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REVIEW

Differentiated thyroid cancer: a focus on post-operative thyroid hormone replacement and thyrotropin suppression therapy

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Abstract

Purpose This review focuses on post-operative thyroid hormone replacement and thyrotropin suppression therapy in patients with differentiated thyroid cancer.

Methods A clinical review.

Results Differentiated thyroid cancers (DTC), including papillary and follicular thyroid cancers, have an excellent prognosis and their management leverages a unique set of clinical tools arising from homology to the normal thyroid follicular cell. Surgery is the cornerstone of initial management, and post-operative care often requires thyroid hormone replacement therapy, which may be approached with the intent of physiologic normalization or used pharmacologically to suppress TSH as part of a DTC treatment.

Conclusion Management of DTC and approaches to TSH suppression are tailored to an individual's risk of DTC recurrence and are adjusted to a patient's clinical status and comorbidities over time with the goal of mitigating risk and maximizing benefit.

Keywords Differentiated thyroid cancer · Thyroid hormone replacement · Levothyroxine · TSH suppression

Introduction

Differentiated thyroid cancer overview

Thyroid cancer is the most common endocrine malignancy, occurring with a global age-standardized incidence of 10.1 per 100,000 women and 3.1 per 100,000 men [1]. Most thyroid carcinomas arise from the thyroid follicular epithelial cell and exist in a broad spectrum of histologic differentiation and behavior, ranging from common indolent classical papillary cancers to rare and aggressive undifferentiated/anaplastic cancers. The majority are considered well-differentiated thyroid cancers (DTCs) which is a collective term for common papillary thyroid cancers (PTCs) and rarer follicular thyroid cancers (FTCs). While PTCs and FTCs exhibit unique clinical features and molecular signatures, they are grouped together because of a close phenotypic resemblance to the thyroid follicular epithelial cell, a comparable excellent prognosis for most patients, and similar management strategies [2]. The incidence of DTC has been rapidly rising over time, mostly due to overdiagnosis of small PTCs [3]. Most patients with DTC present at an early stage and 10-year survival rates approach 99% for American Joint Committee on Cancer Stage I, and 94% for Stage II disease [4].

Management

Similar to the originating thyroid follicular cell, most DTCs express the TSH receptor, the sodium iodide symporter, and thyroglobulin, all of which have been leveraged to develop clinical tools unique to thyroid cancer [5]. The use of supraphysiologic thyroid hormone replacement will suppress TSH through hypothalamic and pituitary feedback inhibition and thereby suppress thyrocyte/cancer function and proliferation. Once normal thyroid tissue is surgically removed and/or ablated, serum thyroglobulin becomes an effective tumor marker. Lastly, the sodium iodine

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exchanger can be co-opted to deliver tumoricidal treatment with beta radiation through radioactive iodine (RAI), which was pioneered in the early 1940s and likely reflects the first "targeted" therapy for cancer [6].

Surgery is the most important initial treatment for DTC and serves as definitive therapy in many cases [7]. Active surveillance is also a well-validated alternative option for small tumors [8]. The American Thyroid Association (ATA) Risk of Recurrence System is widely used to risk-stratify patients after surgery and to guide surveillance intervals, recommended serum TSH suppression targets, and the timing and nature of additional treatments [2]. This review will highlight the importance of thyroid hormone medical therapy in patients with DTC, focusing on its physiologic use in the treatment of post-operative hypothyroidism, as well as its pharmacologic role through suppression of serum TSH.

Thyroid hormone replacement after thyroidectomy

Surgical approach and risk of post-operative hypothyroidism

Total thyroidectomy is defined as the complete removal of thyroid tissue, whereas a near-total thyroidectomy involves leaving a small remnant to reduce the risk of complications; both unequivocally lead to post-operative hypothyroidism. Hemithyroidectomy, otherwise known as partial thyroidectomy or thyroid lobectomy involves removal of a subtotal portion of the thyroid gland including the ipsilateral isthmus. Patients with small, localized tumors without imaging evidence of locoregional lymph node involvement are good candidates for conservative treatment with hemithyroidectomy. After hemithyroidectomy, 23.6–73% of patients require thyroid hormone supplementation to maintain euthyroidism [9, 10]. Multiple predictors for developing a hormone requirement after hemithyroidectomy have been identified, including pre-operative TSH levels >2.0–2.5, and lower thyroid volumes; the effect of female sex and positive anti-thyroid antibodies is debated [11, 12]. Up to two-thirds of patients who develop subclinical hypothyroidism after hemithyroidectomy may experience subsequent TSH normalization without treatment [13].

Physiologic rationale behind thyroid hormone replacement therapy

Under normal conditions, the thyroid produces 80–100 mcg of thyroxine/T4 and 3–6 mcg of triiodothyronine/T3, which are the dominant forms of thyroid hormone in circulation. The majority (80–85%) of systemic T3 is generated extrathyroidally through 5'-monodeiodination of T4 by deiodinase enzymes. T3 exhibits a 10-fold greater affinity for binding intranuclear thyroid hormone receptors compared to T4 and thus thyroxine is mostly considered a pro-hormone. Thyroid hormone receptors exist in two major isoforms with differing tissue distributions, which mediate thyroid hormone's myriad effects on energy homeostasis, metabolism, heat production, organ activity, etc. Thyroid hormone production is tightly regulated by the hypothalamic-pituitary-thyroid axis through a classic endocrine feedback loop. Low levels of circulating thyroxine/thyronine lead to thyrotropin-releasing hormone from the hypothalamus, which in concert with insufficient T4/T3, stimulates TSH secretion from thyrotrophs in the anterior pituitary. TSH binds to thyrotropin receptors on the thyrocyte basolateral membrane and stimulates nearly every step in hormonogenesis including iodine uptake and organification, and thyroid hormone synthesis and release [14, 15].

Practical aspects of post-operative thyroid hormone replacement therapy

The goal of thyroid hormone replacement therapy is the elimination of the signs/symptoms of hypothyroidism and the biochemical normalization of thyroid function tests, of which circulating TSH is most sensitive. The current standard of care involves postoperative initiation of oral levothyroxine, the synthetic but identical levo enantiomer of endogenous human thyroxine. Levothyroxine has an elimination half-life of approximately 6–7 days and oral bioavailability of 60–90%; most absorption occurs in the duodenum and ileum over 2–3 h. Approximately 1.6–1.7 mcg/kg/day (actual body weight) of levothyroxine is needed to normalize serum TSH in anatomically or functionally athyreotic adults, although higher doses (1.9–2.2 mcg/kg/day) are used when the goal is TSH suppression [16]. Levothyroxine is commercially available in tablets, gel capsules, and liquids. Gel and liquid formulations may be more rapidly absorbed [17]. There are many branded and generic products that are identical in their active hormone constituent but differ in excipients. Levothyroxine is typically administered in the morning on an empty stomach 30–60 min before eating, ideally with water, since foods and caloric beverages, especially those containing calcium, iron, and fiber, negatively impact absorption.

A weight-based dose of levothyroxine is typically started the day after total thyroidectomy. After hemithyroidectomy, a serum TSH is usually obtained 4–6 weeks after surgery to assess the adequacy of remnant hormone production. If serum TSH values are not at target, levothyroxine is often initiated at doses between 25–75 mcg; a common titration

strategy involves adjustment in 12.5–25 mcg increments every 6–12 weeks with serial TSH testing that is gradually spaced out after stability [2, 18].

There are several pitfalls that can preclude the achievement of a euthyroid state. Unintentional iatrogenic hyperthyroidism is not infrequent [19, 20]. Patient non-adherence or malabsorption due to concomitant ingestion of levothyroxine with foods/drinks and/or gastrointestinal comorbidities is a common problem, especially since many patients find ideal administration practices to be inconvenient. There is a long list of potentially interfering medications that have been thoughtfully reviewed elsewhere; calcium/iron/multivitamin supplements, proton pump inhibitors, bile acid sequestrants, and phosphorus binders are common culprits [21]. Fluctuations in weight and advancing age can lead to changes in dose requirements over time. Furthermore, several endogenous and exogenous substances can interfere with thyroid hormone testing, the most notable of which is high-dose biotin supplementation, which can cause spurious hyperthyroidism. Anti-animal, anti-TSH, and non-specific cross-linking antibodies in patient sera can lead to persistent TSH abnormalities (typically, elevation). Assay interference should be considered when thyroid function testing does not respond to dose titration as expected, as well as when assay results do not fit with patient signs and symptoms [22].

Is there a role for T3-containing regimens?

While levothyroxine is widely considered a standard of care in the management of hypothyroidism, desiccated thyroid extracts (TEs) and synthetic liothyronine bear mention [18, 23]. Animal-derived TEs containing a mixture of thyroxine and thyronine were the dominant form of thyroid hormone replacement for nearly a hundred years after their first reported use in the early 1880s. Synthetic levothyroxine was synthesized and became available in the 1950s; over the next 30 years, levothyroxine became increasingly popular due to more consistent potency, comparable and then lower cost, and arguably lower rates of iatrogenic thyrotoxicosis, compared to TEs. When research in the 1970s identified that most serum thyronine was generated and regulated by enzymatic deiodination of thyroxine, coupled with levothyroxine's superior ability to fully normalize newly developed TSH, T4, and T3 assays (animal-derived TE has a higher T3:T4 ratio compared to human thyroid tissue), levothyroxine monotherapy quickly grew to supplant TEs in widespread use [24].

Since that time, mounting evidence suggests that levothyroxine monotherapy may not normalize all signs, symptoms, and biochemical markers of euthyroidism in all individuals. Levothyroxine-treated patients have been reported to exhibit a 5–10% lower resting energy expenditure, higher total cholesterol and low-density lipoprotein levels, and modestly higher weight, compared to euthyroid controls [25]. Additionally, a subset of hypothyroid patients report persistent neurocognitive and other non-specific symptoms, and some patients are dissatisfied with current therapy [26]. Lower serum T3 levels, or sub-optimally elevated T4:T3 ratios have been proposed, with some controversy, as possible mechanisms for treatment-refractory symptoms. Calls for expanded study and use of TE and/or synthetic combination therapy with levothyroxine and liothyronine have naturally followed. The identification of deiodinase polymorphisms that may impact peripheral T4-to-T3 conversion and predict a positive response to T3-containing regimens has further intensified the debate. To date, over 17 randomized controlled trials have examined levothyroxine in comparison to TE and/or synthetic combination therapy. Results have been inconsistent, and conclusions/generalizations are hampered by significant methodologic concerns. A recent joint consensus statement from the American, British, and European Thyroid Associations was released to summarize the state of the field and to articulate proper methods for future well-designed clinical trials [27]. Hopefully, future trials will include sufficient symptomatic patients with post-operative hypothyroidism and inform when, in whom, and how combination therapy might be most effectively used.

Thyrotropin suppression therapy

History and benefits of TSH suppression

The development of RAI paved the way for the physiologic basis of TSH suppression in DTC, especially in younger individuals and those with metastatic disease. Prolonged hypothyroidism or TSH injections were observed to stimulate growth and iodine concentration in metastases from DTC [28, 29]. The first published case of TSH suppression therapy for DTC was in 1954, in which a 37-year-old woman with pulmonary metastases was treated with TE after RAI, which led to decreased chest iodine uptake, resolution of chest-X-ray findings, and improvement in pulmonary function [30]. Subsequent work by Mazzaferri revealed a significant drop in the risk of recurrence in patients with DTC > 1.5 cm when treated with total thyroidectomy followed by RAI and TSH suppression therapy [31, 32]. A meta-analysis of similar studies showed this approach led to a relative risk reduction of 71% in the combined endpoint of disease progression, recurrence, and death [33]. However, it was also increasingly recognized that TSH suppression is associated with long-term risks.

Long-term risks of TSH suppression

Long-term risks of TSH suppression for DTC are similar to those seen in cases of subclinical or overt hyperthyroidism, including cardiac morbidity (especially atrial tachyarrhythmias and cardiac remodeling), loss of bone density and higher fracture risk, impaired quality of life, and a question of increased risk of other cancers [34].

The cardiac adverse effects of hyperthyroidism are numerous: left ventricular hypertrophy, higher heart rates and atrial premature beats, and increased systolic function have all been observed in patients with DTC under TSH suppression [35]. Higher rates of atrial fibrillation have been reported, albeit inconsistently; the duration of hyperthyroidism may be more impactful than degree of TSH suppression, although levels <0.1 mIU/L appear enriched in morbidity [36, 37]. Traditional risk factors for atrial fibrillation such as age appear to remain independent risk factors [38]. Interestingly, one study showed that the cumulative risk of RAI was a major risk factor for atrial fibrillation, perhaps due to independent effects on the heart [36]. Higher cardiovascular mortality has also been observed in patients with DTC, with a 3.08 hazard ratio for each 10-fold decrease in geometric mean TSH level [39].

Supraphysiologic thyroid hormone levels accelerate bone turnover more so than bone formation, an effect which is disproportionately seen in post-menopausal women under TSH suppressive therapy for DTC, compared to pre-menopausal women [40]. Age, degree of TSH suppression, and duration of suppressive therapy are all associated with a higher risk of loss of bone mineral density and various markers of bone quality which, coupled with negative effects on muscle strength and weight, create a setup for fractures. Indeed, fracture risks are up to 4-fold higher in post-menopausal women with TSH levels lower than 0.1 mIU/L in one study, although it did not specifically evaluate individuals with DTC [41]. Higher fracture risk with low TSH levels has been confirmed through meta-analytic methods [42].

Quality of life appears to be lower in TSH-suppressed individuals with DTC, although it is challenging to sort out the effects from post-operative hypothyroidism and knowledge of a cancer diagnosis [43, 44]. Lastly, high free T4 levels, but interestingly not low TSH levels, have been associated with a higher risk (HR 1.42) of solid organ malignancies, especially lung and breast cancers.

A risk-adapted approach to TSH suppression

In addition to recognition of the risks of TSH suppression, it is now clear that not all patients benefit, and that the degree and duration of TSH suppression are important. Data supporting TSH suppression are unequivocally strongest for patients with known/active DTC persistence/recurrence or distant metastases, and patients who are at the highest risk for recurrence. However, suppression of TSH below the limit of detectability appears no better than suppression below 0.1 mIU/L [45]. Benefits appear much more modest or even non-existent in patients with low-to-intermediate risk tumors [46]. The National Thyroid Cancer Treatment Cooperative Study Group has been a seminal source of large-volume long-term prospective registry data examining TSH suppression and has demonstrated that moderately suppressed TSH values 0.1–0.4 mIU/L led to better outcomes in the first 5 years of follow-up, but not beyond 5 years [47]. Another large prospective study from the Netherlands demonstrated that median TSH values < 2 mIU/L were associated with better outcomes compared to >2 mIU/L [48].

Contemporary approaches to TSH suppression in DTC rely on a judicious patient risk-adapted, and tailored complication-mitigating approach. To date, the most prescriptive guidelines are the 2015 ATA Guidelines for Thyroid Cancer, in which recommended TSH targets are graded to the risk of DTC recurrence [2]. TSH targets are then modified during dynamic risk-re-stratification, which is performed after initial treatment with thyroid surgery and/or RAI and re-evaluated during subsequent long-term surveillance. An individual's risk factors and comorbidities are used to further personalize TSH targets, with higher risk conditions leading to a stepwise de-escalation of the magnitude of suppression. A summary of ATA risk of recurrence groups and dynamic risk re-stratification category definitions are summarized in Table 1. Risk-adapted TSH targets for each category are represented in Table 2.

An area of active debate is whether patients with low-risk disease, especially those who have undergone lobectomy, need to have serum TSH levels maintained below 2 mIU/L [49]. When using a target of less than 2 mIU/L, 84% of patients required initiation of levothyroxine in one retrospective analysis [50]. Whether or not an optimal TSH target exists is unclear. To our knowledge, the only study to demonstrate the benefit of a specific TSH target after hemithyroidectomy is that by Park et al. which demonstrated a higher risk of recurrence in patients with a TSH > 1.85 mIU/L [51]. In contrast, two large retrospective studies by Lee et al. and Xu et al. did not demonstrate a higher risk of recurrence with TSH levels >2 mIU/L, or even when TSH levels were above the reference range; this finding persisted even amongst patients at intermediate risk of recurrence [52, 53]. A large prospective randomized controlled clinical trial investigated TSH levels between 0.3 and 1.99 uIU/mL versus 2.0 to 7.99 uIU/mL patients post-hemithyroidectomy and is currently underway in Korea [54]. Similar questions about the role of TSH suppression and/or targets arise in the care of patients under active

Table 1 Summary of American Thyroid Association Differentiated Thyroid Cancer Risk of Recurrence and Dynamic Risk Re-Stratification Categories

Category	Definition
ATA Risk of Recurrence	
Low	PTC with complete macroscopic tumor resection and NO evidence of locoregional or distant metastasis, loco-regional tissue invasion, aggressive histology, vascular invasion, radiographic or clinical evidence of nodal disease, >5 N1 micrometastases 2 mm or larger Intrathyroidal encapsulated follicular variant PTC, or Intrathyroidal FTC with <4 foci vascular invasion
Intermediate	DTC with microscopic extrathyroidal extension, RAI-avid metastases on first post-RAI whole body scan, aggressive histologic subtypes, PTC with vascular invasion, clinically evident metastatic adenopathy or >5 involved lymph nodes (but none >3 cm)
High	DTC with gross extrathyroidal extension or residual disease after surgery, distant metastases, FTC with extensive angioinvasion (>4 vessels), involvement of >3 lymph nodes with extranodal extension, or any involved lymph node size >3 cm, post-op Tg suggestive of metastasis
ATA Dynamic Risk Re-Stratification[a]	
Excellent	Negative imaging AND suppressed Tg < 0.2 ng/mL OR TSH-stimulated Tg < 1 ng/mL
Indeterminate	Non-specific imaging findings, faint RAI uptake in thyroid bed on whole-body scanning, detectable suppressed Tg < 1 ng/mL, detectable stimulated Tg < 10 ng/ML OR anti-Tg antibodies are stable or declining in the absence of radiographic evidence of disease
Biochemical Incomplete	Negative imaging AND suppressed Tg ≥ 1 ng/mL OR stimulated TG ≥ 10 ng/mL OR rising anti-Tg antibody titer
Structural Incomplete	Clinical or radiographic structural or functional evidence of disease with any Tg level, whether or not anti-Tg antibodies are present

[a]After treatment with total thyroidectomy

ATA American Thyroid Association

Adapted from Haugen, B. R., et al. (2016). "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 **26**(1): 1–133

Table 2 Summary of American Thyroid Association Differentiated Thyroid Cancer Risk of Recurrence TSH Suppression Goals After Total Thyroidectomy, Tailored by Initial Risk of Recurrence and Dynamic Risk Re-stratification during Follow Up

Initial Post-Treatment and Short-Term Risk Re-stratified TSH Goals ≤5 years after diagnosis					
DTC Risk of Recurrence	Initial TSH Target	Excel-lent	Indeterminate	Biochemical Incomplete	Structural Incomplete
Low	LLR – 2.0	LLR – 2.0	0.1 – LLR	0.1 – LLR	<0.1
Intermediate	0.1 – LLR	LLR – 2.0	0.1 – LLR	0.1 – LLR	<0.1
High	<0.1	0.1 – LLR for ≥ 5 years	<0.1	<0.1	<0.1

Long Term Comorbidity-Graded Risk Re-stratified TSH Targets ≥ 5 years after diagnosis				
Risk Factors	Excellent	Indeterminate	Biochemical Incomplete	Structural Incomplete
No known risk	LLR – 2.0	0.1 – LLR	<0.1	<0.1
Menopause, tachycardia, osteopenia	LLR – 2.0	0.1 – LLR	0.1 – LLR	<0.1
Age > 60, osteoporosis	LLR – 2.0	LLR – 2.0	0.1 – LLR	<0.1
Atrial fibrillation	LLR – 2.0	LLR – 2.0	LLR – 2.0	0.1 – LLR

ATA American Thyroid Association, *LLR* lower limit of the TSH assay-specific reference range

TSH values are reflected in mIU/L

Adapted from Haugen, B. R., et al. (2016). "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 **26**(1): 1–133

surveillance for DTC. Higher TSH levels have been associated with the progression of papillary thyroid microcarcinomas under active surveillance, especially in younger people, in some but not all studies [55–58] Whether administration of levothyroxine to lower TSH levels abrogates risk of progression has not yet been proven. Prospective data are sorely needed, especially given the risk of bias in retrospective studies; levothyroxine is most likely to be offered to patients at higher risk of progression) [59].

While the guidelines have made great strides in canonizing a logical and evidence-based treatment approach, there are ongoing active efforts to better refine risk categories. The observation that 1–2% of patients with low-risk disease are found to have distant metastases emphasizes the need to better articulate the low-risk category so patients can be safely triaged to more conservative therapy [60, 61]. How to better integrate the risk of multifocality, degree, and location of extrathyroidal extension, positive margins, and emerging molecular data are areas of active investigation [62–66]. However, despite the availability of thoughtfully informed guidelines, and evidence that real-world TSH suppression practices significantly exceed the duration and extent of guideline recommendations; effective guideline implementation and dissemination to clinicians may be just as critical as guideline development itself [67].

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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