# Chapter 14
# Papillary Thyroid Cancer

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**Objectives**

1. To understand the presentation of papillary thyroid cancer (PTC)
2. To examine the high-risk features of PTC
3. To discuss the molecular genetics of PTC
4. To understand the surgical indications for PTC
5. To discuss the utility of radioactive iodine remnant ablation and treatment
6. To review the appropriate long-term follow-up for patients with PTC
7. To discuss therapeutic options with tyrosine kinase inhibitors (TKIs) for patients with radioactive iodine refractory metastatic PTC

## Case Presentation

A 25-year-old male with history of asthma, depression, and hypertension was found to have a right palpable thyroid mass on physical exam. His thyroid ultrasound showed a right lower pole nodule measuring 4.7 × 2.4 × 2.7 cm which was described as solid and hypoechoic with irregular borders and a left upper pole nodule measuring 1.7 × 1.2 × 1.0 cm which was described as predominately solid and hypoechoic with microcalcifications. He subsequently underwent an ultrasound-guided

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T. F. Davies (ed.), *A Case-Based Guide to Clinical Endocrinology*,
https://doi.org/10.1007/978-3-030-84367-0_14

fine-needle aspiration (FNA) of these nodules with findings of each nodule as being highly suspicious for papillary thyroid carcinoma (i.e., many enlarged follicular epithelial cells with increased nuclear to cytoplasmic ratio arranged in sheets with papillary structure along with pseudo-intranuclear inclusions, nuclear grooves, multinucleated giant cells, and psammoma bodies). The patient had no known family history of thyroid disorders or malignancy and no personal history of radiation exposure to head and neck. He also denied symptoms of mechanical obstruction, shortness of breath, dysphagia, or other symptoms of hyper- or hypothyroidism. CBC, CMP, thyroid peroxidase, and thyroglobulin antibodies were normal. Thyroid-stimulating hormone (TSH) was 3.2 mU/L (normal 0.8–4.2), and free thyroxine (FT4) was 1.2 ng/dL (normal 0.8–1.8), both within the normal limits.

A total thyroidectomy was recommended. Pathology from the total thyroidectomy demonstrated a 1.1 × 0.9 × 1.0 cm PTC on the left side and a right-sided 4.5 × 2.6 × 1.9 cm PTC with extrathyroidal extension, without angioinvasion, and with inked surgical margins and skeletal muscles negative for malignancy. In total 11 out of 28 lymph nodes were positive for metastatic disease (8 of 14 positive right level IV; 3 of 14 positive left level III). Patient was determined to have stage I PTC (T3aN1). His thyrogen-stimulated I-123 dosimetric-based pre-therapy scan showed two foci of radiotracer uptake in the thyroid bed without scan evidence of metastatic disease in the neck or distant metastases. He received 150 mCi radioactive iodine treatment under Thyrogen® stimulation. He was administered suppressive doses of levothyroxine to maintain a TSH of 0.1 mIU/L. His post-therapy whole body I-131 scan about 10 days after treatment showed two foci of radioiodine uptake in the thyroid bed which were unchanged from his pretherapy scan. His Thyrogen® stimulated thyroglobulin (Tg) was <2.0 ng/mL, and thyroglobulin antibody (Tg Ab) was <20 IU/mL.

One year after his initial surgery, his laboratory studies revealed TSH of 0.2 mU/L and FT4 1.7 ng/dL with unstimulated serum thyroglobulin level < 0.2 mU/L and absence of thyroglobulin antibodies. He had a neck ultrasound followed by Thyrogen® stimulated whole body scan (WBS) 1 year post-operatively, which showed no evidence of local recurrence or distant metastases. However, 2 years post-operatively his stimulated serum thyroglobulin level increased from <0.2 to 5.0 ng/ml with negative thyroglobulin antibodies.

## Fundamentals of Well-Differentiated Thyroid Cancer

Thyroid cancer is the most common endocrine malignancy and accounts for approximately 2.1% of all cancer diagnoses worldwide [1]. According to the American Cancer Society, the projected incidence of thyroid cancer for 2020 is 52,890 new cases (40,170 in women and 12,720 in men) with an estimated 2180 deaths from thyroid cancer (1140 women and 1040 men) [2]. Thyroid cancer death rates have increased at a rate of 0.6% per year from 2008 to 2017 [2]. Mortality rate especially for men over about age 60 is also increasing at a rapid rate.

Differentiated thyroid cancer (DTC) includes both papillary and follicular thyroid cancers, which account for more than 90% of all thyroid cancers, with PTC prevailing (about 80–90% of DTC) followed by follicular thyroid cancer. Over the past approximately 10–15 years, the incidence of PTC cases has been on the rise which is partly attributed to increased early detection of small papillary thyroid carcinomas possibly related to the frequent use of diagnostic head/neck or chest imaging (performed for other medical conditions), leading to incidentally found thyroid nodules which otherwise may not have been diagnosed or become symptomatic. However, the increasing frequency of thyroid cancer cases is not thought to be solely related to overdiagnosis or early detection. If detection alone was the predominant factor, then we would expect early treatment of potentially aggressive cases which should result in an eventual decline in thyroid cancer mortality rates. Yet, the mortality rate and recurrence risk of DTC are higher in men even when adjusted for stage at presentation than in women [3, 4]. This could be attributed to a more aggressive nature of DTC in males.

Most thyroid cancer risk factors are non-modifiable such as female gender and ethnicity. In fact, female gender confers three- to four-fold higher risk of thyroid cancer than men. Additionally, higher thyroid cancer incidence is observed in non-Hispanic whites than Hispanic and African American individuals [1]. Some authors have described modifiable risk factors such as obesity to be associated with increased risk of thyroid cancer [5]. However, the role of obesity in thyroid cancer incidence remains unclear.

Other risk factors associated with PTC include previous exposure to ionizing radiation (particularly at a young age), external neck radiation for treatment of other diseases, and rare hereditary conditions (i.e., Cowden's syndrome). It is worth mentioning that radiation-induced PTCs typically present with *RET* chromosomal rearrangements, whereas sporadic PTCs are more frequently associated with $BRAF^{V600E}$ or *RAS* mutations [6, 7].

Although mortality from thyroid cancer is low, with 10-year survival rates exceeding 90% in PTC patients, the recurrence rate may be greater than 30%, making risk stratification a priority [8]. Prognostic factors such as age ≥55 years, male gender, tumor size >4 cm, follicular histology or tall and columnar cell variants, multifocality, extra-capsular extension, number of lymph node metastases, and rising Tg levels are associated with increased risk of recurrence [8].

Treatment of DTC is individually tailored based on the 2017 revised American Joint Committee on Cancer (AJCC) eighth edition staging guidelines which assess mortality risk, as well as the 2015 American Thyroid Association (ATA) risk stratification guidelines which assess risk of recurrent or persistent disease. Staging is an extremely important tool in management of patients with malignancy. Currently, the TNM (tumor, node, and metastasis) staging system is used which was proposed by the AJCC and International Union Against Cancer Committee (IUCC). Patients <55 years of age are subdivided into stage I or II: stage I, tumor of any size with lymph node metastases and *absence* of distant metastases, and stage II, tumor of any size with lymph node metastases *and* distant metastases.

Patients 55 years and older are subdivided into stages I–IV. Stage I: Tumor is ≤4 cm and localized to the thyroid. Stage II: Tumor is of any size with lymph node metastases *or* extrathyroidal extension invading *only* strap muscles but *absent* distant metastases. Stage III: Tumor is of any size with lymph node metastases and gross extrathyroidal extension invading *beyond* strap muscles into subcutaneous soft tissues, larynx, trachea, esophagus, and/or recurrent laryngeal nerve but *absent* distant metastases. Stage IVa: Tumor is of any size with lymph node metastases and extrathyroidal invasion of prevertebral fascia or encasing carotid artery but *absen* distant metastases. Stage IVb: Tumor is of any size with lymph node metastases and extrathyroidal invasion of mediastinal vessels *and* distant metastases [9].

The 2015 ATA guidelines modified the risk stratification system for DTC to help guide prognostication, post-operative risk assessment, as well as disease management and follow-up. These guidelines have included various factors affecting risk of structural recurrence including extrathyroidal extension (ETE), lymph node involvement, tumor multifocality, and $BRAF^{V600E}$ mutation status, to help guide treatment and surgical intervention and ameliorate treatment-related morbidity.

The 2015 ATA risk stratification divides patients into low-, intermediate-, and high-risk categories. Low-risk patients have no metastases, all their macroscopic tumor has been resected, there is no tumor invasion of locoregional tissues/structures or vascular invasion, there are 0 to ≤5 pathological lymph nodes involved (measuring <0.2 cm in diameter), the tumor lacks aggressive histology, and if I-131 remnant ablation is performed, there is no uptake outside the thyroid bed on the first post-treatment radioactive iodine WBS. The characteristics for intermediate-risk patients include either microscopic tumor invasion into the perithyroidal soft tissues, vascular invasion, pathological lymph nodes >5 (measuring <3 cm in largest dimension), multifocal papillary microcarcinoma with ETE and $BRAF^{V600E}$ mutation, aggressive histology (tall or columnar cell variants), and radioactive uptake in the neck on the first post-treatment WBS. High-risk patients have macroscopic tumor invasion into perithyroidal soft tissues, incomplete tumor resection, pathological lymph nodes ≥3 cm in greatest dimension, follicular thyroid cancer with vascular invasion (>4 foci), distant metastases, and elevated postoperative Tg levels suggestive of distant metastases [10].

Patients can also be reclassified based on their response to initial therapy following thyroidectomy and radioactive iodine ablation or treatment. This model provides a more individualized risk assessment strategy. Based on clinical outcomes using suppressed Tg, stimulated Tg, and imaging studies at any point during follow-up, patients are further divided into four response categories: excellent response, biochemical indeterminate response, structural incomplete response, and indeterminate response. This has been proven to be especially useful in intermediate- and high-risk patients since those who have an initial excellent treatment response have a very low likelihood of disease recurrence [11].

## Molecular Genetics of Papillary Thyroid Cancer

Over recent years, advances have been made in identifying molecular markers from FNA samples that carry both diagnostic and prognostic values in the management of PTC. *BRAF* gene mutations occur in PTC, and in several other carcinomas such as melanoma and lung adenocarcinoma, although the exact *BRAF* mutations may vary. *BRAF* is a B-type Raf kinase, located on chromosome 7. It codes a cytoplasmic serine/threonine kinase and plays a role in regulating the mitogen-activated pathway kinase (MAPK), resulting in cell proliferation, inhibition of differentiation, and apoptosis [12]. The most common *BRAF* mutation in thyroid cancer is a point mutation resulting in change of valine to glutamic acid at codon 600, designated $BRAF^{V600E}$, and accounts for more than 90% of occurrences [12]. The incidence of *BRAF* gene mutations in patients with sporadic PTC ranges from about 40% to 70%. Tumors harboring $BRAF^{V600E}$ mutations are associated with higher rates of regional lymph node metastases, increased risk of recurrence, and persistent disease. *BRAF* mutations may insinuate a poorer prognosis in PTC and are associated with older age, tall cell variant, extrathyroidal extension, and advance disease stage at presentation (stage III and IV) [13]. Additionally, nearly 40% of patients with micropapillary carcinoma (<10 mm) have the $BRAF^{V600E}$ mutation, suggesting that it could be a useful tool for staging in the future [14]. Although *BRAF* mutation is possibly predictive of aggressive behavior of PTC and most studies recommend the use of *BRAF* mutation as a prognostic factor, other studies suggest *BRAF* mutation to be a rare clonal event, indicating its controversial use as a prognostic factor [15]. Given the lack of strong association between *BRAF* mutation and relapse risk, the revised 2015 ATA guidelines do not require application of *BRAF* status for initial risk stratification in DTC. Moreover, *BRAF* is not the only genetic variation found in PTC, as many as 70% of patients with non-familial PTC have some type of gene mutation (i.e., *TERT* promotor, *RET*, *RAS* genes, *NTRK1*, *PTEN, and PIK3CA*).

According to the Bethesda classification system, about 30% of thyroid nodules undergoing FNA biopsy are determined to be atypia of undetermined significance (AUS) (Bethesda category III) or follicular lesion of undetermined significance (FLUS) (Bethesda category IV) representing a diagnostic challenge. Commercial molecular genetic tests were developed to improve diagnostic accuracy of indeterminate thyroid nodules and to help minimize repeat FNAs and/or unnecessary diagnostic surgeries. There are presently several commercially available molecular genetic tests on the market that may be used in conjunction with FNA: *Afirma*® by Veracyte Inc., ThyroSeq® v2 by CBLPath Inc., and ThyGeNEXT® by Interpace Diagnostics Group Inc..

*Afirma* uses genomic sequencing classifier (GSC) to identify genomic profiles of indeterminate nodules which have been confirmed by surgical pathology as either benign or malignant. This system is designed to effectively recognize benign nodules and has a reported sensitivity of 83–100% and negative predictive value of 96%, making it a useful "rule-out test" [16, 17]. ThyGeNEXT utilizes next-generation sequencing (NGS) which tests for DNA mutation panel (e.g., *BRAF*, *RAS*, *TERT*,

*TP53*) and mRNA fusion transcripts and has demonstrated high specificity and positive predictive value, making it an effective "rule-in" test [16, 18, 19]. ThyroSeq v2 also uses NGS to evaluate specific point mutations, gene fusions, alterations, and expressions commonly found in thyroid cancer. It correctly identifies benign and malignant nodules by providing 94% sensitivity, 82% specificity, and 97% negative predictive value, providing both a valuable "rule-out" and "rule-in" test [20].

It is worth mentioning that the clinical utility of these tests is limited in nodules greater than 4 cm, due to high rate of false-negative results. Overall, molecular testing of AUS/FLUS nodules has advanced risk stratification of indeterminate nodules and has helped in distinguishing patients who would benefit from surgical resection versus those who could be managed conservatively. These tests have helped guide our decisions regarding PTC management, but their results should be interpreted with caution and on a case-by-case basis using clinical judgment and evaluation of malignancy risk.

## Surgical Considerations in Papillary Thyroid Cancer

The revised 2015 ATA practice guidelines for the management and treatment of adult patients with DTC differ from the previously published 2009 ATA guidelines. Current guidelines are focused on patient preference and emphasize the importance of patient-centered decision-making. Initial surgical option for patients with a tumor size of >1 cm is near-total or total thyroidectomy, as was performed in our patient. Thyroid lobectomy should be reserved for patients with low-risk disease, micropapillary carcinoma, unifocality, absence of lymph node metastases, and no personal history of prior head and neck radiation or familial thyroid carcinoma. All patients with FNA-proven DTC should be staged pre-operatively and undergo a neck ultrasound with lymph node mapping to further evaluate the contralateral lobe and lymph nodes for the presence of disease [10]. Surgery should ideally be performed by an experienced surgeon performing a high volume number of thyroid surgeries to minimize post-operative complications such as hypoparathyroidism and/or vocal cord dysfunction. Performing prophylactic lymph node dissection at the time of thyroidectomy remains controversial, and surgical expertise is warranted. Postoperatively, serum Tg and Tg Ab should be monitored serially in all patients.

## Utility of Radioactive Iodine Ablation

The 2015 ATA guidelines outline the initial dose of radioactive iodine 131 ($^{131}$I) after total thyroidectomy to be utilized primarily for one of three reasons: (1) remnant ablation (to destroy residual (presumptively) benign thyroid tissue), (2) adjuvant therapy (to decrease recurrence risk and mortality by destroying suspected but unproven metastatic disease), or (3) radioactive iodine therapy (for treatment of

persistent or recurrent disease in high-risk patients). $^{131}$I treatment after total thyroidectomy is the mainstay of management for patients with intermediate- and high-risk disease (evidence of distant metastases, extrathyroidal extension, tumor size >4 cm). For low-risk patients (unifocal or multifocal papillary microcarcinoma <1 cm without high-risk features), the use of remnant ablation is not routinely recommended [10]. In intermediate-risk patients, postsurgical $^{131}$I treatment has shown to improve overall survival in those with aggressive PTC histology, lymph node metastases, tumor >4 cm, or microscopic extrathyroidal invasion particularly in patients aged ≥ 45 years [10]. However, some studies have shown controversial results regarding the utility of postsurgical $^{131}$I treatment on disease recurrence [21]. Additional studies are needed to determine the efficacy of $^{131}$I treatment in intermediate-risk patients.

Radioactive iodine (RAI) administration requires either exogenous TSH stimulation via injection of recombinant human TSH (rhTSH) (Thyrogen®) or withdrawal of thyroid hormone to provoke endogenous rise in TSH. Studies have shown equal efficacy and safety using both methods [22]. Additionally, both methods were found to provide comparable benefit pertaining to progression-free survival and disease-related mortality in patients with metastatic DTC [22]. Conversely, RAI treatment using rhTSH may be more advantageous as it is associated with fewer clinical side effects of hypothyroidism and shorter stimulation of residual tumor as compared to TSH withdrawal method which requires 3–6 weeks of TSH withdrawal. rhTSH is approved by the Food and Drug Administration (FDA) for remnant ablation but not for use in metastatic DTC.

When using TSH stimulation or withdrawal, serum TSH >30 mIU/L is required and is associated with an increased RAI uptake in tumors, although this precise cutoff value has not been studied rigorously. However, regardless of preparation method for RAI remnant ablation or treatment, a low iodine diet (<50 ug iodine/day) should be consumed 7–10 days before and during ablation or treatment and maintained for 1–2 days after $^{131}$I therapy [10]. Checking urine iodine level several days prior to the radioactive iodine scan is important, since excessive total body iodine measured via urinary iodine excretion often results in ablation failure, and this is particularly valuable in regions with high iodine consumption [23].

Indeed, there may be considerable iodine in many foods, such as dairy products, substances made using iodinated flour, seafood, kelp, and sea salt. Amiodarone contains about 37% inorganic iodine by weight and has a half-life of approximately 26–107 days when used chronically, intravenous (IV) radiocontrast agents also contain very high levels of iodine that persist for at least several weeks after administration, and both would preclude the use of RAI as long as the urine iodine concentration is elevated. Thus, it is imperative for clinicians to inquire about history of high-dose iodine exposure when determining the scheduling time of RAI imaging or therapy. Conversely, at times the dietary habits of a patient, as well as previous recent exposure to iodinated IV contrast, may not always be apparent; therefore we recommend routinely measuring a spot urine iodine several days before administering RAI. Although the exact cutoff value has not been determined rigorously, we recommend that a urine iodine value of less than about 150–200 μg/L be used before proceeding with RAI scans and treatment. It should be noted that levothyroxine

contains about 65% iodine which is maintained during radioactive iodine scan and treatment when rhTSH is utilized.

The 2015 ATA guidelines suggest using a low-dose (30–100 mCi) $^{131}$I after total thyroidectomy for remnant ablation in selected low- and intermediate-risk patients who have low-risk disease. There has been uncertainty over the effective $^{131}$I ablative dose in the past. Recent studies have demonstrated that remnant ablation with 30 mCi of RAI is as effective and associated with fewer adverse outcomes (e.g., sialadenitis and xerostomia) than using 100 mCi in low-risk patients [24].

The ATA guidelines also recommend using a dose of 75–150 mCi for adjuvant RAI treatment post-thyroidectomy in those with residual microscopic disease or aggressive tumor histology (e.g., tall cell, columnar cell carcinoma, insular).

As per the 2015 ATA guidelines, there are several approaches to RAI treatment of patients with loco-regional or metastatic disease: fixed high-dose empiric RAI administration using 100–200 mCi of $^{131}$I, RAI therapy based on upper limit of blood and body dosimetry, and quantitative tumor or lesional dosimetry. However, the guidelines do not provide recommendations regarding superiority of one method of RAI treatment over another.

Dosimetric-based $^{131}$I treatment of DTC was initially introduced in the 1960s. Since that time, it has been successfully used in treatment of DTC patients. Dosimetric approach utilizes radioactive iodine isotope 131 and is based on the notion of delivering the highest possible radiation dose which would not cause whole-body retention at 48 hours to result in permanent bone marrow suppression. This allows calculation of maximum tolerable activity or maximum safe dose, enabling doses as high as 630 mCi (200 Rad) to be safely administered. It is generally known that the first RAI treatment has the highest therapeutic effect as DTC is a slow-growing tumor, and therefore lower RAI doses may enable sufficient time for proliferation of the remaining residual thyroid cancer tissue. This is the reason that dosimetric-based $^{131}$I treatment is preferred in patients with distant metastases (especially pulmonary metastases) and renal insufficiency and elderly (>70 years of age) [10].

Two to eight days after RAI remnant ablation or treatment, a post-therapy WBS (in conjunction with or without Single-Photon Emission Computed Tomography/Computed Tomography (SPECT/CT)) is recommended to establish RAI avidity of any structural disease and to determine staging. In high-risk DTC patients with elevated Tg levels (>10 ng/mL) and negative RAI imaging, $^{18}$Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography ($^{18}$FDG-PET/CT) scan is recommended as it confers higher sensitivity. The metastatic lesions/foci which show uptake or increase activity on $^{18}$FDG-PET will not respond to RAI ablation and will likely need to be surgically removed or treated using targeted therapies such as Tyrosine Kinase Inhibitors.

In regard to our case, the patient has metastatic disease to the lymph nodes and therefore received dosimetry-based RAI therapy with 150 mCi of I-131.

Use of RAI in treatment of DTC is a common practice, but it has also been linked to increase risk of development of second primary malignancies in thyroid cancer survivors. The most common secondary malignancies include cancer of salivary glands, stomach, breast, leukemia, and lymphoma [25]. However, the risk for these cancers is relatively low in absolute terms and also remains controversial.

## Hormone Suppressive Therapy and Long-Term Follow-Up

Typically, after initial therapy for PTC, patients are started on exogenous oral levothyroxine ($LT_4$) with a goal to suppress serum thyrotropin (TSH). Suppressing TSH with supraphysiologic doses of $LT_4$ has been shown to decrease the risk of recurrence and helps decrease the likelihood of major adverse events relating to progression of the cancer particularly in high-risk patients.

The 2015 ATA practice guidelines recommend a suppressed TSH <0.1 mU/L in high-risk patients and TSH of 0.1–0.5 mU/L in intermediate-risk patients. Furthermore, they suggest maintaining a TSH of 0.1–0.5 mU/L in low-risk patients with low detectable serum Tg levels and TSH goal of 0.5–2 mU/L in low-risk patients who have undergone lobectomy with undetectable serum Tg levels [10].

Clinicians should carefully evaluate the adverse effects of TSH suppression such as iatrogenic thyrotoxicosis, increased risk of cardiovascular adverse events particularly in elderly, and increased risk of osteoporosis in postmenopausal women. In one cross-sectional study, the rate of atrial fibrillation in PTC patients over the age 60 on TSH suppressive therapy was 17.5% [26]. In a longitudinal study of the Framingham cohort, the risk of developing atrial fibrillation was increased approximately three fold (in patients taking exogenous thyroid hormone or who had endogenous hyperthyroidism) if serum TSH was less than 0.1 mU/L as compared to a population that had normal serum TSH values [27]. Additionally, women >50 years of age with PTC on TSH suppressive therapy may have a significant decrease in their bone mineral density (BMD) 1-year post-thyroidectomy [28]. Thus, the risk of thyroid cancer recurrence should be balanced against the risks of atrial fibrillation and bone loss.

Current 2015 ATA guidelines endorse utilization of four response categories: excellent, biochemical incomplete, structural incomplete, and indeterminate to determine therapeutic response in patients who have undergone total thyroidectomy and RAI remnant ablation, adjuvant or therapeutic treatment based on imaging and Tg/Tg antibodies to help guide long-term disease surveillance and treatment strategies.

The 2015 ATA guidelines suggest that in the absence of contraindications, those patients with persistent disease (structural incomplete response) should maintain a TSH below 0.1 mU/L. Patients with biochemical incomplete response or those who initially presented with high-risk disease but have excellent or indeterminate therapeutic response should aim to keep their TSH between 0.1 and 0.5 mU/L for at least 5–10 years. Lastly, low-risk patients or those free of disease with excellent or indeterminate response to therapy can have TSH levels in the low normal range (0.5–2 mU/L) [10]. Two to three months after definitive treatment, thyroid function tests (TFTs) should be checked to determine the adequacy of TSH suppressive therapy. These general comments regarding suppressive therapy may vary in select patient groups (i.e., elderly, children and adolescents, pregnant women).

Follow-up at 6 months should ascertain disease status of the patient by performing a physical exam, neck ultrasound and baseline (and in some cases TSH-stimulated) Tg and Tg Ab measurement. Tg is only produced within the thyroid gland and is recognized as an excellent biomarker for the presence of residual or recurrent disease in patients

who do not have Tg antibodies. A diagnostic WBS is not necessary in all patients, especially those with negative neck ultrasounds and undetectable basal Tg with absence of Tg Ab. It should, however, generally be performed in high- and intermediate-risk patients, usually at 1-year post $^{131}$I treatment. ATA recommends against performing TSH-stimulated Tg testing in low- and intermediate-risk patients with excellent response to therapy, but annual TFTs, Tg, and neck ultrasounds should be performed. In the subset of patients with detectable Tg, if this value increases, then imaging techniques for localization of disease should be pursued [10]. It is controversial whether performing serial rhTSH stimulated Tg levels that increase over time helps to detect progressive or recurrent disease. One study estimated the chance of a detectable stimulated serum Tg level after having an undetectable stimulated Tg to about 3% [29].

Serum Tg and Tg Abs for patients with DTC should ideally be measured using the same laboratory and the same standardized assays over time to minimize variability in measured values, although this is difficult using commercial laboratories. One of the major pitfalls in using serum Tg as a tumor marker is that Tg measured by methods such as immunometric assays (IMA) or radioimmunoassays (RIA) is subject to interference with Tg autoantibodies which are found in 20–25% of thyroid cancer patients [30]. These assays have thus proven to be unreliable, often resulting in falsely low serum Tg levels when IMA is used and either a falsely low or high Tg levels when RIA is utilized [30]. These variations in Tg levels pose a clinical challenge due to the uncertainty which is brought forth regarding the patient's disease status. In intermediate- or high-risk patients who have elevated Tg antibodies, the periodic use of chest CT or RAI scans is reasonable to identify possible recurrent or persistent disease.

Newer methods have become available which measure Tg via liquid chromatography-tandem mass spectrometry-based assay (LC/MS) that may minimize the autoantibody interference and therefore allow a more accurate quantification of Tg levels in patients with anti-Tg Ab [31]. However, LC/MS has been shown to have low sensitivity for detecting structural disease in those with anti-Tg Abs [30]. Additional clinical studies using this assay are required to assess its clinical utility.

The patient outlined in the case above has had an increase in his stimulated Tg level at 1 year. He will, therefore, need to remain on TSH suppression with TSH goal of 0.1–0.5 mU/L and have a physical exam, repeat TFTs, a neck ultrasound, perhaps TSH-stimulated Tg, and another WBS or chest CT the following year to screen him for local recurrence. Given these findings, the likelihood that he will have detectable neck recurrences requiring surgery or repeat $^{131}$I therapy can be quite high. Therefore, it is imperative that this patient receives close surveillance moving forward.

## Therapeutic Options in Patients with Iodine Refractory Metastatic Disease

Remission after $^{131}$I treatment is achieved only in one third of patients with metastatic DTC [32]. Selected patients with metastatic disease may have $^{131}$I refractory disease; other patients may have no $^{131}$I avid lesions on repeat imaging or have

metastatic DTC that progresses despite repeat $^{131}$I therapy, TSH suppressive therapy, local surgical resection, or focal treatment with external beam radiation. These patients may benefit from novel systemic therapeutic options depending on their age, performance status, extent of their metastatic disease, and prognosis. Systemic therapies for refractory DTC include tyrosine kinase inhibitors (TKIs) which inhibit kinase activity in the last step of the mitogen-activated protein kinase pathway. The FDA-approved TKIs for the treatment of DTC include lenvatinib and sorafenib. These agents have shown to delay disease progression in clinical trials [33–35]. Although these drugs have demonstrated efficacy in treatment of refractory metastatic DTC, they are not without side effects which could include hepatotoxicity, renal toxicity, gastrointestinal toxicity, increased levothyroxine dose requirement, dermatological, neurological, and cardiovascular adverse events to name a few. As a result, the importance of patient-centered decision-making should once again be emphasized as the value of these therapies on overall survival and quality of life remains unknown. Further, these agents should be used by healthcare providers experienced with their use and side effect profile. Patients taking lenvatinib can have cardiovascular events including new or worsening hypertension and QT/QTc prolongation requiring regular blood pressure monitoring as well as baseline and periodic electro- and echocardiograms. Moreover, serious thromboembolic and hemorrhagic events have been reported requiring routine CBC and, in cases of brain metastases, head imaging. Regular physical and neurological exams are needed for early diagnosis of palmar-plantar erythrodysesthesia and reversible posterior leukoencephalopathy syndrome which are unique side effects of lenvatinib [36]. Patients receiving sorafenib are also at risk of developing hypertension and QT prolongation in addition to cardiac infarction or ischemia and require routine monitoring of blood pressure and cardiac function similar to lenvatinib. Patients on sorafenib should also be closely observed for life-threatening bleeding and development of hand-foot skin reaction. Both agents can cause fatigue, bleeding, nausea/vomiting/diarrhea, as well as hepato- and renal toxicity requiring routine measurements of CBC, CMP, and urinalysis [37].

Somatic mutation analysis of the original thyroidectomy cancer sample or of a metastatic lesion could be performed to identify oncogenic activities (e.g., *BRAF*, *RET*, or *TRK*) that would enable targeted therapies. However, these tests are costly and may not be covered by insurance companies, therefore limiting their use. Various clinical trials are available and may be appropriate on a case-by-case basis for patients with RAI refractory metastatic DTC who have failed FDA-approved TKIs and are considered to have disease progression based on response evaluation criteria in solid tumors (RECIST).

There are other systemic therapies currently under investigation which provide a promising future in patients with progressive metastatic RAI refractory DTC.

**Questions**

1. A 51-year-old female was recently diagnosed with PTC. She was found to have a 2.5 cm focus of PTC in the left lobe of her thyroid with metastasis to her level VI lymph nodes, but no evidence of distant metastases.

   What stage is she?

(a) Stage I
(b) Stage II
(c) Stage III
(d) Stage IV

2. What is the goal TSH for the patient described in the case above?

(a) <0.1 mU/L
(b) 0.1–0.5 mU/L
(c) 0.5–2.0 mU/L

3. The presence of antithyroglobulin antibodies increases the accuracy for thyroglobulin antibodies. True or false?

(a) True
(b) False

4. Which of the following characteristics seen in a nodule on neck ultrasound is *not* suspicious for malignancy?

(a) Microcalcifications
(b) Irregular margins
(c) Spongiform appearance
(d) Central vascularity

5. What is the most common molecular marker found in PTC?

(a) *RET*
(b) *Ras* genes
(c) *NTRK1*
(d) *BRAF*

6. What is the most commonly used systemic therapy for patients with RAI refractory metastatic thyroid cancer?

(a) Tyrosine kinase inhibitors
(b) VEGFR inhibitors
(c) Clinical trials
(d) Chemotherapy

**Answers to Questions**

1. (a)
2. (b)
3. (b)
4. (c)
5. (d)
6. (a)

## References


1. Kithara CM & Sosa JA. The changing incidence of thyroid cancer. Nat Rev Endocrinol. 2016;12(11):646–53.
2. American Cancer Society. Cancer facts and figures; 2020. Available at: https://www.cancer.org/cancer/thyroid-cancer/about/key-statistics.html.
3. Jonklaas J, Nogueras-Gonzalez G, Munsell M, Litofsky D, Ain KB, Bigos ST, et al. The impact of age and gender on papillary thyroid cancer survival. J Clin Endocrinol Metab. 2012;97(6):E878–87.
4. Zahedi A, Bondez L, Rajaraman M, Leslie WD, Jefford C, Young JE, et al. Risk of thyroid cancer recurrence is higher in men than in women independent of disease stage at presentation. Thyroid. 2020;30(6):871–7.
5. Schmid D, Ricci C, Behrens G, Leitzmann MF. Adiposity and risk of thyroid cancer: a systematic review and meta-analysis. Obes Rev. 2015;16(12):1042–54.
6. Kebebew E, Weng J, Bauer J, Ranvier G, Clark OH, Du QY, et al. The prevalence and prognostic value of BRAF mutation in thyroid cancer. Ann Surg. 2007;246(3):466–70.
7. Mathur A, Moses W, Rahbari R, Khanafshar E, Duh QY, Clark O, et al. Higher rate of BRAF mutation in papillary thyroid cancer over time: a single-institution study. Cancer. 2011;117(19):4390–5.
8. Chow SM, Law SCK, Chan JKC, Au SK, Yau S, Lau WH. Papillary microcarcinoma of the thyroid – prognostic significance of lymph node metastasis and multifocality. Cancer. 2003;98(1):31–40.
9. Amin MB, Gress DM, Meyer Vega LR, Edge SB. AJCC cancer staging manual. 8th ed. New York: Springer; 2017.
10. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1–133.
11. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid. 2010;20(12):1341–9.
12. Czarniecka A, Oczko-Wojciechowska M, Barczynski M. BRAF V600E mutation in prognostication of papillary thyroid cancer (PTC) recurrence. Gland Surg. 2016;5(5):495–505.
13. Nikiforova MN, Kimura ET, Gandhi M, Biddinger PW, Knauf JA, Basolo F, et al. BRAF mutations in thyroid tumors are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas. J Clin Endocrinol Metab. 2003;88(11):5399–404.
14. Basolo F, Torregrossa L, Giannini R, Miccoli M, Lupi C, Sensi E, et al. Correlation between the BRAF V600E mutation and tumor invasiveness in papillary thyroid carcinomas smaller than 20 millimeters: analysis of 1060 cases. J Clin Endocrinol Metab. 2010;95(9):4197–205.
15. Guerra A, Sapio MR, Marotta V, Campanile E, Rossi S, Forno I, et al. The primary occurrence of BRAF(V600E) is a rare clonal event in papillary thyroid carcinoma. J Clin Endocrinol Metab. 2012;97(2):517–24.
16. Macerola E, Basolo F. Current methodologies for molecular screening of thyroid nodules. Gland Surg. 2018;7(S1):S1–7.
17. Patel KN, Angell TE, Babiarz J, Barth NM, Blevins T, Duh QY, et al. Performance of a genomic sequencing classifier for the preoperative diagnosis of cytologically indeterminate thyroid nodules. JAMA Surg. 2018;153(9):817–24.

18. Lupo MA, Walts AE, Sistrunk JW, Giordano TJ, Sadow PM, Massoll N, et al. Multiplatform molecular test performance in indeterminate thyroid nodules. Diagn Cytopathol. 2020;48(12):1254–64.
19. Labourier E, Shifrin A, Busseniers AE, Lupo MA, Manganelli ML, Andruss B, et al. Molecular testing for miRNA, mRNA and DNA on fine-needle aspiration improves preoperative diagnosis of thyroid nodules with indeterminate cytology. J Clin Endocrinol Metab. 2015;100(7):2743–50.
20. Stewart DL, Carty SE, Sippel RS, Yang SP, Sosa JA, Sipos JA, et al. Performance of a multigene genomic classifier in thyroid nodules with indeterminate cytology: a prospective blinded multicenter study. JAMA Oncol. 2019;5(2):204–12.
21. Lamartina L, Durante C, Filetti S, Cooper DS. Low-risk differentiated thyroid cancer and radioiodine remnant ablation: a systematic review of the literature. J Clin Endocrinol Metab. 2015;100(5):1748–61.
22. Klubo-Gwiezdzinska J, Burman KD, Van Nostrand D, Mete M, Jonklaas J, Wartofsky L. Radioiodine treatment of metastatic thyroid cancer: relative efficacy and side effect profile of preparation by thyroid hormone withdrawal versus recombinant human thyrotropin. Thyroid. 2012;22(3):310–7.
23. Sohn SY, Choi JY, Jang HW, Kim HJ, Jin SM, Kim SW, et al. Association between excessive urinary iodine excretion and failure of radioiodine thyroid ablation in patients with papillary thyroid cancer. Thyroid. 2013;23(6):741–7.
24. Cheng W, Ma C, Fu H, Li J, Chen S, Wu S, et al. Low- or high-dose radioiodine remnant ablation for differentiated thyroid carcinoma: a meta-analysis. J Clin Endocrinol Metabol. 2013;98(4):1353–60.
25. Brown AP, Chen J, Hitchcock YJ, Szabo A, Shrieve DS, Tward JD. The risk of second primary malignancies up to three decades after treatment of differentiated thyroid cancer. J Clin Endocrinol Metab. 2008;93(2):504–15.
26. Abonowara A, Quraishi A, Sapp JL, Alqambar MH, Saric A, O'Connell CM, et al. Prevalence of atrial fibrillation in patients taking TSH suppression therapy for management of thyroid cancer. Clin Invest Med. 2012;35(3):E152–6.
27. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med. 1994;331(19):1249–952.
28. Sugitani I, Fujimoto Y. Effect of postoperative thyrotropin suppressive therapy on bone mineral density in patients with papillary thyroid carcinoma: a prospective controlled study. Surgery. 2011;150(6):1250–7.
29. Klubo-Gwiezdzinska J, Burman KD, Van Nostrand D, Wartofsky L. Does an undetectable rhTSH-stimulated Tg level 12 months after initial treatment of thyroid cancer indicate remission? Clin Endocrinol (Oxford). 2011;74(1):111–7.
30. Azmat U, Porter K, Senter L, Ringel MD, Nabhan F. Thyroglobulin liquid chromatography-tandem mass spectrometry has a low sensitivity for detecting structural disease in patients with antithyroglobulin antibodies. Thyroid. 2017;27(1):74–80.
31. Hoofnagle AH, Roth MY. Improving the measurement of serum thyroglobulin with mass spectrometry. J Clin Endocrinol Metab. 2013;98(4):1343–52.
32. Pacini F, Castagna MG. Approach to and treatment of differentiated thyroid carcinoma. Med Clin N Am. 2012;96(2):369–83.
33. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomized, double-blind, phase 3 trial. Lancet. 2014;384(9940):319–28.
34. Leboulleux S, Bastholt L, Krause T, de la Fouchardiere C, Tennvall J, Awada A, et al. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomized, double-blind, phase 2 trial. Lancet Oncol. 2012;13(9):897–905.

35. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisie R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015;372(7):621–30.
36. Cabanillas ME, Takahashi S. Managing the adverse events associated with Lenvatinib therapy in radioiodine-refractory differentiated thyroid cancer. Semin Oncol. 2019;46(1):57–64.
37. Li Y, Gao ZU, Qu XJ. The adverse effects of Sorafenib in patients with advanced cancers. Basic Clin Pharmacol Toxicol. 2015;116:216–21.