

CLINICAL REVIEW

Well-Differentiated Thyroid Carcinoma: A Review of the Available Follow-Up Modalities

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ABSTRACT

Well-differentiated thyroid carcinoma (WDTC) is among the most curable of thyroid cancers. There is, however, a risk of local and regional recurrence that must be regularly monitored for, by using a variety of follow-up modalities. The purpose of this article is to briefly review the diagnosis, staging, prognosis, and treatment of WDTC, in addition to discussing the various available follow-up modalities such as: measurement of serum thyroglobulin (Tg) by either thyroid hormone withdrawal or recombinant human thyrotropin (rhTSH) stimulation; ^{131}I whole body scanning (WBS); ultrasound (US) examination; additional diagnostic procedures including chest X-ray (CXR), non-contrast Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), Tc-99m bone scans; and reverse transcriptase polymerase chain reaction (rt-PCR). Through detailed discussion of the available follow-up methods, we conclude that conservative therapy (lobectomy plus isthmectomy) requires clinical examination, neck ultrasound, in addition to other imaging studies such as CT or MRI for follow-up; while total or near-total thyroidectomy with post-surgical ablation is best monitored using periodic measurement of Tg levels (in patients with no anti-Tg antibodies) by thyroid hormone withdrawal or rhTSH. For patients positive for anti-Tg antibodies, a new diagnostic tool – rt-PCR – may be warranted.

INTRODUCTION

Thyroid nodules are defined as discrete masses within the thyroid gland. Historically, the prevalence of thyroid nodules within the general population was estimated to be approximately 4-8 %; however, with the advent of improved diagnostic imaging strategies such as ultrasound, that number is estimated to be closer to 50%.¹ Thyroid nodules are classified as benign or malignant, with an associated malignancy risk of 5-10%.¹ That being said, malignant thyroid tumors tend to be slow growing and indolent in nature, with a low potential for morbidity or mortality.² The Canadian Cancer Society estimates that for the year 2003 there were 2,100 (550 male, 1,550 female) newly diagnosed cases of thyroid cancer and, of these, there were 180 deaths due to thyroid cancer (60 male, 120 female).³

Malignant thyroid tumors are classified as well-differentiated thyroid carcinoma (WDTC), undifferentiated carcinoma, medullary carcinoma, thyroid lymphoma, or metastases. The content of this article focuses primarily on follow-up of WDTC, which comprises more than 80% of thyroid carcinomas⁴ and includes both papillary and follicular carcinoma

subtypes. The histological variants of papillary thyroid carcinoma include encapsulated, follicular, tall cell, columnar cell, clear cell, hurthle cell, and diffuse sclerosing carcinomas; those of follicular thyroid carcinoma include minimally invasive, widely invasive, and hurthle cell carcinoma.

Thyroid cancers are two to four times more frequent in women than in men, and are rare in the pediatric population (< 16 years old). The risk of malignancy increases with a history of irradiation to the neck; extremes of age (<20 & >60 years old); excess iodine intake (papillary carcinoma); positive family history; conditions such as Multiple Endocrine Neoplasia (MEN 2), Pendred syndrome (autosomal recessive syndrome characterized by sensorineural hearing loss and thyroid goiter), Gardner's syndrome (familial adenomatous polyposis), and Cowden syndrome (multiple hamartomas); in addition to certain environmental exposures such as hexachlorobenzene and volcanic lava.^{1,4} Prognosis is based on the size, type and histology of the tumor; patient age; presence of metastases; extent of the tumor; and patient gender (males have a worse prognosis).⁵

Table 1a. TNM Staging of Thyroid Carcinomas⁷

	0	1	2	3	4
Tumor (T)		<2cm (limited to thyroid)	2-4cm (limited to thyroid)	>4cm (limited to thyroid)	T4a: Any size, with extension beyond capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or RLN T4b: Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
Nodes (N)	No regional lymph node metastasis	N1a: metastases to level IV N1b: metastases to unilateral, bilateral, contralateral cervical or superior mediastinal lymph nodes			
Metastases (M)	No distant metastases	Distant metastases			

RLN, recurrent laryngeal nerve; level IV, pre-tracheal, para-tracheal, and pre-laryngeal/delphian lymph nodes

Table 1b. Staging of WDTC^{4,7}

Stage	<45 years	>45 years
I	Any T, Any N, M0	T1, N0, M0
II	Any T, Any N, M1	T2, N0, M0
III		T3, N0, M0
IVA		T1-3, N1a, M0 IVC T4a, Any N, M0
IVB		T1-3, N1b, M0 T4b, Any N, M0
IVC		Any T, Any N, M1 Any T, Any N, M1

DIAGNOSIS

Diagnosis of WDTC typically involves palpation of a nodule, visualization by ultrasound, and a fine needle aspiration biopsy. Ultrasound examination aids in assessment of size, location, and characterization of the nodule (cystic, solid, or mixed), and identifies features associated with malignancy such as microcalcifications; irregular or microlobulated borders; vascularity; and finally, presence of marked hypoechoogenicity of the thyroid.^{1,6} Fine needle aspiration (FNA) provides rapid cytological diagnosis, and may be performed blindly by manual palpation, or under direct vision via ultrasound guidance. It should be noted that follicular carcinoma and follicular adenoma are difficult to distinguish using FNA alone, as the sample is unable to demonstrate the invasion of vasculature, lymphatics, or capsule seen with follicular carcinoma in an *en bloc* resection.⁷ Nuclear medicine modalities that use radioactive iodine isotopes (¹³¹I) are useful in the diagnosis of thyroid nodules when TSH is suppressed, and may uncover a hot nodule(s) (a nodule with increased radio-nuclear tracer uptake), which

indicates a decreased likelihood of malignancy in that nodule. In contrast to hot nodules, 14-22% of cold nodules are found to be malignant.¹ Finally, the use of second line modalities such as non-contrast CT scanning are useful in determining tumor extent, the presence of any lymph nodes, or invasion and/or compression of local structures. Early recognition and diagnosis of thyroid cancer is important, as a delay in treatment longer than a year significantly increases mortality rates.⁸

STAGING

While there are many staging systems available for thyroid carcinoma, such as the AMES criteria (age, metastases, extent of primary cancer, size of tumor); the AGES criteria (age, grade of tumor, extent of tumor, size of tumor); and the MACIS (metastases, age, completeness of resection, invasion, size) systems, the TNM system is widely used for WDTC (Table 1).⁷ The National Thyroid Cancer Treatment Cooperative Study Registry composed a staging system that was based on age at diagnosis, tumor histology, size, multiple intra-thyroid foci, extra-glandular invasion, metastases, and tumor differentiation; five-year survival rates are presented in Table 2.⁴ On the basis of these staging systems patients are classified as either high risk or low risk. High-risk patients include some or all of the following characteristics; age under 16 or over 45 years; patients with certain histological subtypes (papillary histological subtypes: tall-cell, columnar-cell, diffuse sclerosing variants; and follicular subtypes: widely invasive, poorly differentiated, hurthle-cell); large tumor size; extra-capsular extension; lymph node metastases.⁴ As with all cancers, staging plays an important role when deciding on therapy.

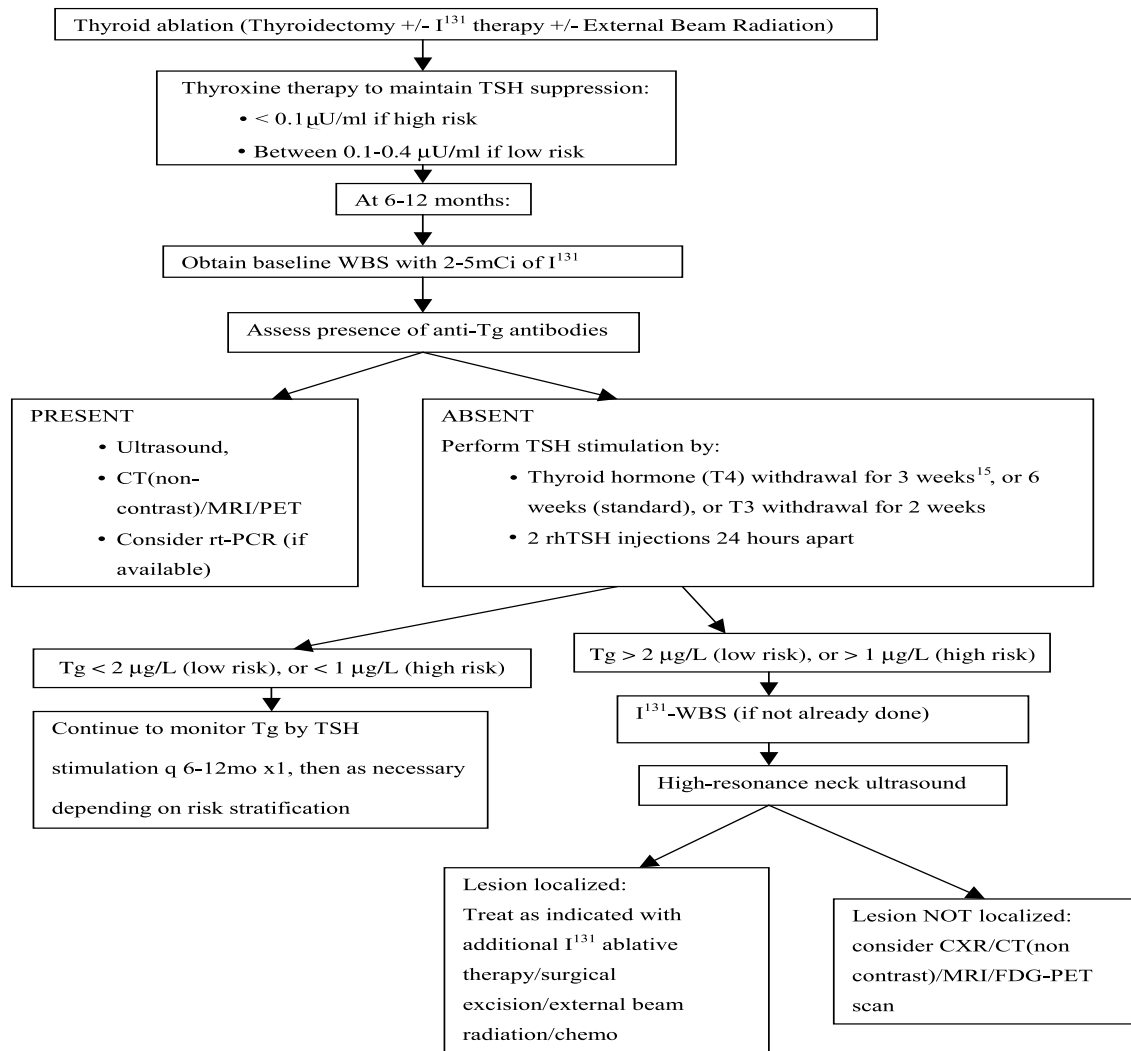


Figure 1. Approach for the Follow-Up of Well-Differentiated Thyroid Carcinoma

TSH, thyrotropin; mo, months; Tg, thyroglobulin; WBS, whole body scan; CT, computed tomography; MRI, magnetic resonance imaging; FDG, fluorine-18 fluorodeoxyglucose; PET, positron emission tomography; rt-PCR, reverse transcriptase polymerase chain reaction; T4, thyroxine; T3, triiodothyronine; rhTSH, recombinant human thyrotropin; CXR, chest x-ray.

Table 2. Five-year Survival Rates for the National Thyroid Cancer Treatment Cooperative Study Registry ⁷

Stage	5-year survival rate (%)	Disease-free survival rate (%)
I	99.8	94.3
II	100	93.1
III	91.9	77.8
IV	48.9	24.6

TREATMENT

Thyroid cancer treatment generally consists of total, or near-total thyroidectomy either alone, or in combination with ablative radioactive iodine (I^{131}), external radiation therapy (for high risk patients), and post-operative suppression of thyrotropin (TSH) with concomitant synthetic thy-

roid hormone supplementation. The decision to undertake total, near-total thyroidectomy, or lobectomy is a highly contentious issue in the arena of thyroid cancer management because the decision is often based upon the staging and extent of the tumor.^{4,5} The extent of surgical procedure must also be weighed against potential post-operative complications such as hypoparathyroidism and damage to the recurrent laryngeal nerve(s). Similarly, low-risk patients considering post-operative radioactive iodine (I^{131}) ablative therapy must consider possible side effects of large doses of I^{131} . Ablative doses are usually between 30-100mCi; however, high doses >200mCi are sometimes warranted for severe disease, and are associated with mild radiation sickness (headache, nausea, vomiting), radiation thyroiditis, radiation sialadenitis, in addition to tongue symptoms such as dry or

burning tongue, bone marrow suppression, pulmonary fibrosis, and the potential for gonadal damage and infertility.⁹ In general, very-low risk patients undergo limited surgery, low risk patients undergo surgery followed by radioactive ablation therapy, and high risk patients (patients with residual micro/macrosopic disease, elderly patients with large tumors, extra-thyroidal extension) are treated similarly to moderate risk patients with consideration of external beam radiation therapy, which decreases the rate of loco-regional recurrence.¹⁰ The most common side effects of external beam radiation are esophagitis, tracheitis, neck fibrosis, and radiation-induced spinal cord necrosis. Patients who undergo near-total or total thyroidectomy, with or without ablative radioactive iodine therapy, are subsequently started on a dosage of thyroid hormone supplements sufficient to maintain TSH suppression $< 0.1\mu\text{gU/ml}$ (high risk patients), or $0.1\text{-}0.4\mu\text{gU/ml}$ (low risk patients).⁴ The effective dose in adults is generally between $2.2\text{-}2.8\mu\text{g/kg}$, a dose that prevents symptoms of hypothyroidism while minimizing adverse cardiac or osteoporotic effects.⁴ Finally, for patients with advanced disease that are not surgical candidates or are non-responsive to other therapies, chemotherapy can be used with the understanding that it is of limited therapeutic benefit, with few studies supporting its use.

FOLLOW-UP

While WDTC is among the most curable of thyroid cancers, it does carry a risk of local or regional recurrence that approaches 10-20 percent.^{4,9} It is, therefore, important to periodically monitor for signs of residual or recurrent disease using a variety of follow-up modalities. Presently, the most recognized screening tools include clinical assessment; measurement of serum thyroglobulin (Tg) by either thyroid hormone withdrawal or recombinant human thyrotropin (rhTSH) stimulation; I^{131} whole body scan (WBS); and ultrasound (US) examination. These modalities, when used either individually or in combination, have similar values for sensitivity and specificity.¹¹

Serum Thyroglobulin (Tg)

Serum Tg is a glycoprotein produced by both normal and neoplastic follicular thyroid tissue. In patients who have undergone total, or near total thyroid ablation, there should be no, or minimal, evidence of Tg. As such, routine monitoring of Tg levels using serum Tg immunoassay detects the presence of persistent thyroid tissue or the recurrence of disease. In monitoring serum Tg one must also assess the presence of anti-thyroglobulin antibodies, which are found in up to 15-25% of thyroid cancer patients, and interfere with Tg immunoassay by producing falsely low or undetectable serum Tg levels.^{2,4,12,13} Any increase in serum Tg concentrations in a patient following total thyroid ablation is considered suspicious and requires further evaluation with I^{131} WBS and other imaging modalities.

Table 3. Thyroglobulin Follow-Up Modalities

Modality	Method	Benefits/Consequences
T4	6 week withdrawal	-free -↓ QOL
T4	3 week withdrawal	-free -minimal effect on QOL
T4→T3	T3x 4weeks (from T4) then 2 week withdrawal	-cost of T3 x 2weeks -↓ QOL
rhTSH	2x 0.9mg injections 24hrs apart (NO withdrawal)	-\$1500 -minimal side effects

TSH, thyrotropin; Tg, thyroglobulin; T4, thyroxine; T3, triiodothyronine; rhTSH, recombinant human thyrotropin; QOL, quality of life.

Thyrotropin Stimulation

Tg production is stimulated by the discontinuation of thyroid hormone replacement therapy, which in turn stimulates TSH and production of Tg glycoprotein. A rise in the serum level of Tg $> 2\mu\text{g/L}$ in low-risk patients, or $>1\mu\text{g/L}$ in high-risk patients (as per staging and initial Tg level), indicates the presence of recurrent/residual thyroid disease.¹³ Measurement of serum TSH-stimulated Tg is accomplished by withdrawal of thyroid hormone thyroxine (T4) therapy for six-weeks, or triiodothyronine (T3) therapy for two-weeks. The six-week hormone withdrawal regimen is associated with prolonged periods of hypothyroidism, which results in significant morbidity, impaired productivity, and reduced quality of life (QOL).¹⁴ The hypothyroid state manifests itself with signs and symptoms such as fatigue, cold intolerance, weight gain, change in appetite, muscle cramps, amenorrhea, constipation, changes in sleep patterns, and changes in appearance. Attempts at rectifying the impact on quality of life include substitution of T4 with T3 therapy for 4 weeks with a subsequent two-week T3 withdrawal period; halving the dose of thyroxine; or a series of intramuscular injections of recombinant human TSH (rhTSH) (Table 3). Golger *et al.* (2003),¹⁵ investigated the adequacy of a three-week vs. traditional six-week T4 withdrawal regimen for the detection of elevated serum Tg levels; the study illustrates that the three-week hormone withdrawal regimen provides adequate Tg stimulation for the detection of recurrent disease, with minimal impact on QOL.¹⁵

Recombinant human thyrotropin (rhTSH) represents an alternate approach to the stimulation of serum Tg and has been demonstrated to avoid the hypothyroid effects associated with T4 withdrawal.^{9,11,16,17} Two doses of 0.9mg of rhTSH are injected 24 hours apart, allowing the elevated serum TSH levels to stimulate the production of serum Tg ($> 2\mu\text{g/L}$ in low risk patients, or $>1\mu\text{g/L}$ in high risk patients), thereby, indicating the presence of any recurrent/residual thyroid disease.¹³ While patients experience no symptoms of hypothyroidism, minor side effects associated with rhTSH include mild nausea and headache.¹⁷

Studies demonstrate that the sensitivity and specificity of rhTSH vs. thyroid hormone withdrawal in the detection of residual/recurrent thyroid cancer are similar (86% sensitive, 91-100% specific).¹¹ While eliminating the negative effects of a hypothyroid state imposed by hormone withdrawal, the diagnostic use of rhTSH is associated with a significant increase in cost (\$1,500) relative to the cost of thyroid hormone withdrawal (free). The difference in cost of rhTSH and thyroid hormone withdrawal has significant implications for patients who are not covered by a health insurer.

Iodine-131 Whole Body Scan (WBS)

Iodine-131 whole body scanning (WBS) relies on thyroid tissue uptake of I¹³¹ in the presence of high serum TSH concentrations (>25 µU/mL). TSH stimulation occurs by either thyroid hormone withdrawal or by administration of rhTSH, and facilitates I¹³¹ uptake thus allowing nuclear imaging of residual/recurrent thyroid tissue. Patients are advised to avoid iodine-containing medications and foods one to two weeks prior to the study. Pregnancy, in women of childbearing age, must be ruled out prior to administration of I¹³¹. WBS is performed 72 hours following the initial dose of 2-5mCi of I¹³¹; this dose minimizes the possibility of thyroid stunning (interference with subsequent uptake of I¹³¹ for several weeks) seen with high doses of radioactive iodine. Scans are examined for the presence of any thyroid tissue uptake which is dependant on the ability of a tumor to concentrate and retain iodine, and is strongly associated with a high likelihood of persistent or recurrent thyroid carcinoma.¹³ While WBS alone has high specificity (100%) for the diagnosis of thyroid cancer, Pacini *et al.* (2003)⁶ reported sensitivities as low as 40%, Kasnar *et al.* (2003)⁶ report a false negative rate of 15%, and recent studies suggest WBS is minimally informative in patients with an undetectable serum Tg.⁶ Mazzaferri and Kloos (2001)⁸ evaluate the use of WBS in follow-up for WDTC, demonstrating that the imaging modality adds almost no diagnostic information to that provided by stimulated serum Tg; this study's results are supported by those of Cailleux *et al.* (2000),¹⁸ who also suggest avoiding the use of WBS in light of its minimal contribution to the diagnosis of recurrent disease. Both studies emphasize the value of serum Tg stimulation as a tool for diagnosing recurrent/residual thyroid cancer. For the purpose of obtaining a control study, a WBS is performed 6-12 months after thyroid ablation. Following that, studies indicate that WBS is only recommended for the localization of the Tg production site in patients presenting with a rise in Tg concentration associated with TSH stimulation.²

Ultrasound

High-resolution ultrasound of the neck is a simple follow-up procedure that provides information about the size, location, and features of small masses within the thyroid area. It also offers the advantage of obtaining FNA samples from suspicious lesions for further cytological examination. In a recent retrospective study by Pacini *et al.* (2003)⁶

rhTSH stimulation, WBS, and neck ultrasound was used to follow 340 patients who have undergone thyroidectomy and I¹³¹ ablation therapy. Results of neck ultrasound and WBS are compared (Table 4)⁶ and illustrate the following: rhTSH is highly sensitive in predicting the presence or absence of active disease; WBS has a low sensitivity; and, neck ultrasound is crucial in the detection of small local disease not detected by either Tg or WBS. In fact, when serum Tg is used in conjunction with ultrasound, the diagnostic sensitivity is increased from 85% to 96.3%.⁶

Table 4. Comparison of Diagnostic Accuracies of Different Tests in Detecting or Excluding Loco-Regional Disease⁶

	Sensitivity%	Specificity%	PPV%	NPV%
Neck US	70	97.5	77.7	92.4
I ¹³¹ WBS	40	100	100	91
Stimulated Tg	78.2	100	100	98.6

US, ultrasound; I¹³¹ WBS, iodine-131, whole body scan; Tg, thyroglobulin

Other Screening Tools

Additional diagnostic and follow-up procedures include chest X-ray (CXR), non-contrast Computed Tomography (CT) (contrast may interfere with subsequent I¹³¹ therapy), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and even bone scans; these studies are warranted when metastatic disease cannot be localized by I¹³¹ imaging, often a result of metastases that fail to concentrate I¹³¹, and an indication of a more aggressive clinical course. CXR, CT, MRI, and bone scans are relatively easy to obtain and are commonly used to localize tumors in the head and neck, chest and bones. Fluorine-18 fluorodeoxyglucose (FDG) PET scans represent a new non-iodine radionuclide-imaging tool able to detect recurrence or metastases with a high degree of sensitivity (80-90%) in patients whose bodies, for whatever reason, are unable to concentrate I¹³¹. PET uses FDG to demonstrate enhanced glucose uptake expected from cancerous cells, thereby localizing the lesion.¹⁹

A relatively new molecular diagnostic screening tool includes using Tg mRNA as a tumor marker to detect the presence of cancer by making use of reverse transcriptase polymerase chain reaction (rt-PCR) technology. rt-PCR detects Tg mRNA in patients with normal functioning thyroid tissue, non-malignant thyroid disease, and in patients with residual/recurrent thyroid disease following surgical and ablative treatment. A prospective study by Grammatopoulos *et al.* (2003)¹² examines 28 patients on TSH suppressive treatment and demonstrates that rt-PCR is a more sensitive and accurate, but less specific, diagnostic tool for the detection of Tg as compared to immunoassay in this patient population (Table 5).¹² The primary benefit of rt-PCR is its use in patients with an elevated serum Tg, and positive anti-Tg antibodies, because it is able to detect Tg mRNA in the presence of anti-Tg antibodies.

Table 5. Comparison of Tg mRNA Assay with Tg immunoassay¹²

	Tg mRNA	Tg immunoassay
Sensitivity	93%	71%
Specificity	70%	80%
Accuracy	84%	75%

Tg mRNA, thyroglobulin messenger RNA

CONCLUSION

Well-differentiated carcinomas occur infrequently in the population and can be diagnosed easily with clinical exam, ultrasound, and FNA. They are among the most curable of cancers when treated with lobectomy, thyroidectomy, and iodine ablative therapy as indicated. The risk of recurrence, however, is considerable and is greater with certain histological variants, and the aforementioned prognostic indicators. As delayed detection and treatment of primary and recurrent/residual disease has a significant effect on mortality, it is important to provide adequate follow-up for patients post-operatively to prevent missed diagnoses. The follow-up of WDTC may differ based on the initial mode of treatment. For conservative therapy (lobectomy plus isthmectomy) I¹³¹ scans and measurement of serum Tg cannot be employed as remaining healthy thyroid tissue is left *in situ* and will produce positive results in all patients. Follow-up then relies on clinical examination, neck ultrasound, in addition to other imaging studies such as CT or MRI. If, however, treatment involves total or near-total thyroidectomy with post-surgical ablation, patients with no evidence of anti-Tg antibodies can be followed using periodic TSH stimulation by thyroid hormone withdrawal or rhTSH, to monitor any rise in Tg >2 µg/L in low risk patients, or >1 µg/L in high risk patients (as per staging and initial stimulated Tg). While a relatively new diagnostic tool, rt-PCR may have an important future role in patients who test positive for anti-Tg antibodies.

In general, following thyroid ablation, patients are maintained on a thyroid hormone supplement regimen at a level that maintains TSH suppression < 0.1µgU/ml if high risk, and between 0.1-0.4 if low risk. This level not only suppresses TSH, but also prevents symptoms of hypothyroidism and minimizes any adverse cardiac and bone effects. A baseline I¹³¹ WBS is then obtained at 6-12 months following initial treatment to assess the presence of any residual thyroid uptake, and provide a control for any future scans. Following that, providing anti-Tg antibodies are negative, TSH stimulated serum Tg levels, by either thyroid hormone withdrawal or rhTSH, are measured at 6-12 month intervals depending on patient risk. Levels are then assessed one more time, after the initial 6-12 month follow-up, and then as necessary thereafter. This is considered, according to recent literature, as sufficient to detect residual/recurrent WDTC. Studies by Pacini (2003)⁶ and Cailleux (2000)¹⁸ indicate that an undetectable serum Tg, in the presence of TSH stimulation, is highly predictive of disease-free status. In conjunction with this, I¹³¹ and WBS, or ultrasound evaluation, can be employed as desired to further

increase the sensitivity of Tg monitoring. With any rise in serum Tg >2µg/L (low-risk), >1µg/L (high-risk), further evaluation is warranted and can include WBS, US, CT, MRI, or PET to localize the presence/absence of thyroid tissue. The localization of recurrent/metastatic uptake may then lead to further ablative treatments with radioactive iodine, surgical intervention, external beam radiation, or chemotherapy as required.

ACKNOWLEDGEMENTS

The authors wish to thank Bosco Lui, Sonja Reichert, and Sarah McMullen.

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