

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MAY 3, 2012

VOL. 366 NO. 18

## Strategies of Radioiodine Ablation in Patients with Low-Risk Thyroid Cancer

Martin Schlumberger, M.D., Bogdan Catargi, M.D., Ph.D., Isabelle Borget, Pharm.D., Ph.D., Désirée Deandreis, M.D., Slimane Zerdoud, M.D., Boumédiène Bridji, M.D., Ph.D., Stéphane Bardet, M.D., Laurence Leenhardt, M.D., Ph.D., Delphine Bastie, M.D., Claire Schvartz, M.D., Pierre Vera, M.D., Ph.D., Olivier Morel, M.D., Danielle Benisvy, M.D., Claire Bournaud, M.D., Françoise Bonichon, M.D., Catherine Dejax, M.D., Marie-Elisabeth Toubert, M.D., Sophie Leboulleux, M.D., Marcel Ricard, Ph.D., and Ellen Benhamou, M.D.,  
for the Tumeurs de la Thyroïde Refractaires Network for the Essai Stimulation Ablation Equivalence Trial\*

### ABSTRACT

#### BACKGROUND

It is not clear whether the administration of radioiodine provides any benefit to patients with low-risk thyroid cancer after a complete surgical resection. The administration of the smallest possible amount of radioiodine would improve care.

#### METHODS

In our randomized, phase 3 trial, we compared two thyrotropin-stimulation methods (thyroid hormone withdrawal and use of recombinant human thyrotropin) and two radioiodine ( $^{131}\text{I}$ ) doses (i.e., administered activities) (1.1 GBq and 3.7 GBq) in a 2-by-2 design. Inclusion criteria were an age of 18 years or older; total thyroidectomy for differentiated thyroid carcinoma; tumor–node–metastasis (TNM) stage, ascertained on pathological examination (p) of a surgical specimen, of pT1 (with tumor diameter  $\leq 1$  cm) and N1 or Nx, pT1 (with tumor diameter  $>1$  to 2 cm) and any N stage, or pT2N0; absence of distant metastasis; and no iodine contamination. Thyroid ablation was assessed 8 months after radioiodine administration by neck ultrasonography and measurement of recombinant human thyrotropin–stimulated thyroglobulin. Comparisons were based on an equivalence framework.

#### RESULTS

There were 752 patients enrolled between 2007 and 2010; 92% had papillary cancer. There were no unexpected serious adverse events. In the 684 patients with data that could be evaluated, ultrasonography of the neck was normal in 652 (95%), and the stimulated thyroglobulin level was 1.0 ng per milliliter or less in 621 of the 652 patients (95%) without detectable thyroglobulin antibodies. Thyroid ablation was complete in 631 of the 684 patients (92%). The ablation rate was equivalent between the  $^{131}\text{I}$  doses and between the thyrotropin-stimulation methods.

#### CONCLUSIONS

The use of recombinant human thyrotropin and low-dose (1.1 GBq) postoperative radioiodine ablation may be sufficient for the management of low-risk thyroid cancer. (Funded by the French National Cancer Institute [INCa] and the French Ministry of Health; ClinicalTrials.gov number, NCT00435851; INCa number, RECF0447.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Schlumberger at the Service de Médecine Nucléaire et de Cancérologie Endocrinienne et Université Paris Sud, Institut de Cancérologie Gustave Roussy, 114 Rue Edouard Vaillant, 94805 Villejuif, France, or at schlumbg@igr.fr.

\*Members of the network who participated in the trial are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2012;366:1663-73.

Copyright © 2012 Massachusetts Medical Society.

**R**ADIOIODINE ( $^{131}\text{I}$ ) IS ADMINISTERED TO patients with thyroid cancer after total thyroidectomy for three reasons<sup>1-3</sup>: first, to eradicate normal-thyroid remnants (ablation) in order to achieve an undetectable serum thyroglobulin level; second, to irradiate any neoplastic focus in order to decrease the risk of recurrence; and third, to perform  $^{131}\text{I}$  total-body scanning for persistent carcinoma.

Successful ablation is defined by the combination of undetectable serum thyroglobulin levels after thyrotropin stimulation and normal results on neck ultrasonography 6 to 12 months after  $^{131}\text{I}$  administration.<sup>2,3</sup> When these criteria are met, approximately 1% of patients have a recurrence.<sup>4-6</sup>

In patients with low-risk thyroid cancer, it is unclear whether the administration of radioiodine provides any benefit after a complete surgical resection, and radioiodine is not recommended in patients with disease that is categorized as consisting of a tumor less than 1 cm in diameter and clinical stage N0.<sup>7-9</sup> Therefore, radioiodine should be used with great care to minimize harm, administer the minimal amount of radioactivity, and involve the best-tolerated methods. Radioiodine may induce lacrimal and salivary-gland disturbances, depending on the amount of radioactivity administered.<sup>10,11</sup> High radioactivity is most effective for the ablation of large normal-thyroid remnants and the eradication of micrometastases.<sup>12,13</sup> However, low radioactivity may be just as effective to ablate small normal-thyroid remnants after total thyroidectomy.<sup>13</sup>

The method used for thyrotropin stimulation is also a matter of debate. The use of recombinant human thyrotropin maintains quality of life,<sup>14</sup> is cost-effective,<sup>15</sup> and reduces the radiation dose delivered to the body as compared with the amount delivered with thyroid hormone withdrawal.<sup>16</sup> Recombinant human thyrotropin and thyroid hormone withdrawal provide similar ablation rates at a dose (i.e., administered activity) of 3.7 GBq.<sup>17</sup> However, the intensity of stimulation may be lower with recombinant human thyrotropin, and discrepant results have been reported with recombinant human thyrotropin when lower doses (1.8 GBq or 1.1 GBq) are administered, with ablation rates either similar to or lower than those obtained with withdrawal.<sup>18-20</sup>

This absence of consensus appears to be largely due to the lack of large, randomized studies.<sup>21-24</sup>

Furthermore, most patients with thyroid cancer are currently treated with total thyroidectomy and have small normal-thyroid remnants; thus, retrospective studies of patients who had been treated with radioiodine for large thyroid remnants are not relevant to current clinical management. Finally, the criteria for ablation have changed, and a diagnostic total-body scan at 6 to 12 months is no longer routinely performed in patients with a normal total-body scan after therapy.<sup>2-5</sup>

Our randomized, open-label, phase 3 trial involving 24 French centers aimed to determine whether the rate of successful postoperative thyroid ablation would be similar among euthyroid patients receiving recombinant human thyrotropin or among hypothyroid patients undergoing thyroid-hormone withdrawal and among those receiving low (1.1 GBq) or high (3.7 GBq)  $^{131}\text{I}$  radioactivity.

## METHODS

### STUDY CONDUCT

All patients provided written informed consent. The study was sponsored by Institut Gustave Roussy. The study was conducted in accordance with the protocol (available with the full text of this article at NEJM.org), which was approved by ethics committees, national authorities, and by each center's institutional review board. The authors vouch for the completeness and accuracy of the data and analyses.

### STUDY PATIENTS

The inclusion criteria were as follows: an age of 18 years or older, low-risk differentiated thyroid carcinoma (papillary or follicular, excluding aggressive histologic subtypes),<sup>25</sup> tumor-node-metastasis (TNM) stage, ascertained on pathological examination (p) of a surgical specimen, of pT1 (tumor diameter  $\leq 1$  cm) and N1 or Nx or pT1 (tumor diameter  $>1$  to 2 cm) and any N or pT2N0,<sup>26</sup> absence of distant metastasis, Eastern Cooperative Oncology Group performance status score of 0 or 1 (i.e., fully active and able to carry on all predisease performance without restriction, and restricted from physically strenuous activity but ambulatory, respectively), no major coexisting conditions (including other cancers) within the previous 5 years, and a negative pregnancy test for women. Patients with a recent history of iodine contamination were excluded.

All patients underwent total thyroidectomy. Lymph-node dissection was performed in patients with evidence of lymph-node involvement, as well as in some patients with no evidence of lymph-node involvement, if part of local practice.<sup>2,3</sup>

Patients were randomly assigned to undergo one of four strategies, each combining one of two methods of thyrotropin stimulation — administration of recombinant human thyrotropin or thyroid-hormone withdrawal — and one of two <sup>131</sup>I activities (1.1 GBq or 3.7 GBq). Randomization was performed between 30 and 120 days after surgery, during which time patients received levothyroxine therapy for at least 28 days (or levotriiodothyronine therapy for 14 days).

Recombinant human thyrotropin (Thyrogen, Genzyme) was administered during treatment with thyroid hormone, at a dose of 0.9 mg intramuscularly on 2 consecutive days, and radioiodine was administered on the day after the second injection. Thyroid-hormone withdrawal consisted of discontinuation of levothyroxine treatment for at least 28 days (or levotriiodothyronine treatment withdrawal for 14 days), with administration of radioiodine when the serum thyrotropin concentration was higher than 30 mIU per liter. Serum thyrotropin, thyroglobulin, and antithyroglobulin antibody levels were measured before radioiodine administration. A <sup>131</sup>I total-body scan was performed 72 to 120 hours after radioiodine administration. The uptake of radioiodine in the thyroid bed (where the thyroid gland was located before its removal) was measured by delineating the thyroid bed on the gamma camera image and comparing the count in this region of interest with that of an external radioactive source with a known activity. Suspicious findings on any total-body scan were reviewed by two of the authors, independently of one another, each of whom was unaware of the treatment assignments. Data from patients with confirmed persistent disease were excluded from the main analysis, because management of their disease may have differed from the planned management.<sup>1-3</sup>

#### OUTCOME ASSESSMENT

The primary outcome was thyroid ablation, assessed at 8±2 months after radioiodine administration with the use of neck ultrasonography<sup>27</sup> and determination of the level of recombinant human thyrotropin-stimulated serum thyroglobulin<sup>28,29</sup> or a diagnostic <sup>131</sup>I total-body scan with 148 to

185 MBq in patients with detectable antithyroglobulin antibody.

Serum thyroglobulin and antithyroglobulin antibody levels were measured 3 days after the second injection of recombinant human thyrotropin at each center. At the completion of the study, serum thyroglobulin measurements were also performed in a central laboratory (Bio-Pathology Department, Institut Gustave Roussy) using the immunometric thyroglobulin Access Immunoassay kit (Beckman-Coulter; functional minimum level of detection, 0.11 ng per milliliter) in samples from patients who had no detectable antithyroglobulin antibody.<sup>28,30</sup>

Neck ultrasonography included the analysis of the thyroid bed and the lymph-node regions. A normal result on ultrasonography was defined by an empty thyroid bed with the jugular and carotid vessels in a medial location or a hyperechoic zone between the trachea and the carotid artery and by the absence of suspicious lymph nodes.

Ablation was considered complete if both the neck ultrasound was normal and the level of recombinant human thyrotropin-stimulated thyroglobulin was less than or equal to 1 ng per milliliter (or, in cases of detectable antithyroglobulin antibody, if the control <sup>131</sup>I total-body scan was normal). Ablation was considered incomplete if suspicious findings on neck ultrasonography were confirmed by cytologic examination and thyroglobulin determination in needle washout fluid or if the level of recombinant human thyrotropin-stimulated thyroglobulin was greater than 1 ng per milliliter (or, in cases of detectable antithyroglobulin antibody, if the control <sup>131</sup>I total-body scan was abnormal — i.e., had abnormal foci of uptake outside the thyroid bed or uptake in the thyroid bed of >0.5%). If any diagnostic test was not performed, the ablation was considered not able to be evaluated. The thyroglobulin levels used to assess thyroid ablation were obtained from each center. Sensitivity analyses were performed with the use of thyroglobulin levels obtained at the central site, with a cutoff level of 1.4 ng per milliliter considered as the optimal threshold to predict long-term recurrence.<sup>30</sup>

Secondary outcomes were symptoms of hypothyroidism, as defined by Billewicz and colleagues<sup>31</sup>; adverse events; and quality of life, ascertained on the basis of the 36-Item Short-Form Health Survey (SF-36) (on which scores range from 0 to 100, with higher scores indicating better

health status).<sup>32</sup> These outcomes were evaluated at the time of randomization, the time of <sup>131</sup>I administration, and 3 and 8 months after <sup>131</sup>I administration.

#### STATISTICAL ANALYSES

Our trial was designed as an equivalence study, with a 2-by-2 factorial design, to answer two questions — first, whether the rate of thyroid ablation with the administration of recombinant human thyrotropin was within 10 percentage points (absolute difference) of the rate obtained with the use of thyroid hormone withdrawal, and second, whether the rate of thyroid ablation with low-dose <sup>131</sup>I (1.1 GBq) was within 10 percentage points of the rate obtained with high-dose <sup>131</sup>I (3.7 GBq). Assuming a two-sided alpha level of 0.05, 80% statistical power, and an ablation rate of 80% in patients treated with 3.7-GBq <sup>131</sup>I or with thyroid-hormone withdrawal, we calculated that we would need to enroll 175 patients per group. Randomization was performed with the use of a variable block size (of 4 or 8),<sup>33</sup> according to study center.

Descriptive quantitative data are expressed as means  $\pm$ SD; qualitative data are expressed as percentages. Significant differences between groups were ascertained by means of analysis of variance (for quantitative variables) or a chi-square test (for qualitative variables). The difference in observed ablation rates and its 95% bilateral confidence interval are also presented. If the confidence interval does not include an absolute difference of 10 percentage points between administration of recombinant human thyrotropin and thyroid hormone withdrawal or between 1.1 GBq and 3.7 GBq, the compared treatments are considered to be equivalent.

The primary analysis was per protocol, considering patients who could be evaluated (i.e., eligible patients without persistent disease and with an assessment of thyroid ablation by means of both types of diagnostic tests). Intention-to-treat analyses included data for patients who could not be evaluated as well as for patients with persistent disease. In sensitivity analyses, thyroid ablation of patients with persistent disease was first considered as incomplete; a maximum-bias hypothesis was also applied, in which thyroid ablation of patients who could not be evaluated or those with persistent disease was considered incomplete in the groups receiving recombinant human thyrotropin or 1.1 GBq and as complete in

groups receiving thyroid hormone withdrawal or 3.7 GBq. Statistical analyses were performed with the use of SAS software (version 9.1).

## RESULTS

From April 2007 through February 2010, 752 patients were enrolled (Table 1). Twenty-three did not receive radioiodine ablation as defined in the protocol: 11 withdrew their consent, 9 were considered ineligible after randomization, and 3 could not be treated with radioiodine (1 for technical reasons and 2 for clinical reasons [insufficient thyrotropin level and myocardial infarction]) (Table 1 and Fig. 1).

#### RADIOIODINE ADMINISTRATION

After surgery and before radioiodine administration, the 729 remaining patients received thyroid hormone therapy for a mean ( $\pm$ SD) of 91 $\pm$ 43 days in the groups receiving recombinant human thyrotropin and 70 $\pm$ 32 days, followed by withdrawal of thyroid hormone for 20 $\pm$ 8 days, in the groups undergoing thyroid hormone withdrawal.

At the time of <sup>131</sup>I administration, the serum thyrotropin level was greater than 30 mIU per liter in 343 of the 360 patients (95%) in the thyroid-hormone withdrawal groups. Radioiodine uptake in the thyroid bed was greater than 0.5% of the administered radioactivity in 590 of the 729 patients (81%) (Table 2).

#### PERSISTENT DISEASE AT ABLATION

Persistent disease was diagnosed in 27 patients with the use of post-ablation total-body scanning (14 patients), post-ablation total-body scanning and neck ultrasonography (8), or neck ultrasonography only (5). As specified in the protocol, data for these patients were excluded from the main analysis.

#### FOLLOW-UP TESTING OF THYROID ABLATION

For the 684 patients who could be evaluated, a follow-up study was performed between 6 and 10 months (average, 8.3 $\pm$ 1.6 months) after <sup>131</sup>I administration; there were no significant differences in the time after <sup>131</sup>I administration in the four groups receiving treatment (two 1.1-GBq groups and two 3.7-GBq groups).

On the basis of the local thyroglobulin determinations, thyroid ablation was considered complete in 631 (92%) of the 684 patients: 600 patients

**Table 1. Initial Characteristics of the 752 Randomized Patients, According to Thyrotropin-Stimulation Method and <sup>131</sup>I Dose.\***

Characteristic	Recombinant Human Thyrotropin		Thyroid Hormone Withdrawal	
	1.1 GBq (N=187)	3.7 GBq (N=187)	1.1 GBq (N=189)	3.7 GBq (N=189)
Age — yr	51±13	48±14	49±13	49±14
Female sex — no. (%)	154 (82)	144 (77)	144 (76)	148 (78)
Days from thyroidectomy to randomization	50±21	50±22	52±21	48±21
Histologic finding — no. (%)				
Papillary	173 (93)	167 (89)	176 (93)	177 (94)†
Follicular	14 (7)	20 (11)	13 (7)	11 (6)
TNM stage and tumor diameter — no. (%)‡				
T1, ≤1 cm	56 (30)	54 (29)	52 (28)	39 (21)
T1, >1 to 2 cm	114 (61)	110 (59)	109 (58)	121 (65)
T2, >2 to 4 cm	17 (9)	23 (12)	26 (14)	27 (14)
T3 or T4	0	0	2 (1)	0
pTNM stage — no. (%)§				
pT1N0	58 (31)	53 (28)	56 (30)	59 (31)
pT1N1	28 (15)	35 (19)	37 (20)	32 (17)
pT1Nx	84 (45)	75 (40)	67 (35)	69 (37)
pT2N0	16 (9)	22 (12)	25 (13)	26 (14)
Other				
pT2Nx	1 (<1)	0	1 (<1)	1 (<1)
pT2N1	0	1 (<1)	0	0
pT3	0	0	1 (<1)	0
pT4	0	0	1 (<1)	0
M1	0	1 (<1)	0	0
Renal carcinoma	0	0	0	1 (<1)
Incomplete surgery	0	0	1 (<1)	0

\* Plus–minus values are means ±SD.

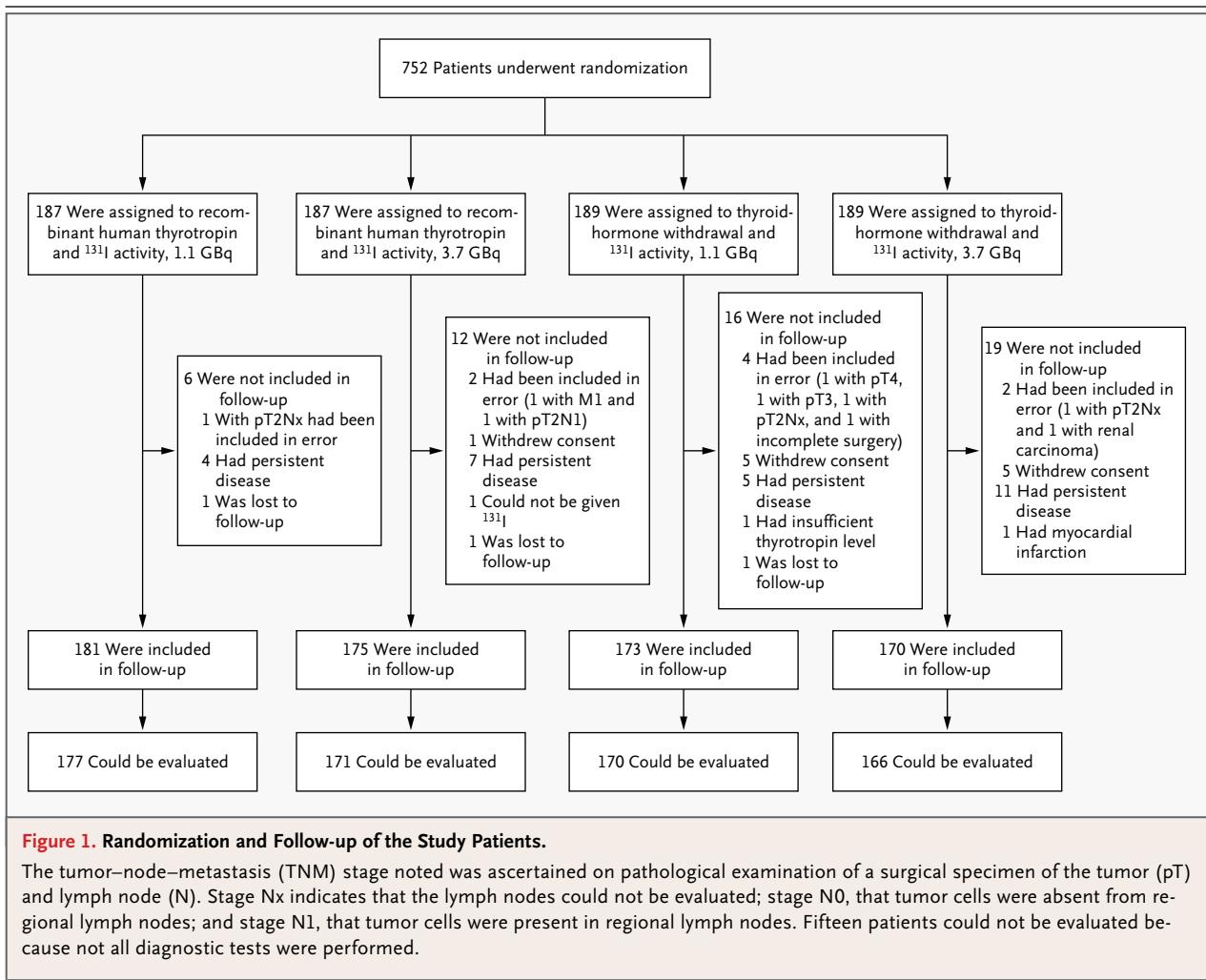
† One of the 177 patients with papillary histologic findings had a renal papillary carcinoma.

‡ The tumor–node–metastasis (TNM) stage for a tumor (T) can range from T0 to T4, with a higher stage indicating worse disease. T3 indicates a tumor with a diameter of more than 4 cm or with minimal extrathyroid extension, and T4 a tumor with more than minimal extrathyroid extension. Tumor diameter could not be determined for one patient in the thyroid hormone–withdrawal group who received 3.7 GBq of <sup>131</sup>I (because the TNM stage was not known), and another patient in the same group was excluded from the analysis owing to renal carcinoma.

§ The TNM stage ascertained on pathological examination of a surgical specimen is shown for the tumor (pT) and lymph node (N). Stage Nx indicates that the lymph nodes could not be evaluated; stage N0, that tumor cells were absent from regional lymph nodes; and stage N1, that tumor cells were present in regional lymph nodes. Data were missing for one patient in the thyroid hormone–withdrawal group who received 3.7 GBq of <sup>131</sup>I. The nine patients with “other” stages were withdrawn from the study after local pathological review revealed their ineligibility.

without detectable antithyroglobulin antibody and with a thyroglobulin level of 1 ng per milliliter or less and normal neck ultrasonography, 23 patients with detectable antithyroglobulin antibody and a normal neck ultrasonography and normal diagnostic total-body scan, and 8 patients with a suspi-

cious neck ultrasonography but with benign cytologic findings and a negative thyroglobulin measurement in the needle washout (Table 3). Thyroid ablation was incomplete in 53 (8%) of the 684 patients: 1 patient with an abnormal diagnostic total-body scan as well as 27 patients with an



elevated thyroglobulin level, 17 with a suspicious neck ultrasonography, and 8 with both.

The rates of complete ablation were estimated at 91.7% and 92.9% in the groups receiving recombinant human thyrotropin and those undergoing thyroid hormone withdrawal, respectively (Table 3), for a difference of –1.2 percentage points (95% confidence interval, –4.5 to 2.2), showing that the two treatments were equivalent. Equivalence was also shown between the two  $^{131}\text{I}$  doses used (see Table 2 in the Supplementary Appendix, available at NEJM.org). There was no interaction between  $^{131}\text{I}$  radioactivity and thyrotropin-stimulation method.

#### SENSITIVITY ANALYSES

Central determination of the serum thyroglobulin level was available for 618 of the 652 patients

without antithyroglobulin antibody (Table 3). Results with central recombinant human thyrotropin-stimulated thyroglobulin determinations or from intention-to-treat analysis were in accordance with those estimated in the per-protocol analysis. For the analysis performed under maximal bias, the 95% confidence interval was just above the margin.

#### FOLLOW-UP OF PATIENTS WITH INCOMPLETE ABLATION

Forty-six of the 53 patients with incomplete ablation (on local determination) had follow-up tests. A second  $^{131}\text{I}$  treatment was administered in 11 of the 46 patients. Four underwent surgery, 3 of whom were found to have recurrent disease. Among the remaining 43 patients, all diagnostic tests were normal in 26 patients, whereas suspicious

**Table 2. Radioiodine Ablation in the 729 Study Recipients, According to Thyrotropin-Stimulation Method and <sup>131</sup>I Dose.\***

Characteristic	Recombinant Human Thyrotropin		Thyroid Hormone Withdrawal	
	1.1 GBq (N=186)	3.7 GBq (N=183)	1.1 GBq (N=179)	3.7 GBq (N=181)
<sup>131</sup> I dose — GBq				
Mean ±SD	1.1±0.2	3.7±0.3	1.1±0.2	3.7±0.1
Range	1.0–3.7	1.1–4.3	1.0–3.7	3.5–4.8
Local determination of antithyroglobulin antibody — no. (%)				
Presence	17 (9)	18 (10)	21 (12)	21 (12)
Absence	169 (91)	165 (90)	158 (88)	160 (88)
Thyroglobulin level at time of <sup>131</sup> I administration in the absence of antithyroglobulin antibody — no./total no. (%)				
≤1 ng/ml	98/169 (58)	97/165 (59)	58/158 (37)	62/160 (39)
>1 ng/ml	68/169 (40)	65/165 (39)	97/158 (61)	96/160 (60)
Missing data	3/169 (2)	3/165 (2)	3/158 (2)	2/160 (1)
Days between <sup>131</sup> I administration and total-body scan	2.4±1.0	3.5±0.9	2.5±1.1	3.6±0.9
Thyroid uptake — no. (%)				
None	11 (6)	4 (2)	4 (2)	6 (3)
Visible (<0.5%)	26 (14)	33 (18)	24 (13)	26 (14)
0.5% to 2%	115 (62)	134 (73)	106 (59)	137 (76)
>2%	33 (18)	10 (5)	44 (25)	11 (6)
Not measured	1 (<1)	2 (1)	1 (<1)	1 (<1)
Pathologic uptake — no. (%)				
Lymph node	1 (<1)	5 (3)	4 (2)	6 (3)
Lung	0	0	0	2 (1)
Both	1 (<1)	0	0	0
Bone	0	2 (1)	0	1 (<1)
Physiological uptake — no. (%)				
Salivary glands	90 (48)	91 (50)	92 (51)	104 (57)
Esophagus	11 (6)	8 (4)	20 (11)	14 (8)
Stomach	125 (67)	120 (66)	132 (74)	129 (71)
Colon	116 (62)	110 (60)	118 (66)	126 (70)

\* Plus–minus values are means ±SD.

findings (suspicious neck ultrasonography or thyroglobulin level >1 ng per milliliter) were still present in 17.

**HYPOTHYROIDISM SYMPTOMS AND QUALITY OF LIFE AT TIME OF RADIOIODINE ADMINISTRATION**

The proportion of patients with symptoms of hypothyroidism was significantly higher in the groups undergoing thyroid-hormone withdrawal than in the groups receiving recombinant human thyrotropin, as measured across all the items on

the Billewicz scale. The SF-36 scale showed that thyroid hormone withdrawal was associated with deterioration of the quality of life, as compared with recombinant human thyrotropin. Three months after ablation, there was no significant difference in the SF-36 or Billewicz scores between the two thyrotropin-stimulation groups (Table 1 in the Supplementary Appendix).

The incidence of salivary problems did not differ significantly between groups, but lacrimal dysfunction (watery eyes) was more frequent

**Table 3.** Follow-up Testing of Thyroid Ablation 6–10 Months after <sup>131</sup>I Administration in the 684 Patients Who Could Be Evaluated, According to Thyrotropin-Stimulation Method and <sup>131</sup>I Dose.

Characteristic	Recombinant Human Thyrotropin		Thyroid Hormone Withdrawal	
	1.1 GBq (N=177)	3.7 GBq (N=171)	1.1 GBq (N=170)	3.7 GBq (N=166)
Neck ultrasonography — no. (%)				
Normal	171 (97)	161 (94)	163 (96)	157 (95)
Suspicious	6 (3)	10 (6)	7 (4)	9 (5)
Cytologic test normal	1 (<1)	3 (2)	1 (<1)	3 (2)
Cytologic test abnormal	0	1 (<1)	0	2 (1)
Cytologic test not performed	5 (3)	6 (4)	6 (4)	4 (2)
Presence of antithyroglobulin antibody — no. (%)				
Total-body scan normal	6 (3)	3 (2)	7 (4)	7 (4)
Total-body scan abnormal	0	0	1 (<1)	0
Total-body scan not performed*	4 (2)	1 (<1)	2 (1)	1 (<1)
Absence of antithyroglobulin antibody				
Local determination				
Thyroglobulin ≤1 ng/ml — no./total no. (%)	157/167 (94)	160/167 (96)	152/160 (95)	152/158 (96)
Central determination				
Thyroglobulin ≤1 ng/ml — no./total no. (%)	148/158 (94)	155/160 (97)	146/152 (96)	142/148 (96)
Thyroglobulin ≤1.4 ng/ml — no./total no. (%)	150/158 (95)	156/160 (98)	146/152 (96)	143/148 (97)
Missing data — no.	9	7	8	10
Thyroid ablation				
With local thyroglobulin determination — no. (%)				
Complete	160 (90)	159 (93)	156 (92)	156 (94)
Incomplete	17 (10)	12 (7)	14 (8)	10 (6)
With central thyroglobulin determination — no./total no. (%)†				
Complete	151/168 (90)	154/164 (94)	150/162 (93)	145/156 (93)
Incomplete	17/168 (10)	10/164 (6)	12/162 (7)	11/156 (7)

\* A total-body scan was not performed in patients with a suspicious finding on neck ultrasonography or a thyroglobulin level greater than 1 ng per milliliter.

† For each column, the total number of patients includes both patients for whom central thyroglobulin determination was available (and who had no detectable antithyroglobulin antibody) and patients with antithyroglobulin antibody.

among patients undergoing thyroid hormone withdrawal along with low-dose <sup>131</sup>I (19%) or high-dose <sup>131</sup>I (25%) than among patients receiving recombinant human thyrotropin (10%) (Table 4). Five unexpected serious adverse events occurred; these are enumerated in Table 4.

## DISCUSSION

The benefits of postoperative radioiodine administration in terms of rates of recurrence and sur-

vival have not been clearly shown in patients with low-risk thyroid cancer after complete surgical resection.<sup>7-9</sup> Because of the unclear degree of benefit, therefore, any therapeutic radioiodine intervention should at least be nontoxic and should maintain the quality of life.

Our randomized, multicenter study of a large number of patients with thyroid cancer shows similar efficacy of thyroid radioablation after preparation with the use of either recombinant human thyrotropin in the euthyroid state or withholding

**Table 4. Adverse Events, According to Thyrotropin-Stimulation Method and <sup>131</sup>I Dose.\***

Adverse Event	Recombinant Human Thyrotropin		Thyroid Hormone Withdrawal	
	1.1 GBq (N=186)	3.7 GBq (N=183)	1.1 GBq (N=179)	3.7 GBq (N=181)
Lacrimal dysfunction at time of ablation — no. (%)	18 (10)	19 (10)	35 (20)	43 (24)
Salivary dysfunction at time of ablation — no. (%)	19 (10)	26 (14)	24 (13)	29 (16)
Serious adverse events†	One hysterectomy	None	One renal stone related to hypercalcemia, one urinary infection, and one case of hypocalcemia	One case of cardiac insufficiency leading to death

\* Adverse events related to hypothyroidism are listed in Table 1 in the Supplementary Appendix.

† The serious adverse events were not thought to be related to treatment.

of thyroid hormone. The efficacy was also equivalent with either low-dose <sup>131</sup>I (1.1 GBq) or high-dose <sup>131</sup>I (3.7 GBq).

The 8-month assessment of ablation included serum thyroglobulin levels measured after the administration of recombinant human thyrotropin in the absence of antithyroglobulin antibodies and neck ultrasonography, on the basis of previous evidence that this is the most reliable combination for assessing ablation.<sup>2,3</sup> The ablation rate in our cohort was higher than the rates reported in previous studies,<sup>12,13</sup> for at least three reasons. First, a total thyroidectomy was performed in all patients, resulting in small remnants of normal thyroid tissue, as shown by the low uptake of <sup>131</sup>I on total-body scan and the low serum thyroglobulin levels at <sup>131</sup>I administration. Second, our patients had low-risk disease, with small T1 or T2 thyroid tumors, with no extension beyond the thyroid capsule and no aggressive histologic subtypes. Third, we did not consider the faint uptake in the thyroid bed that is frequently found on control diagnostic <sup>131</sup>I total-body scans and that has no clinical importance.<sup>4,5</sup>

It is also reassuring that over half our patients with incomplete ablation had a normal evaluation 1 year later, in accordance with a previous study.<sup>34</sup> Thyroglobulin disappears over time, showing that thyroid cells may survive for months after irradiation and may then disappear. Neck ultrasonography findings became normal in some patients, highlighting the fact that abnormalities on ultrasonography should be considered with caution in patients who have undergone total thyroidectomy.

Symptoms of hypothyroidism and quality of life were significantly better in the euthyroid

groups than in the hypothyroid groups, confirming previous results.<sup>14</sup> Lacrimal complications were more frequently observed in patients undergoing thyroid-hormone withdrawal and in those receiving high-dose rather than low-dose <sup>131</sup>I, indicating a relationship with the radiation dose.<sup>35</sup> Conversely, the <sup>131</sup>I radioactivity administered had no apparent effect on symptoms of hypothyroidism or quality of life. Persistent disease was found on ablation in 3% of patients, a rate similar to those in previous studies of patients with low-risk cancer.<sup>36-38</sup>

Whether preparation with recombinant human thyrotropin followed by 1.1-GBq <sup>131</sup>I radioactivity affects long-term outcomes will be revealed only by following patients over time. However, the currently available data are reassuring in showing that less than 1% of patients with low-risk cancer who had normal neck ultrasonography and an undetectable thyrotropin-stimulated serum thyroglobulin level will have a clinical recurrence over a 10-to-15-year period.<sup>4-6</sup> The effect of ablation on the serum titer of antithyroglobulin antibodies has not yet been shown.<sup>39</sup>

In conclusion, this study shows similar rates of thyroid-remnant ablation among patients with thyroid cancer, without evidence of residual disease after surgery, when either 1.1-GBq or 3.7-GBq <sup>131</sup>I is used and when the patient is prepared by means of either recombinant human thyrotropin or withholding of thyroid hormone. A similar ongoing study reached the same conclusions.<sup>40</sup> Thus, the use of recombinant human thyrotropin and a low dose of <sup>131</sup>I for postoperative radioiodine ablation represents an effective and attractive option for the management of low-risk thyroid can-

cer that reduces the amount of whole-body irradiation and maintains the quality of life. Future randomized studies in patients with low-risk thyroid cancer should be permitted to restrict radioablation to patients in whom it is beneficial.

Supported by the French National Cancer Institute (INCa) and the French Ministry of Health under the framework of the Soutien aux Thérapeutiques Innovantes et Coûteuses (STIC) program.

Drs. Leboulleux and Schlumberger report receiving lecture fees from Genzyme. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Sylviane Iacobelli, data manager for the study; Muriel Wartelle, for informatics; Frederic Troalen and Ludovic Lacroix, biologists, for central thyroglobulin determinations; Dana Hartl, surgeon, for proofreading an earlier version of the manuscript; all the clinical research associates, for data collection; and Lorna Saint-Ange, for editing the protocol.

#### APPENDIX

The authors' affiliations are as follows: the Departments of Nuclear Medicine and Endocrine Oncology, Institut Gustave Roussy and University Paris-Sud (M.S., D.D., S.L., M.R.), and the Departments of Biostatistics and Epidemiology, Institut Gustave Roussy (I.B., E.B.) — all in Villejuif; the Department of Endocrinology, Centre Hospitalier Universitaire (CHU) (B.C.), and the Department of Nuclear Medicine, Institut Bergonié (F.B.) — both in Bordeaux; the Department of Nuclear Medicine, Centre Claudius Regaud, Toulouse (S.Z.); the Department of Nuclear Medicine, Centre René Gauducheau, Nantes (B.B.); the Department of Nuclear Medicine, Centre François Baclesse, Caen (S.B.); the Department of Endocrinology, Hôpital Pitié-Salpêtrière (L.L.), and the Department of Nuclear Medicine, Hôpital Saint-Louis (M.-E.T.) — both in Paris; the Department of Nuclear Medicine, CHU, Toulouse (D. Bastie); the Department of Nuclear Medicine, Institut Jean Godinot, Reims (C.S.); the Department of Nuclear Medicine, Centre Becquerel, Rouen (P.V.); the Department of Nuclear Medicine, Institut de Cancérologie de l'Ouest Paul Papin, Angers (O.M.); the Department of Nuclear Medicine, Centre Lacassagne, Nice (D. Benisvy); the Department of Endocrinology, CHU, Lyon (C.B.); and the Department of Nuclear Medicine, Centre Jean Perrin, Clermont-Ferrand (C.D.) — all in France.

#### REFERENCES

- Schlumberger MJ. Papillary and follicular thyroid carcinoma. *N Engl J Med* 1998;338:297-306.
- Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009;19:1167-214. [Erratum, *Thyroid* 2010;20:674-5.]
- Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur J Endocrinol* 2006;154:787-803. [Erratum, *Eur J Endocrinol* 2006;155:385.]
- Cailleux AF, Baudin E, Travaglini JP, Richard M, Schlumberger M. Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer? *J Clin Endocrinol Metab* 2000;85:175-8.
- Pacini F, Capezzone M, Elisei R, Caccarelli C, Taddei D, Pinchera A. 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* 2002;87:1499-501.
- Castagna MG, Brilli L, Pilli T, et al. 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* 2008;93:76-81.
- Hay ID, Thompson GB, Grant CS, et al. Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940-1999): temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. *World J Surg* 2002;26:879-85.
- Jonklaas J, Cooper DS, Ain KB, et al. Radioiodine therapy in patients with stage I differentiated thyroid cancer. *Thyroid* 2010;20:1423-4.
- Bonnet S, Hartl D, Leboulleux S, et al. Prophylactic lymph node dissection for papillary thyroid cancer less than 2 cm: implications for radioiodine treatment. *J Clin Endocrinol Metab* 2009;94:1162-7.
- Kloos RT, Duvuuri V, Jhiang SM, Cahill KV, Foster JA, Burns JA. Nasolacrimal drainage system obstruction from radioactive iodine therapy for thyroid carcinoma. *J Clin Endocrinol Metab* 2002;87:5817-20.
- Mandel SJ, Mandel L. Radioactive iodine and the salivary glands. *Thyroid* 2003;13:265-71.
- Sawka AM, Thephamongkhon K, Brouwers M, Thabane L, Browman G, Gerstein HC. 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* 2004;89:3668-76.
- Hackshaw A, Harmer C, Mallick U, Haq M, Franklyn JA. 131I activity for remnant ablation in patients with differentiated thyroid cancer: a systematic review. *J Clin Endocrinol Metab* 2007;92:28-38.
- Schroeder PR, Haugen BR, Pacini F, et al. 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* 2006;91:878-84.
- Mernagh P, Suebwongpat A, Silverberg J, Weston A. Cost-effectiveness of using recombinant human thyroid-stimulating hormone before radioiodine ablation for thyroid cancer: the Canadian perspective. *Value Health* 2010;13:180-7.
- Hänscheid H, Lassmann M, Luster M, et al. 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* 2006;47:648-54.
- Pacini F, Ladenson PW, Schlumberger M, et al. 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* 2006;91:926-32.
- Barbaro D, Boni G, Meucci G, et al. Radioiodine treatment with 30 mCi after recombinant human thyrotropin stimulation in thyroid cancer: effectiveness for postsurgical remnants ablation and possible role of iodine content in L-thyroxine in the outcome of ablation. *J Clin Endocrinol Metab* 2003;88:4110-5.
- Rosario PW, Xavier AC. Recombinant human thyroid stimulating hormone in thyroid remnant ablation with 1.1 GBq 131-iodine in low-risk patients. *Am J Clin Oncol* 2012;35:101-4.
- Pacini F, Molinaro E, Castagna MG, et

- al. Ablation of thyroid residues with 30 mCi (<sup>131</sup>I): a comparison in thyroid cancer patients prepared with recombinant human TSH or thyroid hormone withdrawal. *J Clin Endocrinol Metab* 2002;87:4063-8.
21. Pilli T, Brianzoni E, Capocchetti F, et al. A comparison of 1850 (50 mCi) and 3700 MBq (100 mCi) <sup>131</sup>-iodine administered doses for recombinant thyrotropin-stimulated postoperative thyroid remnant ablation in differentiated thyroid cancer. *J Clin Endocrinol Metab* 2007;92:3542-6.
22. Chianelli M, Todino V, Graziano FM, et al. Low-activity (2.0 GBq; 54 mCi) radioiodine post-surgical remnant ablation in thyroid cancer: comparison between hormone withdrawal and use of rhTSH in low-risk patients. *Eur J Endocrinol* 2009; 160:431-6.
23. Elisei R, Schlumberger M, Driedger A, et al. 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. *J Clin Endocrinol Metab* 2009; 94:4171-9.
24. Lee J, Yun MJ, Nam KH, Chung WY, Soh EY, Park CS. Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. *Thyroid* 2010;20:173-9.
25. Hedinger C, Williams ED, Sobin LH. Histological typing of thyroid tumours. In: World Health Organization international histological classification of tumours. Berlin: Springer-Verlag, 1988:1-18.
26. Shah JP, Ang KK, Forastiere A, et al. Head and neck sites. In: Greene FL, Page DL, Fleming ID, et al., eds. *AJCC cancer staging handbook*. 6th ed. Chicago: American Joint Committee on Cancer, 2002:89-98.
27. Leboulleux S, Girard E, Rose M, et al. Ultrasound criteria of malignancy for cervical lymph nodes in patients followed up for differentiated thyroid cancer. *J Clin Endocrinol Metab* 2007;92:3590-4.
28. Schlumberger M, Hitzel A, Toubert ME, et al. Comparison of seven serum thyroglobulin assays in the follow-up of papillary and follicular thyroid cancer patients. *J Clin Endocrinol Metab* 2007; 92:2487-95.
29. Spencer C, Fatemi S, Singer P, Nicoloff J, Lopresti J. Serum basal thyroglobulin measured by a second-generation assay correlates with the recombinant human thyrotropin-stimulated thyroglobulin response in patients treated for differentiated thyroid cancer. *Thyroid* 2010;20:587-95.
30. Brassard M, Borget I, Edet-Sanson A, et al. Long-term follow-up of patients with papillary and follicular thyroid cancer: a prospective study on 715 patients. *J Clin Endocrinol Metab* 2011;96:1352-9.
31. Billewicz WZ, Chapman RS, Crooks J, et al. Statistical methods applied to the diagnosis of hypothyroidism. *Q J Med* 1969;38:255-66.
32. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
33. Altman DG, Bland JM. How to randomise. *BMJ* 1999;319:703-4.
34. Baudin E, Do Cao C, Cailleux AF, Leboulleux S, Travagli JP, Schlumberger M. 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* 2003;88:1107-11.
35. Rosário PW, Borges MA, Purisch S. Preparation with recombinant human thyroid-stimulating hormone for thyroid remnant ablation with <sup>131</sup>I is associated with lowered radiotoxicity. *J Nucl Med* 2008;49: 1776-82.
36. Nascimento C, Borget I, Al Ghuzlan A, et al. Persistent disease and recurrence in differentiated thyroid cancer patients with undetectable postoperative stimulated thyroglobulin level. *Endocr Relat Cancer* 2011;18:R29-R40.
37. Toubeau M, Touzery C, Arveux P, et al. Predictive value for disease progression of serum thyroglobulin levels measured in the postoperative period and after (<sup>131</sup>I) ablation therapy in patients with differentiated thyroid cancer. *J Nucl Med* 2004; 45:988-94.
38. Kim TY, Kim WB, Kim ES, et al. Serum thyroglobulin levels at the time of <sup>131</sup>I remnant ablation just after thyroidectomy are useful for early prediction of clinical recurrence in low-risk patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2005;90:1440-5.
39. Chiovato L, Latrofa F, Braverman LE, et al. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. *Ann Intern Med* 2003; 139:346-51.
40. Mallick U. HiLo: multicentre randomised phase III clinical trial of high versus low dose radioiodine, with or without recombinant thyroid stimulating hormone (rhTSH) for remnant ablation for differentiated thyroid cancer. In: Program and abstracts of the 14th International Thyroid Congress, Paris, September 11-16, 2011. abstract.

Copyright © 2012 Massachusetts Medical Society.

POSTING PRESENTATIONS FROM MEDICAL MEETINGS ONLINE

Online posting of an audio or video recording of an oral presentation at a medical meeting, with selected slides from the presentation, is not considered prior publication. Authors should feel free to call or send e-mail to the Journal's Editorial Offices if there are any questions about this policy.