Postoperative Management of Differentiated Thyroid Cancer

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POSTOPERATIVE STAGING

In patients with differentiated thyroid cancer, postoperative staging helps to determine prognosis. Staging also has a role in guiding decisions regarding postoperative radioactive iodine treatment and thyroid hormone suppression therapy, in addition to aiding specific decisions regarding follow-up.1

The UICC (Union Internationale Contre le Cancer) and the American Joint Committee on Cancer (AJCC) have adopted a staging system for differentiated thyroid cancer based on the pathologic tumor-node metastasis (pTNM) system. The sixth edition of the AJCC staging manual presented a revised definition of stages T3 and T4 to reflect the extent of extrathyroidal extension which, along with age, is a major prognostic factor for survival and risk of local recurrence.2–5 Stage T3 represents any primary tumor with minimal extrathyroidal extension or size greater than 4 cm limited to the thyroid. Stage T4a includes a tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, the larynx, trachea, esophagus, or recurrent laryngeal nerve. Stage T4b refers to any tumor that invades prevertebral fascia or encases a carotid artery or mediastinal vessels.2

Patient age at the time of initial diagnosis and therapy is a major determinant of stage in the AJCC/UICC TNM classification. In the absence of distant metastases (M0), all patients younger than 45 years are classified as stage I. In the presence of distant metastases (M1), all patients younger than 45 years are classified as stage II.
Patients 45 years or older with a primary tumor smaller than 2 cm and limited to the thyroid (T1), in the absence of node or distant metastases (N0, M0) are classified as stage I, whereas those 45 years or older with a primary tumor larger than 2 cm but not larger than 4 cm and limited to the thyroid (T2), in the absence of node or distant metastases (N0, M0), are classified as stage II. Patients 45 years or older with T3 disease and/or metastases limited to level VI lymph nodes (N1a, M0) are stage III, whereas those 45 years or older with a more locally invasive primary tumor (T4a or T4b) and/or metastases to any location other than level VI lymph nodes (N1b and/or M1) are classified as stage IV.

The American Thyroid Association (ATA) management guidelines recommend application of the AJCC/UICC TNM classification, based on the premise that the system provides a useful method to describe tumor extent and is also used in cancer registries and epidemiologic studies.\(^1,6\) Several other classification systems have been proposed, each differentially weighing prognostic values such as age, primary tumor size, presence of direct local invasion, multifocality, lymph node involvement, and distant metastases.\(^7\) Each system identifies the majority of patients at low risk of disease-specific mortality, although none have established clear superiority.\(^8\)

AJCC/UICC thyroid cancer staging fails to take into account some known prognostic factors such as histologic subtype, positron emission tomography (PET) positivity, presence or absence of multifocality, vascular invasion, and molecular characteristics.\(^9-12\) In particular, activating mutations of \(BRAF\) have been associated with lymph node metastases, lack of response to radioactive iodine, and increased likelihood of clinically recurrent disease in low-risk patients.\(^13-15\)

Although thyroid cancer staging systems are well suited to predicting cancer-associated mortality, they are relatively insensitive for predicting risk of clinical tumor recurrence. Furthermore, current staging systems rely primarily on data obtained during the initial evaluation, and are not well suited to modification as further studies obtained during follow-up provide key data regarding tumor aggressiveness and response to treatment. With regard to the risk of persistent or recurrent disease, the ATA guidelines designate as low risk those patients with the following characteristics after initial surgery and remnant ablation\(^1:\)

1. Lack of local or distant metastases
2. No evidence of residual macroscopic tumor
3. Absence of tumor invasion of locoregional tissues or structures
4. Lack of vascular invasion or aggressive histologic features (such as tall cell, insular, or columnar cell carcinoma)
5. Lack of radioactive iodine uptake outside of the thyroid bed on the first posttreatment whole body scan (if the patient has been treated with radioactive iodine).

TREATMENT WITH RADIOACTIVE IODINE

Following thyroidectomy in patients with differentiated thyroid cancer, radioactive iodine treatment may be indicated for remnant ablation or for treatment of known residual or metastatic disease.

**Postoperative Remnant Ablation**

Postoperative remnant ablation with radioactive iodine has two main potential benefits.

First, by destroying remaining normal thyroid tissue, remnant ablation increases the sensitivity of subsequent surveillance using serum thyroglobulin levels and radioactive iodine whole body scanning to detect persistent or recurrent disease.
Second, remnant ablation may serve to destroy microscopic thyroid cancer foci remaining in the thyroid bed after surgery. In patients who are at high risk of developing de novo thyroid cancer due to prior radiation exposure or genetic predisposition, remnant ablation has the possible additional benefit of destroying remnant normal thyroid tissue that may harbor the potential to develop into de novo cancer. Several large retrospective studies and a meta-analysis have shown significant reductions in thyroid cancer recurrence and disease-specific mortality in thyroid cancer patients treated with radioactive iodine for remnant ablation.\(^{11,16–20}\) In these studies, the benefit has appeared to be restricted to those patients with tumors larger than 1.5 cm, multicentric disease, locally invasive cancer, or residual disease after surgery.\(^{11,16,21,22}\)

Other studies have shown no such benefits, particularly with regard to low-risk differentiated thyroid cancer.\(^{19,21,23–26}\) An updated systematic review did not confirm a benefit of remnant ablation in early-stage well-differentiated thyroid cancer with regard to either cause-specific mortality or recurrence, although a statistically significant decreased risk of distant metastasis was noted with remnant ablation.\(^{27}\)

In the absence of data from a randomized controlled trial, significant controversy remains regarding the use of postoperative radioactive iodine treatment in patients with low-risk differentiated thyroid carcinoma. The ATA guidelines recommend radioactive iodine treatment for all patients who have distant metastatic disease, primary tumor greater than 4 cm, or evidence of gross extrathyroidal extension. In addition, the guidelines recommend radioactive iodine treatment for selected patients with primary tumor size of 1 to 4 cm limited to the thyroid who, based on tumor size, age, lymph node status, and histology, are predicted to be at intermediate or high risk of thyroid cancer recurrence or death. In the absence of other higher risk features, the ATA guidelines recommend against radioactive iodine treatment of patients with unifocal primary tumor smaller than 1 cm or multifocal cancer when all foci are smaller than 1 cm.\(^{1}\)

**Treatment of Known Residual Locoregional or Metastatic Disease**

Residual local, regional, or metastatic disease may respond to radioactive iodine treatment. In general, radioactive iodine treatment appears to be most effective in patients younger than age 40 years with well-differentiated primary tumors and small-volume metastases.\(^{28}\)

In patients with known residual local or metastatic thyroid cancer after initial surgery, the benefits of postsurgical radioactive iodine treatment are clear. Mazzaferri and Jhiang\(^{11}\) found that thyroid cancer patients with residual local or regional disease after thyroidectomy who were treated with radioactive iodine had an approximately 50% decrease in 30-year recurrence and disease-specific mortality. A subsequent prospective multicenter study in 385 patients with high-risk thyroid cancer found that radioactive iodine treatment improved disease-specific mortality and rates of progression in patients with differentiated thyroid cancer.\(^{20}\)

Iodine-avid pulmonary metastases, particularly micronodular disease, may respond to radioactive iodine treatment, whereas skeletal metastases typically do not show a good response.\(^{29–34}\) FDG-avid metastatic lesions that are detected on PET scanning are generally refractory to radioactive iodine treatment.\(^{35}\)

**PREPARATION FOR RADIOACTIVE IODINE TREATMENT**

**Methods to Increase Thyroid-Stimulating Hormone**

Iodine is taken up and concentrated in normal thyroid follicular cells and, to a lesser extent, differentiated thyroid cancer cells via a membrane sodium-iodide symporter.\(^{36}\)
Iodine uptake is stimulated by thyroid-stimulating hormone (TSH). Postthyroidectomy patients are prepared for radioactive iodine treatment either via withdrawal from thyroid hormone, with an accompanying increase in endogenous TSH levels, or via injection of recombinant human TSH (rhTSH; Thyrogen). The optimal level of TSH elevation is not known. However, data from uncontrolled studies suggest a minimum TSH level of 30 mU/L.\textsuperscript{37,38}

**Withdrawal from thyroid hormone**

Withdrawal from thyroid hormone is the traditional means of preparation for postsurgical remnant ablation and is typically accomplished by withholding levothyroxine (T4; Synthroid) therapy for 6 weeks after total or near total thyroidectomy, although 2 studies have demonstrated a satisfactory TSH elevation after an average duration of less than 3 weeks of T4 withdrawal.\textsuperscript{39,40} To minimize the symptoms of hypothyroidism during T4 withdrawal, patients are commonly treated with the shorter acting hormone liothyronine (T3; Cytomel) during the first 2 to 3 weeks after surgery (or after stopping T4). Typical doses of T3 are 25 $\mu$g twice daily in most patients, or 12.5 $\mu$g twice daily in elderly patients or those with coronary artery disease. However, data from a recent small randomized controlled trial suggest that the administration of T3 makes no difference in hypothyroid symptom scores while significantly delaying the onset of hypothyroidism (32 $\pm$ 4 days vs 17 $\pm$ 9 days needed to reach a TSH level of >30 mU/L in the T3 and control groups, respectively).\textsuperscript{41} Based on these data, it has been suggested that withdrawal preparation for remnant ablation can be simply and effectively accomplished via 2 to 3 weeks of T4 withdrawal without increasing morbidity associated with hypothyroidism. Regardless of the approach used, patients undergoing withdrawal before remnant ablation should undergo testing to confirm TSH elevation before therapy.

**Recombinant human TSH**

rhTSH was approved by the United States Food and Drug Administration (FDA) in 2007 for initial remnant ablation, and is being offered as the method of choice for routine remnant ablation in some centers. The major advantage of using rhTSH is that patients do not need to discontinue T4 therapy and go through a period of overt hypothyroidism in conjunction with radioactive iodine treatment. This agent is given as a 0.9-mg intramuscular injection on 2 consecutive days with a therapeutic dose of I-131 administered 24 hours after the second dose.\textsuperscript{42}

Prospective studies using 30, 50, and 100 mCi of I-131 have shown similar ablation success rates using rhTSH compared with withdrawal, while one prospective study using 30 mCi reported a lower ablation success rate with rhTSH versus hormone withdrawal.\textsuperscript{42-45} One retrospective study found that short-term clinical recurrence rates assessed at a median of 2.5 years after radioactive iodine remnant ablation (median I-131 dose of 108 mCi) were similar for patients prepared with rhTSH and those prepared with thyroid hormone withdrawal.\textsuperscript{46} However, to date there are no published data comparing long-term outcomes of patients treated with radioactive iodine ablation after preparation using rhTSH versus thyroid hormone withdrawal. As such, many providers continue to primarily use thyroid hormone withdrawal for radioactive iodine treatment of intermediate- and high-risk thyroid cancer patients except in cases where iatrogenic hypothyroidism may be particularly high risk (eg, congestive heart failure) or ineffective (eg, pituitary disease).

The economic implications of using rhTSH as preparation for remnant ablation are unclear. While the cost of therapy is much higher when using rhTSH versus hormone withdrawal, several studies have shown that the use of rhTSH may be associated with
substantial productivity benefits due to shorter hospital stays and reduced sick leave.47–50

**Low Iodine Diet and Avoidance of Iodine-Containing Medications**

High levels of iodine reduce uptake of radioactive iodine by normal thyroid cells as well as differentiated thyroid cancer cells. Before administering radioactive iodine, patients should take care to avoid iodine-containing drugs such as amiodarone as well as avoid computed tomography with iodinated intravenous contrast, which can impair the response to I-131 for up to 6 months.51,52 To enhance the effectiveness of radioactive iodine treatment, it is recommended that patients adhere to a low iodine diet for 1 to 2 weeks before treatment.51,53

**Pretherapy Radioactive Iodine Scanning**

Using small amounts of radioactive iodine, a diagnostic scan may be performed to determine the amount of thyroid remnant and presence of metastatic disease before administration of the treatment dose of radioactive iodine. Diagnostic I-131 doses as low as 3 mCi may result in diminished uptake of the subsequent therapeutic dose, an effect referred to as “stunning,” while lower doses are less sensitive for the detection of remaining thyroid tissue and metastases.54–56 The use of low-dose I-123 has been demonstrated to produce high-quality images without stunning. However, widespread I-123 use has been limited by its availability and higher cost.57

**DOSE OF I-131 ADMINISTERED FOR RADIOACTIVE IODINE TREATMENT**

The dose of radioactive iodine may be determined by:

1. Empirical fixed dosing based on tumor stage
2. Upper bound limits defined by whole blood dosimetry
3. Quantitative lesional dosimetry.

There are no data from controlled, prospective trials to suggest superiority of one particular method of dosing radioactive iodine, and current guidelines do not endorse a specific approach.1

Empirical fixed dosing is the simplest and most commonly used form of radioactive iodine dose determination. The optimal dose of I-131 depends on whether treatment is intended solely for remnant ablation or to treat known locoregional or metastatic disease. Patients with low-risk disease, if treated with radioactive iodine for remnant ablation, are typically given a dose of 30 to 100 mCi. Those with larger remnants with higher fractional uptake are paradoxically treated with a lower dose of I-131 in order to decrease the incidence of painful radiation thyroiditis. The ATA guidelines recommend that the minimum activity necessary to achieve successful ablation be used, particularly in low-risk patients.1 A systematic review of retrospective and prospective data comparing the use of low-dose (30 mCi) and high-dose (100 mCi) radioactive iodine concluded that based on available published data, it is not possible to reliably determine whether rates of successful ablation are similar using 30 mCi and 100 mCi.58

Patients with intermediate- or high-risk differentiated thyroid cancer are typically treated with higher activities (100–200 mCi) according to risk, although there is evidence to suggest that this empirical method of radioactive iodine dosing may result in unsafe levels of radiation exposure to bone marrow in the elderly as well as those with diffuse pulmonary metastases.59–62
Posttherapy Radioactive Iodine Scanning

Posttherapy whole body iodine scanning is typically performed 5 to 8 days after radioactive iodine dosing for initial remnant ablation, and represents an import component of staging for differentiated thyroid cancer. When compared with the pretreatment diagnostic scan, posttreatment scanning has been reported to demonstrate additional metastatic foci, most commonly in the neck, lungs, and mediastinum, in 10% to 26% of patients. Disease identified on posttreatment scan may alter cancer staging in approximately 10% of patients and may change plans for therapy in up to 15% of patients.

COMPLICATIONS OF RADIOACTIVE IODINE TREATMENT

At the typical dosages used for postoperative remnant ablation, radioactive iodine treatment is associated with a low risk of adverse events and long-term complications. The most common complications are due to radiation sialadenitis, characterized by pain and swelling in the parotid region, as well as hypogeusia and xerostomia. The incidence of sialadenitis is dose related, occurring in 5% to 40% of patients treated with radioactive iodine. A related complication is nasolacrimal duct obstruction. Mild, self-limited leukopenia and thrombocytopenia may be seen 6 weeks after treatment. An increased risk of pneumonitis and pulmonary fibrosis may also be seen in some patients with diffuse pulmonary involvement. In patients with diffuse pulmonary radioactive iodine uptake, dosimetry studies with a limit of 80 mCi whole body retention at 48 hours should be considered.

Acute complications of radioactive iodine treatment are uncommon. Hemorrhage and edema involving metastatic disease, which can occur 12 hours to 2 weeks after I-131 treatment, is of greatest concern in patients with intracranial and spinal cord metastases. Bone pain may occur following radioactive iodine treatment in patients with skeletal metastases. Patients with a large thyroid remnant can develop radiation thyroiditis, characterized by pain and swelling. Airway compromise rarely may occur. Patients with radiation thyroiditis are treated with prednisone and supportive airway maintenance. In up to two-thirds of patients treated with 200 mCi of I-131, radiation sickness characterized by headache and nausea may occur, typically resolving within 24 hours.

Radioactive iodine treatment may also be associated with an increased risk of secondary malignancies. A multicenter cohort study demonstrated a small, dose-dependent increase in the risk of second primary malignancies in thyroid cancer patients treated with radioactive iodine. Extrapolating data from higher cumulative doses of I-131, the investigators calculated that 100 mCi of I-131 would be associated with an additional 53 solid nonthyroidal malignancies and 3 leukemias during a 10-year period of follow-up of 10,000 patients. In contrast, a large cohort study using the Surveillance, Epidemiology, and End Results (SEER) database compared 10,000 patients administered I-131 for thyroid cancer with 19,000 control cases and found that use of radioactive iodine was not associated with an increased incidence of second primary malignancy during a 5-year follow-up period.

Menstrual irregularities including amenorrhea and oligomenorrhea with a duration of 4 to 10 months may be seen in up to 27% of women treated with radioactive iodine for thyroid cancer. Data from a large retrospective study suggest that pregnancy should be postponed for 1 year following radioactive iodine treatment, because of a higher rate of miscarriage. In men, radioactive iodine treatment may be accompanied by a transient reduction in sperm count and elevation of follicle-stimulating hormone (FSH) levels.
THYROID HORMONE SUPPRESSION

Circulating TSH has a trophic effect on differentiated thyroid cancer cells that express the TSH receptor. Thyroid hormone administered in doses targeted to suppress TSH levels is an important component of the postoperative management of thyroid cancer. Suppression of endogenous TSH using supraphysiologic thyroid hormone levels has been associated with a 27% reduction in adverse clinical events in thyroid cancer patients, although this benefit has not been demonstrated in low-risk patients. Subclinical hyperthyroidism is associated with an increased risk of atrial fibrillation, ventricular hypertrophy, and increased bone turnover; therefore, the appropriate extent of thyroid hormone suppression is determined based on thyroid cancer risk, which in turn is dependent on patient staging and clinical status.

In the absence of specific contraindications, current heuristics target suppression of TSH to less than 0.1 mU/L for initial therapy for patients with stage III and IV disease as well as for all patients with persistent disease. For patients without evidence of persistent disease but at high risk of recurrence, it may be reasonable to adjust TSH suppressive therapy to achieve a TSH level of 0.1 to 0.5 mU/L for 5 to 10 years. Patients without evidence of persistent disease and at low risk of recurrence may be treated to maintain a TSH in the low normal range (0.5–2.0 mU/L).

EXTERNAL BEAM RADIATION

Adjuvant external beam radiation therapy has not been prospectively evaluated in randomized, controlled trials involving patients with thyroid cancer. Several retrospective studies have shown a decreased local recurrence rate after adjuvant external radiation therapy for high-risk disease, whereas others have shown either no benefit or an adverse effect. A single-institution retrospective study including 154 patients older than 45 years with differentiated thyroid cancer and microscopic residual cancer after surgery found that among patients older than 60 years who had extrathyroidal extension but no gross residual disease, external beam radiation therapy was associated with improved 10-year cause-specific survival (81% vs 65%). In one study of 137 patients older than 40 years with extrathyroidal tumor extension, all of whom were treated with thyroidectomy, radioactive iodine, and thyroid hormone suppression, those patients treated with adjuvant external beam radiation therapy had fewer local and regional recurrences.

At present, there are no prospective data to suggest that adjuvant external beam radiation improves locoregional control or disease-specific survival in patients who receive conventional surgery and treatment with radioactive iodine. The ATA guidelines suggest that adjuvant external beam radiation therapy be considered for patients older than 45 years who have grossly visible extrathyroidal extension (T4 disease) and a high likelihood of residual microscopic disease, as well as for patients with gross residual disease that cannot effectively be addressed with further surgery or radioactive iodine treatment. In addition, external beam radiation therapy has an important role in the management of painful bone metastases as well as other unresectable metastatic disease likely to result in fracture, compressive, or neurologic symptoms.

CHEMOTHERAPY

There are no data to support a role for adjuvant chemotherapy in patients with differentiated thyroid cancer. Chemotherapy may be useful in the management of patients...
with progressive, advanced disease that is nonradioactive iodine avid and cannot be addressed through surgery or external beam radiation.

Studies of cytotoxic systemic chemotherapy for advanced thyroid cancer have historically been limited and generally disappointing, with typical response rates of 25% or less. Early reports of partial responses to doxorubicin led to FDA approval for treatment of metastatic thyroid cancer, but durable responses are not common. Results from studies using combination cytotoxic chemotherapy have demonstrated increased toxicity without improved response rates.

Current understanding of cancer biology has led to interest in small molecule chemotherapy agents that target activating mutations of \textit{BRAF}, \textit{RAS}, and translocations producing \textit{RET/PTC} oncogenes, all of which lead to activation of the MAPK pathway. Other treatments are directed at inhibition of proangiogenic growth factor receptors, in particular vascular endothelial growth factor receptor (VEGFR). Numerous recent and ongoing clinical trials have been performed to evaluate these and other novel therapies (for a recent review see Sherman). Overall, partial responses have been infrequent and complete responses not seen in recent monotherapy trials. To date, no novel agent has been shown to prolong survival in patients with advanced thyroid cancer.

Selected patients with advanced, progressive, metastatic thyroid cancer who are appropriate candidates for chemotherapy but unable to participate in a clinical trial may be treated with sorafenib, an oral tyrosine kinase inhibitor targeting VEGFR, \textit{RET}, and \textit{BRAF}. Sorafenib has been approved by the FDA as treatment for advanced renal cell carcinoma and unresectable hepatocellular carcinoma, and is therefore available for off-label use in patients with metastatic thyroid carcinoma. In phase 2 clinical trials, partial responses were seen in 15% to 23% of metastatic thyroid cancer patients treated with sorafenib. In up to 56% of patients, stable disease was observed for at least 6 months. Common toxicities with sorafenib include hand-foot rash, oral mucositis, fatigue, diarrhea, and hypertension. Sorafenib has also been associated with the uncommon development of skin cancers, including squamous cell carcinoma and keratoacanthoma.

**MONITORING**

Detection of persistent or recurrent well-differentiated thyroid cancer relies on monitoring protocols that incorporate a range of testing modalities including measurement of serum thyroglobulin, functional imaging, anatomic imaging, and direct sampling of suspected sites of involvement. Approaches adopted in clinical practice may vary based on a range of factors including the stage of disease at the time of initial treatment, the availability of different imaging and sampling technologies, and the level of institutional experience with the management of advanced cases.

**Thyroglobulin**

Measurement of serum thyroglobulin levels in both suppressed and stimulated states has emerged as a principal modality used to track patients with well-differentiated thyroid cancer. Thyroglobulin is a 660-kDa storage protein that is directly involved in the synthesis and storage of thyroid hormone in normally functioning thyroid tissue. Thyroglobulin may be secreted in detectable levels by remnant normal thyroid tissue that persists after thyroid surgery, or by foci of well-differentiated thyroid cancer that persists after treatment with radioactive iodine. Secretion of thyroglobulin is known to vary in direct relation to changes in TSH levels.
Given the high likelihood that remnants of normal thyroid tissue will be present after initial thyroid surgery, thyroglobulin levels are usually not held to be meaningfully interpretable until an interval of up to 6 months after completion of radioactive iodine treatment. Although measurement in the immediate postoperative period may not provide a reliable index for long-term comparison, it has been shown that thyroglobulin levels that are greater than 2.3 ng/mL 3 weeks after total thyroidectomy are correlated with the presence of cervical lymph node or distant metastases.97

Static thyroglobulin levels checked while patients are maintained on doses of levothyroxine targeted to suppress TSH levels have proven to be a sensitive index of recurrent disease. A thyroglobulin level that is less than 1.0 ng/mL 2 years after thyroid surgery is associated with a low 5-year risk of recurrence.98 By the same token, a previously undetectable or low thyroglobulin level that becomes detectable or demonstrates a relative increase in the setting of adequate TSH suppression usually signifies recurrence.

Accurate measurement of serum thyroglobulin levels may be confounded by the presence of circulating antithyroglobulin antibodies. These antibodies, which are often measured as markers of underlying thyroid autoimmunity, have been shown to be more prevalent in the setting of well-differentiated thyroid cancer. The antibodies may be detected in up to 25% of patients diagnosed with papillary or follicular thyroid cancer in comparison with 10% of general population controls.99 When appreciable titers of antithyroglobulin antibodies are present, a fraction may form complexes with circulating thyroglobulin, precluding accurate measurement of free levels.100 In relative terms, the accuracy of measurement in the presence of antithyroglobulin antibodies may vary depending on the method used to perform the assays. When elevated titers of antithyroglobulin antibodies are present in serum, agglutination assays may not be able to reliably measure thyroglobulin levels less than 10 ng/mL that are readily detected with chemiluminescent assays.101 Discordance has also been noted between thyroglobulin levels measured by radioimmunoassay and immunometric assay in antithyroglobulin antibody-positive sera.99 The degree of discordance noted between these 2 methods has been shown to correlate with the concentration of antibodies present in tested samples. Radioimmunoassays that have been purposefully constructed with a high-affinity first antibody and a species-specific second antibody may be less prone to interference.99

When elevated antithyroglobulin antibody titers have been detected during the course of monitoring, their longevity and variance may serve as a secondary marker of persistent or recurrent disease. A study involving the serial measurement of antithyroglobulin antibodies in patients with undetectable thyroglobulin levels measured by immunometric assay showed that 49% of patients with detectable antibodies (vs 3.4% of patients without antibodies) had evidence of recurrent disease demonstrated through combinations of anatomic imaging, functional imaging, and surgical exploration.102 After treatment of accessible disease, 71% of patients with initially detectable antibodies demonstrated an appreciable decline in titers.

Measurement of thyroglobulin mRNA has been proposed as an alternative method of detecting persistent or recurrent well-differentiated thyroid cancer that may circumvent discrepancies related to the presence of antithyroglobulin antibodies.103,104 A study evaluating reverse transcription-polymerase chain reaction (RT-PCR) measurement of circulating thyroglobulin mRNA in patients with varying degrees of recurrence based on radioactive iodine scanning showed that there were higher rates of positive threshold mRNA levels detectable in cases of more advanced disease.105 When positive threshold mRNA levels were compared with simultaneously measured thyroglobulin levels, they demonstrated greater sensitivity
and equivalent specificity for detection of recurrent disease. Proportionate increases were noted when mRNA levels measured on suppressive doses of levothyroxine were compared with levels measured after TSH stimulation. A study that used RT-PCR to measure circulating thyroglobulin mRNA in patients with treated thyroid cancer over a 12-month period demonstrated a higher degree of correlation with the detection of recurrent disease on radioactive iodine scanning when compared with suppressed thyroglobulin levels.\textsuperscript{106} No interference from antithyroglobulin antibodies was noted in the measurement of serial mRNA levels. Despite its seeming promise, use of thyroglobulin mRNA measurement in clinical practice has been precluded by its current expense and by the low specificity of methods tested to date. An efficacy study that used a similar approach to evaluate patients determined to be disease free after a mean interval of 9.5 years of follow-up showed a high false-positive rate, with detection of high-threshold thyroglobulin mRNA levels in 76% of disease-free patients.\textsuperscript{103} Technical factors related to the nonspecific expression and illegitimate transcription of thyroglobulin mRNA have been cited as potential explanations for this low specificity rate.\textsuperscript{107}

**Monitoring Protocols**

Current approaches to monitoring that involve combinations of different imaging and sampling modalities can be loosely stratified based on:

1. Estimated risk of recurrence extrapolated from the stage of disease at the time of initial treatment
2. Use of radioactive iodine treatment after thyroid surgery
3. Degree of correlation between functional imaging results and suppressed and stimulated thyroglobulin measurements.

**Low-Risk Patients Not Treated with Radioactive Iodine**

Analysis of data collected in tracking thyroid cancer patients treated at the Mayo Clinic over the course of decades has shown that radioactive iodine treatment may be deferred in patients determined to be at low risk for recurrence, without any significant adverse effects.\textsuperscript{108} Those patients determined to have MACIS scores (distant Metastasis, patient Age, Completeness of resection, local Invasion, tumor Size) less than 6 (MACIS score = 3.1 (if aged 39 years) or 0.08 × age (if aged 40 years) + 0.3 × tumor size in cm + 1 (if not completely resected) + 1 (if locally invasive) + 3 (if distant metastases)) on the day of their initial surgery who elected to defer subsequent treatment with radioactive iodine were eventually shown to have a 30-year cause-specific mortality rate of 1% with a 15% cumulative rate of recurrence at any site. This finding, which came under great scrutiny in light of the prior long-standing practice of treating all thyroid cancer patients with radioactive iodine, has had a bearing on the modification of published guidelines related to the management of well-differentiated thyroid cancer. Current ATA guideline recommendations stipulate that the beneficial effects of radioactive iodine may be limited to patients who present with tumors greater than 1.5 cm in maximal diameter or have evidence of residual disease after their initial surgery.\textsuperscript{1} At present, it is unclear as to what extent this shift in outlook has had on the impact on the practice of clinicians who oversee the treatment of low-risk thyroid cancer patients.

In cases where a decision has been made to defer treatment with radioactive iodine after thyroid surgery, monitoring for possible persistent or recurrent disease necessarily relies on anatomic imaging with ultrasonography. Dedicated cervical ultrasonography has proven to be a sensitive and reproducible mode of imaging that allows for
clear visualization of the thyroid bed, paratracheal regions, and lymph node chains, which are the most common sites of local recurrence. Findings noted on ultrasonography can be localized within surgically defined anatomic regions within the neck (Levels I–VI) to allow for precise tracking of changes in appearance or dimension of any suspicious or indeterminate lymph nodes. The accuracy of reported findings may vary to a significant extent in relation to institutional experience and operator expertise in recognizing and characterizing suspicious masses or lymph nodes.

To date, there does not seem to be any consensus regarding the utility of measuring suppressed and stimulated thyroglobulin levels in low-risk patients who have not undergone treatment with radioactive iodine. While it might be anticipated that an undetectable thyroglobulin level would indicate a better prognosis in this situation, it is unclear whether the significance of detectable or increasing levels can be determined in patients who are likely to have varying residual amounts of remnant thyroid tissue after thyroid surgery.

**Low-risk Patients Treated with Radioactive Iodine**

Stimulated whole body radioactive iodine scanning with measurement of a concomitant serum thyroglobulin level is the traditional modality used to monitor the status of patients treated with radioactive iodine after thyroid surgery. Negative whole body scans checked at an appropriate interval after initial treatment are used to demonstrate clearance of remnant thyroid tissue that clarifies interpretation of suppressed and stimulated thyroglobulin levels. Positive whole body scans can be used to localize sites of persistent or recurrent disease to:

1. Determine the need for possible further radioactive iodine treatment
2. Guide further imaging and sampling to confirm suspected sites of metastatic spread.

When stimulated whole body scanning is performed in the setting of possible further administration of therapeutic doses of radioactive iodine, the use of I-123 as a tracer in place of I-131 may offer the benefit of minimizing stunning of tissue that may limit the efficacy of treatment.

**Whole body scanning**

The utility of ongoing monitoring with stimulated whole body scanning in low-risk patients has been questioned with the emergence and refinement of alternative approaches that may increase the detection sensitivity of recurrent disease. A study that compared whole body scanning to measurement of stimulated thyroglobulin levels obtained at 6 to 12 months after treatment with radioactive iodine showed that an undetectable thyroglobulin level during this interval was highly predictive of disease-free status. Stimulated thyroglobulin levels measured after radioactive iodine treatment have been shown to be more predictive of persistent or recurrent disease than levels measured immediately after surgery. The relative magnitude of any change in thyroglobulin levels noted after stimulation may reflect the level of differentiation of responsive tissue. Normal thyroid tissue and well-differentiated thyroid cancer usually demonstrate greater than 10-fold increase in thyroglobulin levels in response to stimulation, whereas less differentiated thyroid cancer is usually marked by a less than 3-fold increase after exposure to elevated TSH levels.

**Recombinant human TSH**

rhTSH administered in a sequence of intramuscular injections has been shown to provide an adequate level of stimulation for the acquisition of whole body scans
used to monitor the status of low- to moderate-risk patients.\textsuperscript{115,119} Use of rhTSH allows patients treated with replacement or suppressive doses of levothyroxine to avoid the unpleasant effects of hypothyroidism precipitated by gradual withdrawal of thyroid hormone to boost levels of TSH secreted by the pituitary gland. Whole body scans acquired after rhTSH stimulation followed by I-123 have been shown to be comparable to those acquired after administration of tracer doses of I-131.\textsuperscript{120}

Studies evaluating low-risk patients have shown that serum thyroglobulin levels measured after administration of rhTSH may be a more sensitive index of persistent or recurrent disease than whole body scanning.\textsuperscript{121,122} One of the larger mixed modality studies evaluating this approach showed that a threshold rhTSH-stimulated thyroglobulin level greater than 1 ng/mL detected active disease in 85\% of cases, whereas whole body scanning was only able to detect active disease in 21\% of cases.\textsuperscript{123} The sensitivity of detection was further enhanced to a level of 96\% when high-resolution ultrasonography was combined with rhTSH-stimulated thyroglobulin measurement. Thresholds of positivity demarcated in guidelines for the management of well-differentiated thyroid cancer tend to be slightly more conservative.\textsuperscript{124} Current ATA guidelines stipulate that rhTSH-stimulated thyroglobulin levels less than 2 ng/mL should be considered to be less significant. Low-risk patients with levels in this range may benefit from continued monitoring with neck ultrasonography and measurement of suppressed thyroglobulin levels. Levels that range between 2 and 5 ng/mL are considered to be significant enough to warrant continued monitoring with neck ultrasonography and repeated measurement of rhTSH-stimulated thyroglobulin levels to track trends.\textsuperscript{115} Levels that rise to greater than 5 ng/mL after rhTSH stimulation are considered to be significant enough to prompt further evaluation with functional or anatomic imaging to search for sites of local recurrence or distant metastasis.\textsuperscript{125,126}

**High-risk Patients**

As most patients determined to be at high risk for persistent or recurrent disease at the time of initial surgery proceed to radioactive iodine treatment, assessments of response usually focus on stimulated whole body scanning and serum thyroglobulin measurement at intervals of 6 to 12 months after administration of therapeutic doses of radioactive iodine. Standard protocols based on withdrawal of thyroid hormone to promote increased secretion of TSH are usually employed as preparatory methods of stimulation. Administration of rhTSH may be considered in cases where comorbidities might be complicated by extended periods of hypothyroidism, but this approach has not been validated as an equivalent method of preparing high-risk patients for whole body scanning. To be effective, thyroid hormone withdrawal protocols aim to boost TSH to levels beyond 30 mU/L immediately before the administration of tracer doses of radioactive iodine.\textsuperscript{39} Trials have shown that withdrawal involving direct cessation of levothyroxine is comparable to more traditional approaches that involve a brief period of transition to liothyronine before complete withdrawal of thyroid hormone.\textsuperscript{40,127} Although most providers have adopted the practice of extending thyroid hormone withdrawal over periods of 3 to 6 weeks, at least one study has shown that the degree of TSH elevation reached after 1 week of thyroid hormone withdrawal is comparable with the degree reached after 3 weeks, with similar responses noted in patients withdrawn immediately after surgery and patients transitioning from suppressive doses of levothyroxine.\textsuperscript{128}

Withdrawal-stimulated thyroglobulin levels measured before initial treatment with radioactive iodine have been shown to have low predictive values.\textsuperscript{129} Levels measured at appropriate intervals after prior radioactive treatment are more likely to reflect the
presence and extent of persistent or recurrent disease. Current ATA guidelines stipulate that withdrawal-stimulated thyroglobulin levels greater than 10 ng/mL after rhTSH stimulation should be considered significant enough to prompt further evaluation with functional or anatomic imaging to search for sites of local recurrence or distant metastasis.

Scan-negative/Thyroglobulin-positive Cases

The increasing sensitivity of refined thyroglobulin assays has led to the identification of many cases where patients who have negative whole body scans after radioactive iodine treatment that appear to be consistent with disease-free states also have detectable thyroglobulin levels that signal the presence of persistent or recurrent disease. This finding, which may be noted in up to 20% of all cases of well-differentiated thyroid cancer, suggests that the thyroid cancer cells that are present have dedifferentiated to a state whereby they have lost the ability to take up and concentrate radioactive iodine but retain the ability to produce thyroglobulin in response to TSH stimulation. Detection of persistent or recurrent disease that may be amenable to further treatment in scan-negative/thyroglobulin-positive cases usually relies on a combination of anatomic imaging and direct sampling. Dedicated ultrasonography performed by experienced operators has proven to be the most reliable modality for the identification of suspicious cervical lymphadenopathy. When ultrasonography has successfully identified an accessible mass or suspicious lymph node, fine-needle aspiration biopsy may be employed to obtain samples for cytopathologic analysis. Samples aspirated from small or cystic lymph nodes often prove to be nondiagnostic due to a lack of sampling of distinct thyroid carcinoma cells. Detection of elevated thyroglobulin levels in aspirate washouts may be useful in identifying metastatic thyroid carcinoma in situations where fine-needle aspiration biopsy samples have been classified as negative or nondiagnostic. A study evaluating aspirate washout samples taken from 168 ultrasonographically detected lymph nodes showed that when standardized preparations diluted in 1 mL normal saline (or undiluted cystic fluid) were assayed for thyroglobulin, a cutoff level of 10 ng/mL had a positive predictive value of 93% for the detection of metastatic well-differentiated thyroid cancer.

When cervical ultrasonography fails to detect any suspicious masses or lymphadenopathy, and thyroglobulin levels increase to markedly elevated ranges that appear to be consistent with a larger burden of persistent or recurrent disease, it may be prudent to focus on imaging of the lung fields to check for evidence of pulmonary metastases. In this circumstance, chest computed tomography (CT) scans have proven to be more sensitive than standard plain film chest radiographs for the detection micronodules representing pulmonary metastases. Interpreting radiologists should be aware of the fact that the presence of micronodules does not always signify active disease. Fibrotic changes that assume the same shape may persist after successful eradication of functional pulmonary metastases with radioactive iodine treatment. Decisions regarding the use of iodinated intravenous contrast in performing chest CT scans should be based on the anticipated likelihood of possible empirical treatment with radioactive iodine. When iodinated intravenous contrast has been used to enhance imaging, it may be necessary to confirm adequate clearance of iodine before proceeding with empirical radioactive iodine treatment. Measurement of spot urine iodine with a threshold level of less than 200 μg/L may help to determine whether there has been adequate clearance of iodine after contrast administration.

Metastatic thyroid cancer that has dedifferentiated to the point of losing iodine avidity may demonstrate avid uptake of 18F-fluorodeoxyglucose (FDG). Studies evaluating FDG-PET scanning in scan-negative/thyroglobulin-positive cases have
shown that static imaging has a positive predictive value of 92% to 100% and a negative predictive value of 27% to 93% for the detection of persistent or recurrent disease.\textsuperscript{131,137,138} False-negative results have been shown to be more common in patients presenting with minimal cervical lymphadenopathy. Positive detection of disease that has a direct impact on plans for management has been shown to be more common in patients presenting with stage IV disease with suppressed thyroglobulin levels of greater than 10 ng/mL. The generalizability of these studies may be limited because they were not blinded and reference standards were inadequately defined for positive findings.\textsuperscript{136} A small study that compared static FDG-PET scanning to rhTSH-stimulated FDG-PET scanning in 7 patients suggested that stimulation may augment the sensitivity of detecting disease.\textsuperscript{139} A larger series that compared preparation modalities in 63 patients showed that while administration of rhTSH increased the total number of foci identified in patients with positive findings, it did not significantly change the overall number of patients with positive findings, and had little to no impact on plans for management in cases where additional foci were identified.\textsuperscript{140}

\textbf{POSTSURGICAL HYPOPARATHYROIDISM}

While transient mild hypocalcemia is commonly noted to develop immediately after surgical resection for thyroid cancer, severe hypocalcemia that persists over the course of days to weeks should raise suspicion that devitalization or inadvertent removal of tissue may have led to postsurgical hypoparathyroidism. Low intact parathyroid hormone (PTH) levels checked 1 hour after surgery may predict the development of postoperative hypocalcemia requiring treatment.\textsuperscript{141} Confirmation of a suspected diagnosis of postoperative hypoparathyroidism relies on detection of low or inappropriately normal PTH levels in tandem with low serum or ionized calcium levels.

Standard treatment of postsurgical hypoparathyroidism involves the administration of calcium carbonate or calcium citrate supplements in combination with vitamin D analogues that act to promote effective absorption.\textsuperscript{142} Calcitriol (Rocaltral), a synthetic form of 1,25-dihydroxyvitamin D\textsubscript{3}, is the most commonly prescribed analogue currently in use in treatment of this disorder. Calcitriol is of high potency and demonstrates a relatively short half-life that reduces the likelihood of sustained vitamin D toxicity. Its principal disadvantages stem from its expense and that it usually has to be administered twice daily to provide effective absorption of dietary and supplemental calcium. Ergocalciferol is an inexpensive synthetic form of vitamin D\textsubscript{2} that demonstrates a markedly lower level of affinity for the vitamin D receptor. Ergocalciferol can be administered once daily in high doses to treat postsurgical hypoparathyroidism, and may serve as an acceptable alternative in cases where extreme sensitivity to the effects of calcitriol limits its use. Doses of vitamin D analogues and calcium supplements are adjusted over time to target serum or ionized calcium levels that are at or just below the lower limits of reference ranges. In some patients, adequate relief of pertainal numbness and digital paresthesias may require treatment with doses that maintain slightly higher serum calcium levels. Loss of PTH-mediated regulation of renal calcium absorption and excretion is known to be associated with an increased risk of progressive renal dysfunction. Twenty-four–hour urine samples can be collected and tracked to guide adjustment of doses of vitamin D analogues and calcium supplements targeted to minimize urine calcium excretion.

Teriparatide (Forteo), a recombinant form of the 1-34 sequence of human PTH used to treat refractory osteoporosis, has been evaluated as a potential hormonal agent for
use in the treatment of postsurgical hypoparathyroidism. An early trial that studied use of teriparatide showed that daily subcutaneous injections effectively maintained serum calcium levels within normal ranges while reducing urine calcium excretion.\textsuperscript{143} The effect was noted to diminish after 12 hours, leading to periods of symptomatic hypocalcemia. Trials that studied twice daily subcutaneous injections showed that more frequent administration allowed for use of lower total daily doses with maintenance of higher average serum calcium levels.\textsuperscript{144,145} Despite its seeming promise, teriparatide has not been adopted for general use in the treatment of postsurgical hypoparathyroidism, principally due to questions and concerns about its efficacy, expense, side effect profile, and potential impact on bone turnover with long-term administration.

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