

A Comparison of Recombinant Human Thyrotropin and Thyroid Hormone Withdrawal for the Detection of Thyroid Remnant or Cancer*

BRYAN R. HAUGEN, FURIO PACINI, CHRISTOPH REINERS, MARTIN SCHLUMBERGER, PAUL W. LADENSON, STEVEN I. SHERMAN, DAVID S. COOPER, KATHRYN E. GRAHAM, LEWIS E. BRAVERMAN, MONICA C. SKARULIS, TERRY F. DAVIES, LESLIE J. DEGROOT, ERNEST L. MAZZAFERRI, GILBERT H. DANIELS, DOUGLAS S. ROSS, MARKUS LUSTER, MARY H. SAMUELS, DAVID V. BECKER, HARRY R. MAXON III, RALPH R. CAVALIERI, CAROLE A. SPENCER, KEVIN McELLIN, BRUCE D. WEINTRAUB, AND E. CHESTER RIDGWAY

Division of Endocrinology, University of Colorado Health Sciences Center (B.R.H., E.C.R.), Denver, Colorado 80262; the Division of Endocrinology, University of Pisa (F.P.), 56124 Pisa, Italy; Klinik und Poliklinik fuer Nuklearmedizin der Universitaet Wuerzburg (C.R., M.L.), Wuerzburg D-97070, Germany; Service de Medecine Nucleaire, Institut Gustave Roussy (M.S.), Villejuif 94805; the Division of Endocrinology and Metabolism, The Johns Hopkins University School of Medicine (P.W.L.), Baltimore, Maryland 21287; the Department of Medical Specialties, M. D. Anderson Cancer Center (S.I.S.), Houston, Texas 77030; the Division of Endocrinology, Sinai Hospital of Baltimore (D.S.C.), Baltimore, Maryland 21215; the Division of Endocrinology, Oregon Health Sciences University (K.E.G., M.H.S.), Portland, Oregon 97201; the Genetics Division, Brigham and Women's Hospital (L.E.B.), Boston, Massachusetts 02115; the Division of Intramural Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (M.C.S.), Bethesda, Maryland 20892; the Division of Endocrinology, Mount Sinai School of Medicine (T.F.D.), New York, New York 10029; the Department of Medicine, University of Chicago Medical Center (L.J.D.), Chicago, Illinois 60637; the Department of Internal Medicine, Ohio State University Health Sciences Center (E.L.M.), Columbus, Ohio 43210; the Thyroid Unit, Massachusetts General Hospital (G.H.D., D.S.R.), Boston, Massachusetts 02114; the Division of Nuclear Medicine, New York Hospital-Cornell Medical Center (D.V.B.), New York, New York 10021; Nuclear Medicine, University of Cincinnati Medical Center (H.R.M.), Cincinnati, Ohio 45267; Nuclear Medicine, Veterans Administration Medical Center (R.R.C.), San Francisco, California 94121; the Department of Medicine, University of Southern California (C.A.S.), Los Angeles, California 90033; Genzyme Transgenics Corp. (K.E.), Boston, Massachusetts 02139; and the Laboratory of Molecular Endocrinology, University of Maryland School of Medicine (B.D.W.), Baltimore, Maryland 21201

ABSTRACT

Recombinant human TSH has been developed to facilitate monitoring for thyroid carcinoma recurrence or persistence without the attendant morbidity of hypothyroidism seen after thyroid hormone withdrawal. The objectives of this study were to compare the effect of administered recombinant human TSH with thyroid hormone withdrawal on the results of radioiodine whole body scanning (WBS) and serum thyroglobulin (Tg) levels. Two hundred and twenty-nine adult patients with differentiated thyroid cancer requiring radioiodine WBS were studied. Radioiodine WBS and serum Tg measurements were performed after administration of recombinant human TSH and again after thyroid hormone withdrawal in each patient. Radioiodine whole body scans were concordant between the recombinant TSH-stimulated and thyroid hormone withdrawal phases in 195 of 220 (89%) patients. Of the discordant scans, 8 (4%) had superior scans after recombinant human TSH administra-

tion, and 17 (8%) had superior scans after thyroid hormone withdrawal ($P = 0.108$). Based on a serum Tg level of 2 ng/mL or more, thyroid tissue or cancer was detected during thyroid hormone therapy in 22%, after recombinant human TSH stimulation in 52%, and after thyroid hormone withdrawal in 56% of patients with disease or tissue limited to the thyroid bed and in 80%, 100%, and 100% of patients, respectively, with metastatic disease. A combination of radioiodine WBS and serum Tg after recombinant human TSH stimulation detected thyroid tissue or cancer in 93% of patients with disease or tissue limited to the thyroid bed and 100% of patients with metastatic disease. In conclusion, recombinant human TSH administration is a safe and effective means of stimulating radioiodine uptake and serum Tg levels in patients undergoing evaluation for thyroid cancer persistence and recurrence. (*J Clin Endocrinol Metab* 84: 3877–3885, 1999)

Received April 22, 1999. Revision received June 30, 1999. Accepted July 7, 1999.

Address all correspondence and requests for reprints to: Bryan R. Haugen, M.D., University of Colorado Health Sciences Center, B151, 4200 E 9th Avenue, Denver, Colorado 80262.

* This work was supported by Genzyme Transgenics Corp. (Boston, MA). Thyroglobulin measurements were supported by NCRR General Clinical Research Center Grant M01-RR-43.

APPROXIMATELY 17,000 cases of thyroid carcinoma are diagnosed in the U.S. each year, and a majority of these are papillary and follicular carcinomas (1). Although most recurrences occur within the first 10 yr, life-long monitoring is required because cancer recurrence may occur many decades after initial diagnosis and treatment (2–4). The most sensitive indicators of thyroid cancer recurrence are

radioiodine whole body scanning (WBS) and serum thyroglobulin (Tg) measurement, particularly when used in combination. Furthermore, Tg levels after withdrawal of thyroid hormone accurately predict the results of radioiodine scanning (5). Periodic withdrawal of thyroid hormone therapy is required to raise endogenous serum TSH levels for radioiodine scanning and enhance serum Tg sensitivity, but causes a wide range of hypothyroid symptoms and signs, and occasional tumor growth (6).

Recombinant human TSH (rhTSH) has been developed to facilitate monitoring for persistent or recurrent thyroid cancer without the attendant morbidity of hypothyroidism (7–9). Recent studies have shown that patients given rhTSH avoid the hypothyroid symptoms and signs seen with withdrawal of L-T₄ therapy (10, 11). These studies also demonstrated that rhTSH stimulates radioiodine uptake in thyroid remnant tissue and metastatic disease. However, in the most recent study, radioiodine WBS after conventional thyroid hormone withdrawal generated superior scans compared with rhTSH scans in 29% of patients with positive scans (11). The superior scans observed with conventional L-T₄ withdrawal were thought to be due in part to lower whole body radioiodine retention and shorter length of TSH elevation observed during rhTSH administration while patients were taking L-T₄. The current study was designed to compare the effects of two different dosing regimens of rhTSH with conventional (levothyroxine) L-T₄ withdrawal on radioiodine WBS. In addition, the likelihood of scans with suboptimal counts for adequate imaging was minimized by requiring uniform dosing of radioiodine and the acquisition of a minimum number of counts for scanning. Finally, serum Tg measurements after rhTSH stimulation were evaluated for disease detection when used alone and in combination with WBS.

Subjects and Methods

Study patients

Two hundred and twenty-nine adult patients with differentiated thyroid cancer requiring radioiodine WBS received rhTSH, and 226 patients completed the study. Written informed consent was obtained from each patient, and the protocol was approved by the institutional review board at each site. All but 1 patient had undergone a total or near-total thyroidectomy, and 83% had received prior radioiodine therapy. Patients who had received previous radioiodine therapy were enrolled at least 4 months after the last treatment. Within 7 days of entry into the study, a serum TSH level of 0.5 mU/L or less during thyroid hormone therapy (THT) was confirmed in each patient. None of the patients had a concurrent major medical disorder or received radiographic contrast agents that could interfere with radioiodine uptake. The use of a low iodine diet was specifically recommended, and a majority of investigators followed a low iodine protocol. Patients received the same diet instructions for both scans.

rhTSH

rhTSH (Thyrogen, Genzyme Corp., Cambridge, MA) was produced as previously described (7, 12). The biological potency was 4 IU/mg protein (Second WHO International Reference Preparation of human TSH for Bioassay 84/703).

Study design (Fig. 1)

To evaluate dosing regimens of rhTSH, patients were randomized into two study arms (Fig. 1). Patients in arm I received 0.9 mg rhTSH,

every 24 h for two doses (Fig. 1A). Twenty-four hours after the second dose of rhTSH, 4 ± 0.4 mCi (148 ± 14.8 megabecquerels) radioiodine were administered orally, and a whole body scan was obtained 48 h later. Whole body images were acquired with a γ -camera after scanning for a minimum of 30 min or a minimum of 140,000 counts. Single (spot) images of body regions were acquired after scanning a minimum of 10–15 min or after obtaining 60,000 counts for a large field of view camera or 35,000 counts for a small field of view camera. These specified conditions were required to account for the differences in iodine retention between the euthyroid (rhTSH) and hypothyroid (withdrawal) phases of the study (10). At least 2 weeks after the second dose of rhTSH, patients were withdrawn from THT and followed until adequate hypothyroidism (TSH, \geq 25 mU/L) was achieved. A repeat dosage of 4 ± 0.4 mCi radioiodine was administered, and WBS was again performed 48 h later. Patients in arm II of the study received 0.9 mg rhTSH IM every 72 h for three doses (Fig. 1B). Twenty-four hours after the third dose of rhTSH, 4 ± 0.4 mCi radioiodine were administered orally, followed by a whole body scan 48 h later. At least 2 weeks after the third dose of rhTSH, patients were withdrawn from THT, and a repeat radioiodine WBS was performed in the same manner as in arm I.

Interpretation of radioiodine scans

Whole body ¹³¹I scans were independently evaluated by three reviewers who were unaware of the order of the scans. Scans were evaluated for technical quality (acceptable, suboptimal, or inadequate) and were classified according to site of uptake and number of lesions (Table 1). The suboptimal or inadequate scans were further classified as poor scan quality, count poor scans, blurred images, missing or unlabeled markers, or other to better define why these scans were not acceptable. The scan classification used for all analyses was the consensus of at least two of the three independent reviewers. Sixty-five percent of scans were given the same classification by all three reviewers, and 31% of scans were given the same classification by two of the three reviewers. Four percent of scans were given different classifications by all three reviewers. If the classification (e.g. 1, 2, or 3) or subclassification (e.g. 2A or 2B) assigned to each scan for a patient was equivalent, the scans were considered concordant. Scans were considered discordant if one scan was given a higher classification or subclassification, and the higher rated scan was considered superior. Furthermore, for concordant scans, the reviewers were also asked if a difference in the number and distribution of lesions between these concordant scans could potentially change the clinical management of the patient. Scans were performed with and without labeled markers (chin, thyroid cartilage, sternal notch, xiphoid process, and iliac crest).

Serum measurements

Baseline serum Tg was measured during THT (TSH, \leq 0.5 mU/L). Serum was obtained on the final day of rhTSH administration in each arm, as well as 24 h, 48 h, 72 h, and 7 days after the final dose of rhTSH (Fig. 1). During the withdrawal phase, serum was obtained on the day of radioiodine administration. All serum Tg assays were performed in duplicate at one institution (University of Southern California, Endocrine Services, Los Angeles, CA) using a RIA employing CRM-457 standardization. The RIA had an analytical sensitivity of 0.2 ng/mL, a functional sensitivity of 0.5 ng/mL, and a reference range for euthyroid subjects of 3–40 ng/mL (13). All samples collected from an individual patient were tested in a single assay run. The basal serum specimen for each patient was screened for the presence of Tg antibodies using a quantitative RIA method with a detection limit of 1.0 IU/mL which was calibrated against the WHO First International Reference Preparation 65/93 (Kronus, San Clemente, CA). Measurements for rhTSH antibodies were performed in each patient at baseline and during the hypothyroid phase before the administration of radioiodine. Samples were analyzed by a validated enzyme-linked immunoassay. Abnormal results were confirmed for antibodies by Western blot analysis.

Hypothyroid symptoms and quality of life measurements

Hypothyroid symptoms and signs were assessed in each patient by the Billewicz scale (14), which is an observer-rated evaluation for 14 symptoms and signs of hypothyroidism. The SF-36 quality of life in-

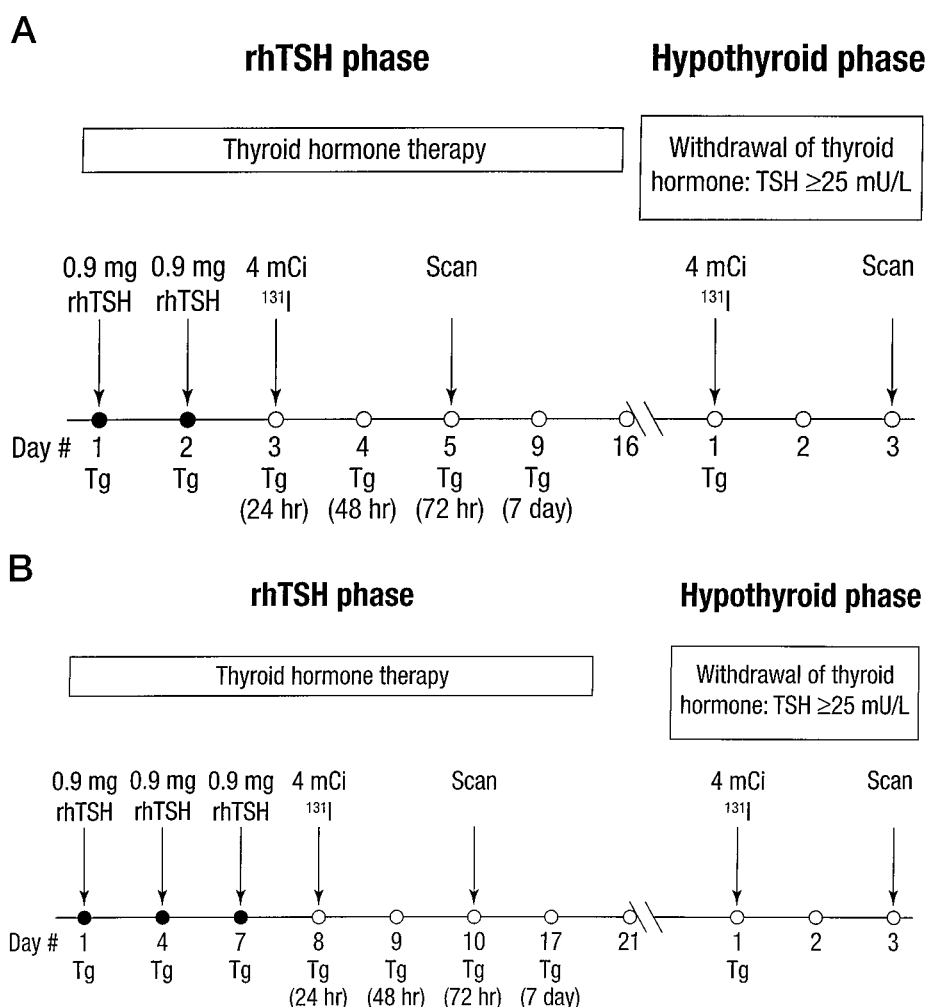


FIG. 1. Protocol for scanning procedures in two study arms. A, Two-dose rhTSH arm. B, Three-dose rhTSH arm.

TABLE 1. Classification of radioiodine scans

Class 0	No uptake
Class 1	Thyroid bed uptake
Class 2	Uptake limited to neck (outside thyroid bed)
A	Solitary focus
B	Multiple foci
Class 3	Uptake in chest
A	Mediastinum
B	Nodular lung uptake
C	Diffuse lung uptake
D	Combination of A, B and/or C
Class 4	Uptake outside neck and chest
A	Solitary skeletal focus
B	Multiple skeletal foci
C	Liver uptake
D	Brain uptake
E	Combination of above

strument is a validated self-administered scale (15). The Billewicz scale and SF-36 instrument were tested in each patient at three points in the study: at baseline on THT, after administration of rhTSH, and after withdrawal of thyroid hormone therapy on the day of radioiodine administration.

Statistical analysis

All statistical tests were two sided, and the significance level (α) used was 0.050. Comparisons between the rhTSH- and withdrawal-mediated scan-

ning techniques were made using the sign test and the continuously adjusted 95% confidence interval. Treatment arm comparisons were made using the Fisher's exact test. Comparisons of serum Tg levels between groups (THT and rhTSH) were performed using the Wilcoxon signed rank test. Comparisons of hypothyroid symptoms and signs on the Billewicz scale and the SF-36 quality of life measures between treatment groups were made using the Wilcoxon signed rank test within each arm.

Results

Study patients

The characteristics of the 229 patients who received rhTSH are shown in Table 2. With the exception of a difference in mean ages (44 vs. 50 yr, between arms I and II, respectively; $P = 0.020$), there were no significant differences between patients receiving the two-dose and three-dose regimens. Disease staging at initial therapy is also shown in Table 2, which is different from radioiodine scan classification at the time of the study (Table 1).

Serum TSH concentrations

Baseline serum TSH concentrations during THT were 0.08 ± 0.17 and 0.10 ± 0.13 mU/L in patients in arms I and II, respectively. Maximal serum TSH concentrations were observed 24 h after the final dose of rhTSH in both arm I

(124 ± 59 mU/L) and arm II (102 ± 44 mU/L). By comparison, mean serum TSH levels during the withdrawal phase were 71 ± 40 and 69 ± 38 mU/L at the time of radioiodine administration in arms I and II, respectively. Patients in the rhTSH phase of arm I had elevated serum TSH levels (≥25 mU/L) for approximately 4 days, whereas patients in arm II had elevated levels for approximately 9 days.

TABLE 2. Demographics of patients entered into the two study arms

Patients	No. of patients (%)	
	Arm I (n = 117)	Arm II (n = 112)
Female	74 (63)	74 (66)
Mean age (yr ± SD) ^a	44 ± 15	50 ± 16
Cancer histology		
Papillary	78 (67)	64 (57)
Follicular variant of papillary	19 (16)	21 (19)
Follicular	17 (14)	22 (20)
Hurthle	3 (3)	5 (5)
Metastatic disease (outside thyroid bed)	19 (16)	30 (27)
Neck	5 (4)	6 (5)
Thoracic	3 (3)	10 (9)
Skeletal	4 (3.5)	11 (10)
Withdrawal scan (-)/Tg ≥10 ng/mL	7 (6)	3 (3)
Thyroidectomy only	18 (15)	21 (19)
Previous radioiodine therapy	99 (85)	91 (81)
Disease stage (AJCC/TNM)		
I	70 (61)	54 (50)
II	22 (19)	22 (20)
III	16 (14)	22 (20)
IV	6 (5)	10 (9)

^a $P = 0.02$, significant difference in the mean age of the patients entered into the two treatment arms.

Comparison of whole body radioiodine imaging after rhTSH administration and after thyroid hormone withdrawal

Of the 229 patients who received rhTSH, 226 completed the study, and 220 had evaluable scans as determined by the independent reviewers. Among these 220 patients, 195 (89%) had concordant scans, 8 (4%) had superior rhTSH scans, and 17 (8%) had superior withdrawal scans (Table 3A). There was no significant difference in the number of superior rhTSH or withdrawal scans within either study arm (arm I, $P = 0.146$; arm II, $P = 0.581$; all patients, $P = 0.108$) or between arms I and II ($P = 0.76$).

One hundred and eight patients (49%) had a positive radioiodine whole body scan (class ≥1) after 1 or both preparatory techniques. Eighty-three patients (77%) had concordant scans, 8 (7%) had superior rhTSH scans, and 17 (16%) had superior withdrawal scans (Table 3B). There was no significant difference in the number of superior rhTSH or withdrawal scans within either study arm (arm I, $P = 0.146$; arm II, $P = 0.581$; all patients, $P = 0.108$) or between arms I and II ($P = 0.78$).

Metastatic disease was defined as disease outside the thyroid bed on a diagnostic or posttherapy scan, and/or an elevated serum Tg (≥10 ng/mL) during thyroid hormone withdrawal in the absence of a positive diagnostic scan at the time of the study. Based on this definition, 49 patients (22%) had metastatic disease. Ten of these patients had an elevated serum Tg as the only evidence of disease (16–18). Thirty-nine patients (80%) had concordant scans, 2 (5%) had superior rhTSH scans, and 8 (16%) had superior withdrawal scans (Table 3C). There was no significant difference in the number of superior rhTSH or withdrawal scans within either study arm (arm I, $P = 0.375$; arm II, $P = 0.375$; all patients, $P = 0.109$).

TABLE 3. Radioiodine scan comparison between rhTSH administration and thyroid hormone withdrawal

Whole body radioiodine scan	Number (%)		
	Arm I (n = 113)	Arm II (n = 107)	All patients
A			
Concordant	101 (89)	94 (88)	195 (89)
Discordant	12 (11)	13 (12)	15 (11)
rhTSH scan superior	3 (3)	5 (5)	8 (4)
Withdrawal scan superior	9 (8)	8 (7)	17 (8)
P	0.146	0.581	0.108
	Arm I (n = 48)	Arm II (n = 60)	All
B			
Concordant	36 (75)	47 (78)	83 (77)
Discordant	12 (25)	13 (22)	25 (23)
rhTSH scan superior	3 (6)	5 (8)	8 (7)
Withdrawal scan superior	9 (19)	8 (13)	17 (16)
P	0.146	0.581	0.108
	Arm I (n = 19)	Arm II (n = 30)	All
C			
Concordant	14 (74)	25 (83)	39 (80)
Discordant	5 (26)	5 (17)	10 (20)
rhTSH scan superior	1 (5)	1 (3)	2 (5)
Withdrawal scan superior	4 (21)	4 (13)	8 (16)
P	0.375	0.375	0.109

Scans were considered concordant when independently assigned the same classification (Table 1). Scans were considered superior when given a higher classification. A, All evaluable patients (n = 220); B, patients with positive scans (n = 108); C, patients with metastatic disease (n = 49). Metastatic disease was defined as disease outside the thyroid bed on diagnostic or posttherapy scan or a serum Tg level of 10 ng/mL or more on THT.

or between arms I and II ($P = 0.85$). Scan results for the 10 individual patients with disease outside the thyroid bed and discordant scans are shown in Table 4. Of the 8 patients with superior withdrawal scans, 5 had negative rhTSH scans (Table 4A). Three of these patients with negative rhTSH scans had thyroid bed uptake (class 1) after withdrawal scanning (patients 1, 5, and 6). Neither of the rhTSH and withdrawal diagnostic scans detected disease in the neck outside the thyroid bed in 1 patient (patient 1) or pulmonary uptake (patients 5 and 6) seen on posttherapy scanning. One of these patients (no. 5) had discordant scans at 48 h, but concordant scans when repeated at 72 h. One patient in each arm of the study had markedly discordant diagnostic scan results (patients 2 and 7), with no uptake after rhTSH and mediastinal or pulmonary uptake after withdrawal, both of which were confirmed at posttherapy scanning. Both patients had elevated serum Tg levels after rhTSH stimulation (38.0 and 13.1 ng/mL, respectively).

Serum Tg after rhTSH administration and after thyroid hormone withdrawal

Maximum serum Tg levels were observed 3 days after the final rhTSH injection in arm I and between 1–3 days after the final rhTSH injection in arm II. Of the 229 patients enrolled in the study, 35 (15%) had detectable serum Tg antibodies. Patients who had undergone previous ablation of thyroid tissue (<1% uptake in thyroid bed) and had negative serum Tg antibodies were further studied. One hundred and five patients had a serum Tg levels of 2 ng/mL or more after thyroid hormone withdrawal. This serum Tg value was chosen because of the assay sensitivity (0.5 ng/mL) and evidence that any detectable serum Tg indicates the presence of thyroid tissue (19). Of these 105 patients, 91 (87%) had a serum Tg of 2 ng/mL or more after rhTSH stimulation, and 52 (50%) had a serum Tg of 2 ng/mL or more during THT. Figure 2 shows a comparison of serum Tg levels during THT, after

stimulation with rhTSH, and after thyroid hormone withdrawal in 58 patients in arm I (Fig. 2A) and 50 patients in arm II (Fig. 2B) with a baseline Tg of less than 2 ng/mL. Median serum Tg levels were less than 0.5, 1.1, and 1.8 ng/mL during THT, after rhTSH, and after hormone withdrawal, respectively, in arm I, and were less than 0.5, 1.2, and 1.8 ng/mL, respectively, in arm II.

To evaluate the ability of rhTSH-stimulated serum Tg levels to detect thyroid remnant or cancer, 46 patients with withdrawal or posttherapy radioiodine uptake in the thyroid bed (class 1) and 30 patients with metastatic disease defined as posttherapy scans with uptake outside the thyroid bed (class ≥ 2) had Tg measurements during THT, after rhTSH stimulation, and after thyroid hormone withdrawal. Tg levels of 2 ng/mL or more and 5 ng/mL or more were used as cut-off values for disease detection. Figure 3A shows the percentage of positive Tg measurements at each cut-off level for the 46 patients with radioiodine uptake in the thyroid bed. An elevated Tg was detected on THT in 22% and 20% of patients at the 2 and 5 ng/mL cut-off levels, respectively, whereas 52% and 35% had elevated Tg levels after rhTSH stimulation using these cut-off values. In comparison, an elevated Tg was detected after thyroid hormone withdrawal in 56% and 43% at the 2 and 5 ng/mL cut-off levels, respectively. For patients with cancer outside the thyroid bed, an elevated Tg level was detected during THT in 80% and 67% of patients at the 2 and 5 ng/mL cut-off levels, respectively (Fig. 3B). In comparison, an elevated Tg was detected after rhTSH stimulation in 100% and 97% of these patients with metastatic disease at these cut-off values. An elevated Tg level was detected in all 30 patients after thyroid hormone withdrawal at both cut-off values. The use of rhTSH to stimulate Tg production from thyroid tumor cells increased detection of radioiodine-concentrating disease over Tg levels measured during THT alone.

Thirty-two patients with rhTSH stimulated Tg levels of 2 ng/mL or more had negative rhTSH and withdrawal diagnostic WBS. This group comprised 23% (32 of 141) of the patients with evaluable Tg measurements (previous radioiodine ablation, Tg antibody negative). All of these patients had a withdrawal Tg of 2 ng/mL or more, and 75% had a withdrawal Tg of 10 ng/mL or more.

Combined use of rhTSH-stimulated Tg and WBS to detect thyroid remnant or cancer

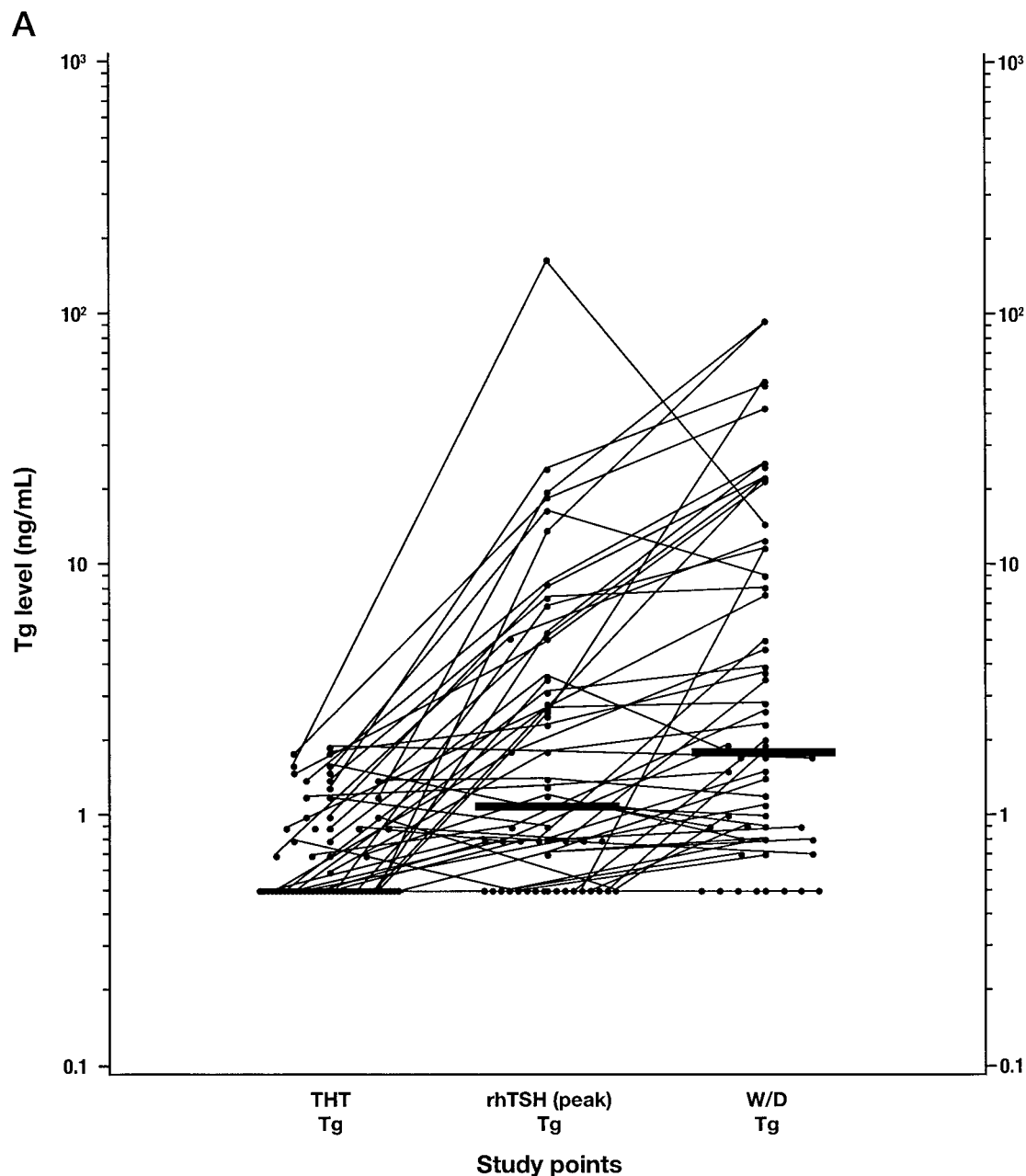
The same 2 groups of patients described above were analyzed for disease detection using the combination of serum Tg and WBS after rhTSH stimulation (Fig. 4). The disease detection rates in the 46 patients with thyroid bed uptake (class 1) after thyroid hormone withdrawal or posttherapy scanning were 93% (43 of 46) and 91% (42 of 46) of patients after rhTSH using the 2 and 5 ng/mL Tg cut-off values, respectively. The disease detection rates in the 30 patients with metastatic disease identified after thyroid hormone withdrawal or posttherapy scanning were 100% after rhTSH at both Tg cut-off values.

TABLE 4. Details of 10 patients with metastatic disease and discordant scans

Patient no.	Whole body scan			Thyroglobulin (ng/mL)		
	rhTSH	W/D	Posttherapy	THT	rhTSH	W/D
A						
Arm I						
1	0	1	2B	2.7	9.5	27.3
2	0	3B	3B	8.7	38.0	69.8
3	1	2B	2B	1.5	16.5	9.0
4	4A	4B	4B	2302	5993	8412
Arm II						
5 ^a	0	1	3B	535	945	1644
6	0	1	3D	882	2225	6692
7	0	3A	3A	2.1	13.1	67.0
8	1	2B	2B	2.0	88.0	34.0
B						
Arm I						
9	1	0	3A	91	2097	1585
Arm II						
10	2A	1	2A	0.5	6.6	7.9

A, Patients with superior withdrawal scans; B, patients with superior rhTSH scans. Definitions of scan classification are given in Table 1.

^a Seventy-two-hour WBS for both rhTSH and W/D was classified as 3B.



Note: Solid line (—) represents median.

FIG. 2. Serum Tg levels at baseline, after rhTSH, and after thyroid hormone withdrawal in patients with a baseline Tg levels below 2 ng/mL. A, Arm I. B, Arm II. Lines connect serum Tg values for an individual patient in each phase of the study. The solid line represents the median Tg for the group.

Clinical changes after rhTSH administration and after thyroid hormone withdrawal

Patients had essentially no symptoms or signs of hypothyroidism after rhTSH administration compared with thyroid hormone withdrawal. There were statistically significant differences between rhTSH administration and thyroid hormone withdrawal in both study arms for all 14 symptoms and signs of hypothyroidism on the Billewicz scale ($P < 0.01$). Patients reported significantly better quality of life scores

(SF-36 instrument) after rhTSH administration compared with those after thyroid hormone withdrawal in areas including performance of physical activities, problems with daily activities as a result of physical health, bodily pain, and emotional problems ($P < 0.01$).

Adverse events

There were no significant differences in the rate of adverse events after rhTSH administration between the 2 study arms

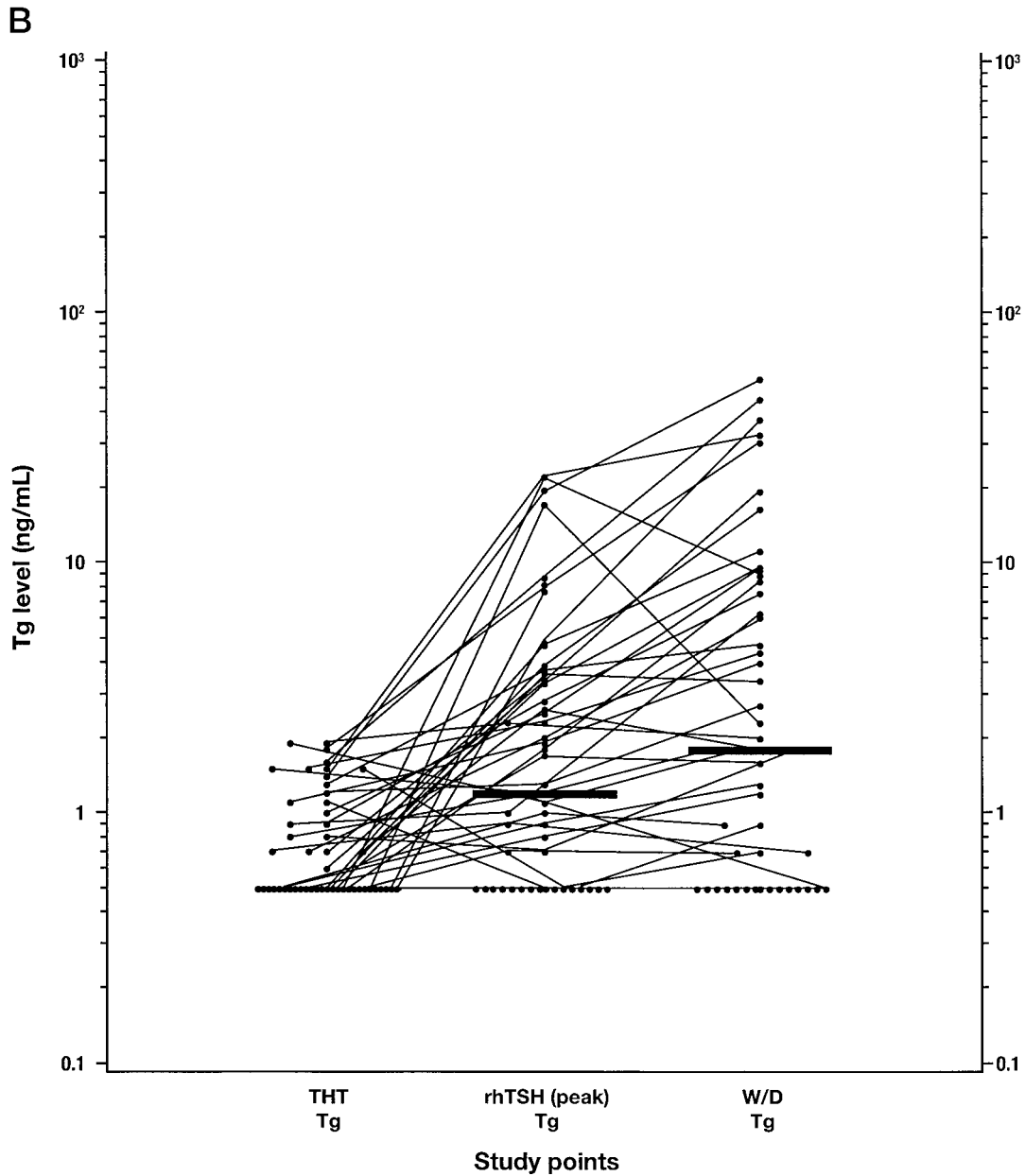


FIG. 2B. Continued.

($P = 0.08$). Headache was the most common event (9.2%) followed by nausea (6.1%) and asthenia (3.5%), which were usually mild and transient. No serious adverse events (life-threatening or requiring hospitalization) were related to rhTSH administration. Four patients had unrelated serious adverse events. Two patients in arm I had chest pain and palpitations 26 and 30 days after rhTSH administration, during the withdrawal phase. One patient in arm I had syncope 52 days after rhTSH administration on the eighth day of thyroid hormone withdrawal. One patient in arm II was hospitalized for nausea and vomiting, uncontrolled diabetes mellitus, and fever 26 days after rhTSH administration during the withdrawal phase. None

of the patients developed antibodies to rhTSH, including 17 patients who had received multiple courses of treatment in previous studies.

Discussion

In this study, we found that rhTSH was a safe and effective means of stimulating radioiodine uptake and serum Tg levels in patients undergoing monitoring for thyroid cancer while remaining on thyroid hormone therapy. rhTSH was well tolerated, with only mild to moderate headache, nausea, or asthenia noted in a minority of patients. None of the patients in this study developed antibodies to rhTSH, including 17

FIG. 3. Elevated serum Tg levels during THT, after rhTSH stimulation, and after thyroid hormone withdrawal. The percentages of patients with serum Tg levels above cut-off values of 2 and 5 ng/mL during THT, after rhTSH stimulation, and after thyroid hormone withdrawal are shown. Detectable disease is defined as positive diagnostic or posttherapeutic WBS after thyroid hormone withdrawal. A, Patients with uptake limited to the thyroid bed (class = 1); B, patients with disease outside the thyroid bed (class ≥ 2).

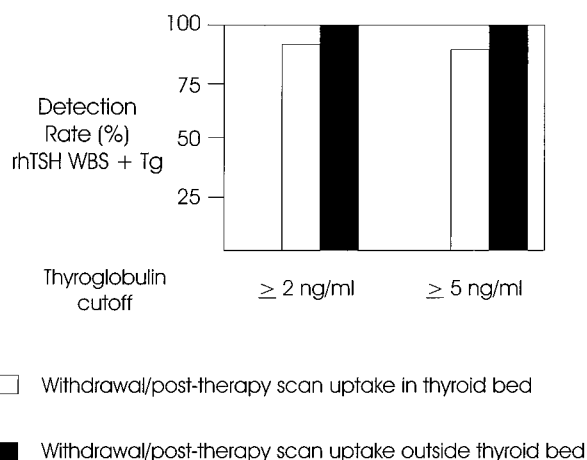
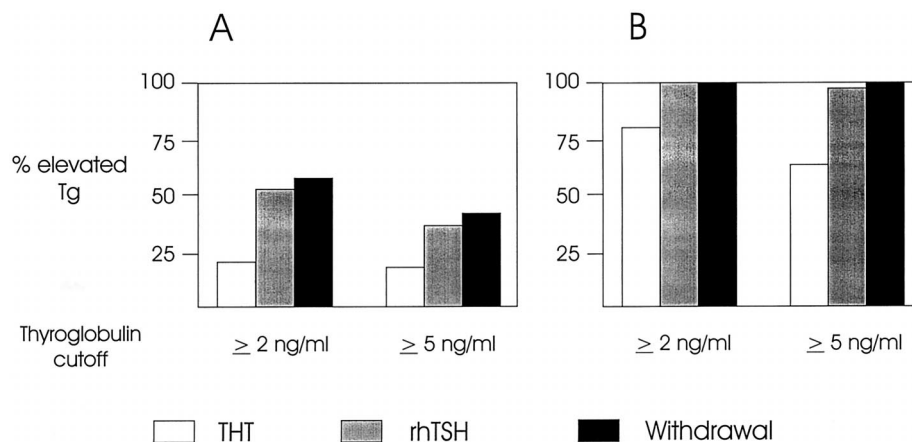


FIG. 4. Disease detection using a combination of WBS and serum Tg after rhTSH stimulation. The percentages of patients with serum Tg levels above cut-off values of 2 and 5 ng/mL in combination with WBS after rhTSH stimulation are shown. Detectable disease is defined as positive diagnostic or posttherapeutic WBS after thyroid hormone withdrawal. Open bars represent uptake limited to the thyroid bed, and closed bars represent uptake outside the thyroid bed (metastatic disease).

patients who had received previous doses of rhTSH, suggesting that rhTSH can be used for multiple administrations.

In a previous study (11), 71% of patients with positive diagnostic scans had an equivalent or superior scan with rhTSH, whereas 95% had equivalent or superior scans using the conventional withdrawal method. This difference was statistically significant in favor of the withdrawal method. The present study was designed to address a number of shortcomings in the previous study, most notably a significantly lower whole body retention of radioiodine after rhTSH stimulation compared with thyroid hormone withdrawal (10). Clearance of radioiodine is decreased by about one third during the hypothyroid withdrawal phase compared with the euthyroid rhTSH phase, leading to a 2-fold increase in whole body retention of radioiodine at 48 h after the radioiodine dose (20). To compensate for this difference, the present study used a slower scanning speed and minimum total count number for each image rather than scanning for a defined period of time, thereby minimizing potential count-poor scans after rhTSH administration. Furthermore,

in the present study, we standardized the dosage of radioiodine to 4 ± 0.4 mCi. Using these methods, we found that 84% of patients with a positive diagnostic scan had an equivalent or superior scan with rhTSH, whereas 93% of the patients had an equivalent or superior scan after thyroid hormone withdrawal. The differences between the rhTSH and withdrawal scans were not statistically significant in either arm of the study, although more discordant scans were superior after thyroid hormone withdrawal. Moreover, we found no significant difference between the two dosing regimens of rhTSH, suggesting that the two-dose regimen is preferable due to the convenience of administration. Following these guidelines for patient preparation, radioiodine dosage, and scanning technique is important to obtain good quality whole body scans.

It has been suggested that even with the availability of rhTSH, conventional thyroid hormone withdrawal is still preferable for detection of residual tissue and cancer in most patients (21). This commentary accurately noted that in the previous study (11), 21 patients had discordant scans, and 18 of these scans were superior after thyroid hormone withdrawal. In the current study, using standardized radioiodine scanning dosage and scanning techniques, we found discordant scans in only 12 patients receiving 2 doses of rhTSH (arm I). Nine of these scans were superior after thyroid hormone withdrawal, and 3 were superior after rhTSH stimulation. Although this difference was not statistically significant, the trend still favored thyroid hormone withdrawal. However, measurement of serum Tg together with WBS after rhTSH greatly improved the detection of remnant tissue or cancer. Specifically, the combination of measuring serum Tg and WBS after rhTSH accurately identified 100% of patients with metastatic disease and 93% of patients with uptake limited to the thyroid bed. In fact, measurement of a serum Tg level alone after rhTSH stimulation predicted thyroid bed uptake in 52% of patients and metastatic disease in 100% of patients using a cut-off level of 2 ng/mL. These results are superior to those obtained while patients were taking THT alone, in which a serum Tg measurement predicted thyroid bed uptake in 22% of patients and metastatic disease in 80% of patients using a cut-off level of 2 ng/mL. Prediction of remnant thyroid tissue or thyroid cancer using serum Tg requires a sensitive and consistent Tg assay and the absence of serum antibodies to Tg. The specific Tg values used in this

study may not be the same in other assays, and these values must be interpreted carefully.

As in the initial phase III study, the rhTSH scan was performed first in each patient, followed by the withdrawal scan. Recent studies have shown that scanning dosages of ^{131}I can cause "stunning" of thyroid tissue, resulting in diminished uptake of a subsequent therapeutic dosage of radioiodine (22, 23). This effect is more pronounced with higher administered activities of ^{131}I . In the present study, 96% of scans were either equivalent or superior after thyroid hormone withdrawal, suggesting that any contribution of stunning may have been small. The potential effect of stunning, however, cannot be excluded in the 4% of scans that were superior using rhTSH. Although the order of scans was not randomized, it was believed inappropriate to perform a withdrawal scan first, resume thyroid hormone therapy for 4–6 weeks, perform the rhTSH scan, and possibly withdraw thyroid hormone therapy again for 4–6 weeks in patients for whom a therapeutic dose of radioiodine was indicated.

In conclusion, rhTSH administration is a safe and effective means of stimulating radioiodine uptake and serum Tg levels in patients undergoing evaluation for thyroid cancer recurrence. No significant differences were seen between the two and three dose rhTSH arms of the study, suggesting that the two-dose rhTSH regimen may be preferable due to ease of administration. As whole body retention of radioiodine is reduced by half in euthyroid patients receiving rhTSH, care must be taken to obtain adequate scans for interpretation, using a minimum number of total counts as a threshold. Patients in this study had essentially no hypothyroid symptoms during administration of rhTSH compared to thyroid hormone withdrawal, and concomitantly fewer effects on job performance, mood state, and general sense of well-being. The use of rhTSH provides an alternative to thyroid hormone withdrawal for patients undergoing evaluation for thyroid cancer persistence and recurrence.

Acknowledgments

We acknowledge the tremendous efforts of the following coordinators and collaborators: Lisa Jensen, R.N.; Nelson Trujillo, M.D.; Prof. A. Pinchera; Dr. F. Lippi; Dr. F. Angelini; M. Lassmann; U. Michalowski; I. Grelle; Eric Baudin, M.D.; Marcel Ricard; Bernard Collot; Marge E. Ewertz, R.N.; Michele Smith, R.N.; Ebrahim Delpassand, M.D.; Naomi Walpert, R.N., M.S.; David Cook, M.D.; Robert Nance, M.D.; Craig Cochran, R.N.; Giuseppe Barbesino, M.D.; Dr. Sanija Bajramovic; Deirdre Maxted; Kathleen Kirby; and Mohammed Al-Adhami, Ph.D.

References

1. Parker SL, Davis KJ, Wingo PA, Ries LA, Heath CW. 1998 Cancer statistics by race and ethnicity. *CA A Cancer J Clinicians*. 48:31–48.
2. Mazzaferrri EL, Jhiang SM. 1994 Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med*. 97:418–428.
3. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. 1990 Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab*. 71:414–424.
4. Hay ID. 1990 Papillary thyroid carcinoma. *Endocrinol Metab Clin North Am*. 19:545–575.
5. Schlumberger MJ. 1998 Papillary and follicular thyroid carcinoma. *N Engl J Med*. 338:297–306.
6. Dow KH, Ferrell BR, Anello C. 1997 Quality-of-life changes in patients with thyroid cancer after withdrawal of thyroid hormone therapy. *Thyroid*. 7:613–619.
7. Szkudlinski MW, Thotakura NR, Bucci I, et al. 1993 Purification and characterization of recombinant human thyrotropin (TSH) isoforms produced by Chinese hamster ovary cells: the role of sialylation and sulfation in TSH bioactivity. *Endocrinology*. 133:1490–1503.
8. Thotakura NR, Desai RK, Bates LG, Cole ES, Pratt BM, Weintraub BD. 1991 Biological activity and metabolic clearance of recombinant human thyrotropin produced in Chinese hamster ovary cells. *Endocrinology*. 128:341–348.
9. Huber GK, Fong P, Concepcion ES, Davies TF. 1991 Recombinant human thyroid-stimulating hormone: initial bioactivity assessment using human fetal thyroid cells. *J Clin Endocrinol Metab*. 72:1328–1331.
10. Meier CA, Braverman LE, Ebner SA, 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.
11. Ladenson PW, Braverman LE, Mazzaferrri EL, 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.
12. Cole ES, Lee K, Kelton C, et al. 1993 Recombinant human thyroid stimulating hormone: development of a biotechnology for detection of metastatic lesions of thyroid carcinoma. *Biotechnology*. 11:1014–1024.
13. Spencer CA, Takeuchi M, Kazarosyan M, et al. 1998 Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement and prognostic significance in patients with differentiated thyroid cancer. *J Clin Endocrinol Metab*. 83:1121–1127.
14. Billewicz WZ, Chapman RS, Crooks J, Day ME, Gossage J, Wayne E, Young J. 1969 Statistical methods applied to the diagnosis of hypothyroidism. *Q J Med*. 150:255–266.
15. Sacham S. 1983 A shortened version of the profile of mood states. *J Person Assess*. 47:305–306.
16. Pacini F, Lippi F, Formica N, Elisei R, Anelli S, Ceccarelli C, Pinchera A. 1987 Therapeutic doses of iodine-131 reveal undiagnosed metastases in thyroid cancer with detectable serum thyroglobulin levels. *J Nucl Med*. 28:1888–1891.
17. Pineda JD, Lee T, Ain KB, Reynolds JC, Robbins J. 1995 Iodine-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan. *J Clin Endocrinol Metab*. 80:1488–1492.
18. Schlumberger M, Arcangioli O, Piekarski JD, Tubiana M, Parmentier C. 1988 Detection and treatment of lung metastases of differentiated thyroid carcinoma in patients with normal chest x-rays. *J Nucl Med*. 29:1790–1794.
19. Spencer CA, Wang CC. 1995 Thyroglobulin measurement: techniques, clinical benefits, and pitfalls. *Endocrinol Metab Clin North Am* 24:841–863.
20. Park SG, Reynolds JC, Brucker-Davis F, et al. 1996 Iodine kinetics during ^{131}I scanning in patients with thyroid cancer: comparison of studies with recombinant human TSH (rhTSH) vs hypothyroidism. *J Nucl Med*. 37:15P–15P.
21. Utiger RD. 1997 Follow-up of patients with thyroid carcinoma. *N Engl J Med*. 337:928–929.
22. Park HM, Perkins OW, Edmonson JW, Schnute RB, Manatunga A. 1994 Influence of diagnostic radioiodines on the uptake of ablative doses of iodine-131. *Thyroid*. 4:49–54.
23. Sisson JC, Shapiro B, Shulkin BL, Gross MD, Ackerman RJ, Zempel S. Diagnostic doses overestimate the absorbed radiation dose to thyroid cancer from ^{131}I therapy [Abstract]. *Proc of the 76th Annual Meet of The Endocrine Soc*. 1994; 203–203.