence of palpable thyroid nodules is 5% in women and 1% in men [2]. As illustrated by this case, common use of anatomic imaging of the neck and chest is associated with an increasing incidence of incidentally found thyroid nodules, with 19% to 67% of randomly selected individuals having thyroid nodules detected on thyroid ultrasound [3]. While the majority of thyroid nodules are benign, the clinical challenge is to accurately diagnose the 5% to 10% of thyroid nodules that are malignant. Some known clinical features associated with increased cancer risk include age >60 years; male gender; radiation exposure history; family history; and a firm, fixed nodule [4]. Ultrasound characteristics that are suggestive of thyroid cancer include irregular borders, prominent intravascular flow, microcalcifications ("starry-night" pattern), and size >4 cm [5]. However, reliance on ultrasound findings alone to predict thyroid cancer is problematic, as the sensitivities range from only 32% to 87% and the specificities range between 39% and 95% [5].

In this case, a small nodule <1.5 cm was found but with multiple concerning features present, and so a fine-needle aspiration was performed. Findings suspicious for papillary thyroid cancer were noted, including scant colloid and distinctive grooved nuclei, although psammoma bodies were absent.

Well-Differentiated Thyroid Cancer

Approximately 23,500 new cases of thyroid cancer are reported each year [6]. The majority are differentiated thyroid cancers (DTCs), 90% of which are papillary or follicular thyroid cancer, with PTC predominating [7]. Recently a new tumor, node, metastases (TNM) staging of thyroid tumors has been adopted [8]. According to this new system, thyroid tumors ≤2.0 cm in size and limited to thyroid gland are classified as T1. This differs from the old staging system where T1 was defined as tumor ≤1 cm. Using extent of disease, tumor size, and age >45 years, patients can then be differentiated into three disease risk categories: very low risk, low to moderate risk, and high risk for disease recurrence and death [9]. Currently, patients with papillary thyroid cancer have a 93% ten-year survival and 100% at 5 years for those considered low risk (stage I, II) [10].

Risk Factors in Thyroid Cancer for Recurrence and Mortality

Multiple studies have attempted to determine characteristics associated with risk for recurrence and mortality. Overall, mortality from thyroid cancer is low, but reoccurrence rates range between 25% and 35% [11]. Most reoccur in the first decade after presentation, but cases of reoccurrence >10 years after initial presentation are encountered. Characteristics including age >45 years, male gender, tumor size >4 cm, follicular histology, multifocality, initial local tumor invasion, and regional lymph node metastasis have been shown to be associated with increased reoccurrence, both distant and local-regional metastases [12]. Multiple studies have looked at thyroid microcarcinomas (<1 cm), which have shown various factors including lymph node metastasis at initial presentation as a significant risk factor for disease reoccurrence [13]. However, few studies have addressed risk factors for smaller tumors falling in the 1- to 1.5-cm range just above the microcarcinoma size cutoff.

One recent study by Pellegriti [14] examined well-differentiated papillary thyroid cancers <1.5 cm, and found that approximately 20% had extrathyroidal invasion or bilateral foci. Additionally, multifocality and lymph node invasion were seen in 30%, with distant metastases in 2.7%. Even more surprising was that over 25% of the patients with tumors <1.5 cm had evidence of persistent/relapsing disease after only an average of about 4 years of follow-up, with 14.4% still having persistent disease at the conclusion of the study. By multivariate analysis, lymph node metastasis at presentation was found as the strongest predictor of development of local metastasis and recurrent disease. Pellegriti's study also revealed increasing aggressiveness of tumor, defined as the presence of multifocality, bilaterality, extrathyroidal invasion, or lymph node involvement, with increasing tumor size, in contrast with another study that found no recurrences in patients with papillary thyroid cancer <1.5 cm [15]. However, in Pellegriti's study, ultimately, tumor size >1 cm was not a significant predictor of recurrent disease with both univariate and multivariate analysis.

Although the overall prognosis is very good for patients with DTC, the ability to make evidence-based management recommendations for patients with small tumors, <1.5 cm, is hindered by a lack of prospective randomized studies.

Surgical Recommendations for Thyroid Cancer

While no uniform opinion exists regarding the initial management of thyroid cancer, present practice guidelines generally recommend near-total or total thyroidectomy for patients with DTC. The lack of consensus stems from the need to rely solely on retrospective trials for current treatment recommendations. However, results from several retrospective studies indicate a higher rate of all-cause specific mortality and recurrence in those not treated with total or near-total thyroidectomy (16–18). Another retrospective study demonstrated decreased mortality and recurrence in low-risk groups undergoing bilateral subtotal resections rather than unilateral

thyroid surgery [11]. The benefit of subtotal thyroidectomy over unilateral lobectomy for smaller DTC, especially microcarcinomas, is still not fully defined. Lobectomy may well be sufficient for management of patients with microcarcinomas, although patients with multifocality are potentially better served by a total thyroidectomy [19]. Interestingly, analysis of X-chromosome inactivation patterns in women with multifocal PTC indicates these foci many times arise as independent tumors [20]. In our case patient, irrespective of the relatively small tumor size, we suggest that the presence of multifocality calls for total thyroidectomy as the appropriate initial surgical approach.

Remnant Ablation for Thyroid Cancer

Following total thyroidectomy, common clinical practice for DTC is remnant ablation with iodine 131 (^{131}I). However, ^{131}I therapy remains controversial, especially in well-differentiated thyroid cancer <1.5 cm. Agreement exists that ablative therapy (using, for example, $\sim$1.85 GBq or 50 mCi) can destroy a functional thyroid remnant and improve the specificity of serum thyroglobulin measurements, thereby aiding in long-term follow-up. Higher ^{131}I doses (5.55 GBq or 150 mCi) are also often used in DTC patients especially, those with high-risk features [21]. For patients with high-risk disease (American Joint Committee on Cancer [AJCC] classification III and IV), a prospective, multicenter, nonrandomized study showed both an improvement in mortality (relative risk [RR], 0.03; confidence level [CI], 0.09 to 0.93) and progression (RR, 0.30; CI, 0.13 to 0.72) for PTC patients undergoing postoperative ^{131}I therapy [22]. However, the majority of patients with thyroid cancer are in low-risk groups (stage I to II). Also, the benefit of ^{131}I on recurrence rates and mortality remains unclear in these cases, with justification of ablation based only on data from retrospective studies. Data to date appear to indicate a potential improvement in recurrence rates with ^{131}I ablation but no definitive reduction in mortality rates.

A review of the existing literature by Haugen [9] concluded that radioiodine therapy does not reduce the risk of reoccurrence or mortality in patients with solitary tumor less than 1.0 to 1.5 cm and no local invasion or lymph nodes present at initial surgery. This conclusion is supported by Hay's [18] study, which found that radioactive iodine in low-risk patients (MACIS <6[*]) did not significantly improve outcome. Furthermore, Mazzaferri's [23] data, which are commonly cited as evidence in favor of ^{131}I ablation, actually revealed a reduction in cancer death ($p<.001$) limited to patients >40 years age and primary tumors ≥ 1.5 cm.

A meta-analysis of 13 studies to evaluate the role of radioiodine remnant ablation/therapy was also recently completed [24]. Overall, the data highlighted a good outcome in patients with DTC, with a mortality rate of only 1.3% to 15%. However,

[*] MACIS < 6, a system which was introduced to eliminate the need for histological grading of the tumor and uses metastasis, age, completeness of resection, invasion and size for initial staging.

the benefit of radioactive iodine was questionable, with only one of six studies examining cancer-related mortality finding a significant benefit [12], but the one study in which radioactive iodine improves the outcome was the largest study and had the longest follow-up. As far as tumor recurrence, postoperative radioactive iodine decreased the risk of recurrence in three studies. Follow-up was between 10 and 16 years, and the recurrence rate was >20%. Three smaller studies did not show improvement in recurrence rates, with recurrence in 3% to 15% and average follow-up of less than 10 years [24]. Results from pooled analysis of 18 studies (8280 patients) with 40% of total receiving ^{131}I were suggestive of a significant treatment effect of ablation for reduction in local-regional recurrence and distant metastases. Ultimately, this meta-analysis concluded that patients with DTC may benefit from radioactive iodine, given the decreased recurrence rate, but the incremental benefit of remnant ablation in low-risk patients treated with radioactive iodine and thyroid hormone suppressive therapy is unclear.

Given the inconsistent conclusions about the use of radioactive iodine in DTC among different centers, the risks of radioactive iodine must also be closely examined. Unfortunately, most of these data are from case reports and small series. One of the biggest concerns in using radioactive iodine is the risk of secondary primary malignancies. Traditional understanding has been that doses below 600 mCi are safe, but recent data seem to indicate an increased risk of chronic myelogenous leukemia even at lower doses. Another study observed a 30% increased risk of secondary primary cancer with a linear relationship between cumulative dose and solid tumors occurrence. Doses greater than 3.7 GBq or 100 mCi were calculated to cause an excess of 53 solid tumors and three leukemias per 10,000 patients over 10 years [25]. Given these concerns, Bal et al. [26] conducted a randomized prospective study looking for the minimal possible effective dose for remnant ablation in cases of DTC. They found that patients receiving 25 to 100 mCi of ^{131}I had similar rates of successful ablation. All the risks of radioactive iodine including sialadenitis, xerostomia, bone marrow suppression, diminished reproductive function, and secondary malignancies need to be discussed prior to the patient's making a definite decision before proceeding with radioactive iodine.

Common clinical practice in remnant ablation and treatment of DTC is withdrawal of thyroid hormone thereby increasing serum TSH in order to optimize the trapping and retention of radiodine. Frequently this leads to impaired quality of life and ability to work secondary to overt symptoms of hypothyroidism such as cognitive impairment, emotional dysfunction, physical fatigue. It may also increase health risk in the elderly and patients with other significant medical problems. Recombinant human TSH (rhTSH) was developed to provide TSH stimulation without thyroid hormone withdrawal. RhTSH has been approve for some time as an adjunct for diagnostic procedures in patients with DTC and just recently was approved for use in thyroid remnant ablation. Some studies have shown comparable rates of remnant ablation with both methods but one study did show that withdrawal was superior. A recent study by Pacini confirmed the non-inferiority of rhTSH preparation of patients for remnant ablation. As no long term data about recurrence or mortality is yet available, caution must be used in selecting appropriate patients for rhTSH

remnant ablation. Stage 1 or stage 2 low risk patients with no evidence of local invasion or local lymph node metastasis as in the above case's presentation should be considered for rhTSH remnant ablation in order to minimize patient discomfort and disruption of their daily activity [27].

In regard to the above case, given the questionable benefit of postiodine ablation in a DTC less than 1.5 cm, the controversy of this therapy and its risks must be clearly discussed with patients. However, the benefits including the ease of long-term surveillance after postablation therapy and the possibility that radioactive iodine may lower the risk of both local and metastatic recurrence that are seen even in microcarcinomas needs also to be considered.

Hormone Suppressive Therapy in Thyroid Cancer

Following initial treatment for thyroid carcinoma, patients are placed on thyroid hormone, usually the oral form of oral levothyroxine (LT_4). The traditional goal is not only to normalize thyroxine (T_4) levels but also to suppress serum thyrotropin (TSH) below the normal range without causing symptomatic thyrotoxicosis. By administering supraphysiologic doses of LT_4, the intent is to directly inhibit tumor growth by negative feedback on pituitary TSH secretion. Thyrotropin's main effect is on differentiated normal thyroid tissue, as the expression of TSH receptors (TSHR) is lower in malignant cells than residual thyroid, which calls into question this common clinical therapy. Other studies have also shown that ThyrCas, the tumoral TSHR alleles, are either deleted or transcriptionally silenced, and that the post-TSHR signaling pathways may be nonfunctional [28]. However, both regression of advanced thyroid cancer by TSH suppression and reduced recurrence rates have been shown on TSH suppression in multiple studies [29]. Drawbacks of these observational studies include absence of randomization, lack of appropriate controls, absence of blinding, inability to isolate the solitary effect of TSH suppression on recurrence, and no risk stratification among patients with different prognostic features [28].

A recent meta-analysis of 10 observational cohort studies of almost 3000 patients, with 69% being on TSH suppression therapy with long-term follow-up, found that patients receiving suppression therapy had a decreased risk of adverse clinical outcomes (RR, 0.73; confidence interval [CI], 0.60 to 0.88; $p<.005$) [28]. This meta-analysis seems to support the overall benefit of suppressive therapy in patients with DTC, yet it still leaves the questions of which patients benefit and to what degree of TSH suppression do patients benefit.

Conflicting data on the benefit of TSH suppression and the degree of TSH suppression has been report in the low-risk patient. It has been suggested that both nonsuppressed serum TSH and elevated serum thyroglobulin are related to an increased risk of DTC recurrence independent of tumor type and tumor stage. Conversely, Cooper [30], who stratified patients into four groups ranging from undetectable to elevated, found that while TSH score category was an independent predictor of disease progression in high-risk patients ($p = .03$), it was not a predictor for disease progression independent of initial tumor stages ($p = .7$). Wang et al [31] assessed three groups—one with recurrence, one without evidence of relapse, and

one without evidence of relapse but thyroglobulin (Tg) levels above 3 ng/mL when off of TSH suppression. From this short-term study they concluded that in patients clinically free of disease and with a Tg level <2 ng/mL, TSH can be kept in the normal range, but in those with active disease and even in those with elevated Tg level >2 ng/mL, TSH should be suppressed. Kamel et al [29] also looked at the degree of TSH suppression but in the setting of Tg levels less than 5 ng/mL, and found that maximal suppression of TSH to <0.1 mU/L did not lead to further suppression of Tg levels, concluding that maximal TSH suppression in patients who have no evidence of active disease seems unnecessary.

Initial TSH suppressive therapy has been proven to benefit patients with DTC, but the degree and duration of TSH suppression is still debated, especially given the long-term side effects of supraphysiologic LT_4 therapy, such as increased cardiac workload, high prevalence of arrhythmia, and reduced bone mass. In the patient presented here, initial suppression of TSH to 0.1 to 0.3 mU/L seems appropriate but may be normalized overtime if long-term surveillance showed an undetectable Tg and negative imaging.

Long-Term Follow-up and Surveillance for Thyroid Cancer

Long-term follow-up and surveillance guidelines for DTC continue to be debated. Optimal long-term surveillance strategies, especially for patients with DTC who appear disease free, are not well established. The National Comprehensive Cancer Network recommends that for all thyroid cancers >1 cm a physical exam should be completed every 3 to 6 months for 2 years, and then annually if the patient is felt to be disease free. Thyroglobulin levels should be measured at 6 and 12 months in those who have received total thyroidectomy with ^{131}I ablation, on or off thyroid hormone suppressive therapy, and a TSH-stimulated radioiodine whole-body scan (DxWBS) every 12 months, until one to two negative scans are documented [32]. An additional caveat is that Tg and DxWBS are less accurate in patients with large remnants, as for optimal sensitivity high TSH levels usually >25 mIU/mL are required. Further large prospective studies are needed to define the most effective follow-up paradigm. As well, given the unpleasant side effects and morbidity associated with patients purposely placed in a hypothyroid state, further studies using synthetic stimulation of TSH with recombinant human TSH (rhTSH) have been completed comparing their effectiveness to withdrawal imagining.

Traditionally, TSH-stimulated DxWBS and Tg levels have been accomplished by withdrawal of suppression therapy, while more recently rhTSH stimulation has become accepted. Multiple studies have shown that patients given rhTSH avoid the symptoms of hypothyroidism, with most demonstrating equivalence between withdrawal LT_4 therapy and rhTSH in WBS. In contrast to an early study, which reported a superior scan using withdrawal WBS in 29% of cases, Haugen [9] found that the difference between withdrawal scan results and rhTSH was not statistically different (93%vs.84%; p =?). The use of rhTSH provides an alternative to thyroid hormone withdrawal in patients undergoing evaluation for thyroid cancer persistence or recurrence (351/5 by Haugen).

The high cost surveillance with RxWBS in low-risk DTC has placed monitoring for recurrence of thyroid carcinoma with only Tg levels in the forefront of discussion. A consensus report on serum Tg levels in DTC stated that Tg measured during thyroid hormone suppression is misleading [33]. The usefulness of stimulated Tg as a clinical marker for persistent disease or disease recurrence is not debated, with recent recommendations by some authors for its use as sole monitor for thyroid carcinoma, especially in low-risk populations. However, stimulated TG alone may be better utilized in those who have had a prior negative DxWBS [34]. The patient presented here underwent testing with both stimulated Tg levels and DxWBS at 1 year. We feel DxWBS continues to be complementary to Tg levels especially in the setting of a positive Tg level, with WBS allowing for tumor localization.

However, the best imaging modality for localization of tumor recurrence/ persistence in low-risk patients is also debated. Many call Tg the gold standard for detecting recurrences and consider WBS useless in the majority of these patients [35]. Since Tg does not allow localization and is undetectable in up to 5% of patients after thyroid hormone withdrawal, some instead recommend thyroid ultrasound (US) for follow-up. A study revealed that WBS did not add any information in metastatic disease, finding foci in only 13 patients, while US uncovered node metastasis in 38 subjects (seven that were Tg negative) [33]. The authors reported a negative predictive value of 98.8% for both negative Tg and US, and concluded that US was beneficial for first follow-up in combination with stimulated Tg levels. Until a definite recommendation can be reached, the most comprehensive initial follow-up for thyroid cancer would be stimulated Tg level and WBS complemented by thyroid US, as this patient received. In regard to long-term follow-up in a patient who is clinically free of disease and has had an undetectable serum Tg level in the past during TSH stimulation, the recommendation is for serum Tg level on FT_4 suppression along with an annual physical exam [33].

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Multiple-Choice Questions

1. A 48-year-old woman recently had a lobectomy for a solitary thyroid nodule and was found on histology to have a 1.5-cm PTC without invasion or extension. What would you further counsel this woman?

   A. Recommend no further treatment was indicated, as lobectomy was curative
   B. Recommend total thyroidectomy and radical neck dissection

C. Recommend total thyroidectomy followed by 100 mCi radioactive iodine therapy
D. Recommend total thyroidectomy and radical neck dissection followed by 30 mCi radioactive active iodine therapy

Suggested answer: C. Explanation: Although of unclear benefit for lesions less than 1.0 to 1.5 cm, total thyroidectomy has been associated with an improvement in mortality and recurrent rates in tumors >1.5 cm. Radioactive iodine treatment is also controversial, with some studies showing improvement in outcomes with ablation and others showing no benefit, but common clinical practice is to give radioactive iodine therapy following surgery, as it appears to reduce morbidity, aid in ease of long-term follow-up, and may reduce mortality.

2. The initial follow-up for patients with well-differentiated PTC should include:

A. US of neck at 12 months postinitial treatment
B. Stimulated whole-body scan (WBS) and thyroglobulin (Tg) levels 6 months to 1 year after initial treatment
C. Continued surveillance annually with Tg and antithyroglobulin levels after 1 or 2 negative stimulated Tg levels and WBS
D. All of the above

Suggested answer: D. Explanation: Although no prospective studies have established long-term follow-up for PTC, current clinical guideline recommend all of the above for continued surveillance for recurrent/residual PTC after initial treatment, especially when primary was greater than 1 to 1.5 cm in size. Less involved follow-up is warranted in cases of microcarcinoma (≤ 1.0 cm).

3. All of these characteristics may be risk factors for increased aggressiveness of PTC except:

A. Psammoma bodies seen on pathology
B. Multifocality of PTC
C. Lymph node metastasis at initial presentation
D. Tumor size >4 cm
E. Age >45 years

Suggested answer: A. Explanation: Studies have showing conflicting results about risk factors for recurrence of PTC but all of the above have been associated with increased aggressiveness of PTC except psammoma bodies, which are seen in up to 50% of patients with PTC.