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Preparation by Recombinant Human Thyrotropin or Thyroid Hormone Withdrawal Are Comparable for the Detection of Residual Differentiated Thyroid Carcinoma

RICHARD J. ROBBINS, R. MICHAEL TUTTLE, RENU N. SHARAF, STEVEN M. LARSON, HEATHER K. ROBBINS, RONALD A. GHOSSEIN, ALEX SMITH, AND WILLIAM D. DRUCKER

Endocrinology and Nuclear Medicine Services, Departments of Medicine (R.J.R., R.M.T., R.N.S., H.K.R., W.D.D.), Pathology (R.A.G.), Radiology (S.M.L.), and Epidemiology and Biostatistics (A.S.), Memorial Hospital for Cancer and Allied Diseases, Memorial Sloan-Kettering Cancer Center, New York, New York 10021

ABSTRACT

Clinical recurrences of differentiated thyroid carcinoma occur in 20% of patients after thyroid surgery. We performed a retrospective analysis of a cohort of patients undergoing routine follow-up testing to detect recurrent thyroid carcinoma over a 2-yr period. One group was prepared for testing by thyroid hormone withdrawal (THW), and the other group remained on thyroid hormone and received injections of recombinant human TSH (rhTSH) before diagnostic whole-body radioiodine scanning (DxWBS). We hypothesized that no differences in the ability to detect residual disease would exist between these 2 groups. Two hundred and eighty-nine patients were examined by both DxWBS and by measurement of the serum thyroglobulin (Tg) response to elevated TSH levels. THW was used for 161 patients, and rhTSH preparation was used for 128 patients. Based on all available testing results, we categorized patients as having metastatic disease, thyroid bed uptake only, or no evidence of disease. We examined the sensitivity, specificity, positive and negative predictive values of the DxWBS, and the stimulated Tg after preparation by THW or rhTSH. Patients with thyroid bed were not considered in accuracy testing. The sensitivity and specificity of the 2 tests were comparable between groups. No significant differences were present in the positive or negative predictive values between groups. The highest negative predictive value (97%) was in patients who had both a negative DxWBS and low stimulated Tg levels after rhTSH. In summary, we were unable to demonstrate a difference in the diagnostic accuracy of DxWBS and/or Tg between patients prepared by either THW or rhTSH. We conclude that preparing patients by rhTSH is diagnostically equivalent to preparing them by THW. (*J Clin Endocrinol Metab* **86:** 619–625, 2001)

DIFFERENTIATED THYROID CARCINOMA is a common malignancy that has a relatively high cure rate (1, 2). Depending on the extent of initial surgery, clinical recurrences will occur in as many as 20% of patients (3–6). Each year in the United States alone, 1200 individuals die of thyroid carcinoma, with papillary thyroid carcinoma accounting for most of the deaths (7). The theory that early detection of residual disease results in the best chance for a long-term cure is the basis for careful monitoring of patients after thyroidectomy.

Standard monitoring for residual thyroid cancer includes clinical examination, measurement of serum thyroglobulin (Tg) levels, and diagnostic whole-body radioactive iodine scanning (DxWBS) (2, 8–10). The serum Tg and the DxWBS are most sensitive at detecting residual disease when patients have elevated serum TSH levels after thyroid hormone withdrawal (THW) (11). The recent availability of recombinant human TSH (rhTSH) provides another means of elevating the TSH level without the need for hypothyroidism (12, 13). The first industry-sponsored prospective paired comparison of THW *vs.* rhTSH found that the THW preparation was statistically better when only the DxWBS was considered (14). A more recent report from the same group found no statistical difference between THW and rhTSH when they considered both the DxWBS and the stimulated Tg as primary end-points (15). One caveat regarding their conclusions was the fact that few patients with distant metastases were included in either study.

The decreased quality-of-life attendant with hypothyroidism, which often follows THW, can be a significant burden on many aspects of the patient's life (16). It is not uncommon for patients to delay or refuse routine evaluations simply to avoid becoming hypothyroid. If the accuracy of testing done after rhTSH (on thyroxine) is the same or better than that after THW, it would be much more acceptable to most patients.

We hypothesized that the ability to detect residual thyroid carcinoma in patients who continued on thyroxine suppression and received rhTSH would not be significantly different from patients after THW. In a retrospective analysis, we compared the diagnostic accuracy of DxWBS and stimulated Tg, alone or in combination, in all thyroid cancer patients undergoing routine follow-up studies at one medical center over a 2-yr period.

Materials and Methods

Patients

The patients in this retrospective study included all individuals who were referred to the Nuclear Medicine section of Memorial Hospital for Cancer and Allied Diseases between January 1, 1998 and December 31,

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Address all correspondence and requests for reprints to: Richard J. Robbins, M.D., Endocrinology Service, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10021.

1999. Testing for residual thyroid carcinoma (DxWBS and Tg) was performed on 373 occasions in 289 different patients. During 1998, patients who could not produce sufficient endogenous TSH or those who could not tolerate hypothyroidism were studied with rhTSH under a compassionate need trial sponsored by the Genzyme Corp. (Cambridge, MA) and the United States Food and Drug Administration. During 1999, all patients had the choice of having the DxWBS performed after THW or with rhTSH while remaining on thyroxine. At the time of the choice, the published information on the accuracy of rhTSH-assisted diagnosis (14) had concluded that scans obtained after THW were more sensitive than those after rhTSH.

DxWBS

Formal dosimetric analysis was performed in each patient based on the blood and whole-body clearance of a tracer dose of ^{131}I (17, 18). Mean scanning doses of ^{131}I were 3.5 mCi (129.5 MBq) for the THW group and 4.2 mCi (155.4 MBq) for the rhTSH group ($P = 0.28$). THW patients were asked to stop their thyroid hormone, 4–6 weeks before the start of diagnostic studies. Some patients were also given triiodothyronine until 2 weeks before the start of testing. Patients in the rhTSH group remained on suppressive doses of thyroxine and received im injections of 0.9 mg rhTSH (Thyrogen, Genzyme Corp.), 24 and 48 h before the administration of ^{131}I. All patients were provided with a low-iodine diet to follow for at least 1 week before dosimetry. For the DxWBS, a whole-body scan in the anterior and posterior projection was obtained using a dual-headed Genesys EPIC imaging system (ADAC Corporation, Malpitas, CA). Both anterior and posterior heads had high-energy general-purpose collimators, peak isotope energy of 364 kilo electron volts with a 20% energy window, a 256 × 256 × 16 matrix, and a scan speed of 8 cm/min. For all patients, a 10-min neck view was obtained at 24 and 72 h after the oral dose of ^{131}I. The neck view was obtained with a 256 × 256 × 16 matrix, 38-cm CFOV with scatter window. Lateral neck views and other spot views were obtained, as required, at the discretion of the nuclear medicine physician.

Whole-body counts were obtained at 0, 2, 4, 24, 72, and 96 h after ^{131}I administration for the THW patients and at 0, 2, 4, 24, 48, 72, and 120 h for the rhTSH patients. A standard fraction of the total dose administered (normally about 1%) is also counted just before patient counting. At each time interval, blood is drawn, and the fractional blood clearance is determined. Total body clearance curves are generated, and the mCi dose that will give a dose of 200 cGy to the blood is calculated using standard techniques (19). After treatment with radioactive ^{131}I, a 1-week posttherapy whole-body scan is performed using identical collimators, with machine settings as described for the 72-h DxWBS, except that the scan speed is increased to 10–15 cm/min, depending on the therapeutic dose administered.

Tg

Serum Tg measurements were performed by the Optiquant IRMA (immunoradiometric assay; Kronus, Boise, ID). This assay has a sensitivity of 0.2 μg/L; however, all readings below 0.5 μg/L are reported to clinicians as: less than 0.5 μg/L. Patients in whom Tg autoantibodies were present were not assigned a specific value, because the reliability of the reading was not assured. For the purposes of statistical analysis, antibody-positive patients were eliminated from any analysis that considered serum Tg. Tg autoantibodies were present in 11 of the hypothyroid patients and in 8 of the rhTSH patients included in the analysis. For the rhTSH group, the baseline Tg was obtained before the first dose of rhTSH, and the stimulated Tg was obtained approximately 72 h after the second dose of rhTSH. In the THW group, the Tg was obtained 48 h before the DxWBS. This was the standard of care during the 2 yr covered by the study.

Other studies

When clinically indicated, the patients underwent standard radiography, computed tomography scans, and magnetic resonance imaging with or without contrast. All radioiodine scans were done no sooner than 6 months after scans with iodinated contrast. Fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning was performed when clinically indicated according to our prior report (20, which showed that FDG could localize disease in patients with negative DxWBS and elevated serum Tg. Cervical ultrasonography performed, using a power Doppler instrument or plain films of any body region, were obtained when clinically indicated (21, 22).

Assignment of clinical status

The final clinical assignment was made by considering all of the clinical information. However, the results of the 1998–99 DxWBS and the stimulated Tg were not considered in assigning the final clinical status for accuracy testing. Eleven patients in whom a clinical status could not be assigned, because of a lack of complementary studies, were not considered in this analysis. Clinical status was judged as having metastatic disease based on the following criteria: 1) patients whose suppressed Tg was more than 2 μg/L, associated with an abnormal radiographic study (computed tomography, magnetic resonance imaging, posttherapy scan, PET, and/or ultrasonography) done within 6 months of the DxWBS, suggestive of a metastatic lesion (n = 108); 2) patients in whom the baseline suppressed Tg was greater than 10 μg/L and who had prior evidence of metastatic disease (n = 7); 3) patients with a low Tg and a positive posttherapy scan (n = 16); or 4) patients who had no other known malignancy and a positive FDG-PET scan (n = 8). Clinical status was judged as no evidence of disease (NED) in patients who had: baseline Tg levels less than or equal to 2 μg/L, NED on physical exam, no positive radiographic studies, and no distant metastases found on the last nuclear medicine evaluation. Finally, patients with no radiographic evidence of distant metastases, in whom the only radioiodine uptake on the most recent DxWBS was in the thyroid bed (TB), were assigned to the TB-only group. For the diagnostic accuracy testing, TB patients were not included in the statistical analyses.

Statistical analyses

The purpose of this study is to examine, retrospectively, whether 2 methods of preparation for diagnostic testing (rhTSH or THW) produce significantly different accuracy in 2 forms of testing (DxWBS and stimulated Tg), as well as in their combined diagnostic accuracy. Because patients in the study were examined annually, repeat visits were common within the 1998–99 period. Out of 373 observed visits, a total of 289 unique patients were analyzed. Because disease is considered to recur at random, patients with multiple visits had a single visit randomly selected to remain in the study. Visits not selected were excluded from analysis, to ensure independence of observations, both between and within samples.

The study compared two preparation methods based on measures of accuracy [sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)] of the various diagnostic tests in reference to a clinical determination. Because patients categorized as TB cannot be proven to either have or not have residual cancer, they were deleted from the statistical comparisons of accuracy. We considered adding the TB patients to the metastatic group or to the NED group for accuracy testing, but there were equally unacceptable biases inherent in those maneuvers (23, 24). For each diagnostic test, the four measures of accuracy are computed for each group, and *P*-values resulting from Fisher's exact test (25) are presented for the difference between preparation methods in both PPV and NPV. In the case of the combined test analysis, the overall test was considered positive if either of the individual tests (DxWBS or stimulated Tg) were positive, and negative only when both tests were negative. S-PLUS for Windows (26) is used for all analyses.

Results

Patient and tumor characteristics

The mean ages, gender, median stimulated Tg levels, and frequency of total thyroidectomy were comparable between the 2 groups (Table 1). Patients in the rhTSH group were slightly older and less likely to be female, compared with the THW group. The histological subtypes, the tumor (T) sizes, nodal (N) status, presence of metastases (M), and American Joint Commission on Cancer staging (27) at initial diagnosis

TABLE 1. Patient and tumor characteristics

	rhTSH	THW
Sample size	128	161
Mean age	45.6	44.2
Female	76 (59%)	103 (64%)
Median stimulated Tg	1.0	4.0
Total thyroidectomy	108 (85%)	151 (94%)
Papillary	111 (87%)	128 (81%)
Follicular	10 (8%)	11 (7%)
Hurthle	5 (4%)	11 (7%)
Tx	16 (12%)	10 (6%)
T1	19 (15%)	14 (9%)
T2	30 (23%)	48 (30%)
T3	11 (9%)	21 (13%)
T4	52 (41%)	68 (42%)
Nx	21 (16%)	39 (24%)
N0	33 (26%)	39 (24%)
N1	74 (58%)	83 (52%)
M0	98 (77%)	131 (82%)
M1	30 (23%)	30 (18%)
Stage I	56 (44%)	73 (45%)
Stage II	19 (15%)	26 (16%)
Stage III	33 (26%)	37 (23%)
Stage IV	20 (16%)	25 (15%)

Stages are AJCC, at initial diagnosis.

were comparable between groups. Patients were judged to be M1 if any distant metastases were discovered by computed tomography, magnetic resonance imaging, chest x-ray, or DxWBS within the first 3 months of the cancer diagnosis. Based on all available clinical information, 66 (51%) of the rhTSH and 73 (45%) of the THW patients had evidence of metastatic thyroid carcinoma. Forty-seven patients (37%) in the rhTSH group and 28 patients (17%) in the THW group were NED. Sixty (37%) patients in the THW group had TB uptake only, compared with 15 patients (12%) in the rhTSH group. The range of TSH levels in the THW group were 2–234 μIU/L for TB patients, 30–576 μIU/L for those judged to be NED, and 0.5–359 μIU/L for patients with metastatic disease. The mean TSH in the THW group, at the time of the DxWBS, was 105.6 μIU/L. Only 5 (3%) of the 162 THW patients had TSH levels below 25 μIU/L. Peak TSH levels were not measured in the rhTSH patients but are usually in the 130–150 μIU/L range, 24 h after the second dose of rhTSH (14, 15, 28). There were only minor differences in tumor characteristics between the groups (Table 1). The median stimulated Tg levels for the rhTSH group were: 1 μg/L for NED, 7.7 μg/L for metastatic disease, and 1 μg/L for TB. The median stimulated Tg levels for the THW group were: 1 μg/L for NED, 38 μg/L for metastatic disease, and 3.2 μg/L for TB. Of the patients judged to be positive for metastatic disease, 59% of the rhTSH and 49% of the THW patients had received ^{131}I treatments before enrollment in the study.

Positive DxWBS scans (Table 2)

Forty-eight percent of the rhTSH group had focal ^{131}I uptake on the DxWBS, compared with 75% of the THW group. The frequencies of bone, cervical, mediastinal, lung, and multicentric uptake were comparable between groups. Uptake in the TB only was present in 40% of the THW group, compared with 15% of the rhTSH group ($P = 0.02$).

TABLE 2. Diagnostic whole body radioiodine scans

	rhTSH	THW
Total scans	128	161
Negative scans	66 (52%)	40 (25%)
Positive scans	43 (33%)	56 (35%)
Bone only	2 (2%)	3 (2%)
Cervical only	17 (13%)	23 (15%)
Lung only	9 (7%)	8 (5%)
Mediastinal only	3 (2%)	2 (1%)
Multiple DM	12 (9%)	20 (12%)
Thyroid bed only	19 (15%)	65 (40%)

DM, Distant metastases.

Negative DxWBS (Fig. 1)

Sixty-six of the rhTSH patients and 40 of the THW patients had negative DxWBS scans (Table 2). Patient and tumor characteristics between these groups were very similar (data not shown). There were 2 false-positive results in the THW group. One had uptake in an inflamed gallbladder and the other had diffuse mediastinal uptake that was judged to be thymus uptake. Eleven patients (4 in rhTSH and 7 in THW) with evidence for metastatic disease had only TB uptake on the DxWBS and were not included in the reduced tables because the result was indeterminate (*i.e.* neither metastatic nor NED). However, 19 (29%) of the rhTSH group and 13 (33%) of the THW group had evidence for metastatic disease. The stimulated Tg levels in these false-negative DxWBS patients ranged from 1.0–5600 μg/L. Only 4 patients in this category had stimulated Tg levels less than 2 μg/L. In the rhTSH patients who had metastatic disease and a negative DxWBS (n = 19), 6 of 9 who were treated with high-dose ^{131}I had uptake in metastatic sites, on posttherapy scans. Ten of 13 patients who had FDG-PET scans demonstrated positive metastatic uptake. Of the 19 patients, 9 had disease in multiple sites, 8 had disease in cervical nodes, 8 had lung uptake, and 3 had bone uptake. Of the THW patients who had negative DxWBS and metastatic disease (n = 13), 5 of 6 who received high-dose ^{131}I had positive posttherapy scans and 5 of 7 who had FDG-PET scans had focal metastatic uptake. Overall, the metastatic lesions were localized in 8 of the 8 THW patients who had either a posttherapy scan or an FDG-PET scan.

Patients with low stimulated Tg levels (Fig. 2)

Another indicator of residual thyroid tissue is a measurable serum Tg in the setting of an elevated TSH. Using a cutoff less than or equal to 2 μg/L as defining a negative stimulated Tg, 54 patients in the rhTSH and 61 patients in the THW group were negative. Of these, 9 in the rhTSH group and 22 in the THW group were TB. The clinical and tumor characteristics of the patients in these cohorts were comparable. Of the patients with low stimulated Tg, 9 (17%) in the rhTSH group and 15 (25%) in the THW group had evidence for metastases. Of the 9 rhTSH patients with low Tg levels and metastases, 8 had uptake in cervical nodes on either the DxWBS or the posttherapy scan. Of the 15 THW patients with low Tg and metastases, 10 had positive cervical nodes and 4 had lung uptake on either the DxWBS or the posttherapy

rhTSH Group

Dx	MET	TB	NED	
"+"	43	0	0	43
TB	4	15	0	19
"-"	19	0	47	66
	66	15	47	128

THW Group

Dx	MET	TB	NED	
"+"	53	1	2	56
TB	7	58	0	65
"-"	13	1	26	40
	73	60	28	161

Reduced Tables (TB Removed):

rhTSH Group

Dx	MET	NED	
"+"	43	0	43
"-"	19	47	66
	62	47	109

THW Group

Dx	MET	NED	
"+"	53	2	55
"-"	13	26	39
	66	28	94

Diagnostic Accuracy Measures (Based on Reduced Tables):

rhTSH Group

Sensitivity: 43/62=0.69
Specificity: 47/47=1.0
PPV: 43/43=1.0
NPV: 47/66=0.71

THW Group

Sensitivity: 53/66=0.80
Specificity: 26/28=0.93
PPV: 53/55=0.96
NPV: 26/39=0.67

P-Values (Difference Between rhTSH and THW)
PPV: P= 0.50
NPV: P= 0.66

FIG. 1. Diagnostic accuracy of the DxWBS. MET, Metastatic disease; +, RAI uptake outside the TB; −, no RAI uptake. Patients with clinical rating of TB were not included in these analyses. ND, Not done. Sensitivity is the ratio of positive DxWBS in MET patients to total number of MET patients; sensitivity is the ratio of negative DxWBS scans in NED patients to total number of NED patients; PPV is the number of positive DxWBS scans in MET patients divided by total number of positive scans; NPV is the number of negative scans in NED patients divided by the total number of negative scans. *P*-values are for Fisher's exact test.

rhTSH Group

Tgb	MET	TB	NED	
"+"	54	4	8	66
"-"	9	9	36	54
	63	13	44	120

THW Group

Tgb	MET	TB	NED	
"+"	56	30	3	89
"-"	15	22	24	61
	71	52	27	150

Reduced Tables (TB Removed):

rhTSH Group

Tgb	MET	NED	
"+"	54	8	62
"-"	9	36	45
	63	44	107

THW Group

Tgb	MET	NED	
"+"	56	3	59
"-"	15	24	39
	71	27	98

Diagnostic Accuracy Measures (Based on Reduced Tables):

rhTSH Group

Sensitivity: 54/63=0.86
Specificity: 36/44=0.82
PPV: 54/62=0.87
NPV: 36/45=0.80

THW Group

Sensitivity: 56/71=0.79
Specificity: 24/27=0.89
PPV: 56/59=0.95
NPV: 24/39=0.62

P-Values (Difference Between rhTSH and THW)
PPV: P= 0.21
NPV: P= 0.09

FIG. 2. Diagnostic accuracy of stimulated Tg level.

scan. FDG-PET scans were performed in 9 of 15, and these scans localized disease in 5 cases. Disease was localized in all 15 by a combination of the posttherapy scan and the FDG-PET scans.

Patients with negative DxWBS and low stimulated Tg levels (Fig. 3)

Thirty-seven patients in the rhTSH group and 25 patients in the THW group had double-negative test results. By definition, no TB patients can be in the double-negative groups. There were 8 false-positives in the rhTSH group and 5 in the THW group. Three patients in the THW group who had metastases (based on other testing) had TB uptake only on the DxWBS and were eliminated from the reduced tables as indeterminate outcomes. One patient (2.7%) in the rhTSH group and 3 patients (12%) in the THW group had metastatic disease. The disease in all 4 patients was localized by either the posttherapy scan or FDG-PET scanning. The 1 patient in the rhTSH group had diffuse lung nodules only seen on FDG-PET scanning, confirmed to be Hurthle cell carcinoma by biopsy. In the THW group, 2 patients had metastases in cervical nodes, localized by ultrasonography and seen on the posttherapy scans. One patient in the THW group had mediastinal and cervical uptake seen on FDG-PET scanning and on the posttherapy scan.

Accuracy testing

Testing was done after eliminating the TB patients as an indeterminate test result. We could not unequivocally conclude that they did or did not have residual cancer. For analysis of the DxWBS testing, 19 of the 128 rhTSH, and 67 of the 161 THW patients were removed from the data, because they had TB status. For analysis of the stimulated Tg testing, we eliminated 13 of the 120 rhTSH patients and 52 of the 152 THW patients who had a TB status. For analysis of the combined test, we eliminated 13 of the 120 rhTSH patients and 55 of the 150 THW patients who had a TB status.

We performed statistical analyses on the predictive values, because these have the most clinical applicability (24). The sensitivity of the DxWBS was slightly better after THW, whereas the specificity was slightly better with rhTSH. The PPV ($P = 0.50$) and NPV ($P = 0.66$) of the DxWBS were comparable between groups (Fig. 1). Using a stimulated Tg greater than 2 μg/L as the definition of a positive Tg response, we found a higher sensitivity in the rhTSH group, whereas the specificity was higher in the THW group. The

rhTSH Group

Tgb/Dx	MET	TB	NED	
"Any+"	62	4	8	74
"-/TB"	0	9	0	9
"-/-"	1	0	36	37
	63	13	44	120

THW Group

Tgb/Dx	MET	TB	NED	
" Any+"	65	31	5	101
"-/TB"	3	21	0	24
"-/-"	3	0	22	25
	71	52	27	150

Reduced Tables (TB Removed):

rhTSH Group

Tgb/Dx	MET	NED	
"Any+"	62	8	70
"-/-"	1	36	37
	63	44	107

THW Group

Tgb/Dx	MET	NED	
"Any+"	65	5	70
"-/-"	3	22	25
	68	27	95

Diagnostic Accuracy Measures (Based on Reduced Tables):

rhTSH Group

Sensitivity: 62/63=0.98
Specificity: 36/44=0.82
PPV: 62/70=0.89
NPV: 36/37=0.97

THW Group

Sensitivity: 65/68=0.96
Specificity: 22/27=0.81
PPV: 65/70=0.93
NPV: 22/25=0.88

P-Values (Difference Between rhTSH and THW)

PPV: P= 0.56
NPV: P= 0.29

FIG. 3. Diagnostic accuracy of combined DxWBS and stimulated Tg testing. Any+, Includes outcomes in which either the DxWBS was positive or the stimulated Tg level was greater than 2 ng/mL; −/−, outcomes in which the DxWBS was negative and the stimulated Tg was equal to or less than 2 ng/mL.

PPV ($P = 0.21$) and the NPV ($P = 0.09$) of the stimulated Tg test were not statistically different between groups, although there was a trend for the NPV to be higher in the rhTSH group (Fig. 2).

When both the DxWBS and the stimulated Tg were considered together as a combined test, the sensitivity and specificity between groups was comparable. The PPV ($P = 0.38$) and the NPV ($P = 0.14$) of the combined test were not different between groups. However, when both the DxWBS and stimulated Tg were negative, only one patient in the rhTSH group had metastatic disease, producing a NPV of 97% (Fig. 3).

We also performed accuracy testing at 0.5 μg/L and at 5 μg/L. As expected, when stimulated Tg levels equal to or above 0.5 μg/L are used to define residual disease, the sensitivities increase (rhTSH = 0.98 and THW = 1.0) and the specificities drop (rhTSH = 0.18 and THW = 0.04). When a stimulated Tg level of 5 μg/L is used, the sensitivities drop (rhTSH = 0.70 and THW = 0.70) and the specificities rise (rhTSH = 0.98 and THW = 0.96). Of the three cutoff levels analyzed, the best balance of specificity and sensitivity (and PPV and NPV) is obtained with the 2-μg/L cutoff.

Discussion

The recent availability of rhTSH is a tribute to the application of molecular biology to human disease (13, 29, 30). From the time of the successful generation of the dimeric rhTSH *in vitro* (31), it took 10 yr for this biological agent to be available in a Food and Drug Administration-approved form. Phase III testing of rhTSH by an international group of thyroid experts revealed potent *in vivo* activity in thyroid cancer patients (14, 15). Pair-wise comparisons of the sensitivity of DxWBS alone in thyroid cancer patients demonstrated a trend for better sensitivity at detecting residual disease after THW, when compared with rhTSH (14). A second industry-sponsored phase III study (15) convincingly demonstrated that, when the DxWBS and the stimulated Tg, after rhTSH, were both considered, 100% of lesions outside the TB could be detected, using hypothyroid testing as the gold standard. Because virtually all of the morbidity and mortality associated with thyroid carcinoma is related to metastatic lesions, this is the disease that patients and clinicians want to detect.

Unfortunately, patients in both phase III studies were generally low-risk, and only a small percentage had distant metastases, raising questions about applicability to high-risk patients. Nevertheless, based on the phase III data, we began to offer all patients the option of having formal dosimetric analysis in preparation for possible ^{131}I therapy after either THW or with rhTSH, while remaining on suppressive doses of thyroxine. In this retrospective analysis, we found that the combination of the DxWBS and the stimulated Tg level had the same PPVs and NPVs whether the patients were prepared by THW or rhTSH. In fact, if both the DxWBS was negative and the stimulated Tg was equal to or less than 2 μg/L after rhTSH, there was only a 3% chance of having metastatic disease, compared with a 12% chance for the THW group. We conclude that the discomfort and reduced quality-of-life that often follows THW are no longer generally necessary, because rhTSH is an equally acceptable preparation.

A number of biases are likely present in our retrospective study. The patients who enrolled in 1998 were only offered the option of rhTSH if they qualified for a Food and Drug Administration-sponsored compassionate-need trial. When the1999 patients made their decision as to which preparation to choose, it was widely believed that the hypothyroid preparation, though more onerous, was more sensitive. It was also known that the cost of the only commercially available form of rhTSH (Thyrogen, Genzyme Corp.) might not be covered by some medical insurance payers. In addition, many patients were referred to us already withdrawn from thyroid hormone, and many of those patients chose to proceed with that route, because they were already partially prepared. Furthermore, individuals who had been through the hypothyroid phase of THW may have been more likely to choose the rhTSH option if their quality of life was poor when they were hypothyroid. Finally, in calculating the accuracy of the testing outcomes, some bias could occur by excluding the TB patients. However, we felt that forcing these patients either into a metastatic or an NED category would induce even greater bias, and we therefore eliminated them from the statistical comparisons.

With an awareness of these potential biases, we decided to retrospectively analyze the ability to detect residual thyroid carcinoma as a function of which type of preparation for the DxWBS was used. Tables 1 and 2 demonstrate that the demographic and tumor characteristics of the two groups were remarkably similar. The main exception was that patients in the hypothyroid group who did not have metastatic cancer were much more likely to have a TB remnant only, and those in the rhTSH group were more likely to have no evidence of residual disease. This again may have been a bias, because patients who had been through hypothyroid testing in the past and knew that they had a low likelihood of residual disease may have been less likely to choose the reduced quality of life of hypothyroidism.

We found metastatic disease in patients who had negative DxWBS, patients with low stimulated Tg levels, and even in a small number of patients who had both negative DxWBS and low stimulated Tg. Although the percentage of such patients was always higher in the THW group than in the rhTSH group, no statistically significant differences were present. We are not aware of any previous publications that have addressed this issue, for comparison.

In our cohort, we found that the sensitivity of the DxWBS was 69% with rhTSH and 80% after THW. This compares to reported THW sensitivities of 48% (32), 50% (33), 55% (34), 57% (35), 71% (36), 78% (37), 80% (38), and 84% (39).

The sensitivity of stimulated Tg to detect residual thyroid carcinoma after thyroidectomy has been reported to be 83% (40), 85% (36), 86% (41), 95% (42, 43), and 97% (35). In our cohort, we found a sensitivity of 86% after rhTSH and 79% after THW. The slightly lower sensitivity in the THW group may be attributable to the spectrum of hypothyroidism that occurs after THW. The wide range of TSH values between 0.5 and 576 μIU/L may reflect the variable presence of remnant normal thyroid, the length of time off thyroxine, and the functional state of the malignant thyroid cells. On the other hand, there seems to be a relatively similar rise in TSH levels after two doses of rhTSH, with peak level in the 130 μIU/L range (14, 15).

We chose to statistically compare the predictive values of the various tests because this seems to provide the clinician with information that patients can use in decision making. No significant differences in the predictive values of the tests were found between groups. When both a negative DxWBS and a stimulated Tg $\leq$ 2 μg/L were found, a nonsignificant trend toward a higher NPV was present in the rhTSH group. In that group, we found that 97% of our patients had no evidence of distant metastases. The NPVs were comparable, between groups, for the DxWBS alone and for the stimulated Tg alone.

In a recent publication, Cailleux *et al.* (44) recommended that, after a remnant ablation, it may be best to first test the Tg level after THW, before doing a DxWBS. For those with levels below 1 μg/L, they recommend no scanning, because significant disease is rare; whereas those with Tg levels above 10 μg/L should be scanned with 100 mCi (3.7 GBq), because the scans with 2–5 mCi (74–185 MBq) are too insensitive. This is an interesting proposal that will need independent confirmation.

Our results indicate that the accuracy of detecting significant residual or recurrent thyroid carcinoma is not significantly different whether the patient is prepared by THW or with rhTSH. From a strictly diagnostic perspective, there was no advantage, in our patients, of using the THW approach. The only patients for whom the THW approach seems reasonable, at present, are those for whom there is a high likelihood that a therapeutic dose of radioiodine would be given within a short time after the results of the DxWBS and the stimulated Tg. On the other hand, patients who have a low or unknown likelihood of needing a therapeutic dose of radioiodine could be offered the rhTSH approach. The cost of rhTSH is also a significant factor to be weighed by the patient and the attending physicians, with the cognizance that several weeks of hypothyroidism may result in a reduced quality of life, including possible lost time at work or at school. Based on our findings, the final choice between rhTSH and THW preparation will not need to consider the accuracy of diagnostic testing, which seems to be comparable.

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References

1. **Schlumberger M.** 1998 Papillary and follicular thyroid carcinoma. N Engl J Med. 338:297–306.
2. **Mazzaferri E.** 1999 An overview of the management of papillary and follicular thyroid carcinoma. Thyroid. 9:421–427.
3. **Hay I, Bergstralh E, Goellner J, Ebersold J, Grant C.** 1993 Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery. 114:1050–1058.
4. **Mazzaferri E, Jhiang S.** 1994 Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med. 97:418–428.
5. **Ruegemer J, Hay I, Bergstralh E, Ryan J, Offord K, Gorman C.** 1988 Distant metastases in differentiated thyroid carcinoma: a multivariate analysis of prognostic variables. J Clin Endocrinol Metab. 67:501–508.
6. **Hay I, Bergstralh E, Grant C, et al.** 1999 Impact of primary surgery on outcome in 300 patients with pathologic tumor-node-metastasis stage III papillary thyroid carcinoma treated at one institution from 1940 through 1989. Surgery. 126:1173–1181.
7. **Landis S, Murray T, Bolden S, Wingo P.** 1999 Cancer statistics. CA Cancer J Clin. 49:8–31.
8. **Ozata M, Suzuki S, Miyamoto T, Liu R, Fierro-Renoy F, DeGroot L.** 1994 Serum thyroglobulin in the follow-up of patients with treated differentiated thyroid cancer. J Clin Endocrinol Metab. 79:98–105.
9. **Feld S.** 1996 AACE Clinical practice, guidelines for the diagnosis and management of thyroid nodules. Endocr Pract. 2:78–84.
10. **Singer P, Cooper D, Daniels G, et al.** 1996 Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. Arch Intern Med. 156:2165–2172.
11. **Mazzaferri E.** 1999 NCCN thyroid carcinoma practice guidelines. Oncology. 13:391–442.
12. **Meier C, Braverman L, Ebner S, et al.** 1994 Diagnostic use of recombinant human thyrotropin in patients with thyroid carcinoma (phase I/II study). J Clin Endocrinol Metab. 78:188–196.
13. **Weintraub B, Szkudlinski M.** 1999 Development and *in vitro* characterization of human recombinant thyrotropin. Thyroid. 9:447–450.
14. **Ladenson P, Braverman L, Mazzaferri E, et al.** 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.
15. **Haugen B, Pacini F, Reiners C, et al.** 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.
16. **Dow K, Ferrell B, Anello C.** 1997 Quality-of-life changes in patients with

thyroid cancer after withdrawal of thyroid hormone therapy. Thyroid. 7:613–619.
17. **Benua R, Cicale N, Sonenberg M, Rawson R.** 1962 The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. Am J Roentgenol. 87:171–179.
18. **Leeper R.** 1973 The effect of 131I therapy on survival of patients with metastatic papillary or follicular thyroid carcinoma. J Clin Endocrinol Metab. 36:1143–1152.
19. **Furhang E, Larson S, Buonopong P, Humm J.** 1999 Thyroid cancer dosimetry using clearance fitting. J Nucl Med. 40:131–138.
20. **Wang W, Macapinlac H, Larson S, et al.** 1999 ^{18}F-fluoro-2-deoxyglucose positron emission tomography localizes residual thyroid cancer in patients with negative diagnostic ^{131}iodine whole body scans and elevated serum thyroglobulin levels. J Clin Endocrinol Metab. 84:2291–2302.
21. **Wu C, Shih J, Chang Y, Lee S, Hsieh F.** 1998 Two-dimensional and three-dimensional power Doppler sonographic classification of vascular patterns in cervical lymphadenopathies. J Ultrasound Med. 17:459–464.
22. **Robbins R, Drucker W, Hann L, Tuttle RM,** Advances in the detection of residual thyroid carcinoma. Adv Intern Med. In press.
23. **Simel D, Feussner J, Delong E, Matchar D.** 1987 Intermediate, indeterminate, and uninterpretable diagnostic test results. Med Decis Making. 7:107–114.
24. **Begg C.** 1987 Biases in the assessment of diagnostic tests. Stat Med. 6:411–423.
25. **Fleiss JL.** 1981 Statistical methods for rates and proportions. 2nd ed. New York: Wiley and Co.
26. **SPlus.** 1995 S-PLUS for Windows reference manual. 3.3 ed, vol 1. Seattle, WA: Statistical Sciences, Inc.
27. **American Joint Committee on Cancer.** 1997 American Joint Committee on Cancer. Cancer staging manual, 5th ed. Vol II. Philadelphia-New York: Lippincott-Raven Publishers.
28. **Adler M, Macapinlac H, Robbins R.** 1998 Radioiodine treatment of thyroid cancer with the aid of recombinant human thyrotropin. Endocr Pract. 4:282–286.
29. **Dracopoli N, Rettig W, Whitfield G, et al.** 1986 Assignment of the gene for the beta subunit of thyroid-stimulating hormone to the short arm of human chromosome 1. Proc Natl Acad Sci USA. 83:1822–1826.
30. **Guidon P, Whitfield G, Porti D, Kourides I.** 1988 The human thyrotropin beta-subunit gene differs in 5′ structure from murine TSH-beta genes. DNA. 7:691–699.
31. **Wondisford F, Usala S, DeCherney G, et al.** 1988 Cloning of the human thyrotropin β-subunit gene and transient expression of biologically active human thyrotropin after gene transfection. Mol Endocrinol. 2:32–39.
32. **Ronga G, Fiorentino A, Fragasso G, Fringuelli F, Todino V.** 1986 Complementary role of whole body scan and serum thyroglobulin determination in the follow-up of differentiated thyroid carcinoma. Ital J Surg Sci. 16:11–15.
33. **Grunwald F, Kalicke T, Feine U, et al.** 1999 Fluorine-18 fluorodeoxyglucose positron emission tomography in thyroid cancer: results of a multicentre study. Eur J Nucl Med. 26:1547–1552.
34. **Lubin E, Mechlis-Frish S, Zatz S, et al.** 1994 Serum thyroglobulin and iodine-131 whole-body scan in the diagnosis and assessment of treatment for metastatic differentiated thyroid carcinoma. J Nucl Med. 35:257–262.
35. **Van Sorge-van Boxtel R, Van Eck-Smit B, Goslings B.** 1993 Comparison of serum thyroglobulin, 131I and 201Tl scintigraphy in the postoperative follow-up of differentiated thyroid cancer. Nucl Med Commun. 14:365–372.
36. **Obiols G, Simo R, Burgos R, et al.** 1997 Differentiated thyroid carcinoma, 1972–1992. Follow-up, detection of recurrences and prognostic factors. Med Clin (Barc). 109:738–743.
37. **Unal S, Menda Y, Adalet I, et al.** 1998 Thallium-201, technetium-99m-tetrofosmin and iodine-131 in detecting differentiated thyroid carcinoma metastases. J Nucl Med. 39:1897–1902.
38. **Dadparvar S, Krishna L, Brady L, et al.** 1993 The role of iodine-131 and thallium-201 imaging and serum thyroglobulin in the management of differentiated thyroid carcinoma. Cancer. 71:3767–3773.
39. **Brendel A, Guyot M, Jeandot R, Lefort G, Manciet G.** 1988 Thallium-201 imaging in the follow-up of differentiated thyroid carcinoma. J Nucl Med. 29:1515–1520.
40. **Muller-Gartner H, Schneider C.** 1988 Clinical evaluation of tumor characteristics predisposing serum thyroglobulin to be undetectable in patients with differentiated thyroid cancer. Cancer. 61:976–981.
41. **Harvey R, Matheson N, Grabowski P, Rodger A.** 1990 Measurement of serum thyroglobulin is of value in detecting tumour recurrence following treatment of differentiated thyroid carcinoma by lobectomy. Br J Surg. 77:324–326.
42. **Hay I.** 1989 Prognostic factors in thyroid carcinoma. Thyroid Today. 12:1–9.
43. **Gallowitsch H, Mikosch P, Kresnik E, Unterweger O, Gomez I, Lind P.** 1998 Thyroglobulin and low-dose iodine-131 and technetium-99m-tetrofosmin whole-body scintigraphy in differentiated thyroid carcinoma. J Nucl Med. 39:870–875.
44. **Cailleux AF, Baudin E, Travagli JP, Ricard M, Schlumberger M.** 2000 Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer? J Clin Endocrinol Metab. 85:175–178.

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