Chapter 22
Surveillance of Treated Thyroid Cancer Patients and Thyroid Hormone Replacement and Suppression

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Epidemiology

Differentiated thyroid cancer is increasing in incidence. The Surveillance, Epidemiology, and End Results (SEER) program database estimates that there will be 62,450 new cases of thyroid cancer in 2015, representing 3.8 % of all new cancers, and there will be 1950 deaths resulting from thyroid cancer. The incidence has been rising at about 5 % per year [1]. Thyroid cancer affects women more than men resulting in 47,230 of the 62,450 estimated cases to be in women. Deaths estimated in 2015 will occur in 1080 women and 870 men [2]. The yearly incidence has nearly tripled from 4.9 per 100,000 in 1979 to 14.3 per 100,000 in 2009 [3]. Nearly two out of three thyroid cancers will be detected in patients under 55 [3]. Overall, the 5-year survival for differentiated thyroid cancer is 97.9 % [1]. Many investigators feel the rise in incidence is due to detection earlier of small thyroid cancers with radiologic intensity; however, some studies have shown a rise in larger tumors being diagnosed as well [4]. Several authors including Vigneri et al. feel that thyroid cancer incidence is increasing due to two processes: (1) increased detection and (2) increased incidence due to thyroid-specific carcinogens that are not fully recognized nor studied; this latter point is the focus of ongoing investigations [5]. Almost the entire increase in incidence can be attributed to papillary thyroid cancers. Additionally, 25 % of the new thyroid cancers diagnosed in 1988–1989 were <1 cm compared to 39 % in 2008–2009 [3].

Approximately 88 % of all differentiated thyroid cancers (DTC) are papillary thyroid cancer (PTC) (and its various subtypes), while 8 % are follicular thyroid cancer [6]. DTC can occur at any age, but has a median age of diagnosis of 49 years,

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with approximately 39 % of new cases diagnosed prior to the age of 45 years. Women are about three times more likely to develop DTC [1]. By the year 2019, one study predicts that papillary thyroid cancer will be the third most common cancer in women at a healthcare cost of $19–21 billion in the United States alone, representing a major growing healthcare concern [7].

Prognosis

Overall prognosis for DTC is quite good. The goals of initial therapy (specifically surgery) are to (1) remove the primary tumor and any disease that has extended beyond the thyroid capsule including nodal metastases that are clinically significant; (2) minimize the risk of disease recurrence; (3) facilitate radioactive iodine ablation, adjuvant, or therapeutic, when appropriate; (4) permit accurate staging and risk stratification of the disease and prognostication; (5) permit accurate long-term surveillance for disease recurrence; and (6) minimize treatment-related morbidity [8].

In patients who have PTC tumors >1 cm with no extrathyroidal extension or vascular invasion, their risk of death is nearly 0 % and risk of recurrence on average is 2 % [9]. Patients with clinical N1 disease will have an overall risk of recurrence of 13–42 %, whereas those with pathological N1 disease will have a 7–14 % risk of recurrence [10]. Those with larger metastases and extra-nodal extension are at the highest risk for recurrence [10]. In terms of survival, stage I and II patients have a near 96–99.7 % relative 5-year survival rate vs. 91 % for stage III and 50 % for stage IV [11, 12].

Surveillance of DTC

Although most patients with DTC have a favorable long-term survival, up to 30 % of patients may experience a recurrence overall, but this is very dependent on initial staging and clinical findings [13]. Clinically evident disease recurrence has been reported up to 30 or 40 years after initial therapy, but large retrospective studies consistently show that the vast majority of recurrences are detected within 10–15 years after initial therapy [14].

Short-term and long-term surveillance strategies continue to evolve based on ongoing scientific investigations. Typically, current surveillance regimens for most patients with DTC include serial thyroglobulin measurements coupled with cervical ultrasound at a minimum to identify residual or recurrent disease, which commonly occurs within the thyroidectomy bed or lateral cervical lymph node chains [15]. In order to recommend how best to provide surveillance for a patient with treated thyroid cancer in the postoperative setting, it is important to use all of

the available clinical data to individually risk-stratify patients [12]. This would include the original pathology report; pre- or postoperative neck imaging, which is typically in the form of an ultrasound; and postoperative serum thyroglobulin levels. A careful analysis of these data points can provide initial estimates for risk of recurrence, risk of having persistent disease, disease-specific mortality, and TSH suppression goals; it can guide providers in choosing the best imaging modalities for surveillance [16]. Tailoring a risk-stratified approach to individual patient care could lead to a more cost-effective approach, and possibly higher quality of life by reducing the burden of adverse treatment effects, and the stress and costs of ongoing surveillance. Providers are encouraged to stage patients post-operatively to provide prognostic information that is of value when considering disease surveillance and therapeutic strategies. In addition, this allows tracking of patients for communication among other healthcare professionals, tracking by various cancer registries and for research purposes [8].

The first-line therapy in nearly all patients is surgery, followed by radioactive iodine in some intermediate- and high-risk patients. The ATA has developed risk categories to help guide clinicians in initial treatment and subsequent surveillance as defined below.

ATA low-risk patients include papillary thyroid cancer with all of the following:

- No local or distant metastases.
- All macroscopic tumor has been resected.
- No invasion into locoregional tissues.
- Tumor does not have aggressive histology including tall cell, insular, columnar cell, Hurthle cell, or follicular cell thyroid carcinoma (FTC).
- No vascular invasion.
- No I131 uptake outside the thyroid bed if an I123 or I131 scan is done.
- Clinical N0 or ≤5 pathological N1 micrometastases (<0.2 cm in largest dimension).
- Intrathyroidal, encapsulated follicular variant of PTC.
- Intrathyroidal, well-differentiated FTC with capsular invasion and no or minimal (<4 foci), vascular invasion.
- Intrathyroidal, papillary microcarcinoma (<1 cm), unifocal, or multifocal, including V600E BRAF mutated if known.

ATA intermediate-risk patients include:

- Microscopic invasion into the perithyroidal soft tissues (minimal extrathyroidal extension [ETE])
- Cervical lymph node metastases or I131 uptake outside the thyroid bed on post-treatment scan done after thyroid remnant ablation
- Tumor with aggressive histology or vascular invasion (e.g., tall cell, insular, columnar, Hurthle cell, hobnail, or FTC)
- Papillary thyroid cancer with vascular invasion

- Clinical N1 or >5 pathological N1 with all involved LNs <3 cm in largest dimension
- Intrathyroidal, PTC with primary tumor 1–4 cm, and V600E BRAF mutated if known
- Multifocal papillary microcarcinoma with extrathyroidal extension and BRAF 600E mutated (if known)

ATA high-risk patients include:

- Macroscopic tumor invasion into the perithyroidal soft tissues (gross ETE)
- Gross residual tumor
- Distant metastases
- Postoperative serum thyroglobulin suggestive of distant metastases
- Pathologic N1 with any metastatic LN ≥ 3 in largest dimension
- FTC with extensive vascular invasion (>4 foci)

[Adapted from the new American Thyroid Association guidelines, reference [8]]

Although most DTCs have a very favorable long-term prognosis, the disease can recur many years after initial diagnosis leading the provider to decide on a long-term plan for how best to provide surveillance for these treated thyroid cancer patients. No evidence of disease (NED) is defined as stimulated thyroglobulin <1 ng/ml with no other radiological or clinical evidence of disease. Studies looking at estimates of patients in each risk category who subsequently were characterized as no evidence of disease (NED) after total thyroidectomy and RAI remnant ablation found that 78–91 % of low-risk patients were NED; intermediate-risk patients, 52–64 % NED; and high risk, 31–32 % NED [8, 17–20]. Over a follow-up period of 5–10 years, structural disease recurrence was found in less than 1–2 % of ATA low-risk patients and 8 % of intermediate-risk patients who underwent thyroid surgery without RAI ablation as initial therapy [21–23].

It is also important to consider the clinical significance of "persistent disease." In ATA low-risk patients, 70–80 % of persistent disease is manifest by abnormal serum thyroglobulin levels (suppressed or stimulated thyroglobulin >1 ng/ml) without identifiable structural disease, whereas in intermediate-risk patients, this ranges from 29 to 51 % and in high-risk patients 19–21 % [17, 20]. When counseling patients on risk of recurrence and tailoring surveillance strategies, the original pathology provides critical data. For example, patients with unifocal intrathyroidal papillary microcarcinomas experience structural disease recurrence of 1–2 % [24, 25] which increases to 5–6 % in 2–4 cm intrathyroidal PTCs [26] and 8–10 % in intrathyroidal PTCs >4 cm [26]. Intermediate-risk patients with locoregional lymph node involvement can have a risk of structural disease recurrence of 4 % in patients with fewer than five metastatic lymph nodes, 5 % if all lymph nodes involved are <0.2 cm, 19 % if more than five lymph nodes are involved, 21 % if >10 lymph nodes, 22 % if macroscopic lymph nodes are clinically evident (CN1 disease), and 27–32 % if any metastatic nodes are greater than 3 cm [10, 27].

Ultimately, all imaging (including structural and functional), biochemical, and cytopathological data should be used for a dynamic, ongoing redefinition of

clinical status to assess the individual response to therapy at each follow-up visit over time. This re-evaluation should direct intensity of surveillance and follow-up.

Surveillance of Treated Thyroid Cancer in the First Year Post Initial Therapy

The intensity of surveillance should depend on the original risk stratification of the patient. We now have a better understanding that risk stratification is ongoing at each visit, and dynamic. As patients move through the first year and beyond following initial therapy, providers need to undertake dynamic risk stratification based on available data and use this to re-evaluate their management plans. Our newest guidelines recommend putting patients into categories of "excellent response, biochemical incomplete, structural incomplete, and indeterminate".

Excellent response implies negative imaging, and either undetectable suppressed thyroglobulin or TSH-stimulated thyroglobulin <1 ng/ml. Patients who achieve an excellent response will have a 1–4 % risk of recurrence and a <1 % disease-specific death risk [8]. If patients are able to achieve this, they typically can undergo a decrease in intensity and frequency of follow-up and the degree of TSH suppression [8].

Patients who experience a biochemical incomplete response are characterized by negative imaging and a suppressed thyroglobulin >1 ng/ml, or a stimulated thyroglobulin >10 ng/ml, or a rising thyroglobulin antibody level. At least 30 % of these patients will spontaneously evolve to NED, 20 % will achieve NED after additional therapy, 20 % develop structural disease, and <1 % will experience disease-specific death [8]. Patients in this category who have stable or declining serum thyroglobulin levels should undergo continued observation with ongoing TSH suppression in most patients. Rising thyroglobulin or thyroglobulin antibody values should prompt additional investigations and potentially additional therapies [8].

Patients who fall into the category of structurally incomplete response will exhibit structural or functional evidence of disease with any thyroglobulin level +/− thyroglobulin antibodies. Patients in this category will continue to have persistent disease, despite additional therapy, 50–85 % of the time. The disease-specific death rate may be as high as 11 % with locoregional metastases, and 50 % with structural distant metastases. Patients with structural incomplete response may undergo additional treatments, or ongoing observation depending on multiple clinicopathologic factors including size, locations, rate of growth, RAI avidity, PET avidity, and specific pathology of the structural disease [8].

Indeterminate response includes patients with nonspecific findings on imaging studies or faint uptake in thyroid bed on RAI scanning; detectable non-stimulated thyroglobulin, but less than 1 ng/ml; detectable stimulated thyroglobulin but less than 10 ng/ml; or stable or declining thyroglobulin antibodies in the absence of

structural of functional disease. Of these patients, 15–20 % will have structural disease identified during follow-up. In the remainder, the nonspecific changes are either stable or resolve. Less than 1 % will experience disease-specific death. Patients in this category should undergo continued observation with appropriate serial imaging of the nonspecific lesions and serum thyroglobulin monitoring. Nonspecific findings that become suspicious over time should be evaluated further with additional imaging or undergo therapy [8].

Thyroglobulin and cervical neck ultrasound are cornerstones of surveillance. Measurement of serum thyroglobulin is an important modality to monitor patients for persistent or recurrent disease. Following initial therapy, patients at low risk of recurrence and death can be followed with a suppressed thyroglobulin every 6–9 months in the first 2 years with no need to obtain a stimulated thyroglobulin value if there are no other suspicious clinical concerns [16]. These patients should undergo at least one follow-up neck ultrasound [16] keeping in mind that surveillance ultrasounds in this low-risk population are more likely to have false positives and lead to more procedures, including follow-up ultrasounds, FNA, and more patient anxiety.

Long-Term Surveillance of Treated Thyroid Cancer Patients

Long-term surveillance strategies also need to be individualized based on original risk of recurrence and mortality of the thyroid cancer patient. Determining accurate surveillance for possible recurrence in patients presumed disease-free is the major goal of long-term follow-up. Highly specific tests allow recognition of patients unlikely to experience disease recurrence so that less aggressive, more cost-effective, and safe management strategies can be deployed. Patients with higher risks of recurrence should be monitored more aggressively since early detection of recurrent disease is thought to offer the best opportunity for most effective care.

Most recurrences of DTC occur within the first 5–8 years after initial treatment; however, recurrences may occur even decades later, particularly in patients with PTC [28]. Long-term follow-up is guided by the evaluation of how the patient responded to therapy in the first 1–2 years of original diagnosis [12]. At each subsequent visit, patients should be classified as having one of the following clinical outcomes to direct long-term surveillance [12, 17]:

- Excellent response: no clinical or biochemical or structural evidence of disease
- Biochemical incomplete response: abnormal thyroglobulin levels in the absence of localized disease
- Structural incomplete response: persistent or newly identified locoregional or distant metastases
- Indeterminate response: nonspecific biochemical or structural findings that cannot be classified as either benign or malignant confidently

When defining an excellent response or a biochemical incomplete response, the extent of the initial therapy is key. In patients who have undergone total

thyroidectomy and RAI remnant ablation, an excellent response is defined as a stimulated thyroglobulin value of <1 ng/ml or a highly sensitive non-stimulated thyroglobulin of <0.2 ng/ml with negative imaging and commonly a normal postoperative neck ultrasound. In patients who underwent total thyroidectomy without subsequent RAI therapy, a non-stimulated thyroglobulin value of <1 ng/ml is considered an excellent response. In patients treated with less than total thyroidectomy, non-stimulated thyroglobulin values less than 20 ng/ml are considered an excellent response. This equals about 50 % of the thyroglobulin expected from a normal thyroid. Any thyroglobulin value above these ranges is considered biochemical incomplete response in the absence of confirmed structural disease.

Patients classified as having an excellent response to therapy should have a decrease in the intensity of their surveillance and frequency of follow-up. They should have their TSH goal raised to 0.5–2 mU/L and be seen for physical exam and non-stimulated thyroglobulin levels yearly with surveillance neck ultrasound at 3–5-year intervals. Patients originally classified at ATA intermediate or high risk who then achieve an excellent response to therapy may benefit from closer follow-up and more intense suppression for a few more years.

Patients who demonstrate a biochemical incomplete response to therapy defined as an abnormal thyroglobulin in the absence of structurally identifiable disease should continue to be monitored every 6 months with ongoing TSH suppression and yearly neck ultrasound for several more years. Patients with stable or declining thyroglobulin values should continue routine surveillance and TSH suppression, while those with rising thyroglobulin should prompt additional imaging modalities and evaluation.

Patients deemed to have a structural incomplete response to therapy could require additional imaging or therapy depending on several clinical factors including location, rate of growth, FDG or RAI avidity, and pathology.

Patients with an indeterminate response to therapy defined as a nonspecific, biochemical, or structural imaging should continue on mild TSH suppression (0.1–0.5 mU/L) with 6-month follow-up visits for 2–3 years with yearly neck ultrasound. After that time, most patients can be reclassified [12, 17]. In summary, in terms of clinical decision making and algorithms for those who underwent partial thyroidectomy and are ATA low risk, follow-up should consist of possibly serum thyroglobulin levels and ultrasound; radioactive iodine scanning is not indicated. The TSH goal is 0.5–2 mU/L in most cases [8]. If there is an excellent response to therapy, non-stimulated thyroglobulin levels can be followed every 12–24 months with periodic neck ultrasounds [8].

In patients who received total thyroidectomy and are ATA low risk, we recommend routine use of postoperative serum thyroglobulin, and postoperative ultrasound can be used, with consideration of radioactive iodine scanning. Radioactive iodine treatment is typically not given, but if it is, low-dose ablation such as 30 mCi can be used for initial therapy [8]. Initial TSH goal is 0.1–0.5 mU/L if thyroglobulin is >0.2 and 0.5–1 mU/L if thyroglobulin <0.2. Response to therapy is evaluated by serum thyroglobulin and ultrasound, and if excellent response is detected, TSH is

allowed to be 0.5–2 mU/L [8]. Once an excellent biochemical response is demonstrated, unstimulated thyroglobulin can be measured at 12–24 month intervals with periodic neck ultrasounds [8].

In ATA intermediate-risk patients who have undergone total thyroidectomy +/− prophylactic central neck and/or lateral neck dissections, routine use of postoperative serum thyroglobulin is recommended, and postoperative RAI scanning and ultrasound are to be considered [8]. For RAI remnant ablation, lower doses such as 30 mCI is generally favored over higher doses, and for adjuvant therapy, doses up to 150 mCI are administered in the absence of distant metastases [8]. The initial TSH goal is 0.1–0.5 mU/L. The response to therapy is evaluated by thyroglobulin measurement, ultrasound, and consideration of whole-body scanning. If there is an excellent response to therapy, the TSH goal can be allowed to come up to 0.5–2 mU/L and the patient be followed by periodic non-stimulated thyroglobulin and neck ultrasound imaging [8].

In ATA high-risk patients who have undergone total thyroidectomy+/− prophylactic central neck and/or lateral neck dissections, routine use of postoperative thyroglobulin is recommended, and postoperative RAI scanning and ultrasound are to be considered [8]. RAI should be considered, and adjuvant therapies up to 150 mCi are administered in the absence of distant metastatic disease. For known structural disease, 100–200 mCi or dosimetry is generally used [8]. Initial TSH goal is <0.1 mu/L. Initial response to therapy is assessed via thyroglobulin measurement and neck ultrasound, and consideration should be given to CT/MRI and/or FDG/PET scanning as well as whole-body scanning [8]. If there is an excellent response to therapy, the TSH goal should then become 0.1–0.5 mU/L for at least 5 years with yearly follow-up of thyroglobulin for 5 years and consideration of ultrasound +/−CT/MRI. If there is a biochemical or structural incomplete response, the TSH goal should be <0.1 indefinitely in the absence of contraindications [8].

Long-term survivorship care is becoming more recognized as an important area that requires future research. The American Cancer Society estimates that over 63,000 thyroid cancers were diagnosed in 2014, but there were only 1900 deaths [29]. There are over 50,000 thyroid cancer survivors alone in the United States [30]. Despite this, there remains a small amount of peer-reviewed literature on survivorship care.

Thyroglobulin in Patients With and Without RAI Treatment

Thyroid cells are assumed to the be the only source of thyroglobulin in the human body, and hence circulating thyroglobulin levels serve as a biochemical marker of persistent or recurrent disease in DTC follow-up [31]. Thyroglobulin is a large glycoprotein that in normal thyroid tissue is found in the follicular colloid where it serves as a substrate for thyroid hormone synthesis. Since it is only produced by normal or well-differentiated malignant thyrocytes, it serves as a suitable tumor

marker [32]. Thyroglobulin assays became available in the 1980s and have greatly improved in sensitivity and precision [33], and have become a cornerstone in surveillance of patients post initial treatment. Since thyroglobulin has a half-life of 65 h, the levels typically nadir 4–6 weeks post-surgery [33].

The Presence of Thyroglobulin Antibodies and Challenges with Interpreting Thyroglobulin Levels

Most thyroglobulin assays are immunometric, but unfortunately are prone to interference from autoantibodies to thyroglobulin, which can occur in approximately 25 % of thyroid cancer patients and 10 % of the general population, particularly in patients with Hashimoto's thyroiditis [34, 35].

The presence of thyroglobulin antibodies may cause a falsely low serum thyroglobulin measurement [36]. Given this, it is recommended to measure concomitant serum thyroglobulin antibodies when measuring serum thyroglobulin. No method reliably eliminates thyroglobulin antibody interference, but radioimmunoassays (RIA) for thyroglobulin may be less prone to antibody interference [37–39]. RIA assays, however, are often not as sensitive (lower limit of detection) compared to immunometric assays. Recurrent or progressive disease should be suspected in patients with rising positive antithyroglobulin antibodies, while falling levels may indicate successful therapy [40, 41]. In most patients who have undergone total thyroidectomy and RAI remnant ablation, thyroglobulin antibodies tend to disappear over a median of 3 years in patients without recurrent or persistent disease [42–44]. Several studies have shown an increased risk of recurrence or persistent disease associated with either a new appearance of antithyroglobulin antibodies or a rising titer, and thus should prompt further investigation [40, 42, 45, 46].

Imaging Modalities Used in Surveillance of DTC

Ultrasound

Ultrasound is widely used in patients with both thyroid nodules and thyroid cancer from initial detection, diagnosis, preoperative planning, and finally to postoperative surveillance. Cervical ultrasound is well suited for surveillance since most recurrences of differentiated thyroid cancer and metastases occur within the thyroid bed and in the cervical lymph node chains; it is low cost and noninvasive without radiation exposure [15]. Once a patient has had either total thyroidectomy or partial thyroidectomy, ultrasonography can be used to monitor the thyroid bed for recurrence or for evaluating for suspicious nodules in the remaining thyroid [47].

Ultrasonography can also evaluate for abnormal appearing lymph nodes in the central compartment (in a postsurgical neck) and in the lateral compartments [47].

Differentiated thyroid carcinoma, especially PTC, has been found to involve cervical lymph node metastases in 20–50 % of patients in several studies [48–50], and may be present even in the stetting of a primary tumor that is small and intrathyroidal [51, 52]. However, the clinical significance of small volume, occult lymph node metastases is still unclear.

Abnormal lymph nodes on ultrasound examination may include calcifications, cystic changes, rounded shape, hyperechogenicity, absence of a fatty hilum, abnormal vascularity, and an increased short-axis diameter [53]. Nodal microcalcifications and cystic changes are highly indicative of malignancy, and several studies have shown these two characteristics together to have reported specificities near 100 % [54]. No single sonographic feature, however, is adequately sensitive to identify malignant cervical lymph nodes with thyroid cancer.

Normal thyroid remnant tissue appears as vascular lobules of tissue with the same echogenicity of surrounding tissue. Once patients have undergone radioablation, thyroid remnants may appear as hypoechoic, heterogeneous nodules, without internal vascularity [55]. On the other hand, thyroid bed malignant recurrences typically appear as well-defined hypoechoic oval nodules. Sometimes vascularity and microcalcifications can be seen [56]. Since these features are not specific, many entities need to be considered in the differential diagnosis for recurrence, including remnant thyroid, fibrosis, suture granulomas, reactive lymph nodes, and fat necrosis [56].

If an abnormal lymph node or soft tissue is appreciated on ultrasound, confirmation of malignancy with FNA for cytology and/or measurement of thyroglobulin in the needle washout is recommended, particularly if surgical intervention will be recommended [57].

Nuclear Medicine Imaging: I123 vs. I131

Nuclear medicine imaging was once the mainstay imaging modality in the surveillance of thyroid cancer but has largely been replaced by cervical ultrasound as the primary imaging modality. Some studies have reported that whole-body scintigraphy (WBS) has a sensitivity for detection of local recurrence of 20 % vs. cervical ultrasound at 70 % [58]. Routine use of diagnostic WBS for surveillance is not recommended for low-risk patients who did not show uptake outside of the thyroidectomy bed on their initial posttreatment WBS. We still employ diagnostic WBS in patients with intermediate or high risk of recurrence. Additionally, patients with elevated or rising thyroglobulin levels with negative cervical ultrasound should also undergo WBS to assess for recurrence of radioiodine-avid disease [15].

Some thyroid cancers become radioiodine refractory. By definition this includes (1) disease that does not take up iodine at known sites of metastatic disease, (2) continued growth of disease despite RAI therapy and confirmed uptake, (3) distant

disease that grows over a 1-year period after RAI, and (4) total cumulative dose of RAI of >600 mCi [59]. It is estimated that 5–15 % of patients will develop RAI refractory disease [60]. The 5-year disease-specific survival rate in DTC that is deemed non-RAI avid is 66 % [61], and the 10-year survival rate is only 10 %. Studies have shown that the overall median survival for patients with RAI refractory disease and distant metastases is 2.5–3.5 years [62].

Cross-Sectional Imaging: CT and MRI

The utilization for computed tomography (CT) and magnetic resonance imaging (MRI) is much less common for surveillance given the advantages and efficacy of ultrasound, particularly in surveillance of treated, lower-risk DTC, as ultrasonography is the preferred method coupled with thyroglobulin determination. One could employ CT in patients with positive serum thyroglobulin levels and negative cervical ultrasound, although, in some circumstances, PET-CT may be more useful. Many use CT of the chest for surveillance of pulmonary metastases in higher-risk patients or those with known previous metastases, as this is a frequent location for metastases in PTC [15]. CT can detect both macro- and micronodular lung disease, in addition to military disease, the latter of which can be missed on WBS or PET imaging due to limited resolution [63].

MRI is not generally used for routine surveillance, but can be utilized to further define anatomy and presence of invasion for aggressive recurrences. In these cases, it can aid in surgical planning. Some studies have shown MRI to be comparable to ultrasonography for detection of recurrence, but US is less invasive, less costly, and easier to perform [64]. Lastly, MRI can be valuable for localizing retroesophageal/retrotracheal tumors and mediastinal disease [15]. The sensitivity of MRI for the detection of cervical metastases in some studies has been shown to be around 30–40 % [65]. MRI can be affected by respiratory artifacts and may be more difficult to interpret than CT scanning, especially in low-volume nodal disease [66].

Positron Emission Tomography with FDG (PET Scan)

PET scanning is generally not useful in patients with no evidence of recurrence or who maintain radioiodine avidity. It is however useful in patients who have a recurrence that is no longer radioiodine avid. When tumors dedifferentiate, there is a decrease in sodium-iodide symporter expression and an increase in glucose transporter-1 expression, the transporter by which FDG is taken up by cells. In this circumstance, PET scan becomes a valuable imaging modality [67]. It is recommended to obtain a PET scan in patients with a negative whole-body I123 or I131 scan and a stimulated thyroglobulin >5–20 ng/ml [8].

TSH Suppression

Goals and Rationale

After total thyroidectomy, thyroxine therapy is required for all patients to maintain TSH levels, whether or not radioactive iodine is given. Partial thyroidectomies may not require thyroxine therapy. Levothyroxine also can limit potential TSH stimulation of tumor growth by keeping the serum TSH suppressed. The American Thyroid Association guidelines for the treatment of thyroid cancer recommend that low-risk disease patients maintain a serum TSH level between 0.1 and 0.5 mU/L until the patient demonstrates an excellent response to therapy, which usually occurs in the first 6–12 months. At that point, the TSH can be kept between 0.5 and 2.0 mU/L. This latter level is also recommended in patients who have undergone lobectomy only for their low-risk disease. For ATA intermediate-risk disease, the serum TSH level should be 0.1–0.5 mU/L [8]. Obviously, the patient's comorbidities, such as active heart disease or bone loss, may dictate that lower doses be utilized. Per the guidelines published in 2015, those patients who have demonstrated an excellent biochemical response can have their serum TSH level kept at 0.5–2.0 mU/l, while for those with an indeterminate response, it may be more appropriate to aim for a TSH level of 0.1–0.5 mU/L, and unless they have age >60 years, osteoporosis, or atrial fibrillation, then their goal is best kept at 0.5–2.0 mU/L [8]. For those patients with no known risks and a biochemical incomplete response or known structural disease, their serum TSH goal should be <0.1 mu/L [8]. Those with active atrial fibrillation tend to be the highest-risk patients for worsening of cardiac disease from serum TSH over-suppression, and unless they have structural disease, their goal should be kept at 0.5–2.0 mU/L. If structural disease is present, even with atrial fibrillation, patients' serum TSH level should be kept at 0.1–0.5 mU/L [8]. Once patients remain disease-free for 5–10 years, the TSH can be allowed to come into the normal range [12]. Practice guidelines recommend combining patient comorbidity with tumor prognostic indicator (excellent response, indeterminate, biochemically incomplete, and structurally incomplete) to determine the best-suited TSH suppression goal [8].

The data supporting TSH suppression to below the normal range impacting thyroid cancer morbidity and mortality is controversial. There is a lack of general consensus as to what degree of suppression is needed across stages to best reduce recurrence and thyroid cancer-related death. It is thought that most well-differentiated thyroid carcinomas express TSH receptors on their cell membrane and respond to TSH stimulation by increasing the expression of several thyroid-specific proteins, such as thyroglobulin, and thus increasing rates of cell/tumor growth [68]. Goitrogens, iodine deficiency, and partial thyroidectomy may promote the development of thyroid cancer, but these tumors can be prevented by the oral administration of levothyroxine or by hypophysectomy, both of which reduce or suppress the secretion of TSH [69]. DTC tissues have functional TSH receptors,

and thyroid cancer cells in primary culture respond to TSH stimulation by activating the cyclic-AMP cascade that promotes cell growth [70]. TSH receptors and other thyroid-specific proteins are not well expressed in poorly differentiated thyroid cancers [71]. The first study published describing the regression of PTC in two patients treated with thyroid extracts was published by Dunhill in 1937 [72]. Many years later, Mazzaferri and Jiang published a retrospective analysis of 30 years of follow-up data showing that patients treated with thyroxine therapy had 25 % fewer recurrences and 50 % fewer cancer deaths than those who did not receive hormonal therapy and who had serum TSH levels within the hypothyroid range [73]. Based on these findings and others, suppressing TSH became a cornerstone to therapy in patients with DTC. Although earlier studies found that TSH suppression below physiological levels have reduced thyroid cancer recurrence and disease-specific mortality, this has remained controversial and not well studied by large randomized controlled trials. There are risks to long-term suppression including iatrogenic thyrotoxicosis, bone loss, arrhythmia, angina, and others. Sugitani and Fujimoto evaluated 441 patients with a proven diagnosis of PTC who were randomized to receive serum TSH suppression to <0.01 μU/ml or to not receive any TSH suppression. They excluded patients with tumors less than 1 cm or patients too high risk to undergo suppression (already with known heart disease or bone loss). At 5 years of median follow-up, disease-free survival and recurrence did not differ among these two groups [74]. Carhill et al. performed a multi-institutional disease registry evaluating 4941 patients with DTC. Of these, 88 % had PTC, 8 % had follicular thyroid cancer (FTC), and 4 % had Hurthle cell carcinoma (HCC). Median follow-up was 6 years, but ranged from 0 to 25 years. TSH suppression was graded as serum TSH level undetectable, TSH subnormal but detectable, TSH normal range, and TSH above normal range. In all stages, moderate TSH suppression (subnormal but detectable) was shown to have improved overall and disease-specific survival. Even in the presence of distant metastases, TSH suppression to undetectable levels was not found to improve overall survival above modest TSH suppression. This suggests there may be no benefit across any stage to suppress TSH to an undetectable level [75]. Wang et al. studied 771 patients with ATA low- or intermediate-risk DTC to see if a median TSH <0.4 μU/ml vs. a median TSH >0.4 μU/ml improved recurrence over a median follow-up of 6.5 years. Osteoporosis incidence was evaluated in women only. They found that suppression of serum TSH level <0.4 μU/ml did not change recurrence rates in low- to intermediate-risk patients with DTC but did increase osteoporosis incidence in women [76]. Studies have shown that doses of levothyroxine that reduce circulation TSH to <0.4 mIU/L induce maximum suppression of serum thyroglobulin [77], suggesting that increasing the degree of TSH suppression beyond this point may not further decrease tumor function [78]. Others have found that serum thyroglobulin continues to decline when TSH is further suppressed to levels that are undetectable <0.01 mIU/L [79]. These findings have added to the controversy of optimal TSH suppression levels in patients with thyroid cancer.

Morbidity Associated with TSH Suppression

For decades, all patients with thyroid cancer were put on thyroid hormone suppression to suppress serum TSH to undetectable levels. We now have a better understanding that with suppression comes the price of morbidity, including bone loss, arrhythmias, particularly atrial fibrillation, and symptoms of hyperthyroidism. We also have a better understanding of long-term mortality and the often favorable prognosis in most patients with DTC. Given this, it is critical to weigh the risks and benefits of thyroid hormone suppression at each follow-up visit.

Bone Loss

Bone loss is a concern in patients with overt and subclinical hyperthyroidism, particularly in elderly patients. Since patients with DTC often undergo TSH suppression as part of their therapy, it is important to consider the effects on bone metabolism and clinically significant bone loss. In postmenopausal women, several studies have reported a negative effect of long-term serum TSH suppression on the bone mineral density (BMD) of patients with DTC [80, 81], while other studies have not confirmed such a negative effect [82, 83]. BMD analysis is important because it is correlated with the risk of fracture in postmenopausal women [84]. Wang et al. retrospectively examined a total of 771 patients (569 women) with ATA low or intermediate DTC with a mean age of 48 +/− 14 years who underwent thyroidectomy between the years 2000–2006. They were followed for a median of 6.5 years. They were divided into two groups, a median serum TSH level of >0.4 mIU/L or <0.4 mIU/L. Primary outcomes were structural recurrence of thyroid cancer, postoperative development of atrial fibrillation, and osteoporosis (the latter in women only). A total of 5.6 % of patients recurred (43/771) and 3.9 % (29/739) developed osteoporosis. The rates of recurrences were similar among the two groups, but patients suppressed to a TSH of <0.4 mIU/L were at a higher risk for osteoporosis (HR 2.1, $p=0.05$) compared to those patients with a TSH of >0.4 mIU/L [81]. Gomes de Melo et al. performed a cross-sectional study that assessed BMD and risk factors for decreased BMD in 109 postmenopausal women under TSH suppression for DTC therapy. They compared this cohort to age-matched, euthyroid women as a control. They found that low body mass index and low serum TSH levels were correlated with lower BMD, but there was no increased prevalence of osteopenia or osteoporosis compared to the age-matched, euthyroid controls [85]. Sugitani and Fujimoto performed a randomized controlled trial in female patients with PTC. They were randomized to suppressive therapy or non-suppressive therapy. The mean TSH in the suppressed group was 0.07 mU/L ($n=144$) and 3.14 mU/L ($n=127$) in the non-suppressed group. They measured annual lumbar spine BMD. They found that there were significant decreases in T scores within the first year postoperatively in the suppressed group in women ≥50 years old but not those <50 years of age. In the non-suppressed group, there was no significant decline in lumbar spine BMD until

5 years postoperatively [86]. One can appreciate that risk factors for lower BMD and fracture risk should be taken into account along with benefits of TSH suppression when treating patients for DTC.

Atrial Fibrillation

Hyperthyroidism has a well-known association with atrial fibrillation (AF) [87]. Even subclinical hyperthyroidism has been shown to have a greater risk of AF in patients over the age of 60 years [88]. Abonowara et al. evaluated 136 patients with a mean age of 52 years (85 % female and mean follow-up of 11 years) to evaluate the risk of developing AF. The mean serum TSH level was 0.17 mIU/L and 14 patients were found to have AF. The mean age of those patients with AF was 61.6 years vs. 51.4 years in those patients who did not develop AF. The prevalence of AF in this study was 10.3 % in DTC patients over the age of 60 years, which is >17.5 % higher than the rate of published data for the incidence of AF in the normal population of the same age group [89]. In addition to AF, other important cardiovascular risk factors can develop in young and middle-aged patients undergoing long-term TSH suppression therapy including increased heart rate, increased left ventricular mass, increased mean arterial pressure, and diastolic dysfunction [90].

Symptoms of Hyperthyroidism

TSH-suppressive therapy can also be associated with signs of hyperthyroidism including insomnia, racing heart, tremor, palpitations, diarrhea, excessive sweating, anxiety, heat intolerance, and weight loss. Several studies have shown that TSH-suppressive doses of levothyroxine can impair quality of life as measured by psychological, social, and physical items, particularly when the serum TSH is undetectable [90].

Conclusion

Thyroid cancer overall has a favorable long-term prognosis and low risk of death in most cases. Risk of recurrence can be estimated based on original pathology and clinical data at time of initial treatment. At each follow-up visit, patients should be re-evaluated and considered in either one of four categories: (1) excellent response, (2) biochemical incomplete response, (3) structural incomplete response, or (4) indeterminate response. This information should then be used to guide the clinician in long-term surveillance decisions. Ongoing risk stratification is essential to guide surveillance strategies and degree of desired TSH suppression, weighing the risks and the benefits. Lifelong suppression is no longer recommended in patients who have been shown to have an excellent response to treatment. Over surveillance and

over treatment with thyroxine can lead to anxiety in the patient, unnecessary studies, and morbidity. Ongoing dynamic risk stratification at each visit can avoid negative outcomes while providing appropriate surveillance to patients with treated DTC.

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