Current Guidelines for Postoperative Treatment and Follow-Up of Well-Differentiated Thyroid Cancer

Jenny Y. Yoo, MD, Michael T. Stang, MD*

KEYWORDS

• Thyroid cancer • Radioactive iodine • I^{131} • TSH suppression

KEY POINTS

- The pathology and demographics of well-differential thyroid cancer patients define specific risk groups.
- Adjuvant radioactive iodine is recommended for moderate- to high-risk patients after surgical resection.
- Administration of thyroxine to suppress TSH levels is a cornerstone of long-term therapy.
- Long-term follow-up is guided by serum thyroglobulin measurements and cervical ultrasound to detect recurrent disease.

Well-differentiated thyroid carcinoma (WDTC) is predominately a surgical disease with respect to the primary tumor, locoregional advanced disease, and the treatment of cervical neck recurrences. However, the multidisciplinary approach to postoperative management of thyroid cancer is central in minimizing the risk of recurrence and surveying patients long-term in a cost-effective manner to detect clinically significant disease recurrence that warrants further treatment. Because long-term survival from WDTC is good with 10-year survival of 93% for papillary thyroid cancer (PTC) inclusive of all stages it is vital to appropriately treat the patients that are at higher risk of complications from their disease burden without overtreating those patients with a low risk of thyroid cancer–related adverse outcome.[1]

For the purpose of this article, the discussion is inclusive of the postoperative treatment of adult differentiated carcinoma processes derived from follicular epithelial cells and comprises PTC, follicular (FCC), and oncocytic follicular (Hürthle or oxyphillic cell [HCC]) subtypes.

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Division of Endocrine Surgery, Department of Surgery, University of Pittsburgh, 3471 Fifth Avenue, Kaufman Building, Suite 101, Pittsburgh, PA 15213, USA
* Corresponding author.
E-mail address: stangmt@upmc.edu

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In the past two decades, there has been a dramatic and sustained rise in incidence and detection of these well-differentiated thyroid tumors. Most of the rise in incidence is caused by the detection of PTC and likely the consequence of increased sensitivity of imaging modalities and pathologic identification of subclinical microscopic tumors. With the relative rapid increase in the diagnosis of WDTC, clinicians caring for this epidemic of thyroid cancer need guidance in providing algorithmic care from rational guidelines formed out of extensive literature review and consensus expert opinion. In our own clinical treatment of patients with thyroid cancer, postoperative care and surveillance is directed predominately by guidelines laid out by the American Thyroid Association (ATA) as initially published in 2006 and revised in 2009, with the anticipated third iteration due in 2015, and guidelines established through the National Comprehensive Cancer Network® (NCCN®), with the current version published in 2015.[2–4] Use of such guidelines is not to discredit the recommendations made through other vigorous reviews and the expert opinion of very relevant professional organizations involved in promoting improved WDTC care.[5–8]

ASSIGNMENT OF RISK

Most patients with WDTC who have undergone a total thyroidectomy with or without appropriate lymphadenectomy have relatively excellent prognosis for long-term survival and very low disease-specific mortality.[9,10] However, there is an inherent risk of growth of occult persistent disease and this is often reflected as a locoregional cervical neck or mediastinal recurrence.[9,10] This is especially true for PTC, which accounts for most cases of WDTC. As reasoned, the ultimate goal in the postoperative management of patients with WDTC is to maximize disease-free recurrence with appropriate and measured treatments that serve benefit to those patients with a real risk of adverse outcome from recurrent disease while not overtreating most patients that have minimal risk of recurrence following surgical removal of the primary tumor alone.

Specific factors have been identified that permit a more individualized estimation of recurrence rate and survival and help guide long-term oncologic adjuvant treatment and surveillance strategies. Of these, the patient's age at the time of presentation and tumor stage are two of the most important prognostic factors.[11–14] As one would expect, age is an independent variable in the long-term risk of mortality, with older patients more likely to succumb to disease burden. The inflection point of increased risk of death begins in the fourth decade and escalates for those greater than 60 years of age.[9] Risk of tumor recurrence, however, is more bimodal as it pertains to age at diagnosis. The risk of recurrence is highest for those with age less than 20 and greater than 60.[9,12–14] Male sex also portends more aggressive disease when compared with that of female cohorts.[10]

As with any other cancer, tumor biology has a profound influence on the expected long-term outcome. For WDTC, this is best represented by the pathologic features of the primary tumor including tumor size, tumor histology, extrathyroidal extension (ETE), vascular invasion, and the extent of metastatic lymph node involvement. Clearly, small tumors (<1 cm) conventionally referred to as microcarcinomas would be expected to have favorable outcomes and are addressed separately. Larger tumors (>1.5 cm) are associated with a higher risk of recurrence and disease-specific mortality.[9] Indeed, there is an incremental increase in the risk of distant metastasis with increasing tumor size.[15]

Certain histologic variants of WDTC portend a more concerning risk of recurrence and/or disease-specific mortality. Among these are variants of PTC including tall-cell, insular, columnar, and diffuse sclerosing variants.[10,16–20] Conversely, follicular

variant PTC carries a very favorable risk profile and is especially true with evidence of clear demarcation or complete encapsulation.[21,22] Conventional follicular and oncocytic follicular carcinomas are largely considered to have more aggressive tumor biology especially with larger tumors and advanced age.[23–25] However, tumors with evidence of minimal invasion as defined by microscopic capsular disruption are considered to have a favorable biology and low risk of recurrence.[26,27]

Ten percent of WDTC exhibit evidence on anatomic pathology of tumor extension through the outer thyroid capsule into the immediate perithyroidal soft tissue.[9] Such extension is variable and designated as either minimal ETE (American Joint Committee on Cancer [AJCC] T3) or macroscopic and extensive (AJCC T4a). The risk of recurrence significantly correlates to the degree of ETE. For minimal ETE, risk of recurrence is 3% to 9%, whereas recurrence rates for T4a disease is 23% to 40%.[28–33] Further, intrathyroidal extension observed as vascular invasion has been shown to correlate with tumor recurrence (16%–30%), high rate of distant metastasis (12%–35%), and long-term adverse outcomes.[34–38]

Lymph node metastasis in the context of WDTC is common and observed in most patients (62%–81%) when detailed lymph node dissection is performed.[39–42] However, it is clear from large retrospective series and observational studies that not all lymph node metastasis carry the same clinical significance because the real risk of recurrence ranges from 2% to 38%.[41,43–46] To an extent, this holds true even in patients managed without lymph node dissection or adjuvant treatment with radioactive iodine (RAI).[40,46] To more clearly synthesize the abundant and varied data for lymph node metastasis and risk of recurrence or adverse outcome, an ATA taskforce clarified the characteristics of lymph node metastasis to be considered at low risk or higher risk.[47] Micrometastasis (<0.2 cm in largest diameter) in five or fewer nodes are classified as lower-risk disease with an estimated risk of recurrence of 5% without further treatment.[47] More than five metastatic lymph nodes, clinically apparent N1 disease (detected with either preoperative imaging or intraoperatively), or any metastatic focus greater than 3 cm are classified as higher risk of recurrence with risk of recurrence greater than 20%.[47] Identification of extranodal extension is also an important indication of biology and the risk of recurrence is 2% for patients with less than or equal to three lymph nodes exhibiting extranodal extension rising to 38% for those with greater than three lymph nodes demonstrating extranodal extension.[46]

The extent of data available regarding the various risk factors for recurrence and disease-specific morbidity for a given presentation of WDTC has resulted in several different staging systems all establishing a relative prognostic score. The AJCC TNM staging system is considered the most useful for prediction of the risk of death from thyroid cancer.[3,43] However, the AJCC TNM staging system does tend to fall short in its overall clinical relevance in predicting recurrence of WDTC.[13,48] Other common prognostic scoring methodologies used within the literature in analyzing large prospective and retrospective clinical cohorts include AGES (*A*ge, tumor *G*rade, *E*xtent, and *S*ize), AMES (*A*ge, *M*etastasis, *E*xtent, and *S*ize), MACIS (*M*etastasis, *A*ge, *C*ompleteness of resection, *I*nvasion, and *S*ize), EORTC (European Organization for Research and Treatment of Cancer), and NTCTCS (National Thyroid Cancer Treatment Cooperative Study) among other more institutional-specific scores (Ohio State University and Memorial Sloan Kettering Cancer Center).[9,13,49–53] Such scoring systems alternatively weigh the typical prognostic variables to better define the outcome end point they were designed to measure. Overall, none of the scoring systems have shown over time to provide primacy in the ability to predict outcome whether it is recurrence or disease-specific mortality.[13,27,54,55] A simplified three-tier risk staging

system was proposed as part of the 2009 ATA guidelines (**Table 1**) to more specifically address the risk of clinical recurrence and has proved to be well validated in its approach.[56–59] This more relevant risk stratagem provides the basis for the key components in the postoperative care of WDTC patients as it pertains to adjuvant treatment with RAI and thyroid-stimulating hormone (TSH) suppression, in addition to establishing the tempo and intensity of long-term surveillance.

An important consideration in long-term postoperative care of WDTC patients is to be cognizant that the initial staging as specified by the AJCC TNM stage does not change over time; however, because most patients live decades following diagnosis, the biology of the disease may evolve with time. Most WDTC persistent disease remains indolent in nature and escalation of treatment is infrequently needed. For some patients with thyroid cancer, nonetheless, the response to therapy is incomplete and/or the clinical course transforms and with that the ongoing risk of recurrence, disease progression, and risk of disease-specific death may change over time. Thus, the multidisciplinary team tasked with long-term treatment of each patient should provide an ongoing reassessment of the risk of recurrence as their clinical data emerges with the response to therapy and clinical course.[3,36,38]

THE INCIDENTAL PAPILLARY THYROID MICROCARCINOMA

The detection of small PTC lesions (<1 cm), termed microcarcinomas (PTMC), has been steadily increasing over the last four decades and accounts for a large portion of the steady rise observed in overall number of PTC over that same timeframe.[60] These are typically found incidental to the original indication for thyroid surgery and are very-low-risk lesions with essentially zero risk of disease-specific mortality and less than 1% risk of distant metastasis.[61,62] The risk of locoregional recurrence is 2.4% despite studies reporting 60% of PTMC are associated with lymph node metastasis.[42,63] Patients with PTMC have an excellent overall prognosis and most pertinent studies demonstrate no significant improvement in recurrence rate or increased

Table 1
A simplified three-tier risk staging system

Low Risk	Intermediate Risk	High Risk
Absence of local or distant metastasis	Evidence of microscopic extrathyroidal extension into perithyroidal tissue	Macroscopic tumor invasion of perithyroidal structures
Complete macroscopic tumor resection	Presence of cervical lymph node metastasis	Incomplete resection of the primary tumor
No tumor invasion of locoregional tissues or structures	Evidence of aggressive histology[a] or vascular invasion	Distant metastasis
Absence of vascular invasion or predominate aggressive histology[a]	Evidence of I^{131} uptake outside the thyroid bed on posttreatment whole-body RAI scan	Serum Tg levels out of proportion to I^{131} uptake observed on posttreatment whole-body RAI scan
No I^{131} uptake outside the thyroid bed on posttreatment whole-body RAI scan		

[a] Insular, columnar, tall-cell, solid, and diffuse sclerosing variants.

Adapted from Cooper DS, Doherty GM, Haugen BR, et al. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19(11):1180; with permission.

survival after total thyroidectomy versus thyroid lobectomy with or without RAI treatment in the context of PTMC.[64,65] Accordingly, the ATA and NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) do not advocate the use of RAI ablation or completion thyroidectomy for these tumors because of the low risk of recurrence and metastatic potential.[3,4] If PTMC is discovered following diagnostic lobectomy whether unifocal or multifocal, periodic surveillance of the contralateral lobe with high-resolution ultrasound (US) is adequate for postsurgical management.[4]

COMPLETION THYROIDECTOMY

Not all patients have the amenity of a preoperative diagnosis of WDTC and anywhere from 5% to 75% of patients with nondiagnostic, atypia of undetermined significance, follicular lesion, or suspicious for malignancy cytology (Bethesda System for Reporting Thyroid Cytopathology I, III, IV, and V) on fine-needle aspiration (FNA) biopsy have a clinically significant malignancy diagnosed on anatomic pathology following the initial surgical resection.[66] Many of these patients receive a diagnostic lobectomy because of the uncertainty of the indeterminate cytology reporting categories. For these patients, the first step in postoperative care involves the decision to proceed with completion thyroidectomy. This often requires a multidisciplinary approach and clear communication between the endocrine surgeon, endocrinologist, and nuclear medicine specialist involved in posttreatment plans.

Total thyroidectomy for patients with primary tumors greater than or equal to 1 cm yields lower recurrence rates and higher survival rates.[67] As such, the treatment of choice is total thyroidectomy if the tumor is biopsy proved preoperatively. Current guidelines prescribe that if a total thyroidectomy was warranted with a preoperative diagnosis of WDTC, then completion thyroidectomy should be offered.[3] This is especially true for those patients that are to be recommended RAI treatment or those where active surveillance is more of a concern.[3,4] Conversely, patients with low-risk purely intrathyroidal PTC (favorable histology, such as follicular variant <4 cm) and without evidence of ETE or only minimally invasive FCC less than 2 cm may be considered to have definitive therapy with thyroid lobectomy alone.[4,21,44,68]

Treatment or attempt at ablation of the remaining contralateral lobe of the thyroid with RAI is not recommended under circumstances where it can be removed surgically.[3,69] Circumstances that can present a challenge with respect to completion thyroidectomy are cases where the recurrent laryngeal nerve is injured at the initial resection and the patient is left with a vocal fold motion deficit. This also highlights the vital importance of laryngoscopy in the postoperative setting to document any deficit and proceed with treatment if needed.

RADIOACTIVE IODINE TREATMENT

In the context of surgical oncology and adjuvant oncology treatment, there are few treatments that are more “targeted” than that of RAI. A hallmark of follicular-derived thyroid epithelial cells is their ability to import via the sodium-iodine symporter and retain iodine in the process of organification. Such activity provides for a reasonable cellular retention time and potentiates radiopharmacologic imaging and treatment. Postoperative treatment with radioactive I^{131} is primarily applied for three reasons. First, RAI ablates or eliminates any remaining normal thyroid tissue and facilitates the specificity of thyroglobulin (Tg) as a tumor marker in long-term surveillance. This is of more significance in the low-risk and some intermediate-risk group patients that otherwise may never have disease recurrence but could observe an increase in Tg over time because of growth of any normal thyroid remnant tissue from incomplete

thyroidectomy. Second, RAI serves as an adjuvant treatment of intermediate-risk patients to destroy remaining occult small foci of WDTC and potentiating a decrease in long-term risk of recurrent disease. Finally, RAI may be administered in a true therapeutic fashion for those high-risk patients with macroscopic residual disease or distant metastatic disease.

The 2009 ATA guidelines and current version of NCCN Guidelines for the treatment of WDTC patients with RAI are reasonably congruent (**Table 2**).[3,4] In general, both sets of guidelines define a set of patients at low risk of recurrence for whom there is little documented benefit in administering either an ablative or adjuvant dose of RAI. Certainly for those patients at high risk of recurrence there is relative uniformity in recommending an empiric therapeutic dose of RAI. For all other WDTC patients in between as either low risk with tumors 1 to 4 cm or intermediate risk with only a low-volume of nodal metastasis, the use becomes more selective and inherently subjective. Furthermore, for those patients in the intermediate-risk group or those with low risk of recurrence but tumors greater than 4 cm the multidisciplinary team must determine the appropriate empiric dose range to treat, whether that is more consistent with an ablative dose (30–100 mCi) or an adjuvant dose (100–200 mCi).

With respect to the less common WDTC histology of FCC and HCC, widely invasive tumors or those exhibiting vascular invasion should prompt RAI treatment in all cases. For tumors greater than 2 cm or those with only a few foci of vascular invasion, consideration of RAI treatment should follow best clinical judgment.[4] Tumors with evidence of minimal invasion as defined by microscopic capsular disruption do not typically warrant RAI treatment.[3,4,26,27]

The actual RAI doses for each of stated intent of simple remnant ablation, adjuvant treatment, and therapeutic dosing vary to a degree across the ATA and NCCN Guidelines.[3,4] However, some generalizations can be made with respect to empiric dosing. An ablative dose is typically 30 to 100 mCi (ATA) with the NCCN favoring more restrained use with 30 mCi for most ablative intents and in some cases of low to intermediate risk of recurrence (see **Table 2**, NCCN Selective Use). Adjuvant and therapeutic treatment dosing tends to overlap and typically ranges from 100 to 200 mCi for those in the intermediate- and high-risk groups, favoring 200 mCi for those at highest risk (ATA).[3] The NCCN Guidelines more specifically recommend doses of 100 to 175 mCi for known lymph node metastasis, 150 to 200 mCi for incompletely resected tumor remaining in the thyroid bed, and 200 mCi for those patients with evidence of distant metastasis.[4] Because of the risk of pulmonary fibrosis, patients with diffuse pulmonary metastasis are recommended not to exceed a dose of 150 mCi.[4] The role of other dosing strategies, such as lesional dosimetry or upper limit blood- and body-based dosimetry, in the initial postoperative treatment is less well defined and is most appropriate to consider for patients with significant distant metastatic disease, diffuse pulmonary metastasis, or medical comorbidities, such as renal failure, that potentiate the possibility of significant toxicity with the upper limits fixed empiric dosing.[3,70,71]

Preparation for RAI imaging and treatment includes induction of an iodine deficient state and elevation of the TSH level to maximize the response of remaining normal thyroid tissue and any persistent tumor burden. It is vital for the multidisciplinary care team to inquire about potential exposures to high levels of iodine, such as intravenous contrast or amiodarone. Spot urine iodine can be measured to guide in the timing of RAI because most patients with urinary iodine concentrations greater than 135 μg/L following high-dose iodine return to baseline within 60 days.[72] Patients are instructed to maintain a low-iodine diet ($\leq$50 μg/day) for at least 1 to 2 weeks before receiving RAI.[3,4,73] Useful resources for patients regarding complying with a low-iodine diet are

Table 2
Recommendations for the use of RAI

	Not Recommended	Selective Use	Recommended	Recommended
		Ablative (30–100 mCi) or adjuvant dosing (100–200 mCi)	Ablative (30–100 mCi) or adjuvant dosing (100–200 mCi)	Therapeutic dosing 100–200 mCi
ATA[c]	Most low risk	Low risk with tumor 1–4 cm[a] Intermediate risk: age <45 nodal metastasis only[a] Intermediate risk: age >45 nodal metastasis only (AJCC T1-2 N1a)[a] Intermediate risk: any age with minimal ETE only (AJCC T3 with tumor <4 cm)[a]	Low risk with tumor >4 cm[a] Most intermediate risk[a]	High risk
[NCCN][d]	PTC: unifocal or multifocal classic variant PTC with all primary tumors <1 cm without ETE, absence of anti-Tg antibodies and unstimulated Tg <1 ng/mL FCC/HCC: primary tumor <2 cm without ETE or vascular invasion, absence of nodal or distant metastasis and absence of anti-Tg antibodies	PTC: tumor 1–4 cm or high-risk histology or lymphovascular invasion or lymph node metastasis or macroscopic multifocal (>1 cm) or positive anti-Tg antibodies or unstimulated Tg 1–5 ng/mL[b] FCC/HCC: primary tumor 2–4 cm or minor vascular invasion or lymph node metastasis or positive anti-Tg antibodies or unstimulated Tg 1–5 ng/mL[b]	PTC: primary tumor >4 cm or gross extrathyroidal extension or unstimulated Tg >5 ng/mL[b] FCC/HCC: primary tumor >4 cm or gross extrathyroidal extension or extensive vascular invasion or unstimulated Tg >5 ng/mL[b]	PTC, FCC, and HCC: known or suspected distant metastasis or incomplete resection or primary tumor

[a] Suspected or known residual disease based on clinical judgment or demonstrated on pretherapy WBS should prompt treatment with 100 to 200 mCi. In the absence of known or suspected residual disease based on clinical judgment or pretherapy WBS, dosing of 30 to 100 mCi should be used.
[b] If pretherapy WBS shows no thyroid bed uptake and Tg <1 ng/mL then follow without ablation. With thyroid bed uptake only proceed with remnant ablation dose of 30 mCi. For patients with proved metastatic disease proceed with empiric dosing 100–200 mCi.
[c] Cooper DS, Doherty GM, Haugen BR, et al. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167–214. PMID: 19860577.
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found through the ATA (http://www.thyroid.org/faq-low-iodine-diet/) and the Thyroid Cancer Survivors Association (http://thyca.org/rai.htm#diet).

Recombinant Human Thyrotropin Versus LT4 Withdrawal in an Iodine Deficient State

Traditionally, RAI had been administered in the setting of levothyroxine (LT4) withdrawal to elevate the TSH level to a goal of greater than 30 mU/L, which is the level shown necessary to adequately concentrate iodine with remnant thyroid and persistent tumor.[3,4] Comparable results are achieved by simply administering recombinant human thyrotropin (rhTSH) before RAI without the need to discontinue LT4. In several randomized controlled trials, low- to intermediate-risk patients demonstrated equivalent ablation with rhTSH versus LT4 withdrawal.[74–78] The role of rhTSH in high-risk patients is less clear and it is still recommended to use LT4 withdrawal in this patient cohort in the absence of medical comorbidities that preclude a prolonged hypothyroid state.[3]

Pretreatment whole body scan (WBS) with either 1.5 to 3 mCi I^{123} or low activity 1 to 3 mCi I^{131} is controversial in whether it confers long-term benefit because it rarely changes the RAI dosing treatment algorithm.[79–82] The concern, typically, is whether iodine administered for the pretreatment WBS "stuns" the targeted tissue and inhibits activity of the impending ablative dose.[83,84] As such, the use of pretreatment scans is selective and recommended if the information gathered is anticipated to change management (ie, low-risk patients undergoing remnant ablation with unexpected uptake outside the thyroid bed may prompt higher empiric dosing of I^{131} or the finding of diffuse pulmonary metastasis limiting RAI dosing in limiting pulmonary toxicity).[3,4] Optimal I^{131} treatment is subsequently administered within 72 hours to maximize treatment.[3,85] Following administration of I^{131}, posttherapy WBS done within 2 to 10 days is strongly recommended to detect clinically unapparent disease, which can be present in 10% to 25% of cases, and guide ongoing assessment of risk of recurrence and subsequent surveillance.[3,4,86,87]

Treatment with I^{131} is well tolerated; however, the multidisciplinary care team needs to be aware of and clinically evaluate all patients administered I^{131} for the potential short- and long-term complications that can arise. The more common side effects of RAI are related to iodine avidity of epithelial cells with the salivary glands and lacrimal ducts. Temporary or permanent dysfunction of these tissues can lead to salivary gland dysfunction, xerostomia, dental carries, dysgeusia, sialadenitis or parotiditis, and lacrimal duct obstruction. The likely best management of such symptoms in the early posttreatment period is adequate hydration.

THYROID-STIMULATING HORMONE SUPPRESSION

The 2009 ATA and current NCCN Guidelines for adults with WDTC recommend TSH suppression as an important adjunct in the long-term treatment of patients at intermediate and high risk of recurrence.[3,4] The upcoming 2015 ATA guidelines will likely continue this recommendation with modification based on the degree of response to therapeutic interventions.[88] The theoretic benefit and goal of therapy is in inducing hyperthyroxemia with oral LT4 suppressing hypothalamic thyrotropin-releasing hormone and subsequent pituitary TSH production. This relative suppression of TSH relegates its potential to stimulate the growth of nascent disease. The rationale for this treatment is based on studies demonstrating benefit of improved overall survival, disease-specific survival, prevention of major adverse clinical events, and restrained progression of metastatic disease in high-risk patients.[89–92] No such benefit has been demonstrated, however, for those patients with low risk of recurrence.[52,53] Current management guidelines offer congruent recommendations with respect to the degree of

TSH suppression for each risk stratification (**Table 3**).[3,4] Initial T4 dosing is weight based at 1.6 μg/kg/day and is titrated to achieve the goal TSH level within the first 6 to 12 postoperative weeks. Once a patient has maintained sustained appropriate levels, the TSH level should be monitored at least once in any give 12-month period.[3]

The consequences of sustained TSH suppression should not be ignored and this is especially true in older patients or those with ischemic heart disease. Supraphysiologic dosing of LT4 can potentiate cardiac arrhythmias and exacerbate angina symptoms, respectively.[3,93] Sustained elevation of serum thyroxine levels can lead to decreased bone density and is particularly pertinent in postmenopausal women; therefore, the concurrent use of calcium and vitamin D supplementation is advised, as is consideration of antiresorptive therapy when appropriate.[94,95]

POSTOPERATIVE ADJUNCTS FOR HIGH-RISK PATIENTS

Locally advanced WDTC with invasion into the aerodigestive tract or other vital structures of the head and neck, such as the carotid artery, is a surgical challenge even for high-volume thyroid surgeons. Every reasonable effort should be pursued to achieve a complete resection while preserving function. However, in those cases where complete resection is not possible and there is likely persistent aerodigestive tract invasion, treatment with external beam radiation should be considered as an adjunct to RAI treatment. This is especially true for tumors that lack iodine avidity on initial WBS.[3,4]

Conventional cytotoxic chemotherapeutic agents generally elicit a poor response for thyroid cancer and adjuvant systemic chemotherapy is enthusiastically not recommended in any circumstance for WDTC.[3,4,96] The future use of systemic treatment with targeted inhibitors to sensitize WDTC to RAI treatment is promising but its role in the routine care of more advanced cases is still uncertain.[97]

SURVEILLANCE

Following surgery and RAI when necessary, long-term surveillance entails a thorough physical examination of the surgical site and cervical lymph nodes, imaging, and laboratory values including degree of TSH suppression and Tg as a marker of tumor persistence/recurrence. This should be typically re-evaluated in the first 6 to 12 months

Table 3
TSH suppression range goal

	ATA[b]	[NCCN][c]	
Low risk	0.1–0.5 mU/L	—	Mild suppression[a]
Intermediate risk	<0.1 mU/L	Complete treatment response/remission Incomplete treatment response	Mild suppression[a] <0.1 mU/L
High risk	<0.1 mU/L	—	<0.1 mU/L

[a] Slightly below or above the laboratory lower level of normal reference (0.5 mU/L for most centers).

[b] Cooper DS, Doherty GM, Haugen BR, et al. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167–214. PMID: 19860577.

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following initial treatment to establish a response to therapy and aid in the tempo of subsequent follow-up.[3,4]

Serum Tg is a highly sensitive and specific tumor marker in the context of WDTC. Tg measurement is integral in the long-term surveillance of patients with WDTC. Because Tg is a protein product exclusively of thyroid follicular origin, complete elimination of all normal and carcinoma-related thyroid cells from the body results in negligible or undetectable Tg levels. Tg is measured in most laboratories via immunometric assays and it is recommended that calibration be done against the CRM-457 international standard.[3,4] Furthermore, there is variability between different assays and has led to the recommendation that for a given patient the same assay be used consistently in the long-term follow-up to avoid clinical confusion regarding the real risk of persistent disease or the tempo of progression.[3,98,99] One key consideration in the use of Tg assays is the presence or absence of anti-Tg autoantibodies (TgAb) because these can dramatically interfere with conventional immunometric assays and provide for situations of falsely reported low Tg levels. Tg antibodies should be quantitatively measured every instance when Tg levels are assessed and with interpretation of the Tg level accordingly.[3,4] Furthermore, in the absence of TgAbs, the sensitivity of serum Tg assessment can be significantly enhanced with rhTSH stimulation and is used at pertinent times for assessing WDTC patients for their level of response to surgery and RAI treatment or the risk of persistent disease.[3,4,100]

When done well, high-resolution US (high frequency probe $\geq$10 MHz) is a sensitive imaging modality in the detection of cervical neck persistent/recurrent disease.[101] It is important that long-term follow-up neck US include all compartments of the neck with documentation of any enlarged or suspicious lymphadenopathy and thyroid bed remnant. Suspicious features on US include lymph nodes that demonstrate a loss of fatty hilum, rounded profile, cystic appearance, punctations concerning for microcalcifications, and a more chaotic vascular distribution.[102] Any suspicious lymph node identified in long-term follow-up with a suspected focus of thyroid cancer on shortest axis of 8 mm or greater in the central neck and 10 mm in the lateral neck should undergo cytologic evaluation with an US guided FNA.[103] To increase the sensitivity, all FNAs of potential recurrent cervical disease should be accompanied with a wash of a FNA pass into saline and quantified via routine Tg assay and consideration of levels greater than 10 ng/mL to be positive.[3,104,105]

It is the combination of serum Tg measurement and US that provides for the most sensitive assessment of WDTC in long-term cancer surveillance.[106] Interpretation of either result should rely on the other in the overall valuation of the data and the clinical judgment of whether a patient is tumor free or has recurrent disease. For example, a low detectable Tg level with a negative US may represent a patient with microscopic persistent cervical nodal disease that is of minimal long term morbidity, a high Tg level with a negative neck US may represent a patient with concern for persistent distant metastatic disease, and a low Tg level with a concerning neck US for bulky recurrent disease may represent a patient with a dedifferentiating process.

For patients managed with total thyroidectomy alone without RAI treatment, a negative US at the initial posttherapy assessment done at 6 to 12 months and a low unstimulated Tg level with undetectable TgAbs can be assured of a continued low risk of recurrence and surveyed further at 12 month or longer intervals. In the same subset of patients but with a detectable Tg level (TgAb negative), attention should be directed at the degree of thyroid remnant left from surgery and the Tg level judged accordingly. Long-term stability of the unstimulated Tg level without a rise and continued negative neck US is reassuring for low risk of recurrence. For patients with elevated TgAbs and

a negative US, continued closer follow-up is warranted until there is resolution of TgAbs.

For patients managed with RAI ablative treatment, a negative US at the initial post-therapy assessment done at 6 to 12 months with an unstimulated Tg less than 1 ng/mL should be assessed then with a rhTSH-stimulated Tg level. If stimulated levels remain less than 1 ng/mL the patient is at low risk of recurrence and can be followed annually with unstimulated Tg levels and selective use of neck US. For this same subset of patients but with stimulated Tg levels of 1 to 2 ng/mL, closer follow-up is warranted following the trend of Tg over time and continued interval neck US interrogation. For patients with an initial stimulated Tg level greater than 2 ng/mL, the risk of recurrent disease is more significant and in the context of a negative neck US the patient should be considered for possible stimulated diagnostic RAI WBS to document sites of possible recurrent disease.[3,107]

For patients at high risk or recurrent disease and Tg greater than 10 ng/mL or concern for progressive recurrent disease with up-trending Tg levels over time and negative imaging by neck US and negative imaging on stimulated RAI WBS, consideration should be given to the addition of PET–computed tomography imaging. The use of ^{18}F-fluorodeoxyglucose-based imaging has been shown to have an enhanced sensitivity and specificity in non-iodine-avid WDTC disease.[108] This is principally true in the context of more aggressive histologic subtypes, such as tall-cell PTC and HCC.[108]

TREATMENT OF RECURRENCE

After initial surgical treatment with or without RAI treatment, WDTC may exhibit locoregional recurrence in 15% to 30% of patients.[9,10,109] Because all of these disease recurrences can be considered persistent disease from the primary tumor and the initial surgery would have included this nascent cervical neck disease had it been detectable at the time of the original surgery, it is reasonable to consider that there is a clear role for surgery in the management of cervical neck recurrence. However, the surgical treatment of cervical recurrence needs to be tempered by weighing the risks of reoperation against the potential benefit of resecting what may be rather indolent disease. Studies have illustrated that most small-volume recurrent cervical nodal metastasis in the central compartment (91%) and lateral neck (71%) demonstrate minimal growth ($\leq$1 mm per year) over 3 to 5 years of observation and can be cautiously observed.[110,111] Moderate to large volume and locally invasive recurrent disease can portend long-term disease-specific adverse outcome.[112,113] Such locoregional recurrences are best managed surgically and should be considered when feasible with the understanding that it may not result in biochemical cure in most cases.[114]

The risks of operating in a previously dissected neck compartment are increased significantly compared with initial surgery and the challenge such surgery can entail is related to postoperative adhesive disease and the distortion of normal anatomy. In the case of development of structural disease in a previously undissected neck compartment, the risks are minimal and the benefit is significant and should be pursued in most cases exclusive of poor surgical candidates or evidence of persistent distant metastatic disease.[3,4] The pursuit of resection in a previously dissected compartment is more guarded and the threshold for surgery is set slightly higher. In general and when feasible, a reoperative surgery for persistent or recurrent disease should avoid “berry-picking” and proceed in a compartment-orientated dissection to include all tissue within the compartment with recurrence[3,4,103]; however, often some patients with WDTC have undergone several surgeries for neck recurrence and may present cases where a more focused dissection is warranted.[115] We find

that this is best directed with surgeon-performed intraoperative US to plan and direct the approach and extend the dissection for recurrent disease.[115]

The angst for most thyroid surgeons relates to what qualifies as an actionable structural disease recurrence. An ATA taskforce has more recently provided some clarity for this issue with a synthesis of the available published data and expert opinion on appropriate management of recurrent cervical nodal WDTC disease.[103] In general, highly suspicious or biopsy-proved (inclusive of positive FNA Tg wash) neck recurrences of the central compartment (level VI) greater than or equal to 8 mm in the shortest axis measurement should be considered for reoperative compartment dissection, as should lateral neck compartments (levels I, II, III, IV, V) greater than or equal to 10 mm be considered.[103] A volume of disease below these limits should be observed.

RADIOACTIVE IODINE REFRACTORY DISEASE

For patients that demonstrate disease that is initially or becomes noniodine avid the treatment choices become significantly more limited. External beam radiation therapy is an option for patients with isolated unresectable cervical neck disease that has not responded to RAI. In the context of extracervical isolated or oligometastatic disease, directed stereotactic radiosurgery is considered. This is especially true for palliation if the lesions are symptomatic, present risk of pathologic fracture, risk of spinal cord compromise, or intracranial mass effect.[3,4] As a final option, systemic therapy with either a Food and Drug Administration–approved (for WDTC) kinase inhibitor or through a clinical trial should be considered for patients that have progressive disease despite all other treatment modalities.

SUMMARY

The postoperative management of WDTC requires a multidisciplinary approach and constant communication among all stakeholders including the patient. Most patients are going to have a long, uneventful clinical course and should be reassured of such when appropriate based on all available clinical data. It is fundamental to have rational clarity regarding what is and is not concerning. Long-term care should avoid situations of trying to treat the surgeons or endocrinologists and excessively pursue microscopic disease or a mild biochemical persistence of Tg. Instead, the focus needs to remain on treating the patient when it is going to serve a real benefit and avoid unnecessary surgery or radioactive treatment when it is unlikely to alter the disease course. The management guidelines will continue to evolve and it is essential that physicians and surgeons who treat WDTC maintain competency in this respect.

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