Follow-Up of Low-Risk Differentiated Thyroid Cancer Patients Who Underwent Radioiodine Ablation of Postsurgical Thyroid Remnants after Either Recombinant Human Thyrotropin or Thyroid Hormone Withdrawal

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Background: We previously demonstrated comparable thyroid remnant ablation rates in postoperative low-risk thyroid cancer patients prepared for administration of 3.7GBq ^{131}I (100 mCi) after recombinant human (rh) TSH during T_4 (L-T4) therapy *vs.* withholding L-T4 (euthyroid *vs.* hypothyroid groups). We now compared the outcomes of these patients 3.7 yr later.

Patients and Methods: Fifty-one of the 63 original patients (28 euthyroid, 23 hypothyroid) participated. Forty-eight received rhTSH and serum thyroglobulin (Tg) sampling. A ^{131}I whole-body scan was performed in 43 patients, and successful ablation was defined by criteria from the previous study. Based on the criterion of uptake less than 0.1% in thyroid bed, 100% (43 of 43) remained ablated. When no visible uptake instead was used, five patients (four euthyroid, one hypothyroid) had minimal visible activity. When the TSH-stimulated Tg criterion was used, only two of 45 (one euthyroid, one hypothyroid) had a stimulated Tg level greater than 2 ng/ml.

Results: No patient in either group died, and no patient declared disease free had sustained tumor recurrence. Nine (four euthyroid, five hypothyroid) had received additional ^{131}I between the original and current studies due to detectable Tg or imaging evidence of disease; with follow-up, all now had a negative rhTSH-stimulated whole-body scan and seven (three euthyroid, four hypothyroid) had a stimulated serum Tg less than 2 ng/ml.

Conclusions: In conclusion, after a median 3.7 yr, low-risk thyroid cancer patients prepared for postoperative remnant ablation either with rhTSH or after L-T4 withdrawal were confirmed to have had their thyroid remnants ablated and to have comparable rates of tumor recurrence and persistence. **(*J Clin Endocrinol Metab* 94: 4171–4179, 2009)**

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Abbreviations: CI, Confidence interval; DTC, differentiated epithelial thyroid cancer; rhTSH, recombinant human TSH; RxWBS, therapeutic WBS; Tg, thyroglobulin; Tg-Ab, Tg antibody; WBS, whole-body scanning.

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Postsurgical thyroid remnant ablation is a key element in treatment for selected differentiated epithelial thyroid cancer (DTC) patients (1, 2). In high-risk patients, nonrandomized trials have shown lower rates of tumor recurrence when adjunctive radioiodine is used (3–5). Ablation of remnant thyroid tissue also improves the accuracy of long-term patient monitoring with serum thyroglobulin (Tg) and radioiodine whole-body scanning (WBS) (6, 7). Because postoperative thyroid remnant ablation requires TSH activation of tissue, the traditional approach of preparation for radioiodine therapy has been to withhold thyroid hormone therapy to induce an endogenous TSH rise (1). Although this strategy is effective, it causes clinical hypothyroidism with unpleasant symptoms (8) and, in some settings, the need for longer hospitalization compared with patients prepared by recombinant human TSH (rhTSH) (9).

In a previous prospective randomized trial (10), we demonstrated comparable successful postsurgical ^{131}I thyroid remnant ablation rates in two groups of low-risk DTC patients who were prepared for administration of 3.7 GBq ^{131}I with either endogenous TSH stimulation induced by 4 or more weeks of thyroid hormone withdrawal or by rhTSH. Successful ablation was achieved in all patients in both groups, based on the primary prospectively defined criterion for thyroid remnant ablation: either no visible uptake or less than 0.1% thyroid bed uptake of the administered ^{131}I activity on imaging performed 8 months after therapy. Similarly, based on the secondary criteria of no visible uptake alone or a stimulated serum Tg level less than 2 ng/ml at 8 months, there were no significant differences between the hypothyroid and euthyroid patient groups. In the current study, we reexamined most patients from both of the original groups 3 or more years later to determine whether current TSH-stimulated testing confirmed that the comparability of thyroid remnant ablation success had persisted and whether there has been any difference in patients' clinical outcomes.

Subjects and Methods

Study objectives and design

This open-label study was designed to provide follow-up information about patients who had previously undergone postsurgical ^{131}I thyroid remnant ablation after preparation with either withdrawal of thyroid hormone therapy or rhTSH while euthyroid on thyroid hormone therapy, as has been previously described (10). Eight months later, all of these patients had undergone follow-up rhTSH-stimulated diagnostic WBS and serum Tg measurement. The current study involved patients from all nine sites that participated in the previous trial, including four centers in the United States, two in France, and one each in Italy, Germany, and Canada.

The primary objective of the study was to confirm, after a median follow up of 3.7 yr (range 3.4–4.4 yr), whether there was comparable persistence of thyroid remnant ablation in patients who had been prepared for 100 mCi (3.7 GBq) ^{131}I therapy by thyroid hormone withdrawal (hypothyroid group) *vs.* rhTSH administration while on L-T_4 therapy (euthyroid group). Secondary objectives of the study were: 1) to determine whether there were patients with clinically documented recurrences of thyroid cancer; 2) to assess the patients' current rhTSH-stimulated serum Tg concentrations, as an indicator of residual disease or normal thyroid tissue; and 3) to confirm the long-term safety of previous rhTSH exposures.

Study patients

In the original remnant ablation trial, 63 patients (61 with papillary thyroid cancer and two with follicular thyroid cancer) had been randomized to preparation for postthyroidectomy thyroid remnant ablation by one of the two methods. However, only 61 of these patients were eligible for recruitment to enroll in this follow-up study; one was ineligible due to the presence of lung metastases on a posttherapy scan in the earlier trial, and another had not received the full rhTSH dose in preparation for radioiodine therapy. For women of child-bearing potential, a negative serum human chorionic gonadotropin pregnancy test was required. Patients gave written informed consent for review of their medical records to capture medical information because the 8-month follow-up visit in the original study and to undergo additional diagnostic testing under this protocol.

Fifty-one of the 61 eligible patients (23 hypothyroid and 28 euthyroid) participated in the current follow-up study by providing their interim medical histories. The demographic, clinical, and histopathological features of these 51 patients are reported in Table 1. Features of the 10 patients (four euthyroid and six hypothyroid), who did not participate, principally due to the inconvenience of testing procedures or recent extensive routine diagnostic follow-up, did not differ from those of enrolled patients in the current study (Table 2). Thus, exclusion of these 10 patients did not result in any apparent bias. Because three of the 51 enrolled patients could not be given rhTSH for various reasons (*i.e.* breast-feeding in one case and rhTSH-stimulated testing having been recently performed for routine follow-up in two cases), 48 of the 51 enrolled patients (21 hypothyroid and 27 euthyroid) received rhTSH for diagnostic testing in this protocol. Among these 48 patients, 43 agreed to receive 4 mCi ^{131}I to perform the WBS. In 47 of the 48, serum Tg determinations were completed; in two of these 47 cases, they were uninterpretable because of the presence of serum Tg antibody (Tg-Abs) at a level interfering with Tg measurement (>30 U/ml). Thus, reliable rhTSH-stimulated Tg data were obtained in 45 patients (20 hypothyroid and 25 euthyroid).

Patients' median time of follow-up, which was defined as the period between earlier ^{131}I ablation and the date of signing the consent form for participating in the current follow-up study, was 3.7 yr (range 3.4–4.4 yr).

Assessments of outcome

To assess current status, patients underwent rhTSH-stimulated diagnostic WBS, static neck imaging, and serum Tg measurement. Recombinant TSH (rhTSH, TSH alfa, Thyrogen; Genzyme Corp., Cambridge, MA) was administered as 0.9 mg im per day for 2 consecutive days. The WBS and static neck imaging

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TABLE 1. Demographic, clinical, and histopathological characteristics of study patients

Parameter	Hypothyroid group (n = 23)	Euthyroid group (n = 28)	Overall (n = 51)
Age at remnant ablation (yr)			
Mean (SD)	48 (13)	49 (12)	48 (12)
Median (range)	45 (24–67)	52 (24–71)	49 (24–71)
Gender, n (%)			
Female	18 (78)	23 (82)	41 (80)
Male	5 (22)	5 (18)	10 (20)
Race, (%)			
Caucasian	23 (100)	27 (96)	50 (98)
Black	0	1 (4)	1 (2)
Weight (kg)			
n	22	25	47
Mean (SD)	69.8 (14.0)	77.2 (18.3)	73.8 (16.7)
Median (range)	71.0 (46.0–95.0)	72.6 (50.2–121.0)	72.6 (46.0–121.0)
Height (cm)			
n	22	25	47
Mean (SD)	162 (9)	167 (9)	165 (10)
Median (range)	161 (145–182)	167 (149–186)	163 (145–186)
BMI (kg/m^2)			
n	22	25	47
Mean (SD)	26.7 (5.8)	27.4 (5.5)	27.1 (5.6)
Median (range)	26.8 (18.7–45.0)	25.9 (18.4–42.4)	26.2 (18.4–45.0)
Thyroid cancer type, n (%)			
Papillary	20 (87)	25 (89)	45 (88)
Follicular	0	0	0
Combined (considered papillary cancer patients)	3 (13%)	3 (11%)	6 (12%)
TNM			
T1	3 (13%)	7 (25%)	10 (20%)
T2	17 (74%)	19 (68%)	36 (71%)
T3	0	0	0
T4	3 (13%)	2 (7%)	5 (10%)
NX	1 (4%)	1 (4%)	2 (4%)
N0	12 (52%)	18 (64%)	30 (59%)
N1	6 (26%)	7 (25%)	13 (25%)
N1a	2 (9%)	1 (4%)	3 (6%)
N1b	2 (9%)	1 (4%)	3 (6%)
MX	3 (13%)	3 (11%)	6 (12%)
M0	20 (87%)	25 (89%)	45 (88%)
M1	0	0	0

BMI, Body mass index; TNM, tumor node metastasis.

were performed 48 ± 6 h after oral administration of 4 ± 0.4 mCi ^{131}I, which was given 24 ± 6 h after the second injection of rhTSH. All images were read by three independent nuclear medicine specialists, who were blinded to the original treatment. Static cervical images were assessed for uptake both visually and after quantification. If a majority of readers considered ^{131}I uptake to be visible in the thyroid bed, the percentage of administered ^{131}I activity then residing in the thyroid bed was calculated

TABLE 2. Characteristics of original study patients not enrolled in the current study

Patient	Age (yr)[a]	Sex	Thyroid cancer type	Original TNM
Former euthyroid group				
1	54	F	Follicular	T2NxMx
2	27	F	Papillary	T2N0M0
3	45	M	Papillary	T1N1M0
4	29	M	Papillary	T2N0M0
Former hypothyroid group				
5	37	F	Papillary/follicular	T1NxMx
6	32	F	Follicular	T2NxMx
7	52	F	Papillary	T2N0M0
8	47	F	Papillary	T2N0M0
9	33	F	Papillary	T2N0M0
10	62	M	Papillary	T2N0M0

TNM, Tumor node metastasis.

[a] Patient ages were defined at screening for the ablation study.

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using the same standardized procedure applied in the 8-month follow-up assessments. The definition of successful ablation by scanning was no visible thyroid bed uptake or, if visible, less than 0.1% uptake in the thyroid bed (11).

Blood samples for Tg and TSH measurement were obtained on d 1 (before rhTSH administration) and d 5 (3 d after the second rhTSH injection). Circulating anti-Tg-Abs were also measured on d 1. Successful ablation was defined by the previously described criteria used in the original ablation study (10).

The general safety and tolerability of rhTSH were monitored through patient-reported adverse events and changes in laboratory assessments for routine chemical and hematological parameters. In addition, safety also was verified by changes in vital signs (including blood pressure, temperature, heart rate, and respiratory rate) and medical history or physical examination findings.

Laboratory measurements

Patients' blood was taken at the screening visit for measurement of TSH and free T_4 concentrations and independently measured at each respective study site using standard immunoassay procedures. Other blood samples were collected on d 1 and 5, immediately centrifuged, and stored at −20 C and then shipped to a central laboratory (Department of Endocrinology, University of Pisa, Pisa, Italy) for determinations of serum Tg and Tg-Ab levels.

Serum Tg determination was performed using the same immunometric assay (Diagnostic Products Corp., Los Angeles, CA) used in the previous ablation study. The functional sensitivity of this method was of 0.9 ng/ml, standardized against the certified reference material for human Tg (12). Tg assays were performed within 1 month from the receipt of samples. All of each patient's samples were analyzed in the same assay run.

Tg-Abs were measured with an immunoenzymometric assay (AIA PACK TgAb system; TOSOH Bioscence NV, Tessenderlo, Belgium). Samples with a potentially interfering level of Tg-Ab (*i.e.* >30 U/ml in the central laboratory) were excluded from final analyses of stimulated Tg values. To exclude further any possible interference of Tg-Ab, a second data analysis using a lower cutoff of interference (>5 U/ml) also was performed.

Although Tg released by cervical nodes with tumor or a distant metastasis could confound the Tg-based analysis of the elimination of normal thyroid remnant tissue, the data also were examined using a definition of successful ablation of a rhTSH-stimulated serum Tg level less than 2 ng/ml in the absence of interfering Tg-Abs. Yet another analysis of the rate of ablation using a stimulated serum Tg level less than 1 ng/ml was also performed.

Mean serum TSH and free T_4 concentrations were similar for both groups at screening. Although several TSH and free T_4 values were minimally out of range in patients in both groups, none of these abnormalities was considered clinically significant.

Biostatistical considerations

In this follow-up study, the study population was limited to the patients who completed the original remnant ablation study and consented to participate in the current follow-up study. The same noninferiority methodology used in the original study was again applied in the analysis of the ablation rates calculated using the criteria defined for the primary end point (10). In the present study, this statistical strategy was also applied for the interpretation of the serum Tg values. Noninferiority was considered achieved if there was less than 20% difference between treatment groups (*i.e.* euthyroid group minus hypothyroid group), meaning that the lower bound of the 95% confidence interval (CI) was not more negative than −20%.

The standard $\alpha = 0.05$ was used to assess statistical significance. Missing or invalid data were not imputed. Patients were grouped according to their treatment assignments in the original study for comparison.

Results

Clinical outcomes

None of the 63 patients who participated in the original trial had died at the time of this follow-up study. Among the 51 patients enrolled in the current study, their interim medical histories revealed that nine patients (five hypothyroid and four euthyroid) had undergone additional ^{131}I treatments. Furthermore, two of them (one hypothyroid and one euthyroid) along with one additional patient who did not receive further ^{131}I treatments (former euthyroid) had been surgically treated for metastatic cervical lymph node disease identified by neck ultrasound and confirmed by fine-needle aspiration cytology; none of these patients' lesions were iodine avid (Table 3). In the previous study, these nine patients who required further treatment with additional ^{131}I had been considered ablated based on the criterion of absent neck radioiodine uptake, but none of the nine had definitive serum Tg evidence of absent thyroid tissue, due to either persistently detectable TSH-stimulated serum Tg (n = 5) or uninterpretable serum Tg due to the presence of potentially interfering Tg-Ab levels (n = 4). In one of these nine patients, there had been possible evidence of a small thyroid remnant by ultrasound, whereas in four patients there had been evidence of persistent thyroid bed or regional cervical lymph node metastases that had been shown at the posttherapeutic WBS (RxWBS). Similarly, the three patients who underwent surgery all had negative WBS but had detectable levels of serum Tg or interfering Tg-Ab and evidence of suspicious cervical adenopathy at neck ultrasound. In the current follow-up study, seven of the nine ^{131}I retreated patients underwent rhTSH stimulation, and all seven had a negative rhTSH-stimulated WBS, whereas two of these seven (one hypothyroid and one euthyroid) still had a rhTSH-stimulated serum Tg greater than 2 ng/ml, likely reflecting persistent tumor in cervical nodes. The other two of the nine ^{131}I retreated patients did not agree to undergo repeat rhTSH stimulation. None of the 51 patients in this follow-up study had been declared free of disease but then had suffered a tumor recurrence.

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TABLE 3. Patients who received subsequent ^{131}I therapy following 8-month postablation testing

Treatment group	Sex/age	Original TNM	Total additional ^{131}I (mCi)	Comment	Stimulated Tg at 8 months control in the first study (ng/mL)	Neck uptake at 8 months control in the first study (%)
Euthyroid	F/47	T2N0M0	150	Tg-Ab positive; thyroid bed uptake (RxWBS)[a]	0.99	0.07
Euthyroid	M/37	T2N0M0	260	Physical exams, stimulated Tg and neck ultrasound suggestive of residual tumor; node biopsy: tumor; uptake in thyroid bed (two RxWBS)[a]	1.60	<0.004
Euthyroid	F/68	T2N1Mx	193	Bed uptake (RxWBS)[a]	0.99	0.015
Euthyroid	F/31	T1N0M0	150	Serum hypo-Tg: 7.4 ng/ml, and possible remnant (neck ultrasound)	3.70	0.005
Hypothyroid	F/65	T2N1M0	260	Serum hypo-Tg: 5.6 ng/ml	3.10	<0.013
Hypothyroid	F/75	T2NxM0	100	Serum hypo-Tg: 12.4 ng/ml	44.0	<0.009
Hypothyroid	F/40	T2N0M0	280	Serum hypo-Tg: 10 ng/ml	4.30	<0.006
Hypothyroid	F/43	T1N1M0	260	Tumor in neck (CT scan)	2.50	0.011
Hypothyroid	M/40	T4N0M0	251	Tg-Ab positive; tumor in neck (neck ultrasound); lymph node aspirations: tumor; pathological uptake in neck (RxWBS); PET scan positive for tumor[a]	32.0	<0.01

In addition to the radioiodine therapies given after the end of the initial ablation study, two of these nine patients (one hypothyroid and one euthyroid) had residual noniodine-avid metastatic lymph nodes identified by neck ultrasound and fine-needle aspiration cytology and excised by surgery. A third patient with neck node metastases not able to take up iodine (belonging to the euthyroid group) directly underwent surgery with no other ^{131}I treatments. TNM, Tumor node metastasis; CT, computed tomography.

[a] All of these RxWBS comments are referring to interval studies obtained outside the first study and this second follow-up study.

Persisting efficacies of thyroid remnant ablation after hypothyroidism and rhTSH

The long-term outcome of the original ablation procedure was analyzed in the 43 patients who completed both rhTSH-stimulated WBS and rhTSH-stimulated Tg testing in the current protocol. They included the above described nine patients who had received further treatments after the first study, which, of course, confounds the assessment of efficacy of the original ablation procedure. Considering all 43 patients who consented to scanning, based on the criterion of no visible uptake, or uptake less than 0.1% in the thyroid bed, (the predefined primary end point of the study), 100% of patients in both the hypothyroid and euthyroid groups remained ablated. It is worth noting that formal confidence intervals could not be calculated for these results because 100% of patients were ablated in the two groups. When the more strict but subjective criterion of no visible uptake was used, faint residual visible thyroid bed uptake was identified in five subjects (one hypothyroid and four euthyroid). Consequently, 94% of the hypothyroid and 84% of euthyroid patients were considered to have been persistently ablated by using that criterion, with no clinically significant difference between the two groups (95% CI −23.2, 7.4) (Table 4). This indicates that this study was unable to prove noninferiority with regard to the no visible uptake end point, perhaps due to the small sample size, although the finding of trace thyroid bed uptake (which was quantitated to be very low in this study) is generally believed in most low-risk patients to be a finding of little or no clinical significance.

When the secondary end point of rhTSH-stimulated serum Tg was used as the criterion for successful ablation, 45 patients could be considered and all but two (one hypothyroid and one euthyroid) had rhTSH-stimulated Tg less than 2 ng/ml, corresponding to comparable ablation rates of 95 and 96%, respectively (95% CI −11.3, 13.3). When a more stringent rhTSH-stimulated serum Tg criterion, less than 1 ng/ml, was applied, all but four patients (two hypothyroid and two euthyroid) were considered to have been successfully ablated, corresponding to comparable ablation rates of 90 and 92%, respectively (95% CI −14.9, 18.9) (Table 4). Two patients (one hypothyroid and one euthyroid) had serum Tg-Ab levels greater than 30 U/ml that excluded them from the main Tg analyses. When the more stringent criterion of greater than 5 U/ml was used, nine patients (four hypothyroid and five euthyroid)

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TABLE 4. Comparison of 8-month and current study result for evaluable patients

	8-month postablation testing in original study		3- to 4-yr postablation testing in current study	
	Hypothyroid group (n = 30)	Euthyroid group (n = 33)	Former hypothyroid group (n = 21)	Former euthyroid group (n = 27)
Patients included in scan analysis/all original patients	28/30	32/33	18/21	25/27
Patients with no visible uptake or less than 0.1%/patients in scan analysis	28/28 (100%)	32/32 (100%)	18/18 (100%)	25/25 (100%)
Patients included in scan analysis/all original patients	28/30	32/33	18/21	25/27
Patients with no visible uptake/patients in scan analysis	24/28 (86%)	24/32 (75%)	17/18 (94%)	21/25 (84%)
Patients with serum Tg measured and no interfering TgAb/all original patients	21/30	24/33	20/21	25/27
Patients with serum Tg less than 2 ng/ml/all patients with Tg analyzed	18/21 (86%)	23/24 (96%)	19/20 (95%)	24/25 (96%)
Patients with serum Tg measured and no interfering TgAb/all original patients	21/30	24/33	20/21	25/27
Patients with serum Tg less than 1 ng/ml/all patients with Tg analyzed	18/21 (86%)	20/24 (83%)	18/20 (90%)	23/25 (92%)

were excluded. The findings and conclusions regarding comparable serum Tg evidence of ablation were not different when either cutoff was used (data not shown).

Comparison of the rhTSH-stimulated serum Tg in the present study with rhTSH-stimulated serum Tg values 8 months after radioiodine ablation in our original study showed that all patients with levels less than 1 ng/ml in the earlier study were confirmed to remain less than 1 ng/ml in the present. Only eight cases (four hypothyroid and four euthyroid) had a rhTSH-stimulated serum Tg above cutoff levels in the first study (five cases >2 ng/ml and three cases >1 ng/ml but <2 ng/ml). Three of these patients, although serum Tg positive, also had potentially interfering titers of Tg-Ab. Unfortunately, comparison of the two rhTSH-stimulated serum Tg values in these patients cannot be accurately performed because six of these patients were retreated. Consequently, both these retreatments and the reduction in level of interfering Tg-Ab antibodies alter the results of serum Tg measurement. In the sole patient from this cohort who had not been treated with radioiodine during the interim and who initially had no interfering anti-Tg-Abs, the rhTSH-stimulated serum Tg decreased from 1.8 to less than 1 ng/ml.

Safety and tolerability of rhTSH

Retreatment with rhTSH for diagnostic testing during this follow-up study was well tolerated. One or more treatment emergent adverse events were reported by two patients (9%) in the former hypothyroid group and six patients (21%) in the former euthyroid group. Because all patients were euthyroid on T_4 when receiving rhTSH in this follow-up study, it was not clear how original treatment assignment more than 3 yr previously would have been relevant to the incidences of minor adverse events reported in this study. For all eight of these patients, no action or medications were prescribed for any of these adverse events and all patients recovered promptly and spontaneously.

Discussion

We previously demonstrated that the rates of successful postsurgical remnant ablation (determined 8 months after

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^{131}I treatment) in patients with low-risk DTC were similar whether patients were prepared for radioiodine therapy after rhTSH administration or thyroid hormone withdrawal (10). Besides a similar rate of ablation, a significantly better quality of life and lesser time lost from work has been documented in euthyroid patients prepared with rhTSH administration (13–15). In addition, the mean absorbed radiation dose to the blood, which can be considered as an indicator for bone marrow exposure, was lower than with comparable therapy in hypothyroid patients (11, 16). In the current study, we demonstrate that patients prepared with rhTSH and thyroid hormone withdrawal still have comparable rates of successful remnant ablation and have manifested similar clinical outcomes after approximately 4 yr of follow-up, which is the period with the highest risk of recurrent disease (3). Although the number of enrolled patients in this follow-up study was, of necessity, relatively small, statistical analysis of our results showed no difference in the rates of successful ablation between the two groups.

In the present study, all patients who were considered ablated at 8 months after radioiodine therapy according to the criterion of neck uptake being invisible or less than 0.1% of the administered activity were confirmed to have negative rhTSH-stimulated radioiodine scanning a median 3.7 yr later based on the same criterion. These results suggest that there is no need to repeat radioiodine scanning in these patients during their subsequent follow-up. When the criterion of TSH-stimulated serum Tg detectability was applied, the majority of patients similarly had no biochemical evidence of persisting thyroid tissue: 40 of 45 patients based on a stimulated Tg less than 1 ng/ml and 43 of 45 based on a stimulated Tg less than 2 ng/ml. Although there is an apparent increase in the successful ablation rate based on Tg criteria in this report *vs.* our original study, this difference is attributable to disappearance of Tg-Abs in several patients and to a modest decrease overall size of the study population. In fact, TSH-stimulated serum Tg testing performed several years after the remnant ablation revealed similar rates of cure, regardless of the preceding mode of TSH stimulation used to facilitate ablation.

Recently Tg assays with higher sensitivity than that used in the present work have been developed, and the question of whether a more sensitive Tg assay provides more clinically useful information than the Tg assay used after recombinant TSH stimulation is under investigation (17, 18). However, because consistency dictated our use of the same Tg assay as in the first study and its functional sensitivity was 0.9 ng/ml, we cannot comment on lower values with confidence.

Differentiated thyroid cancer recurrence is defined as the reappearance of tumor (either locally in thyroid bed, in neck nodes, or as distant metastatic disease) after a well-documented disease-free period. Such recurrences are becoming less common because of earlier primary treatment of thyroid cancer patients and more stringent criteria for definitive cure, *i.e.* undetectable TSH-stimulated serum Tg in the absence of interfering serum Tg-Abs, and negative cervical ultrasound in addition to negative radioiodine WBS (6, 7). In this study, we have shown that no patient had a definite recurrence of tumor in the sense that they had been declared disease free but then suffered tumor recurrence during the follow-up period. All patients with rhTSH-stimulated serum Tg less than 1 ng/ml at the 8-month evaluation in the original study again demonstrated a rhTSH-stimulated serum Tg less than 1 ng/ml in the present study. Although there are emerging data showing that patients with low detectable levels of rhTSH-stimulated serum Tg may avoid further treatment because the serum Tg may spontaneously decline over the time (19–21), we observed only one patient demonstrating this phenomenon, so we cannot draw any conclusion regarding this issue.

It is important to keep in mind that low stage of disease presentation was a criterion for inclusion in the original remnant ablation trial (10). All patients had been stage T2 or T4 with minor invasion of the thyroid capsule, N0-N1, and M0 or T0-T1, N1, and M0 (22). Furthermore, T_4 tumors were later considered ineligible because some participating centers routinely treated such patients with ^{131}I activities larger than 100 mCi or external radiotherapy. Consequently, the findings of this study, like its predecessor, may or may not apply to patients presenting with higher stages of disease.

In recent years, as serum Tg assay sensitivity has been progressively increased, it has become clear that when serum Tg remains undetectable after TSH stimulation in the absence of interfering serum Tg-Ab, its negative predictive value for subsequent disease recurrence is very high (20, 23), whereas persistently detectable serum Tg indicates persistence of functioning thyroid cells (24, 25). In contrast, the predefined criterion of no visible uptake or, if visible, less than 0.1% uptake is relevant for initial assessment in studies of the ablation of the normal thyroid remnant tissue because serum Tg could arise from tumor in cervical nodes. In our original study, 100% of the patients were considered successfully ablated based on this scan criterion, whereas a lower ablation rate (85–95%) was reported based on TSH-stimulated serum Tg testing. The ^{131}I treatments and/or surgery subsequently required for some patients in this study during follow-up prove that small amounts of residual either normal or malignant thyroid tissue may not be detected routinely using a 4 mCi ^{131}I diagnostic WBS as has been noted in other series (24, 25).

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With the more stringent criterion of no visible uptake, ablation rates were found in the original study to be 86 and 75% in the hypothyroid and euthyroid groups, respectively, although the clinical meaning of trace thyroid bed uptake remains uncertain. Recall that for the original ablation study, radioiodine scanning had to be the primary end point because the goal of the study treatment was the elimination of the normal thyroid remnant tissue rather than the sterilization of all residual tumor in neck nodes. In other words, rhTSH plus ^{131}I was intended to eliminate the thyroid remnant, but this one-time use was not thought likely to eliminate all tumor cells, especially if there was no detectable uptake in tumor tissue or if located in nodes. As a matter of fact, most patients recognized as requiring subsequent treatment had a neck uptake less than 0.1% on WBS but had detectable serum Tg levels. This confirms the observation that serum Tg is a more sensitive test than a radioiodine scan to detect residual functioning thyroid cells, benign or malignant (26–28). However, the need for further treatments was unrelated to the mode of TSH stimulation for earlier remnant ablation because among the nine patients requiring ^{131}I retreatment, five originated from the hypothyroid group and four from the euthyroid group. These findings are similar to those of Tuttle *et al.* (29), who recently reported comparable clinical recurrence rates in 320 patients who earlier underwent radioiodine remnant ablation after rhTSH stimulation *vs.* 74 patients who were ablated after thyroid hormone withdrawal. Although the study by Tuttle *et al.* was retrospective and nonrandomized, the substantial number of thyroid cancer patients analyzed makes it valuable in supporting the comparability of the two methods.

In the present follow-up study, we showed that rhTSH can be safely administered to enhance ^{131}I uptake for remnant ablation in patients with low-risk DTC, with no long-term adverse effects observed over several years of follow-up. Although a number of the study patients received one or more cycles of rhTSH administration during the interim period to monitor their statuses, none developed apparent rhTSH-related adverse events of importance. This confirms the much larger clinical experience with repeated rhTSH use for diagnostic testing.

In conclusion, the current study performed a median 3.7 yr after postsurgical ^{131}I thyroid remnant ablation found no differences in the success of thyroid remnant ablative radioiodine therapy or clinical outcomes between patients prepared by endogenous TSH stimulation by withholding thyroid hormone therapy *vs.* exogenous rhTSH in the euthyroid state. There were no differences between the two approaches in eliminating thyroid remnants or in instances of residual disease detected. These findings confirm that rhTSH is an effective and safe alternative to thyroid hormone withdrawal in preparing low-risk DTC patients for the postsurgical thyroid remnant ablation. This study also confirms that rhTSH-stimulated serum Tg measurement is a highly sensitive indicator of residual disease or normal tissue and one that is superior to radioiodine scanning. Finally, we confirmed the long-term safety of repeated rhTSH exposures.

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References

1. **Mazzaferri EL, Robyn J** 1996 Postsurgical management of differentiated thyroid carcinoma. Otolaryngol Clin North Am 29:637–662
2. **Schlumberger MJ** 1998 Papillary and follicular thyroid carcinoma. N Engl J Med 338:297–306
3. **Mazzaferri 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
4. **Mazzaferri EL** 1997 Thyroid remnant 131I ablation for papillary and follicular thyroid carcinoma. Thyroid 7:265–271
5. **Sawka AM, Thephamongkhol K, Brouwers M, Thabane L, Browman G, Gerstein HC** 2004 Clinical review 170: a systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. J Clin Endocrinol Metab 89: 3668–3676
6. **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
7. **Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W** 2006 European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 154:787–803
8. **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
9. **Borget I, Remy H, Chevalier J, Ricard M, Allyn M, Schlumberger M, De Pouvourville G** 2008 Length and cost of hospital stay of radio-

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iodine ablation in thyroid cancer patients: comparison between preparation with thyroid hormone withdrawal and thyrogen. Eur J Nucl Med Mol Imaging 35:1457–1463

10. **Pacini F, Ladenson PW, Schlumberger M, Driedger A, Luster M, Kloos RT, Sherman S, Haugen B, Corone C, Molinaro E, Elisei R, Ceccarelli C, Pinchera A, Wahl RL, Leboulleux S, Ricard M, Yoo J, Busaidy NL, Delpassand E, Hanscheid H, Felbinger R, Lassmann M, Reiners C** 2006 Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: results of an international, randomized, controlled study. J Clin Endocrinol Metab 91:926–932
11. **Hänscheid H, Lassmann M, Luster M, Thomas SR, Pacini F, Ceccarelli C, Ladenson PW, Wahl RL, Schlumberger M, Ricard M, Driedger A, Kloos RT, Sherman SI, Haugen BR, Carriere V, Corone C, Reiners C** 2006 Iodine biokinetics and dosimetry in radioiodine therapy of thyroid cancer: procedures and results of a prospective international controlled study of ablation after rhTSH or hormone withdrawal. J Nucl Med 47:648–654
12. **Feldt-Rasmussen U, Profilis C, Colinet E, Black E, Bornet H, Bourdoux P, Carayon P, Ericsson UB, Koutras DA, Lamas de Leon L, DeNayer P, Pacini F, Palumbo G, Santos A, Schlumberger M, Seidel C, Van Herle AJ, De Vijlder JJ** 1996 Human thyroglobulin reference material (CRM 457). 1st part: assessment of homogeneity, stability and immunoreactivity. Ann Biol Clin (Paris) 54:337–342
13. **Mernagh P, Campbell S, Dietlein M, Luster M, Mazzaferri E, Weston AR** 2006 Cost-effectiveness of using recombinant human TSH prior to radioiodine ablation for thyroid cancer, compared with treating patients in a hypothyroid state: the German perspective. Eur J Endocrinol 155:405–414
14. **Schroeder PR, Haugen BR, Pacini F, Reiners C, Schlumberger M, Sherman SI, Cooper DS, Schuff KG, Braverman LE, Skarulis MC, Davies TF, Mazzaferri EL, Daniels GH, Ross DS, Luster M, Samuels MH, Weintraub BD, Ridgway EC, Ladenson PW** 2006 A comparison of short-term changes in health-related quality of life in thyroid carcinoma patients undergoing diagnostic evaluation with recombinant human thyrotropin compared with thyroid hormone withdrawal. J Clin Endocrinol Metab 91:878–884
15. **Borget I, Corone C, Nocaudie M, Allyn M, Iacobelli S, Schlumberger M, De Pouvourville G** 2007 Sick leave for follow-up control in thyroid cancer patients: comparison between stimulation with thyrogen and thyroid hormone withdrawal. Eur J Endocrinol 156:531–538
16. **Luster M, Sherman SI, Skarulis MC, Reynolds JR, Lassmann M, Hänscheid H, Reiners C** 2003 Comparison of radioiodine biokinetics following the administration of recombinant human thyroid stimulating hormone and after thyroid hormone withdrawal in thyroid carcinoma. Eur J Nucl Med Mol Imaging 30:1371–1377
17. **Iervasi A, Iervasi G, Ferdeghini M, Solimeo C, Bottoni A, Rossi L, Colato C, Zucchelli GC** 2007 Clinical relevance of highly sensitive Tg assay in monitoring patients treated for differentiated thyroid cancer. Clin Endocrinol (Oxf) 67:434–441
18. **Rosario PW, Purisch S** 2008 Does a highly sensitive thyroglobulin (Tg) assay change the clinical management of low-risk patients with thyroid cancer with Tg on T_4 <1 ng/ml determined by traditional assays? Clin Endocrinol (Oxf) 68:338–342
19. **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
20. **Castagna MG, Brilli L, Pilli T, Montanaro A, Cipri C, Fioravanti C, Sestini F, Capezzone M, Pacini F** 2008 Limited value of repeat recombinant human thyrotropin (rhTSH)-stimulated thyroglobulin testing in differentiated thyroid carcinoma patients with previous negative rhTSH-stimulated thyroglobulin and undetectable basal serum thyroglobulin levels. J Clin Endocrinol Metab 93:76–81
21. **Baudin E, Do Cao C, Cailleux AF, Leboulleux S, Travagli JP, Schlumberger M** 2003 Positive predictive value of serum thyroglobulin levels, measured during the first year of follow-up after thyroid hormone withdrawal, in thyroid cancer patients. J Clin Endocrinol Metab 88:1107–1111
22. **Sobin LH, Fleming ID** 1997 TNM classification of malignant tumors, fifth edition (1997). Union Internationale Contre le Cancer and the American Joint Committee on Cancer. Cancer 80:1803–1804
23. **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
24. **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 patients with detectable serum thyroglobulin levels. J Nucl Med 28:1888–1891
25. **Pineda JD, Lee T, Ain K, 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
26. **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
27. **Mazzaferri EL, Kloos RT** 2002 Is diagnostic iodine-131 scanning with recombinant human TSH useful in the follow-up of differentiated thyroid cancer after thyroid ablation? J Clin Endocrinol Metab 87:1490–1498
28. **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
29. **Tuttle RM, Brokhin M, Omry G, Martorella AJ, Larson SM, Grewal RK, Fleisher M, Robbins RJ** 2008 Recombinant human TSH-assisted radioactive iodine remnant ablation achieves short-term clinical recurrence rates similar to those of traditional thyroid hormone withdrawal. J Nucl Med 49:764–770

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