Management of Papillary Thyroid Cancer: An Overview for the Primary Care Physician

Case Study and Commentary, Paulino Tallon de Lara, MD, Elizabeth H. Holt, MD, PhD, Glenda G. Callender, MD, David Cheng MD, PhD, and Hari A. Deshpande, MD

ABSTRACT

• **Objective:** To review management of papillary thyroid cancer.
• **Methods:** Review of the literature.
• **Results:** Papillary thyroid cancer is the most common endocrine malignancy. The standard treatment for papillary thyroid cancer is thyroidectomy. Adjuvant therapy includes lifelong thyroid-stimulating hormone suppression and radioiodine therapy. Local recurrence is common and is normally treated with surgery and/or radioiodine. Metastatic radioiodine-resistant disease is a more infrequent event.
• **Conclusion:** The incidence of papillary thyroid cancer is rapidly increasing. Surgery remains the cornerstone of treatment.

Papillary thyroid cancer is the most common endocrine malignancy and accounts for the majority of cancers of the thyroid. The incidence of papillary thyroid cancer is rapidly increasing [1]. Although increasing detection has been proposed as a possible factor [2], some studies reject this hypothesis, reporting increase in the incidence of larger tumors [3]. Papillary thyroid cancer is characterized by a low mortality but a high recurrence rate [1], posing challenges not only to the endocrinologist and oncologist but also to the general practitioner.

The most frequent presentation of papillary thyroid cancer is a palpable thyroid nodule, cervical lymphadenopathy, or incidental detection on imaging. Locally advanced disease can present with hoarseness or voice alteration. Common risks factors include history of radiation exposure during childhood (the most important risk factor), thyroid cancer in a first-degree relative, family history of a thyroid cancer syndrome (such as Werner syndrome, Cowden syndrome, Carney complex, or familial polyposis), and female sex (2.5:1). Thyroid nodules in the context of an autoimmune thyroiditis may have a higher risk of malignancy [4].

CASE STUDY

**Initial Presentation**

A 49-year-old man with no significant past medical history presents with a painless mass in the anterior part of his neck.

**History, Physical Examination, and Initial Investigations**

He has no other symptoms, no weight changes, no history of radiation exposure to the neck, and no family history of malignancy. Physical exam shows a mass in the left thyroid lobe. There is no evidence of cardiac arrhythmias, tremors, or ophthalmologic abnormalities. Thyroid-stimulating hormone (TSH) level is 2.8 mIU/L (normal range, 0.4–4.5 mIU/L) and free thyroxine (T4) level is 1.1 ng/dL (normal range, 0.8–1.5 ng/dL). An ultrasound scan of the neck shows enlargement of the left lobe of thyroid gland, containing multiple complex lesions, the largest measuring 2 x 3 cm, with calcification as well as 3 enlarged lymph nodes in the left level IV. Fine-needle aspiration of the thyroid mass is positive for papillary carcinoma.

**What is the approach to the initial evaluation of a thyroid nodule?**

Initial diagnostic evaluation includes history, physical examination, and TSH measurement; nonfunctioning nodules, associated with normal or high values of TSH, carry a higher risk of malignancy [5]. Cervical ultrasound should be performed in all patients with nodules. Fine-needle aspiration (FNA) should be used to evaluate non-
functioning nodules > 1 cm or subcentimeter nodules with suspicious ultrasound features or if the patient has major risk factors (history of ionizing radiation exposure, external beam radiation exposure, family or personal history of papillary thyroid cancer, or FDG-PET [fluorinated glucose positron emission tomography]-positive thyroid nodules). Scintigraphy can be used to evaluate the need for ultrasound and FNA in patients with low TSH values [6,7]; hyperfunctioning nodules are at low risk for malignancy and do not require biopsy.

**What is initial treatment of papillary thyroid cancer?**

Surgery is the primary treatment for papillary thyroid cancer. Unlike for many cancers, surgical removal of the primary tumor is indicated even in the presence of metastatic disease [8]. Total or near-total thyroidectomy is used to treat patients with tumors > 1 cm or with tumors < 1 cm and associated risk factors (eg, contralateral nodules, affected lymph nodes, metastasis, history of radiation, first-degree family history of papillary thyroid cancer, or age > 45 years) [6]. There is a lower risk of recurrence in patients treated with total thyroidectomy versus lobectomy in papillary thyroid cancer [9,10]. Thyroid lobectomy may be used in small (< 1 cm) unifocal tumors without the presence of the associated risk factors listed above.

Patients with central or lateral neck lymph node involvement should also undergo central-compartment (level VI) neck dissection. Therapeutic lateral neck compartmental lymph node dissection is recommended in patients with biopsy-proven metastatic lateral cervical adenopathy [6,7]. The role of unilateral or bilateral prophylactic central-compartment nodal dissection (PCND), that is, lymph node dissection in the level VI compartment of neck in patients without evidence of lymphadenopathy, is controversial. The data for the possible benefit of PCND are inconclusive [11] although the ATA recommends the procedure for locally invasive T3 and T4 tumors [6].

The American Thyroid Association (ATA) and National Comprehensive Cancer Network (NCCN) guidelines [6,7] recommend a preoperative cervical ultrasound in patients with biopsy-proven papillary thyroid cancer to evaluate the presence of disease in the cervical lymph nodes, especially in the lateral and central compartments, and in the contralateral thyroid lobe. If suspicious lymph nodes are found, FNA confirmation is necessary only if this would change management. Systematic use of other preoperative imaging studies, such as CT or MRI, is not recommended [6,7].

**Surgical Treatment**

The patient underwent a total thyroidectomy with bilateral central neck dissection and selective supraclavicular left-sided lateral neck dissection. Lymph nodes on both sides of the neck (paratracheal nodes) as well as the left supraclavicular nodes were removed. Pathology showed multifocal papillary cancer with extracapsular extension to the paratracheal soft tissue, 14/14 lymph nodes affected, stage IVA T4N1,M0.

**How is papillary thyroid cancer staged?**

Thyroid cancer is normally staged using 2 classifications. The TNM classification system for differentiated thyroid cancer (papillary and follicular thyroid cancer) designed by the American Joint Committee on Cancer (AJCC) is the most frequently used and predicts survival, but was not developed to predict recurrence. The ATA risk stratification system can be used to classify patients into low-, medium- or high-risk for recurrence [6] (Table).

**How should this patient be treated after surgery? Is any adjuvant therapy indicated?**

**TSH Suppression**

In an effort to reduce risk of recurrence, patients should receive lifelong suppression of TSH using supraphysiologic doses of levothyroxine after total thyroidectomy. This is based upon the hypothesis that TSH is a growth factor for thyroid cancer cells [12,13]. Although a meta-analysis [14] supports the efficacy of TSH suppression therapy, some authors have questioned its widespread use, especially in light of the adverse effects of its use over the long term [15]. Many support its use only in high-risk patients [16], arguing that there is no evidence of benefit for low-risk patients [17]. This view is reflected in the ATA guidelines, which recommend TSH suppression below 0.1 mU/L for high-risk and intermediate-risk pa-
tients, while normal or slightly below normal TSH levels are recommended for low-risk patients [6]. Adverse effects of TSH suppression therapy are derived from the induced mild thyrotoxicosis, including cardiovascular and skeletal manifestations. Notably, elderly patients have a higher risk of cardiovascular side effects [18] such as atrial fibrillation, diastolic dysfunction, tachyarrhythmias, increased heart rate or increased left ventricular mass. Likewise, postmenopausal women are most susceptible for skeletal effects such as decreased mineral bone density and fractures [19].

### Radioiodine Ablative Therapy

Radioactive iodine (RAI or radioiodine) therapy is based on the capacity of thyroid tissue to take up and retain iodine, specifically, radioiodine. This capacity is present but reduced in papillary and follicular cancer cells.

Radioiodine remnant ablation is performed after surgery, acting as adjuvant therapy by destroying remnant pathological or normal thyroid tissue. The destruction of normal thyroid tissue is useful as it increases the reliability of thyroglobulin testing and radioiodine scanning in the detection of recurrent or metastatic disease. Moreover, remnant ablation has been shown to prevent new thyroid neoplasias in high-risk patients (ie, those with history of radiation exposure). Radioiodine ablative therapy has been shown to reduce recurrence and cause-specific mortality [20] in certain subgroups; however, patients with low mortality risk do not seem to benefit from this therapy [21,22]. Its use is recommended in patients with distant metastases, tumors > 4 cm, or with extrathyroidal extension. It is also recommended for selected patients with tumors 1–4 cm who have high-risk features (such as lymph node involvement, history of radiation, or others previously mentioned) when there is an intermediate to high risk of recurrence or death from thyroid cancer [6]. Lymph node involvement can occur in up to 50% of cases [39] and normally responds to radioiodine therapy.

Since TSH increases radioiodine uptake by normal or pathological thyroid cells, TSH stimulation is required for radioiodine therapy. This can be done by endogenous TSH elevation or by recombinant human TSH (rhTSH). The former can be achieved by either stopping thyroxine 2 to 3 weeks prior to the remnant ablation, or by withdrawing thyroxine and switching to liothyrionine for 2 to 3 weeks followed by a discontinuation of liothyrionine for 2 weeks. Both approaches seem to produce the same incidence of hypothyroid symptoms [23]. Thyroxine therapy can be resumed 2 to 3 days after radioiodine ablative therapy. Recombinant human TSH can be used with equal efficacy in place of thyroxine withdrawal [24], with the advantage of not producing transitory hypothyroidism. It is especially recommended for patients who are unable to tolerate hypothyroidism or who cannot achieve an adequate TSH level. Short-term recurrence rates are similar in patients treated with rhTSH or thyroxine withdrawal [25].

In addition, a low-iodine diet for 1 or 2 weeks is recommended for patients undergoing radioiodine remnant ablation. The rationale is that a high-iodine diet or iodine exposure (ie, amiodarone treatment or intravenous contrast) can decrease radioiodine uptake by papillary cancer cells due to further dilution of radioactive iodine in an expanded endogenous non-radioactive iodine pool.

### Table. ATA Risk Classification System

<table>
<thead>
<tr>
<th>Classification</th>
<th>Requirements</th>
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<tr>
<td><strong>Low risk</strong></td>
<td>All of the following:</td>
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<tr>
<td></td>
<td>• No local or distant metastases</td>
</tr>
<tr>
<td></td>
<td>• No tumor invasion of locoregional tissues or structures</td>
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<td></td>
<td>• All macroscopic tumor has been resected</td>
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<td></td>
<td>• No aggressive histology or vascular invasion</td>
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<tr>
<td></td>
<td>• If $^{131}$I is given, there is no $^{131}$I uptake outside the thyroid bed on the first whole-body radioactive iodine scan post treatment</td>
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<tr>
<td><strong>Intermediate risk</strong></td>
<td>Any of the following:</td>
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<td></td>
<td>• Cervical lymph-node metastases or $^{131}$I uptake outside the thyroid bed on the post treatment whole body radioactive iodine scan</td>
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<tr>
<td></td>
<td>• Tumor with vascular invasion or aggressive histology</td>
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<td></td>
<td>• Microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery</td>
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<tr>
<td><strong>High risk</strong></td>
<td>Any of the following:</td>
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<td></td>
<td>• Distant metastases</td>
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<td></td>
<td>• Incomplete tumor resection</td>
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<td></td>
<td>• Macroscopic tumor invasion</td>
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<td></td>
<td>• Possible thyroglobulin levels out of proportion to what is seen on the post-treatment scan</td>
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Patients with suspected high iodine levels can be screened using spot urinary levels [26].

Commonly, a diagnostic scan using low activities of iodine-131 is performed prior to radioablation to avoid the controversial “stunning effect” [27] from any exposure to sublethal radiation in a diagnostic dose. In stunning, the diagnostic RAI dose decreases uptake of a subsequent therapeutic dose. Alternatively, we use [I-123] radioiodine at very low dose (1.4 mCi) in pre-ablation patients. Uptake in the thyroid bed occurs in 75% to 100% of patients, commonly due to remnant normal thyroid tissue [28].

The typical activity used for RAI ablative therapy is 30–100 mCi. The administration of high activities (150–200 mCi) of [I-131] radioiodine has been used to treat recurrent or metastatic disease. This treatment can be very effective, especially in young patients [29].

Side Effects and Contraindications

Common side effects of radioiodine treatment include sialadenitis, radiation thyroiditis, tumor hemorrhage or edema, nausea, transient oligospermia or amenorrhea and nasolacrimal duct obstruction. Moreover, patients treated with radioiodine have a modest increased risk of developing other malignancies [30].

[I-131]Radioiodine must be avoided in pregnancy and in breastfeeding [31]. Indeed, breast tissue has a strong tendency to uptake iodine so breastfeeding should be stopped 5 to 8 weeks before radioiodine treatment, otherwise it can lead to a false-positive radioiodine scan in the chest [32], or worse, deliver radioiodine to the baby with detrimental effects and potential ablation to the baby’s thyroid gland.

Patients treated with radioiodine are advised to drink abundant water after the treatment in order to increase its renal elimination. If no stool elimination occurs in 14 to 24 hours, laxatives may be indicated to eliminate radioiodine from the gastrointestinal track. In addition, patients are advised to avoid sexual contact, avoid sharing bed, utensils, towels, toothbrushes, razors, and avoid public transportation and public places among other measures to avoid exposing the population to radiation [33]. The duration of this restriction depends on the dose administered.

Adjuvant Treatment in this Patient

As the patient was at high risk for recurrence, he received TSH suppression therapy to levels < 0.1 mIU/L. He was referred to nuclear medicine for I-131 treatment. However, at 3 months following thyroidectomy, thyroglobulin measurement showed an elevation (40.5 ng/mL). Ultrasound showed enlarged lymph nodes at level II at the right and at level II at the left. A FNA of left neck node was positive for papillary thyroid cancer.

How should the patient be treated now?

Treatment of Locoregional Metastatic Disease

The best treatment for residual disease or local recurrences is surgery. ATA guidelines recommend compartmental lateral and/or central neck dissection for patients with persistent or recurrent disease confined to the neck [6]. Radioiodine can be an alternative when recurrent disease is not visible on imaging. Other treatments that can be used for local recurrences or isolated metastases when surgery is not possible are radiofrequency ablation [34], chemo-embolization [35], or ethanol ablation [36]. External beam radiotherapy, which is discussed later, could also be used in selected cases.

Further Treatment

The patient underwent a bilateral modified radical neck dissection followed by adjunctive radioiodine therapy. His initial radioiodine scan showed mild uptake in the neck at the site of his prior surgery. He received treatment with 215 mCi, then 6 months later he was treated with 250 mCi, as his scan showed continued mild uptake. Eleven months later his radioiodine scan showed no uptake and thyroglobulin levels remained stable at 14.4 ng/mL.

One year later, in a follow-up blood analysis he was found to have an elevated thyroglobulin level (90.4 ng/mL). A PET/CT scan showed multiple bone metastases. A neck ultrasound revealed enlarged lymph nodes in the right thyroid bed.

How common is radioiodine-refractory thyroid cancer?

Radioiodine-refractory thyroid cancer in patients with progression of disease despite radioiodine therapy, or
with non-radioiodine-avid lesions [37], is uncommon. It has a poor prognosis with a median survival of 3 to 6 years after diagnosis. It is more frequent in older patients. These lesions are often hypermetabolic and hence [F-18] FDG-avid [38], with a worse prognosis. In one study of patients with metastatic differentiated thyroid cancer, the 10-year overall survival rate was 56% in patients with radioiodine-avid lesions but only 10% in patients with non-radioiodine-avid lesions [38].

• Is the bone a common place for metastasis? Where else should we expect to find a lesion?

Metastatic Pattern
The most common sites for distant metastasis of papillary thyroid cancer are the lungs and the bone. The 10-year survival rate of papillary thyroid cancer patients with lung metastases is between 30% and 50% [38,39]; the prognosis is better in patients < 45 years and with radiodine uptake [40]; indeed, patients with pulmonary metastasis seen only in 131-I scans and not on CT or chest x-ray have a longer survival [41]. Pulmonary metastasis can be treated with radioiodine if they are radioiodine-avid. With this treatment complete remission is possible, although it is extremely difficult to achieve in macronodular metastasis.

Bones are the second most common place for distant metastases. Bone metastases seem to have a worse response to treatment with an unfavorable prognosis [42]. Pamidronate (a bisphosphonate) and denosumab (a RANK ligand inhibitor) have been used to prevent skeletal related events, including pathologic fractures and cord compression, in bone metastases from other cancers such as breast and prostate, and may also be useful in thyroid cancer, although this has not yet been studied [43,44]. Moreover, surgical resection of isolated bone metastasis seems to improve survival [45].

Skin, liver, and brain metastasis, although uncommon, can also occur. There are also reported rare cases of metastasis in the breast, parotid, larynx, pharynx, adrenal glands, pituitary, kidney, liver, orbit, the sphenoid sinus, choroid plexus, pancreas, and skeletal muscles [46].

• Which treatments can we offer to a patient with metastatic disease refractory to radioiodine?

Chemotherapy and Treatment of Radioiodine-Resistant Disease
Therapeutic options for patients with metastatic papillary thyroid cancer resistant to radioiodine and TSH suppression are limited. Cytotoxic drugs do not play a major role in the treatment of refractory metastatic papillary thyroid cancer, and new research is mainly focused on tyrosine kinase inhibitors (TKIs) with a considerable number of clinical trials either completed or ongoing.

Tyrosine kinases are enzymes that transfer phosphate groups from adenosine triphosphate to proteins. In tumor cells their signaling paths promote proliferation, avoidance of apoptosis, invasion, angiogenesis, and metastasis. TKIs are small molecules that are able to inhibit tyrosine kinase function even at very low intracellular concentrations. Some of them inhibit various tyrosine kinases and are known as multi-kinase inhibitors (MKIs).

Sorafenib
Sorafenib (400 mg twice daily) is an oral MKI that targets RAF, platelet-derived growth factor receptor, vascular endothelial growth factor receptors 2 and 3, RET and c-Kit [47]. It was approved in November 2013 for patients with radioiodine-refractory differentiated thyroid cancer [48]. Three phase II studies had previously evaluated sorafenib in papillary thyroid cancer, showing a partial response in 15% to 31% of patients and a progression-free survival up to 79 weeks [49–51]. Common adverse effects included weight loss, fatigue, rash, hypertension and the main dose-limiting toxicity—a hand-foot syndrome consisting of swelling, reddening, numbness, and desquamation on palms and soles [52].

Approval of the drug was based on the DECISION trial [52]. A total of 417 patients were randomized (207 to sorafenib and 210 to placebo), of which 57% had papillary thyroid cancer. The primary endpoint of progression-free survival (PFS) was significantly higher in the sorafenib arm, (median, 10.8 months) compared with placebo (median, 5.8 months) (hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.45–0.75, P < 0.001). Median overall survival had not been reached in either arm [52]. The PFS of 5.8 months in the placebo arm confirmed that the group of patients in this study had a rapidly progressing disease, unlike the majority of patients with RAI-sensitive disease.

Selumetinib
Radioiodine re-sensitization was addressed in a study using selumetinib, an inhibitor of mitogen-activated protein
kinase kinase (MAPK kinase or MEK). Preclinical models had shown that radioiodine-refractory tumors exposed to inhibitors of this enzyme were able to uptake radioiodine again. Twenty patients with radioiodine-refractory thyroid cancers were treated with selumetinib for 4 weeks and 12 showed increased radioiodine uptake following the treatment. Furthermore, 8 of these patients went on to show responses clinically to retreatment with radioiodine [53]. Further studies with this agent will be needed to determine its place in treating patients with differentiated thyroid cancer.

**External Beam Radiotherapy and Local Treatment for Metastases**

The role of external beam radiotherapy in papillary thyroid cancer is mainly for symptom management. Local radiation can be used in patients with refractory metastatic disease or in lesions that do not uptake radioiodine. Examples include painful bone metastasis or brain metastasis that cannot be treated with surgery. In addition, radiofrequency ablation, chemo-embolization, or ethanol ablation can be used in certain patients.

**Sequence of Treatments**

In the setting of symptomatic metastatic, radioiodine-resistant disease, we prefer to use a TKI, normally sorafenib, as a first-line treatment. For second-line treatments, enrollment in a clinical trial is an option. Over 70% of patients with metastatic papillary thyroid cancer have mutations of the enzyme BRAF kinase. Vemurafenib is an inhibitor of this enzyme and appears to have some activity in patients with RAI-refractory thyroid cancer in early clinical trials [54–58]. Other TKIs such as sunitinib can also be used. Doxorubicin is only used in cases when a patient is not eligible for a trial and the off-label use of another TKI is contraindicated.

**Further Treatment in this Patient**

The patient received a trial of sorafenib. He showed disease stabilization that lasted 5 months. The treatment was stopped due to adverse effects (loss of weight and vomiting) and progression of the disease. He was then enrolled in a trial of vemurafenib. He stopped treatment because of adverse events related to the medication and currently has stable disease.

**Summary**

Papillary thyroid cancer is the most common endocrine malignancy. It is characterized by low mortality but high recurrence rate and can have a considerable impact on quality of life. Any anterior neck nodule, especially in a patient with a history of neck irradiation, should raise concern for this disease. Surgery remains the cornerstone of treatment. Adjuvant therapy includes lifelong TSH suppression and radioiodine therapy. Local recurrence is common and is normally treated with surgery and/or radioiodine. Metastatic radioiodine-resistant disease is a more infrequent event. Thyroid cancer has a tendency to metastasize to the bones and lungs. Metastatic radioiodine-resistant disease is often treated with TKIs such as sorafenib. Enrollment in clinical trials is recommended as second-line therapy in radioiodine-resistant metastatic disease.

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