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Radioiodine Ablation of Thyroid Remnants after Preparation with Recombinant Human Thyrotropin in Differentiated Thyroid Carcinoma: Results of an International, Randomized, Controlled Study

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Context: After surgery for differentiated thyroid carcinoma, many patients are treated with radioiodine to ablate remnant thyroid tissue. This procedure has been performed with the patient in the hypothyroid state to promote endogenous TSH stimulation and is often associated with hypothyroid symptoms and impaired quality of life.

Objective and Intervention: This international, randomized, controlled, multicenter trial aimed to compare the efficacy and safety of recombinant human TSH (rhTSH) to prepare euthyroid patients on L-thyroxine therapy (euthyroid group) to ablate remnant thyroid tissue with 3.7 GBq (100 mCi) ^{131}I, compared with that with conventional remnant ablation performed in the hypothyroid state (hypothyroid group). Quality of life was determined at the time of randomization and ablation. After the administration of the 131-I dose, the rate of radiation clearance from blood, thyroid remnant, and whole body was measured.

Results: The predefined primary criterion for successful ablation was "no visible uptake in the thyroid bed, or if visible, fractional uptake less than 0.1%" on neck scans performed 8 months after therapy and was satisfied in 100% of patients in both groups. A secondary criterion for ablation, an rhTSH-stimulated serum thyroglobulin concentration less than 2 ng/ml, was fulfilled by 23 of 24 (96%) euthyroid patients and 18 of 21 (86%) hypothyroid patients ($P = 0.2341$). Quality of life was well preserved in the euthyroid group, compared with the hypothyroid group, as demonstrated by their lower pretreatment scores on the Billewicz scale for hypothyroid signs and symptoms, 27 ± 7 *vs.* 18 ± 4 ($P < 0.0001$) and their significantly higher Short Form-36 Health Assessment Scale scores in five of eight categories. Euthyroid patients had a statistically significant one third lower radiation dose to the blood, compared with patients in the hypothyroid group.

Conclusions: This study demonstrates comparable remnant ablation rates in patients prepared for ^{131}I remnant ablation with 3.7 GBq by either administering rhTSH or withholding thyroid hormone. rhTSH-prepared patients maintained a higher quality of life and received less radiation exposure to the blood. **(*J Clin Endocrinol Metab* 91: 926–932, 2006)**

INITIAL TREATMENT FOR patients with differentiated epithelial-derived (papillary and follicular) thyroid carcinoma is total or near-total thyroidectomy, which is often followed by ^{131}I ablation of remnant thyroid tissue (1). The rationale for thyroid remnant ablation is to decrease the risk of clinical tumor recurrence (2) and improve the sensitivity and specificity of follow-up testing with periodic serum thyroglobulin measurement and radioiodine scanning (3, 4). In current medical practice, remnant ablation is performed after thyroid hormone has been withheld, which increases endogenous TSH release to promote radioiodine uptake in remaining thyroid cells. Frequently this is associated with the physical and psychological side effects of hypothyroidism, which can have a profound negative impact on the patient's quality of life (5).

Recombinant human TSH (rhTSH, TSHα, Thyrogen, Genzyme Corp., Cambridge, MA) has been developed as a source of exogenous TSH. Clinical studies have shown that admin-

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Abbreviations: rhTSH, Recombinant human TSH; SF-36, Short Form-36.

istration of rhTSH to thyroid cancer patients remaining on thyroid hormone therapy promotes radioiodine uptake and thyroglobulin production by thyroid cells with comparable efficacy with hypothyroidism for diagnosing residual cancer and preserving the patient's quality of life (6). A few uncontrolled pilot studies have been performed exploring the efficacy of 131-I ablation after preparation with rhTSH. Specifically, a lower rate of successful ablation was found using 30 mCi (1.1 GBq) after rhTSH, compared with the same dose after thyroid hormone withdrawal in one study (7). In contrast, another study (8) using a 30-mCi (1.1 GBq) standard activity found that similar rates of ablation were achieved after rhTSH and thyroid hormone withdrawal, although this study protocol included the withdrawal of L-thyroxine for 4 d before ablation, rendering the results difficult to compare directly. A third study (9) found no difference in ablation rate when preparing the patients with thyroid hormone withdrawal or rhTSH using individual doses of radioiodine determined by dosimetric studies. The present prospective, randomized, multicenter study was designed to investigate whether preparation of patients with rhTSH while on L-thyroxine therapy results in a comparable rate of successful postoperative thyroid ablation, compared with preparation by withdrawal of thyroid hormone when using a fixed dose of 100 mCi (3.7 GBq) of 131-I.

Subjects and Methods

Aim of the study

This randomized, controlled, open-label study involved four centers in Europe and five in North America. The primary objective of the study was to determine whether thyroid remnant ablation in T_4-treated euthyroid patients after preparation with rhTSH results in a comparable ablation rate to treating patients in the hypothyroid state. To test this hypothesis, the primary criterion for successful ablation was defined as "no visible uptake, or if visible, less than 0.1%" on a whole-body radioiodine scan performed 8 months after radioiodine therapy. A second objective was to evaluate the safety profile of rhTSH when used for thyroid remnant ablation. Other objectives were to compare the quality of life in both groups and the uptake and retention of radioiodine in the remnant thyroid tissue as well as radiation exposure to the blood and whole body in both groups.

Inclusion criteria

Study patients were 18 yr or older with newly diagnosed differentiated papillary or follicular thyroid carcinoma, the sole previous treatment for which had been total or near-total thyroidectomy within 2 wk before enrollment. Patients were all staged T2 or T4 with minor invasion of the thyroid capsule, N0-N1, and M0 or T0-T1, N1, and M0 (10). T4 tumors were no longer eligible after a protocol amendment because concern arose that patients with T4 tumors might alternatively be treated routinely with radioiodine doses higher than 100 mCi or external radiotherapy at some centers. However, six T4 patients already enrolled before the study amendment. For women of child-bearing potential, a negative serum human chorionic gonadotropin pregnancy test was required. As assessed by the principal investigator at each site, patients had no clinically significant abnormalities of hematological or blood chemistry testing for routine analytes, including serum creatinine concentration. No patients had major concurrent medical disorders, including other malignancies within the past 5 yr; and no patient had a recent history of drugs affecting thyroid or renal function, including iodine-containing medications or radiocontrast agents.

Study design

All patients provided written informed consent to participate in the study. The protocol was approved by each site's institutional review board and/or independent ethics committee.

Within 14 d after thyroidectomy, eligible patients were randomized to either the euthyroid group, which received rhTSH to prepare for radioiodine therapy, or the hypothyroid group, from which thyroid hormone treatment was withheld before radioiodine therapy. Patients in the euthyroid group received L-thyroxine therapy for 4–6 wk until their serum TSH concentration was 5 mU/liter or less. Then 0.9 mg rhTSH (Thyrogen) was administered im on 2 consecutive days; and 24 h later, 3.7 GBq (100 mCi) ^{131}I was administered. Subsequently whole-body probe measurements and blood collections were conducted at 2, 6, 24, 48, 72–96 h, and 96–168 h to obtain time-activity curves. Patients also underwent whole-body scanning and remnant neck imaging at 48, 72–96 h, and 96–168 h after ablation.

Patients randomized to the hypothyroid group did not receive thyroid hormone therapy postoperatively. The serum TSH concentration was reassessed at 4–6 wk until the patient's TSH was greater than 25 mU/liter. The patients received a 3.7 GBq (100 mCi) ^{131}I activity followed by posttreatment imaging and dosimetry measurements at the same intervals as the euthyroid group. Thereafter these patients commenced L-thyroxine therapy.

Dosimetric procedures were developed and assessed centrally by one of the participating centers (University of Würzburg) based on earlier studies (11, 12) and adjusted to the higher activities used in this study. A full description of the technical aspects of the study and the theory of the dosimetry is presented elsewhere (13). A manual with detailed instructions to the dosimetric measurements and the data extraction was distributed to all participating centers before the beginning of the study. All data with respect to dosimetry were transmitted to Würzburg at which the dosimetry calculations were performed using identical evaluation procedures for each patient. The absorbed dose to the blood was calculated using a modified approach described in detail by Hänscheid *et al.* (13) based on the medical internal radiation dose (MIRD) formalism and S values from Akabani and Poston (14). The remnant uptakes and the corresponding areas were determined by quantitative evaluation of the scintigram remnant counts, applying appropriate background corrections.

Eight ($\pm$1) months after ablation, rhTSH-stimulated (0.9 mg/d for two doses) whole-body scan and spot views of the neck (48 h after the administration of 150 MBq ^{131}I as tracer activity) and serum thyroglobulin testing were performed.

Assessment of outcome

The neck and whole-body scans performed 8 $\pm$ 1 months after ablation and 48 h after the administration of the diagnostic activity were evaluated in a blinded manner by three independent readers. If a majority of the readers considered radioiodine uptake to be visible in the thyroid bed, the percentage of ^{131}I uptake in the thyroid bed was calculated.

Symptoms of hypothyroidism and quality of life were assessed using the Billewicz scale and Short Form-36 (SF-36) scores at baseline, 2 wk after randomization, immediately before ^{131}I ablation, and 1 month after ablation.

Safety was monitored throughout the study by assessment of vital signs and any changes in medical history or physical examination and by complete blood count (complete blood count, platelet, and differential white blood cell count), routine biochemical parameters (urea nitrogen, creatinine, liver function tests, total cholesterol, and triglycerides), and urinalysis.

Measurement of serum TSH, thyroglobulin, and urinary iodine excretion

TSH determinations were performed at the individual sites using standard immunoassay procedures. Thyroglobulin measurements were performed in a central laboratory (Department of Endocrinology, University of Pisa), using an immunometric assay (Diagnostic Products Corp., Los Angeles, CA) with a functional sensitivity of 0.9 ng/ml, standardized against the certified reference material for human thyro-

globulin (15). In the same laboratory antithyroglobulin antibodies were measured using an immunoradiometric assay method (ICN Pharmaceuticals, Inc., Asse Relegem, Belgium). Patients with a potentially interfering level of antithyroglobulin autoantibodies were not considered for statistical analysis of serum thyroglobulin changes.

Urinary iodine excretion over 24 h was determined 2 d before ^{131}I administration (hypothyroid group) or within 2 d before rhTSH administration (euthyroid group) and at the 8-month assessment. Iodine measurements were performed in a central laboratory (Boston Medical Center, Boston, MA) using a colorimetric method (16).

Biostatistical considerations and sample size

Patients were randomized in 1:1 ratio into the two treatment arms based on a blocked and stratified randomization scheme, with permuted blocks of 4 and stratification by site to ensure balance between the treatment arms in each site. A box was provided to each clinical site that contained a batch of sealed randomization envelopes numbered sequentially. On confirmation that a potential patient met all entry criteria, an envelope would be drawn, starting with the lowest number, and opened to reveal the treatment group to which the patient was assigned.

This study was designed to answer the question whether successful ablation with the euthyroid rhTSH treatment is within 20% of the hypothyroid treatment. The comparison was based on standard noninferiority framework (17) in which difference of 20% in outcome was considered a clinically meaningful difference. For such designs, it is implicit that the 95% confidence interval around the difference in the observed ablation rates is calculated instead of conducting a hypothesis test. If the 95% confidence interval does not include the 20% clinically relevant difference, then the inference is that the euthyroid treatment is not inferior to the hypothyroid treatment by more than the prespecified difference. Assuming a successful ablation rate of 93% in the overall patient population, it was calculated that with 25 patients in each arm, the probability of finding the predefined noninferiority relationship, if such relationship truly exists, was 79%. Although this statistical approach was developed for the analysis of the primary end point (*i.e.* absence of visible uptake or, if present, less than 0.1%), the same analysis was also used for other ablation endpoints without adjusting the definition of significance, using χ^2 analysis.

Other statistics included Student *t* test and Wilcoxon rank sum test for difference between groups (for serum TSH, serum thyroglobulin, urinary iodine excretion, and radioiodine kinetics).

Results

Patient inclusion

The first patient was enrolled on December 17, 2001. The last patient completed the final study visit on September 26, 2003. Sixty-six patients provided informed consent, three were found ineligible, leaving 63 patients for intent-to-treat analyses. Thirty of these patients were randomized to the hypothyroid group and 33 to the euthyroid group. In the hypothyroid group, two patients were excluded from the final analysis: one due to discovery of lung metastases on the posttherapy whole-body scan and one because the neck scan was uninterpretable due to a positioning error. In the euthyroid group, one patient was ineligible for the final analysis due to a mistake in the reconstitution of one rhTSH dose in preparation for ^{131}I ablation. As shown in Table 1, patients in the two arms of the study were not significant different in their baseline characteristics.

Serum TSH

Immediately before radioiodine ablation in the hypothyroid group and before rhTSH administration in the euthyroid

TABLE 1. Patient demographics and characteristics of intent-to-treat cohort at baseline

	Hypothyroid (n = 30)	Euthyroid (n = 33)	*P*
Age (yr)			
Mean (SD)	43.2 (12.5)	44.5 (12.2)	0.6899
Median (range)	41.0 (20.0–63.0)	47.0 (20.0–68.0)	
Gender, n (%)			
Female	24 (80)	26 (79)	
Male	6 (20)	7 (21)	
Weight (kg)			
Mean (SD)	69.5 (14.4)	75.6 (16.9)	0.1259
Median (range)	68.0 (48.6–95.8)	73.0 (48.6–125)	
Height (cm)			
Mean (SD)	164 (10)	168 (9)	0.1443
Median (range)	162.8 (148–188)	167 (149–193)	
BMI			
Mean (SD)	25.7 (3.8)	26.9 (5.4)	0.3256
Median (range)	25.9 (19.3–33.0)	25.9 (17.8–44.8)	
Histology, n (%)			
Papillary	29 (97)	32 (97)	0.6601
Follicular	1 (3)	1 (3)	
TNM, n (%)			
T0 1 (1.5)[a]	0	1 (3.0)	0.4025
T1 12 (19.%)	4 (13.3)	8 (24.2)	
T2 44 (69.8)	22 (73.3)	22 (66.7)	
T4 6 (9.5)	4 (13.3)	2 (6.1)	
N0 36 (57.1)	16 (53.3)	20 (60.6)	0.7741
N1 22 (35.0)	11 (36.7)	11 (33.3)	
NX 5 (7.9)[b]	3 (10.0)	2 (6.1)	
M0 54 (85.7)	25 (83.3)	29 (87.9)	0.6066
MX 9 (14.3)[c]	5 (16.7)	4 (12.1)	
M1 0	0	0	

TNM, Tumor node metastasis.

[a] This patient presented with apparent cervical lymph node metastasis, but no primary tumor could be identified.

[b] Regional lymph nodes could not be assessed in five patients.

[c] The presence of distant metastases could not be assessed in nine patients.

group, the mean (± SD) serum TSH concentration in the euthyroid group was 1.1 ± 1.3 mU/liter, whereas in the hypothyroid group, it was 83 ± 51 mU/liter. At month 8, the median serum TSH concentrations in the euthyroid and hypothyroid groups were not significantly different, 0.0 mU/liter (range 0.0–96.0 mU/liter) and 0.0 mU/liter (range 0.0–1.6 mU/liter), respectively. The extremely high serum TSH level (96.0 mU/liter) in the euthyroid group was due to one patient who mistakenly was not taking their L-thyroxine.

Results of the posttherapy scan at the time of ablation and the control radioiodine scan at 8 months

Thyroid bed uptake was identified in each patient on the postablation scans. Mean (± SD) and median areas in the scans obtained 48 h after ablation were 16 ± 10 and 14 cm^2 in the hypothyroid group, and 19 ± 17 and 19 cm^2 in the euthyroid group, and were not significantly different.

Based on the primary end point of no visible uptake, or if visible, less than 0.1% uptake, scans performed 8 months after therapeutic radioiodine administration (Table 2) showed that all patients who had evaluable results in both groups had been successfully ablated. Based on the criterion of no visible uptake alone, 24 of 32 euthyroid patients (75%) and 24 of 28 hypothyroid patients (86%) had their thyroid residues successfully ablated ($P = 0.300$).

Serum thyroglobulin

Serum thyroglobulin levels at study entry were comparable in the euthyroid and hypothyroid groups, 11 ± 16 and 34 ± 127 ng/ml, respectively ($P = 0.331$). Immediately before administering rhTSH to euthyroid patients, their serum thyroglobulin concentrations had fallen to 1.5 ± 1.9 ng/ml on thyroxine therapy, whereas in the hypothyroid group, it remained 22 ± 47 ng/ml ($P = 0.025$), reflecting their differing states of endogenous TSH stimulation. At 1 and 8 months after radioiodine therapy, serum thyroglobulin levels were low or undetectable, with no significant differences between the two groups. Immediately before diagnostic rhTSH administration at month 8, serum thyroglobulin concentrations were less than 2 ng/ml in all patients in both groups. Three days after the second dose of rhTSH, the serum thyroglobulin was 2 ng/ml or greater in one euthyroid group patient and five hypothyroid group patients. Although the study was not specifically designed to examine the success of ablation based on serum thyroglobulin concentration, these data were also analyzed. When successful ablation was defined as rhTSH-stimulated serum thyroglobulin concentration less than 2 ng/ml in the subset of patients without interfering antithyroglobulin antibodies (Table 3), 23 of 24 euthyroid patients (96%) and 18 of 21 hypothyroid patients (86%) were considered successfully ablated. The 95% confidence interval for difference in ablation rates was −7 to 27%, demonstrating that the response to radioiodine treatment in the euthyroid group was not clinically inferior to that in the hypothyroid group. Furthermore, no difference was found by χ^2 analysis ($P = 0.2341$). Using a cut-off for rhTSH-stimulated serum thyroglobulin of less than 1 ng/ml, the 95% confidence interval for difference in ablation rates ranged from −24 to 19%, failing to exclude the predefined clinically relevant difference of 20%, but no significant difference was found by χ^2 analysis ($P = 0.826$).

Urinary iodine excretion

Urinary iodine concentrations before ablation were not significantly different in the euthyroid and hypothyroid groups, 12 ± 9 and 9 ± 8 μg/dl, respectively ($P = 0.157$), indicating no significant impact of the additional iodine content of administered L-thyroxine in the euthyroid group. At month 8 before the follow-up scan, mean urinary iodine levels in euthyroid and hypothyroid groups were again comparable, 15 ± 17 and 15 ± 8 μg/dl, respectively ($P = 0.837$).

Radioiodine kinetics

Analysis of the thyroid remnant tissue radioiodine kinetics showed that the fractional uptake 48 h after the ^{131}I administration tended to be lower in the euthyroid group than the hypothyroid group (Table 4), although the difference was not statistically significant ($P = 0.096$). The effective half-life in remnant tissue was significantly shorter in the hypothyroid group ($P = 0.011$), whereas the mean residence time in remnant tissue was shorter in the euthyroid group (0.9 ± 1.27 h) than the hypothyroid group (1.4 ± 1.51 h), but the difference was not statistically significant ($P = 0.109$). The dose to the blood was significantly lower in the euthyroid group (0.109 ± 0.028 mGy/MBq administered activity) than in the hypothyroid group (0.167 ± 0.061 mGy/MBq; $P < 0.0001$).

Quality of life

Mild and transient symptoms around the time of radioiodine ablation were noted in eight patients in each group. The most frequent symptoms in the euthyroid group were nausea (four patients), fatigue (two patients), and taste loss (two patients). In the hypothyroid group, symptoms included fatigue (three patients), nausea (two patients), and skeletal pain (two patients).

There was a highly significant difference ($P < 0.0001$) at wk 4 between Billewicz scores of the two groups, with patients in the hypothyroid group having higher mean total scores immediately before ablation and 1 month after ablation, com-

TABLE 2. Results of thyroid remnant ablation at month 8 based on ^{131}I thyroid bed uptake

Uptake in thyroid bed	Hypothyroid (n = 28), n (%)	Euthyroid (n = 32), n (%)	95% CI of difference in ablation rate (euthyroid minus hypothyroid)
No visible uptake or uptake <0.1%	28 (100)	32 (100)	Not applicable
No visible uptake	24 (85.7)	24 (75.0)	(−30.5 to 9.1)
Visible uptake <0.1%	4 (14.3)	8 (25.0)	
Visible uptake >0.1%	0	0	

CI, Confidence interval.

TABLE 3. Results of thyroid remnant ablation at month 8 based on rhTSH-stimulated serum thyroglobulin level

rhTSH-stimulated serum thyroglobulin (ng/ml)	Hypothyroid (n = 21), n (%)	Euthyroid (n = 24), n (%)	95% CI on difference in ablation rate (euthyroid minus hypothyroid)
<2	18 (85.7)	23 (95.8)	−6.85 to 27.09
>2	3 (14.3)[a]	1 (4.2)[b]	
<1	18 (85.7)	20 (83.3)	−23.5 to 18.7
<1	3 (14.3)[a]	4 (16.7)[c]	

CI, Confidence interval.
Individual values of rhTSH-stimulated thyroglobulin: [a] 2.5–4.3–44 ng/ml; [b] 3.7 ng/ml; [c] 1.3–1.6–1.8–3.7 ng/ml.

pared with baseline (2 wk after randomization). The most common complaints of patients in the hypothyroid group, as opposed to those of the euthyroid group, were cold intolerance (50 *vs.* 21%), weight increase (60 *vs.* 21%), constipation (43 *vs.* 3%), slow movements (50 *vs.* 12%), cold skin (47 *vs.* 12%), and periorbital puffiness (50 *vs.* 0%). One month after ablation, mean Billewicz scores for patients in the hypothyroid group returned to the level seen in the euthyroid group.

The SF-36 scale showed that the status of the euthyroid group improved in seven of eight physical and mental domains between baseline and wk 4, whereas the hypothyroid group experienced a decrease in quality of life in seven of eight SF-36 domains. The change from baseline in the euthyroid group was significantly different from that in the hypothyroid group in five of eight SF-36 domains (Table 5).

Discussion

This study demonstrates comparable efficacy of thyroid remnant radioablation when thyroid cancer patients are prepared by either administering rhTSH in the euthyroid state or withholding thyroid hormone for endogenous TSH stimulation. A fixed 3.7 GBq (100 mCi) ^{131}I therapeutic activity was selected because it has been associated with a high rate of successful ablation when delivered to hypothyroid patients (18). Although lower activities, *e.g.* 1.1 GBq (30 mCi) ^{131}I, have been used by some centers with good results (19), when this dose was given 48 h after rhTSH administration in a previous controlled trial, the ablation rate was reported to be only 54% (7). In contrast, higher rates of ablation, comparable with those after preparation by hypothyroidism, have been observed in patients prepared with rhTSH using 1.1 GBq (30 mCi) after 4 d withdrawal of L-thyroxine (8) and individualized activities between 3.3 and 8.5 GBq ^{131}I (9). Our study shows that a standard ^{131}I activity of 3.7 GBq (100 mCi) is sufficient to ablate most, if not all, thyroid remnants using either preparatory technique.

The 8-month follow-up scans to assess ablation were performed after rhTSH preparation, based on previous evidence that the results of diagnostic whole-body scans obtained after rhTSH are not significantly different from those obtained after thyroid hormone withdrawal (6, 20, 21). Using the predefined scan criterion of no visible uptake, or if visible, less than 0.1%, all patients in both groups were ablated. Several studies have shown that minimal visible remnants in the thyroid bed have no clinical importance and do not affect the subsequent follow-up and outcome (22, 23). Nevertheless, even using the more restrictive criterion of no visible uptake alone, the difference between ablated patients in the euthyroid or hypothyroid group was marginal (75 and 86%, respectively) and not statistically significant ($P = 0.300$).

In the absence of circulating antithyroglobulin antibodies, TSH-stimulated serum thyroglobulin measurement, either after hormone withdrawal or after rhTSH stimulation, is well accepted as the most sensitive marker of residual thyroid tissue after surgery and remnant ablation (3, 21). Consequently, we considered a level of rhTSH-stimulated serum thyroglobulin less than 2 ng/ml at the 8-month control as an additional criterion of successful ablation. Using this measure, the rate of successful ablation was not different between the euthyroid (96%) and hypothyroid groups (86%). A sim-

TABLE 4. Summary of ^{131}I kinetics in remnant tissue (ITT population)

Parameter	Hypothyroid (n = 29)	Euthyroid (n = 33)	*P* value
48-h uptake in remnant tissue (%)[a]			
Mean (SD)	0.9 (1.1)	0.5 (0.7)	0.0969
Median	0.5	0.3	
Range	0.006–4.3	0.003–3.4	
Residence time in remnant tissue (h)[b]			
Mean (SD)	1.4 (1.5)	0.9 (1.3)	0.1098
Median	0.8	0.4	
Range	0.01–5.9	0.01–6.6	
Effective half-life in the remnant (h)[c]			
Mean (SD)	48.0 (52.6)	67.6 (48.9)	0.0116
Median	26.9	51.1	
Range	16.0–192.5	17.3–192.5	
Dose to blood (mGy/MBq)			
Mean (SD)	0.167 (0.061)	0.109 (0.028)	<0.0001

[a] Uptake, Percentage of activity retained in tissue.
[b] Residence time, Integral of the time-activity curve divided by the administered activity expressed in hours.
c Effective half-life, For a monoexponential decay, time after which the activity drops by 50%, a combination of biological excretion and physical decay, expressed in hours.

TABLE 5. SF-36 scores in 8 domains for both groups (ITT population)[a]

SF-36 domains	Euthyroid group (n = 33)		Hypothyroid group (n = 30)	
	Baseline	Week 4	Baseline	Week 4
Physical functioning	82.0 ± 18.5	84.5 ± 18.3	71.0 ± 26.5	57.8 ± 29.4
Role-physical	43.0 ± 44.6	58.3 ± 38.9	36.7 ± 36.4	22.5 ± 34.3
Bodily pain	57.8 ± 28.3	67.4 ± 23.6	54.1 ± 27.1	55.0 ± 22.4
General health	68.2 ± 18.4	66.1 ± 20.8	67.8 ± 15.1	61.6 ± 21.2
Vitality	46.6 ± 22.2	54.5 ± 22.5	55.7 ± 23.3	36.4 ± 21.3
Social functioning	62.1 ± 24.3	74.2 ± 21.4	67.5 ± 24.5	53.3 ± 28.4
Role-emotional	46.9 ± 43.9	57.6 ± 44.3	50.0 ± 44.4	31.1 ± 41.0
Mental health	61.4 ± 18.8	71.0 ± 20.1	64.3 ± 18.4	58.8 ± 16.5
Mental component summary	40.0 ± 10.0	45.2 ± 11.9	44.4 ± 12.0	38.5 ± 9.8
Physical component summary	46.2 ± 7.5	47.6 ± 7.7	42.5 ± 7.2	40.0 ± 9.9

[a] The change from baseline in the euthyroid group is significantly different from that in the hypothyroid group in five of the eight domains: physical functioning, $P = 0.016$; role-physical, $P = 0.018$; vitality, $P < 0.0001$; social functioning, $P < 0.0001$; mental health, $P = 0.002$.

ilar trend was observed when the thyroglobulin cut-off level was lowered to 1 ng/ml, although the 95% confidence interval for successful ablation did not exclude a clinically significant 20% difference between the two groups. These thyroglobulin findings are clinically relevant because several centers currently assess the success of ablation with only rhTSH-stimulated serum thyroglobulin measurement without diagnostic whole-body scanning, at least in low-risk patients. Indeed, serum thyroglobulin measurements combined with the results of neck ultrasound examination have been reported by several groups to be the best indicator of complete remission/persistent disease in the follow-up after initial treatment (3, 20, 24, 25).

Symptoms and signs of hypothyroidism as well as subjective perceptions of quality of life were, as expected, significantly better in euthyroid than hypothyroid group patients, as assessed by the results of previously validated survey instruments (Billewicz scale and SF-36). Patients were enrolled in this study soon after being diagnosed with thyroid cancer while recovering from thyroidectomy. Such patients can be expected to have a poor perception of their quality of life, as is reflected by the SF-36 scores in both groups at study entry. During withdrawal of thyroid hormones, SF-36 scores decreased even further in patients in the hypothyroid group in seven of the eight SF-36 domains; whereas in patients in the euthyroid group, SF-36 scores improved in seven of the eight SF-36 domains. The difference between the two groups probably resulted from both an amelioration of immediate postoperative symptoms in rhTSH-treated patients and a deterioration in patients withdrawn from thyroid hormones. This confirms that prevention of hypothyroidism by use of rhTSH for remnant ablation avoided the worsening of subjectively experienced quality of life in patients who already were in a fragile psychological condition soon after being diagnosed with thyroid cancer.

The kinetics of thyroid remnant and whole-body kinetics of radioiodine represent another important issue in our study. A detailed presentation of the theoretical and methodological background of the dosimetric investigations goes beyond the scope of this paper and is described elsewhere (13), including a discussion of the observed differences of the iodine kinetics after thyroid hormone withdrawal and stimulation with rhTSH. Fractional remnant uptakes and residence times tended to be higher in the hypothyroid than the euthyroid group, whereas the half-life of tissue residence in remnants was lower. Only the difference of the half-lives was statistically significant. The radiation dose to the blood, a surrogate measure for radiation dose to the bone marrow, was significantly lower (−35%) in the euthyroid group than in the hypothyroid group. These findings suggest that using rhTSH to prepare for thyroid remnant ablation reduces the blood radiation dose and potential risk of radiation-induced malignancies (26, 27).

Our urinary iodine excretion data indicate that the modest additional stable iodine intake before radioiodine treatment in the thyroxine-treated euthyroid patients did not produce a significantly higher urinary iodine level than in the hypothyroid patients. This contrasts with an earlier report of higher mean urinary iodine excretion in patients undergoing thyroid ablation with rhTSH than hypothyroid patients (8). The median urinary iodine levels in both or our groups were well below the approximately 20 μg/dl threshold conventionally considered to have the potential for interference with effective thyroid remnant uptake of radioiodine.

A final important issue that could not be addressed in our study is whether preparation for remnant ablation with rhTSH *vs.* thyroid hormone withdrawal has an impact on patients' long-term outcomes, particularly disease recurrence. This can be answered only by following these cohorts of patients in future years.

In conclusion, these study findings demonstrate comparable thyroid remnant ablation rates in thyroid cancer patients without evidence of remaining disease after surgery when prepared for ^{131}I therapy by either administering rhTSH or withholding thyroid hormone. rhTSH-prepared patients sustained a better quality of life and received less radiation exposure to blood. Thus, the use of rhTSH for postoperative radioiodine thyroid remnant ablation represents an effective and attractive option in the postoperative management of patients with thyroid cancer.

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