0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(1):82–87

doi: 10.1210/jc.2006-0993

Monitoring Thyroglobulin in a Sensitive Immunoassay Has Comparable Sensitivity to Recombinant Human TSH-Stimulated Thyroglobulin in Follow-Up of Thyroid Cancer Patients

Robert C. Smallridge, Shon E. Meek, Melissa A. Morgan, Geoffrey S. Gates, Thomas P. Fox, Stefan Grebe, and Vahab Fatourechi

Division of Endocrinology and Metabolism (R.C.S., S.E.M., M.A.M., G.S.G., T.P.F.), Mayo Clinic College of Medicine, Jacksonville, Florida 32224; and Department of Laboratory Medicine and Pathology (S.G.) and Division of Endocrinology (V.F.), Mayo Clinic College of Medicine, Rochester, Minnesota 55905

Context: Most thyroglobulin (Tg) assays have a sensitivity of 0.5–1 ng/ml. A minority of patients with undetectable T_4-suppressed Tg levels have a recombinant human TSH (rhTSH)-stimulated Tg above 2 ng/ml and identifiable residual disease.

Objective: The objective was to determine whether a Tg assay with improved sensitivity could eliminate the need for rhTSH stimulation when baseline Tg is below 0.1 ng/ml.

Design: A retrospective study of two academic endocrine practices was conducted.

Population: A total of 194 patients undergoing rhTSH stimulation participated in the study.

Results: Of the 80 patients with Tg below 0.1 ng/ml, two (2.5%) had rhTSH-stimulated Tg above 2 ng/ml. One other patient with stimulation to 0.3 ng/ml and negative ^{123}I scan had an ultrasound-detected malignant lymph node resected. None had $^{131}I/^{123}I$ imaging after rhTSH stimulation suggestive of local recurrence or distant metastasis. If T_4-suppressed Tg was 0.1–0.5 or 0.6–2.0 ng/ml, rhTSH Tg was above 2 ng/ml in 24.2 and 82.4%, respectively.

Conclusions: Patients with differentiated thyroid carcinoma and a T_4-suppressed serum Tg below 0.1 ng/ml rarely have a rhTSH-stimulated Tg above 2 ng/ml, and none of these patients had ^{131}I or ^{123}I imaging after rhTSH stimulation suggestive of local recurrence or distant metastasis. We recommend monitoring such patients with a T_4-suppressed Tg level and periodic neck ultrasonography. An increase in T_4-suppressed serum Tg to a detectable level or the appearance of abnormal lymph nodes by physical or ultrasound exam should prompt further investigation. **(*J Clin Endocrinol Metab* 92: 82–87, 2007)**

THYROID CARCINOMA comprises 1–2% of all malignancies, with more than 30,000 new cases in 2006 in the United States (1). Overall mortality is less than 10%, and for young patients with well-differentiated forms is less than 1% (2). However, the recurrence rate is not inconsequential at 10–20%. Because the cancer may reappear after many years, patients require prolonged follow-up.

Several diagnostic procedures enable physicians to monitor patients and detect recurrences early. Radioactive iodine scans, performed while hypothyroid or after recombinant human TSH (rhTSH), permit detection of local disease and distant metastases. Neck ultrasonography is particularly helpful in identifying locoregional soft tissue and lymph node disease, the most frequent locations for recurrence. Thyroglobulin (Tg) is established as an excellent biomarker for persistent or recurrent disease.

Although an undetectable serum Tg after thyroidectomy and ^{131}I ablation suggests that patients are free of disease, several studies have determined that a minority of patients, under the influence of TSH stimulation, have a rise in serum Tg (3–13). The source of Tg in some instances is from a thyroid bed remnant, but in others is residual cancer. These observations have resulted in recommendations that all patients periodically have a rhTSH stimulation test and that those whose Tg increases above 1–2 ng/ml have further imaging and possibly therapy.

Many patients are unlikely to have a recurrence, but the sensitivity of Tg assays is such that it has been difficult to distinguish them from individuals with persistent disease without resorting to rhTSH stimulation. The purpose of this study was to review our experience since 2001, when a more sensitive Tg assay with a functional sensitivity of 0.1 ng/ml was introduced, enabling the use of a clinical cutoff value of 0.1 ng/ml. The results suggest that patients with a Tg below 0.1 ng/ml while taking T_4 suppression do not require a TSH-stimulated Tg measurement.

First Published Online October 31, 2006

Abbreviations: CT, Computed tomography; rhTSH, recombinant human TSH; Tg, thyroglobulin; WBS, whole-body scan.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Patients and Methods

Patients

Charts were reviewed retrospectively after Mayo Clinic Institutional Review Board approval to determine which patients had biochemical responses to rhTSH. The time of study was from August 2001, when the Mayo Medical Laboratory changed to a more sensitive Tg assay, until

March 2006. Of 79 consecutive patients having rhTSH tests at Mayo Clinic Jacksonville (MCJ) after ^{131}I ablation, 47 (59%) had baseline Tg below 0.1 ng/ml, with no interfering Tg antibody, and comprised the initial test population. Of the remaining 32 patients, 13 had baseline serum Tg of 0.1–0.5 ng/ml, nine had Tg of 0.6–2 ng/ml, four had Tg above 2 ng/ml, and six had interfering Tg antibody. A second population was derived from 115 rhTSH tests performed at Mayo Clinic Rochester (MCR) (70 consecutive cases from September 2001 to April 2003, and 45 from September 2004 to June 2005). Thirty-three patients (29%) had baseline Tg below 0.1 ng/ml, 20 had baseline Tg of 0.1–0.5 ng/ml, eight had Tg of 0.6–2 ng/ml, 30 had Tg above 2 ng/ml, and 20 had positive Tg antibody. Four were excluded due to incomplete laboratory results.

Initial therapy

The MCJ patients with baseline Tg below 0.1 ng/ml were 16–76 yr old (median age, 43 yr) at the time of thyroid surgery. Eight had completion thyroidectomies at a later date (six within 9 wk, one within 2 yr, and one 9 yr later). All patients received at least one ablation dose of ^{131}I, seven received two doses, and two received three or more doses. All 33 MCR patients had received ^{131}I ablation. Patients' ages at the time of their rhTSH test ranged from 22–80 yr at MCJ and 22–73 yr at MCR.

Tumor characteristics

At MCJ, twice as many patients with baseline Tg below 0.1 ng/ml had T1 tumors [26 of 47 (55%) *vs.* 9 of 33 (27%)], but the percentage with T1 + T2 tumors was similar, with 36 of 47 (77%) at MCJ *vs.* 24 of 33 (73%) at MCR. More patients at MCJ than at MCR were free of lymph node metastases [35 of 47 (74%) *vs.* 15 of 33 (45%)] (Table 1). These differences are not unexpected because at MCR, lower risk patients usually do not receive ^{131}I ablation and, hence, were less likely to have a rhTSH test. The pathology (Table 1) was predominantly papillary at both locations.

rhTSH testing

Patients received rhTSH (0.9 mg im) on d 1 and 2. ^{131}I (3.6–4.8 mCi; median, 4.1 mCi) was given orally on d 3, whereas neck uptake and body scan were performed on d 5 at MCJ. Serum TSH was measured on d 1, 3, and 5 at MCJ and d 1 and 3 at MCR, whereas Tg was measured on d 1 and 5 at MCJ and d 1 and 4 at MCR. At MCR, only three patients were scanned after ^{131}I and had serum Tg measurements on d 5. All other patients received ^{123}I and had Tg measurements on d 1 and 4 with whole-body scan (WBS) on d 4. In patients with baseline Tg below 0.1 ng/ml, at MCJ baseline TSH ranged from less than 0.1 to 9.4 mIU/liter, with TSH no greater than 0.4 in 40 patients and only one being greater than 1.7 mIU/liter. At MCR, baseline TSH ranged from less than 0.01 to 7 mIU/liter (median, <0.05), with three above 2 mIU/liter. Peak TSH levels after rhTSH ranged from 79.7 to 337.2 mIU/liter at MCJ and 81 to 257 mIU/liter at MCR.

TABLE 1. Clinical and pathological characteristics: baseline Tg < 0.1 ng/ml

	MCJ	MCR
Sex, no. (%)		
Male	13 (28)	8 (24)
Female	34 (72)	25 (76)
Age, median (range)		
Initial surgery	43 (16–76)	47 (17–72)
rhTSH study	54 (22–80)	52 (22–73)
TNM classification		
T1N0M0	19	3
T1N1M0	3	6
T1N0M1	1	0
T1N0MX	1	0
T1N1MX	1	0
T1NXM0	1	0
T2N0M0	8	8
T2N1M0	2	6
T2NXM0	0	1
T3N0M0	3	1
T3N1M0	1	1
T3N0M1	1	0
T4N0M0	1	3
T4N1M0	1	2
T4N1M1	1	0
TXN0M0	1	0
TXN1M0	0	2
TXN1M1	1	0
TXNXMX	1	0
Pathology		
Papillary	37	27
Follicular	6	4
Hürthle cell	4	2

Tg assay

In August 2001, our laboratory changed from a manual immunoradiometric Tg assay with a lowest reportable value of 0.5 ng/ml to the automated chemiluminometric Beckman Coulter Access Tg immunoassay. We had assisted Beckman in validation of this assay and are, therefore, very familiar with its performance characteristics. Method comparison with our previous assay was performed in 224 patient samples, of which 146 had Tg levels of less than 50 ng/ml in our original assay. In these 146 individuals, Demming-regression showed a slope of 0.922 (confidence interval, 0.88 to 0.97), an intercept of −0.78 (confidence interval, 0 to −1.42), and an r of 0.96. Our validation also showed that the Beckman-specified lowest reportable level of 0.1 ng/ml corresponded to the functional assay-sensitivity (coefficients of variation no greater than 20%), whereas the limit of detection, defined as at least 95% likelihood that no detectable analyte is present (calculated as zero-calibrator value plus 2 SD; multiple runs of 20 replicates each), was 0.065 ng/ml.

Since the introduction of the assay, we have run three sets of controls (low, medium, and high) at least once every 4 h during hours of testing. Controls have been sourced commercially (medium and high controls; Nichols Institute Diagnostics, San Juan Capistrano, CA) or prepared in-house from patient pools (low control). The various batches of low controls have run between 0.07 and 4.5 ng/ml, most commonly between 0.4 and 0.6 ng/ml, with typical coefficients of variation of 8% or less. To ensure lot-to-lot consistency, every new reagent lot is compared with the existing lot by Passing Bablok linear regression analysis of duplicate measurements of at least 40 patient samples that span the analytical range (0.1–500 ng/ml). Any lot with an intercept that is statistically significantly different from zero or any with a slope that exceeds ±10% is rejected. Each lot that appears acceptable is then further tested by running the existing controls at least 20 times. If the values fall into the existing ±2 SD ranges, the new lot is accepted. Although this approach maximizes assay reproducibility, there are some inevitable fluctuations in assay performance over time, and the laboratory considers all levels below 0.1 ng/ml as having uncertain reproducibility and being potentially compatible with the absence of analyte. All values below 0.1 ng/ml are therefore not precisely quantified and are reported as below 0.1 ng/ml, in line with Beckman's reporting recommendations.

Results

Serum Tg levels

At MCJ, only one of 47 (2.1%) patients with a baseline Tg below 0.1 ng/ml had a rhTSH-stimulated Tg above 2 ng/ml. In contrast, 2 of 13 (15.4%) with a baseline Tg of 0.1–0.5 and 8 of 9 (88.9%) if 0.6–2 ng/ml had a rhTSH-stimulated Tg above 2 ng/ml. Figure 1, A–C, depicts the individual Tg results after rhTSH at MCJ. Thirty-two patients (68%) with undetectable T_4-suppressed Tg had no increase after rhTSH, and an additional 12 patients had stimulated Tg levels no greater than 0.4 ng/ml. Serum Tg increased to 1.0 ng/ml in two patients (one of whom had $T_xN_1M_1$ disease 27 yr earlier) and to 3.0 ng/ml in one. To determine whether the results were generalizable across practices, a subset of patients from the endocrinology division at MCR was reviewed. Although patients had some differences in their clinical characteristics,

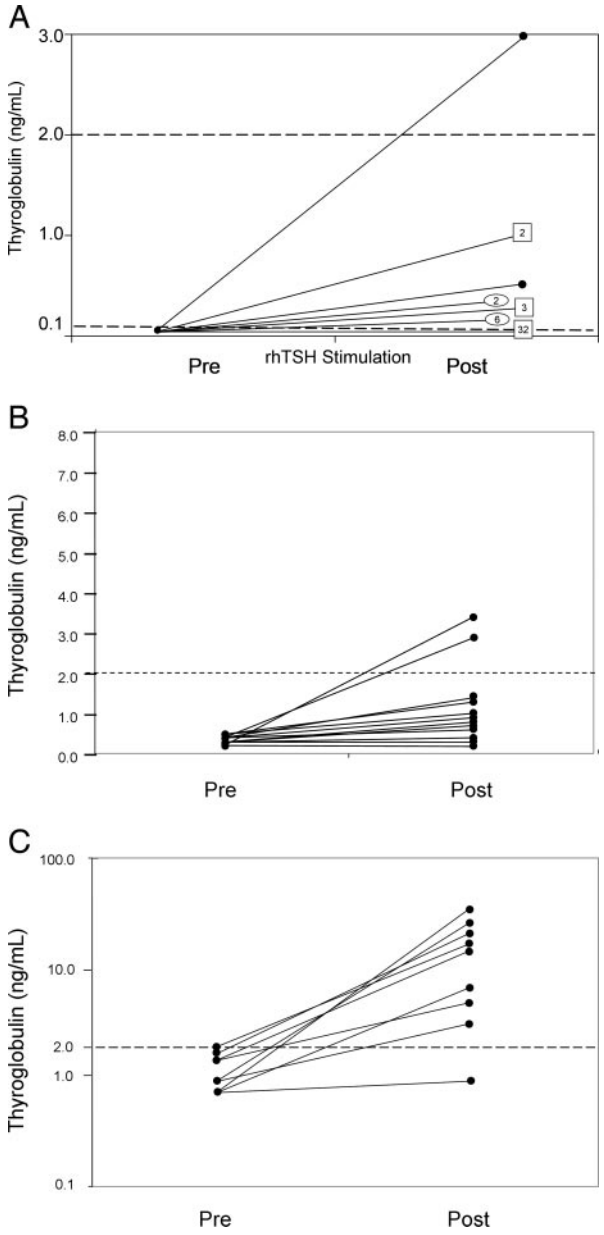

FIG. 1. Serum Tg levels before and after rhTSH stimulation in 69 patients followed at MCJ. A, Forty-seven patients with T_4-suppressed Tg below 0.1 ng/ml; numbers in *circles* and *squares* indicate number of patients. B, Thirteen patients with baseline Tg of 0.1–0.5 ng/ml. C, Nine patients with baseline Tg of 0.6–2 ng/ml (logarithmic scale).

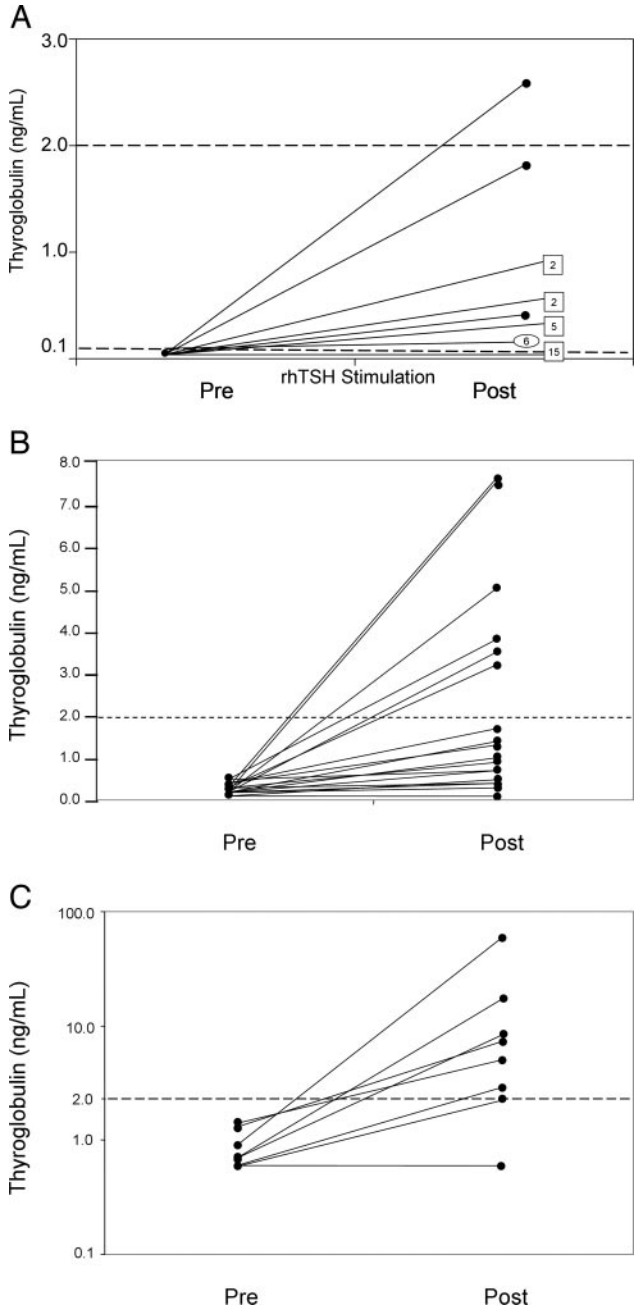

FIG. 2. Serum Tg levels before and after rhTSH stimulation in 61 patients followed at MCR. A, Thirty-three patients with T_4-suppressed Tg below 0.1 ng/ml; numbers in *circles* and *squares* indicate number of patients. B, Twenty patients with baseline Tg of 0.1–0.5 ng/ml. C, Eight patients with baseline Tg of 0.6–2 ng/ml (logarithmic scale).

the results in patients at both sites whose baseline TSH was below 0.1 ng/ml were quite similar. Figure 2A illustrates the 33 patient responses to rhTSH stimulation at MCR. In 15 (45.4%), Tg remained undetectable after rhTSH, and in 17 the levels were less than 2 ng/ml. In one individual, Tg rose to 2.5 ng/ml. At MCR, 6 of 20 (30%) of patients with baseline Tg of 0.1–0.5 and 6 of 8 (75%) with Tg of 0.6–2 ng/ml had rhTSH-stimulated Tg above 2 ng/ml (Fig. 2, B and C). When results from both sites are combined, 2.5, 24.2, and 82.4% of patients had rhTSH above 2 ng/ml when baseline Tg was below 0.1, 0.1–0.5, or 0.6–2 ng/ml, respectively (Fig. 3). To further characterize the clinical status of all 80 patients who had undetectable baseline Tg, their imaging studies were reviewed.

Thyroid scans (baseline Tg < 0.1 ng/ml)

At MCJ, neck uptake at 48 h was 0.0–0.7% in 42 patients and was not measured in four. One patient had a small amount of residual thyroid bed tissue and a 1.2% neck bed uptake. Forty of the 47 patients had no visible uptake on imaging, and three had no scans. Four patients had uptake

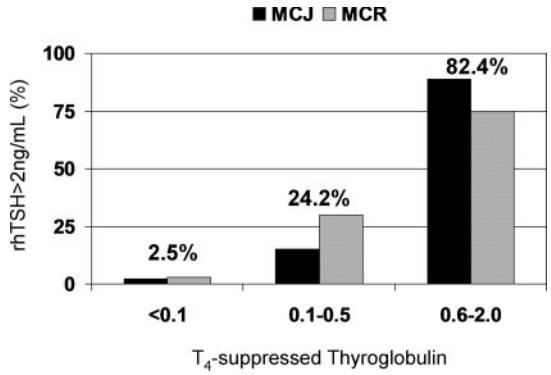

FIG. 3. rhTSH-stimulated Tg increases directly with T_4-suppressed Tg.

(0.06–0.22%) visualized in the central neck; of these four, three had received a single 29 mCi ^{131}I ablation dose, and one who had follow-up 16 months later without intervening therapy had a negative scan (and uptake decreased from 0.14 to 0.04%). At MCR, all patients had WBSs. Three had faint visible thyroid bed uptake (0.08%, 0.2%, and not reported in one). Thirteen with no visible image had uptakes of 0.01–0.2%, but none showed any foci of recurrent thyroid cancer, nor were they treated with ^{131}I.

Other imaging (baseline Tg < 0.1 ng/ml)

Neck ultrasonography (n = 39) or computed tomography (CT) scan of neck (n = 2) or chest (n = 6) was performed in 42 of 47 patients at MCJ at the time of rhTSH test and/or during follow-up of almost 4 yr; in all, there was no tissue, minimal thyroid bed tissue, and/or benign-appearing neck lymph nodes. Four of five patients without neck ultrasound or CT had negative ^{131}I WBS. Three patients each had a single tiny lung nodule on chest CT scan; all were unchanged at 10, 10, and 24 months of follow-up. At MCR, all patients had neck ultrasound and, if Tg was above 2 ng/ml, a chest CT scan; imaging studies did not show evidence of recurrent cancer.

Follow-up testing (baseline Tg < 0.1 ng/ml)

At MCJ, five patients had follow-up rhTSH tests 16 to 39 months after their initial test. Peak rhTSH-stimulated Tg levels remained within 0.1 ng/ml of the original value in three patients, increased from 0.4 to 0.6 ng/ml in one, and decreased from 3.0 to 1.7 ng/ml (39 months later) in one. Follow-up imaging tests were performed, including neck ultrasounds, chest CT scans, and chest x-rays in 26 patients. There were no lesions detected that were deemed worrisome or that were treated.

Of the 33 MCR patients with T_4-suppressed Tg below 0.1 ng/ml, one had a stimulated Tg of 2.5 ng/ml (Fig. 2A). WBS was negative, and a neck ultrasound showed an indeterminate 5-mm nodule in the thyroid bed that was unchanged 1 yr later. Another patient had a stimulated Tg of 1.4 ng/ml, with negative WBS and ultrasound. Four patients had stimulated Tg of 0.5–0.9 ng/ml. All had neck ultrasound, and three had WBS, with no evidence of recurrence. Thirteen patients had stimulated Tg of 0.1–0.4 ng/ml; one, whose Tg increased to 0.3 ng/ml after rhTSH, developed a neck node tumor recurrence 1 yr later, which was excised (at the time of surgery, her T_4-suppressed Tg was < 0.1 ng/ml). All others had negative neck ultrasounds and WBS. Two patients with rhTSH-stimulated Tg levels of 0.2 and 0.3 ng/ml had tiny indeterminate lung nodules on chest CT scan (one had sarcoidosis, the other a breast cancer history). Nodules were unchanged 20 and 25 months later.

Discussion

The development of Tg assays and rhTSH has provided the means for physicians to detect residual (or recurrent) thyroid cancer much earlier than 30 yr ago, when diagnostic tools were limited to physical examination, ^{131}I scans after T_4 withdrawal, and chest x-rays. The combined use of serum Tg and WBS after rhTSH stimulation is particularly effective in identifying small residual foci of thyroid tissue (either thyroid remnant and/or cancer). Heuristically, one would presume that earlier detection and treatment of recurrent disease would lead to better outcomes, but definitive evidence is lacking that ^{131}I therapy of microscopic disease benefits the low-risk patient whose survival approaches 100% (2).

The current study reports our experience of more than 4.5 yr using a serum Tg assay with a clinical detection limit of 0.1 ng/ml, considerably lower than the 0.5 to 1.0 ng/ml levels reported by others. Our data show that in 80 patients with T_4-suppressed Tg below 0.1 ng/ml, Tg remained undetectable in 47 (58.8%) after rhTSH; in 97.5% (78 of 80) Tg was below 2 ng/ml. The remaining two patients had Tg rise to 3.0 and 2.5 ng/ml, respectively. The first patient, a 42-yr-old woman who presented with T4N1M0 disease in 1993, has been followed for the past 7.5 yr at MCJ. Her most recent Tg after rhTSH has decreased to 1.7 ng/ml, and she remains free of detectable disease. Spontaneous decreases in serum Tg have been reported (13, 14). The second patient, who presented with T1NxM0 tumor in 1990 at age 46, had positive cervical lymph nodes resected twice at MCR and two ^{131}I therapies before her rhTSH test. She has a 7-mm indeterminate neck nodule that has been stable for 5 yr and negative CT and bone scans and post-^{131}I therapy scan. Five patients had tiny indeterminate pulmonary nodules, stable on CT scan for 10–25 months. The significance of these nodules is unclear, and further follow-up is indicated. However, when patients at high risk for lung cancer had screening CT scans, 69% had indeterminate lung nodules; with follow-up, 99% were believed benign (15). Because our patients had an undetectable or barely detectable rhTSH-stimulated Tg, it is unlikely that these lesions are related to thyroid cancer.

Only one of 80 patients had treatment for recurrent disease. This patient had a stimulated Tg of only 0.3 ng/ml, but neck ultrasound detected a lymph node that was resected. ^{123}I imaging after rhTSH stimulation did not detect the lymph node metastasis in this patient. Thus, a rare patient may have detectable disease even with a very low serum Tg and a negative rhTSH-stimulated ^{123}I image, which supports the importance of neck ultrasonography.

Several studies have shown that rhTSH is effective in stimulating both ^{131}I uptake and Tg levels (3–10), although occasionally Tg does not increase (4, 10). Using Tg assays with

sensitivities of 0.5–1.0 ng/ml, some patients with an undetectable T_4-suppressed Tg have a stimulated Tg above 2 ng/ml that is indicative of metastatic disease. It has been proposed that the use of a stimulated Tg alone, without a diagnostic ^{131}I scan, is sufficient to detect disease (6, 8, 10), although some authors favor inclusion of ^{131}I scans (7, 9) or neck ultrasonography (12).

Robbins *et al.* (9) have questioned the use of a stimulated Tg alone in an unselected population. They performed rhTSH tests in 366 patients, 13.7% of whom had a stimulated Tg no greater than 2 ng/ml yet had evidence of metastatic disease. These results could be explained in part by the patient population, because 40% had stage 3 or 4 disease. Also, Tg antibody was assessed using a recovery assay, which could underestimate the number of patients with antibody positivity. In the low-risk patients, 8% had locoregional disease with a stimulated Tg no greater than 2ng/ml, whereas none who had a prior negative diagnostic scan had evidence of disease if Tg remained below 2 ng/ml. The authors concluded that a diagnostic WBS should be performed with rhTSH testing in unselected patients. Pacini *et al.* (12) studied 294 patients whose L-T_4 suppressed Tg was undetectable (<1 ng/ml). In 85%, stimulated Tg remained below 1 ng/ml. Four patients had residual disease, three being detectable by ultrasound. The authors proposed that the combination of a neck ultrasound and a stimulated Tg above 1 ng/ml (their assay) or above 2 ng/ml (other assays) would detect the few patients needing additional evaluation.

A Consensus Report (11) was published by the investigators cited above and included thyroid cancer specialists from other medical centers. They concluded that undetectable T_4-suppressed Tg levels were insufficient to exclude residual disease. They reviewed eight studies (784 patients without clinical disease and suppressed Tg < 1 ng/ml). After rhTSH, 21% of patients had a Tg above 2 ng/ml, with one third having metastatic disease. Conclusions were: 1) Tg assays should have a functional sensitivity of at least 1 ng/ml; 2) "tumor is rarely found when the serum Tg value is less than 2 μg/liter after rhTSH stimulation"; and 3) further annual testing is unnecessary (beyond T_4-suppressed Tg) in low-risk individuals with an undetectable (<1 ng/ml) stimulated Tg.

Kloos and Mazzaferri (13) provided follow-up on 101 patients whose initial rhTSH-stimulated Tg remained below 0.5 (n = 63), increased to 0.6–2.0 (n = 18), or rose to above 2 ng/ml (n = 20). Only 2 of 81 patients (2.5%) whose initial rhTSH-Tg increased to less than 2 ng/ml had recurrent thyroid cancer during follow-up. In one patient, serum Tg antibody became positive, both negating the utility of the Tg value and suggesting the recurrence of thyroid antigenic tissue. The second patient had a rise in T_4-suppressed Tg to a detectable level (0.5 ng/ml). Both patients had recurrent cervical lymph nodes identified by ultrasound. Thus, in neither of the positive patients was a rhTSH-stimulated Tg necessary to recognize recurrent thyroid cancer.

In a Letter to the Editor (14), the authors of the Consensus Report stated "in the future, using even more sensitive serum Tg assays may indeed render TSH stimulation unnecessary to identify patients with persistent tumor." Most authors agree that if a rhTSH-stimulated Tg remains below 2 ng/ml, the likelihood of finding detectable, treatable disease is small. Giovanella *et al.* (16), using a Tg assay with a sensitivity of 0.2 ng/ml, reported a negative predictive value of 99% when T_4-suppressed Tg and neck ultrasound were used to monitor low-risk patients. Our results are consistent with these observations. Only 2 of 80 patients with a baseline Tg below 0.1 ng/ml had a rhTSH-stimulated Tg above 2 ng/ml. In one, follow-up showed that her Tg rose only to 1.7. The other patient, who had undergone multiple treatments for neck lymph nodes, had a single subcentimeter node, stable for 5 yr. Kloos and Mazzaferri proposed that a "small TSH-stimulated rise in Tg to no higher than 2 ng/ml is not usually a serious matter but requires follow-up with neck ultrasonography," and annual rhTSH testing is unnecessary if the initial value remains below 0.5 ng/ml (13). Furthermore, the recently published American Thyroid Association (ATA) management guidelines propose that Tg "unstimulated or stimulated levels greater than 2 ng/ml that increase over time may represent recurrent disease" (17).

Our results are in agreement with these reports. We propose that by using a Tg-immunoassay with a cutoff 5- to 10-fold lower than reported by others (3–10, 12, 13), it is possible to follow patients with differentiated thyroid cancer and a T_4-suppressed Tg below 0.1 ng/ml without the need to perform rhTSH stimulation. We recommend that ATA guidelines be followed if T_4-suppressed Tg is detectable (17) because 24–82% of such patients had an rhTSH-stimulated Tg above 2 ng/ml. It should be emphasized that the study conditions at MCJ and MCR were not identical because rhTSH-stimulated Tg at MCR was measured 1 d earlier. Although the standard procedure for Tg measurement is 72 h after the last rhTSH injection (*i.e.* d 5), Pacini *et al.* (6) observed that peak rhTSH-stimulated Tg occurs earlier (24–48 h after rhTSH) in 32% of patients. Similarly, in a phase 3 trial (4), serum Tg levels appeared to be similar 2 and 3 d after rhTSH (Haugen, B., personal communication).

The economic impact of this strategy is significant. Most patients with differentiated thyroid carcinoma are low risk, and only about 10–20% will have a recurrence. The cost of a single rhTSH stimulation test (Florida Medicare fees) at MCJ is $1,861 [includes pharmacy, two Tg and two TSH measurements (d 1 and 5), and a ^{131}I uptake and scan]; the cost without the uptake and scan is $1,517. The cost of a single T_4-suppressed serum Tg and TSH is $44, and a neck ultrasound is $90. Prices for various insurance carriers and for uninsured patients exceed these figures by up to three times. A rhTSH test requires the patient to visit the clinic on 4 separate days within a week (three visits if a scan is not performed), compared with a one-time visit for a baseline lab test and ultrasound. The intangible costs for time lost from work were not calculated.

In summary, when a sufficiently sensitive Tg assay is used, we found that patients with differentiated thyroid carcinoma (not all of whom were low risk) and a T_4-suppressed serum Tg below 0.1 ng/ml rarely have a rhTSH-stimulated Tg above 2 ng/ml, and only one had demonstrable disease by ultrasound despite numerous imaging studies. Several patients had indeterminate lesions and required longer surveillance. For now, we feel that monitoring such patients with a T_4-suppressed Tg level and periodic neck ultrasound imaging is recommended, although additional studies using

Tg assays with improved sensitivity and longer follow-up are needed. An increase in serum Tg to detectable level or appearance of abnormal lymph nodes should prompt further investigations. The only caveats are that the testing laboratory has to ensure consistent assay performance over time and that patients should always be tested with the same highly sensitive assay because assays from different manufacturers, even if sufficiently sensitive, might not always yield comparable results.

Acknowledgments

Received May 8, 2006. Accepted October 24, 2006.

Address all correspondence to: Robert C. Smallridge, M.D., Division of Endocrinology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, Florida 32224. E-mail: smallridge.robert@mayo.edu.

Disclosure Statement: S.E.M., M.A.M., G.S.G., T.P.F., and V.F. have nothing to declare. S.G. consults for Diagnostic Hybrids, Inc. R.C.S. consulted one day in 2005 for Astra Zeneca. He received expenses, but no honorarium.

References

1. **Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ** 2006 Cancer statistics, 2006. CA Cancer J Clin 56:106–130
2. **Hay ID, Grant CS, van Heerden JA, Goellner JR, Ebersold JR, Bergstralh EJ** 1992 Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. Surgery 112:1139–1146; discussion, 1146–1147
3. **Ladenson PW, Braverman LE, Mazzaferri EL, Brucker-Davis F, Cooper DS, Garber JR, Wondisford FE, Davies TF, DeGroot LJ, Daniels GH, Ross DS, Weintraub BD** 1997 Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. N Engl J Med 337:888–896
4. **Haugen BR, Pacini F, Reiners C, Schlumberger M, Ladenson PW, Sherman SI, Cooper DS, Graham KE, Braverman LE, Skarulis MC, Davies TF, DeGroot LJ, Mazzaferri EL, Daniels GH, Ross DS, Luster M, Samuels MH, Becker DV, Maxon 3rd HR, Cavalieri RR, Spencer CA, McEllin K, Weintraub BD, Ridgway EC** 1999 A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. J Clin Endocrinol Metab 84:3877–3885
5. **Robbins RJ, Tuttle RM, Sharaf RN, Larson SM, Robbins HK, Ghossein RA, Smith A, Drucker WD** 2001 Preparation by recombinant human thyrotropin or thyroid hormone withdrawal are comparable for the detection of residual differentiated thyroid carcinoma. J Clin Endocrinol Metab 86:619–625
6. **Pacini F, Molinaro E, Lippi F, Castagna MG, Agate L, Ceccarelli C, Taddei D, Elisei R, Capezzone M, Pinchera A** 2001 Prediction of disease status by recombinant human TSH-stimulated serum Tg in the postsurgical follow-up of differentiated thyroid carcinoma. J Clin Endocrinol Metab 86:5686–5690
7. **Haugen BR, Ridgway EC, McLaughlin BA, McDermott MT** 2002 Clinical comparison of whole-body radioiodine scan and serum thyroglobulin after stimulation with recombinant human thyrotropin. Thyroid 12:37–43
8. **Pacini F, Capezzone M, Elisei R, Ceccarelli C, Taddei D, Pinchera A** 2002 Diagnostic 131-iodine whole-body scan may be avoided in thyroid cancer patients who have undetectable stimulated serum Tg levels after initial treatment. J Clin Endocrinol Metab 87:1499–1501
9. **Robbins RJ, Chon JT, Fleisher M, Larson SM, Tuttle RM** 2002 Is the serum thyroglobulin response to recombinant human thyrotropin sufficient, by itself, to monitor for residual thyroid carcinoma? J Clin Endocrinol Metab 87:3242–3247
10. **Wartofsky L** 2002 Management of low-risk well-differentiated thyroid cancer based only on thyroglobulin measurement after recombinant human thyrotropin. Thyroid 12:583–590
11. **Mazzaferri EL, Robbins RJ, Spencer CA, Braverman LE, Pacini F, Wartofsky L, Haugen BR, Sherman SI, Cooper DS, Braunstein GD, Lee S, Davies TF, Arafah BM, Ladenson PW, Pinchera A** 2003 A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 88:1433–1441
12. **Pacini F, Molinaro E, Castagna MG, Agate L, Elisei R, Ceccarelli C, Lippi F, Taddei D, Grasso L, Pinchera A** 2003 Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. J Clin Endocrinol Metab 88:3668–3673
13. **Kloos RT, Mazzaferri EL** 2005 A single recombinant human thyrotropin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. J Clin Endocrinol Metab 90: 5047–5057
14. **Mazzaferri EL, Robbins RJ, Braverman LE, Pacini F, Haugen BR, Wartofsky L, Braunstein GD, Ladenson PW, Pinchera A** 2003 Author's response: a consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 88:4508–4509
15. **Swensen SJ, Jett JR, Hartman TE, Midthun DE, Sloan JA, Sykes AM, Aughenbaugh GL, Clemens MA** 2003 Lung cancer screening with CT: Mayo Clinic experience. Radiology 226:756–761
16. **Giovanella L, Ceriani L, Ghelfo A, Keller F, Sacchi A, Maffioli M, Spriano G** 2006 Thyroglobulin assay during thyroxine treatment in low-risk differentiated thyroid cancer management: comparison with recombinant human thyrotropin-stimulated assay and imaging procedures. Clin Chem Lab Med 44: 648–652
17. **Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Sherman SI, Tuttle RM** 2006 Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 16:109–142