ORIGINAL ARTICLE

Thyroidectomy without Radioiodine in Patients with Low-Risk Thyroid Cancer

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ABSTRACT

BACKGROUND

In patients with low-risk differentiated thyroid cancer undergoing thyroidectomy, the postoperative administration of radioiodine (iodine-131) is controversial in the absence of demonstrated benefits.

METHODS

In this prospective, randomized, phase 3 trial, we assigned patients with low-risk differentiated thyroid cancer who were undergoing thyroidectomy to receive ablation with postoperative administration of radioiodine (1.1 GBq) after injections of recombinant human thyrotropin (radioiodine group) or to receive no postoperative radioiodine (no-radioiodine group). The primary objective was to assess whether no radioiodine therapy was noninferior to radioiodine therapy with respect to the absence of a composite end point that included functional, structural, and biologic abnormalities at 3 years. Noninferiority was defined as a between-group difference of less than 5 percentage points in the percentage of patients who did not have events that included the presence of abnormal foci of radioiodine uptake on whole-body scanning that required subsequent treatment (in the radioiodine group only), abnormal findings on neck ultrasonography, or elevated levels of thyroglobulin or thyroglobulin antibodies. Secondary end points included prognostic factors for events and molecular characterization.

RESULTS

Among 730 patients who could be evaluated 3 years after randomization, the percentage of patients without an event was 95.6% (95% confidence interval [CI], 93.0 to 97.5) in the no-radioiodine group and 95.9% (95% CI, 93.3 to 97.7) in the radioiodine group, a difference of −0.3 percentage points (two-sided 90% CI, −2.7 to 2.2), a result that met the noninferiority criteria. Events consisted of structural or functional abnormalities in 8 patients and biologic abnormalities in 23 patients with 25 events. Events were more frequent in patients with a postoperative serum thyroglobulin level of more than 1 ng per milliliter during thyroid hormone treatment. Molecular alterations were similar in patients with or without an event. No treatment-related adverse events were reported.

CONCLUSIONS

In patients with low-risk thyroid cancer undergoing thyroidectomy, a follow-up strategy that did not involve the use of radioiodine was noninferior to an ablation strategy with radioiodine regarding the occurrence of functional, structural, and biologic events at 3 years. (Funded by the French National Cancer Institute; ESTIMABL2 ClinicalTrials.gov number, NCT01837745.)

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The majority of patients with thyroid cancer are at low risk for recurrence (<5%),[1-3] and their risk of cancer-related death is even lower.[4] After thyroidectomy, radioiodine (iodine-131) is generally administered both to ablate residual normal thyroid tissue and to treat persistent disease. Two large, randomized trials have shown that in patients with low-risk thyroid cancer, the postoperative administration of low-activity radioiodine (1.1 GBq) after injections of recombinant human thyrotropin was noninferior to the administration of high-activity radioiodine (3.7 GBq) after withdrawal of thyroid hormone treatment with respect to the ablation success rate at 1 year and the recurrence rate at 5 years.[5-8]

There is a consensus to avoid radioiodine administration in patients with a unifocal microcarcinoma (≤10 mm in diameter), but the benefits of radioiodine administration in other patients with low-risk thyroid cancer remain controversial.[4,9] In patients with pathological tumor–node–metastasis (pTNM) stage 1 disease, retrospective studies have shown inconsistent results regarding the usefulness of radioiodine administration.[10,11] The pTNM staging system predicts the risk of thyroid cancer–related death and was used until recently for the decision regarding postoperative administration of radioiodine.[12,13] The risk of recurrence was defined by the risk stratification recommended by the American Thyroid Association.[4] On the basis of this stratification, retrospective studies have not shown benefits of postoperative radioiodine administration in patients with low-risk disease.[14,15] Nevertheless, the absence of prospective studies that address this question has been used as an argument in favor of recommending the use of radioiodine in all patients with low-risk thyroid cancer.

We conducted the randomized, phase 3 Essai Stimulation Ablation 2 (ESTIMABL2) trial involving patients with low-risk thyroid cancer to assess the noninferiority of a follow-up strategy that does not include the postoperative administration of radioiodine as compared with radioiodine administration (ablation with 1.1 GBq after stimulation with recombinant human thyrotropin) with respect to the percentage of patients without an event during 3 years after randomization.

Methods

Trial Oversight

The ESTIMABL2 trial was performed within the Tumeurs de la Thyroïde Refractaires Network with support from the French Ministry of Health through a grant from the National Cancer Institute. All the patients provided written informed consent. The trial was conducted in accordance with the protocol (available with the full text of this article at NEJM.org), which was approved by a central ethics committee and by national authorities. Data were gathered by all the authors and were analyzed by the first and last authors. The manuscript was reviewed by all the authors before submission for publication. All the authors assume responsibility for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Patients were adults (≥18 years of age) with a differentiated thyroid carcinoma (papillary, follicular, or oncocytic [Hürthle-cell cancer]), with a multifocal pT1a tumor (a diameter of each lesion of ≤1 cm and a sum of the longest diameters of the lesions of ≤2 cm) or a pT1b tumor (>1 cm and ≤2 cm); with both tumor stages, patients had a nodal status of N0 (no evidence of regional node involvement) or Nx (regional lymph nodes cannot be assessed in the absence of neck dissection), in the absence of extrathyroidal extension (Table S1 in the Supplementary Appendix, available at NEJM.org). Patients who had aggressive histologic subtypes (tall-cell, clear-cell, columnar-cell, and diffuse sclerosing variants of papillary thyroid cancer, poorly differentiated) were excluded from the trial.[16]

Two to five months before randomization, eligible patients had undergone total thyroidectomy with or without dissection of cervical lymph nodes (neck dissection), according to ongoing protocols, with complete tumor resection. In addition, all the patients had undergone postoperative neck ultrasonography without the detection of suspicious abnormalities.

Procedures

Patients were randomly assigned to undergo postoperative administration of radioiodine (radioiodine group) or not to undergo such administration (no-radioiodine group), with stratification according to the trial site and lymph-node status (N0 or Nx). In the radioiodine group, while patients were receiving thyroid hormone treatment, 1.1 GBq (30 mCi) of radioiodine was administered 24 hours after the second intramuscular injection of recombinant human thyrotropin

(Thyrogen, Sanofi), which was given at a dose of 0.9 mg on 2 consecutive days. Whole-body scanning and single-photon-emission computed tomography (SPECT) of the neck were performed 2 to 5 days after radioiodine administration.

The follow-up protocol was consistent with the standard of care in France and consisted of the measurement of thyroglobulin and thyroglobulin antibodies in all patients at 10 months and yearly thereafter. Thyroglobulin was measured while the patient was receiving thyroid hormone treatment, except for the measurement at 10 months after randomization in the radioiodine group, in whom the measurement was performed after stimulation with recombinant human thyrotropin. Ultrasonography of the neck was performed in all patients 10 months and 3 years after randomization. No diagnostic radioiodine scanning was performed after the whole-body scanning that was performed after therapy.

PRIMARY AND SECONDARY END POINTS

The primary objective was to assess noninferiority in the no-radioiodine group as compared with the radioiodine group with respect to the percentage of patients without a functional, structural, or biologic event during 3 years after randomization. An event was a composite end point that consisted of several criteria.

In the radioiodine group only, events included the presence of foci of radioiodine uptake outside the thyroid bed on postablation whole-body scanning or on SPECT (functional event) that resulted in additional treatment (radioiodine administration or surgery). In both groups, events included abnormal findings on ultrasonography of the neck (structural events), which were defined as a suspicious lymph node or thyroid mass associated with abnormal cytologic findings or with a serum thyroglobulin level in the aspirate fluid of more than 10 ng per milliliter or an elevated level of thyroglobulin or thyroglobulin antibodies (biologic events). In the radioiodine group, in the absence of thyroglobulin antibodies, an elevated thyroglobulin level was defined as a value of more than 5 ng per milliliter (after the receipt of recombinant human thyrotropin or during thyroid hormone treatment) or a value of more than 1 ng per milliliter during thyroid hormone treatment on two consecutive measurements obtained 6 months apart. In the no-radioiodine group, in the absence of thyroglobulin antibodies, an elevated thyroglobulin level was defined as a value of more than 5 ng per milliliter during thyroid hormone treatment or a value of more than 2 ng per milliliter during thyroid hormone treatment on two consecutive measurements obtained 6 months apart. In the two groups, the detection of a thyroglobulin antibody titer above the upper limit of the normal range or an increase in the thyroglobulin antibody titer by more than 50% between two measurements performed 6 months apart was also considered to be part of the composite criteria. Serum samples for the measurement of thyroglobulin and thyroglobulin antibodies that were obtained at randomization and at the 10-month and 3-year follow-up visits were assessed both locally and in a central laboratory (Table S2).[17]

Secondary end points were quality of life, anxiety, fear of recurrence, and dysfunction of lacrimal and salivary glands. Questionnaires were administered to all the patients at the time of randomization, after radioiodine administration during hospitalization in the radioiodine group or 2 months after randomization in the no-radioiodine group, and at 10 months and 3 years after randomization in the two groups.

PROGNOSTIC FACTORS

Prognostic factors for an event were evaluated with the use of univariate logistic regression. A post hoc analysis comparing the percentages of patients with no evidence of disease (as defined by the 2015 guidelines of the American Thyroid Association as an "excellent response" to treatment) was performed in the two groups at 10 months and at 3 years. An excellent response at 10 months was defined as normal findings on neck ultrasonography with a thyroglobulin level of less than 1 ng per milliliter after the administration of recombinant human thyrotropin (in the radioiodine group) or during thyroid hormone treatment (in the no-radioiodine group) in the absence of an elevated level of thyroglobulin antibodies. An excellent response at 3 years was defined as normal findings on neck ultrasonography with a thyroglobulin level of less than 0.2 ng per milliliter (in the radioiodine group) and a level of less than 1 ng per milliliter (in the no-radioiodine group) during thyroid hormone treatment in the absence of an elevated level of thyroglobulin antibodies. Results were assessed after review of findings from both local and central laboratories.[4]

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Radioiodine (N=389)	No Radioiodine (N=387)
Age — yr	52.2±13.4	52.6±13.5
Female sex — no. (%)	319 (82.0)	323 (83.5)
Interval between thyroidectomy and randomization — days	92.1±23.2	91.2±23.6
Histologic analysis — no. (%)		
Papillary	372 (95.6)	372 (96.1)
Follicular	13 (3.3)	11 (2.8)
Oncocytic: Hürthle cell	4 (1.0)	4 (1.0)
Largest tumor dimension — mm	13.4±3.6	13.7±3.9
Primary tumor–node–metastasis stage — no. (%)		
pT1aN0	26 (6.7)	23 (5.9)
pT1aNx	56 (14.4)	42 (10.9)
pT1bN0	143 (36.8)	148 (38.2)
pT1bNx	164 (42.2)	174 (45.0)
Multifocality — no. (%)	178 (45.8)	156 (40.3)
Neck dissection performed — no. (%)†	171 (44.0)	171 (44.2)
Central only	69 (17.7)	77 (19.9)
Central and lateral	74 (19.0)	65 (16.8)
Lateral only	26 (6.7)	27 (7.0)
Unknown	2 (0.5)	2 (0.5)

* Plus–minus values are means ±SD. The percentages may not total 100 because of rounding.
† Neck dissection was performed according to ongoing protocols at each trial center.

MOLECULAR ANALYSIS

The objective was to describe the type and number of molecular alterations, according to the occurrence of an event (Table S2). For this purpose, we designed a nested case–control study in which cases were patients with an event and controls were patients without an event, regardless of which randomized treatment had been received. Each case patient was paired with two controls on the basis of five criteria: pT classification (pT1a or pT1b), histologic results (papillary or follicular), sex, age group (≤55 years or >55 years), neck dissection (yes or no), and treatment group (radioiodine or no radioiodine).

STATISTICAL ANALYSIS

We designed our trial as a noninferiority study to answer the question of whether the percentage of patients without an event in the no-radioiodine group would be noninferior to that in the radioiodine group, with a between-group difference of less than 5 percentage points at 3 years. We calculated that the enrollment of 750 patients would provide the trial with 90% power to determine the noninferiority margin, assuming that 95% of the patients in the radioiodine group would not have an event at 3 years and including the potential loss to follow-up; a P value of less than 0.05 was considered to indicate statistical significance.

Descriptive quantitative data were expressed as means and standard deviations; qualitative data were expressed as percentages and 95% confidence intervals. We calculated the difference in the observed percentages of patients without an event and its 95% one-sided confidence interval, which was equivalent to a two-sided 90% confidence interval, because the trial was designed to use one-sided hypothesis testing at an alpha level of 0.05. We used logistic regression to perform an analysis of the primary end point after adjustment for stratification factors as a test of robustness.

The primary analysis included all the patients who could be evaluated in the per-protocol population (i.e., all the patients whose treatment and 3-year follow-up had adhered to the study protocol); patients who had been followed for fewer than 3 years were excluded from the primary population. The percentage of patients without an event during the trial period was calculated without consideration for the timing of the event during that period. A sensitivity analysis was performed in the intention-to-treat population that included the results for all the patients until their last participation in the trial in order to consider those who could not be evaluated at 3 years. We report the between-group difference in event-free survival at 3 years using a time-to-event analysis and its two-sided 90% confidence interval.

For secondary end points, results are reported as point estimates and 95% confidence intervals, since the statistical analysis plan did not include a provision for correcting for multiple comparisons. Thus, the widths of the confidence intervals have not been adjusted for multiplicity, so they should not be used to infer definitive treatment effects. All the analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

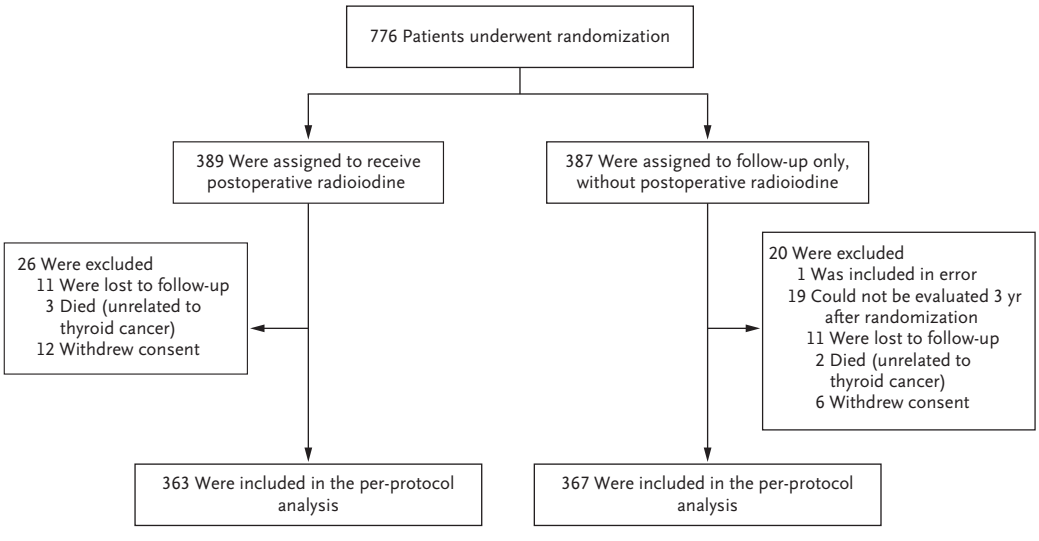

Figure 1. Enrollment and Follow-up.

The five listed deaths that occurred during the trial period were from pulmonary embolism, sarcomatoid lung cancer, and aneurysm rupture in the radioiodine group and heart failure and peritoneal cancer in the no-radioiodine group.

RESULTS

TRIAL POPULATION

From May 2013 through March 2017, a total of 776 patients underwent randomization at 35 centers in France (Table 1 and Table S3). The mean age of the patients was 52 years, and 83% were women. Histologic analyses revealed mostly papillary tumors (95.9%), and pTN stages were mostly pT1b N0 or Nx (81.1%). One patient did not meet the inclusion criteria, and 45 patients (5.8%) could not be evaluated at 3 years after randomization (Fig. 1).

PRIMARY END POINT

Among the 730 patients who could be evaluated at 3 years, the percentage without an event was 95.6% (95% confidence interval [CI], 93.0 to 97.5) in the no-radioiodine group and 95.9% (95% CI, 93.3 to 97.7) in the radioiodine group, for a between-group difference of −0.3 percentage points (two-sided 90% CI, −2.7 to 2.2), which met the noninferiority cutoff for the nonuse of radioiodine. Similar results were obtained in the intention-to-treat population and after adjustment for stratification factors (Tables S4 and S5).

Primary events occurred in 16 of 367 patients (4.4%) in the no-radioiodine group and in 15 of 363 patients (4.1%) in the radioiodine group. Events consisted of functional or structural abnormalities in 8 patients and biologic abnormalities with respect to levels of thyroglobulin or thyroglobulin antibodies in 23 patients with 25 events (Table 2).

Overall, subsequent treatments (surgery, radioiodine administration, or both) were performed in 4 patients in the no-radioiodine group and in 10 in the radioiodine group. Other patients were followed without additional treatment. Adverse events occurred in 30 patients, and no adverse events were determined by the investigators to be related to treatment (Table S6). There were no thyroid-related deaths.

QUALITY-OF-LIFE SCORES

In the two groups, the patients had similar scores regarding quality of life, anxiety, distress, and fear of recurrence (Table S7 and Fig. S1). The frequency of salivary or lacrimal dysfunction was also similar in the two groups at all time points, except for lacrimal discomfort, which was more common in the radioiodine group at 2 months after randomization (Table S8).

PROGNOSTIC FACTORS FOR EVENT OCCURRENCE

A higher risk of events was observed in patients with a tumor size of less than 14 mm and in patients with a postoperative serum thyroglobulin

Table 2. Number and Type of Events Occurring during 3 Years (Per-Protocol Population).*

Variable	Radioiodine (N=363)		No Radioiodine (N=367)		Between-Group Difference†
	no.	*% (95% CI)*	*no.*	*% (95% CI)*	*percentage points (90% CI)*
Primary composite end point					
No primary event during 3 yr	348	95.9 (93.3 to 97.7)	351	95.6 (93.0 to 97.5)	−0.3 (−2.7 to 2.2)
Occurrence of event during 3 yr	15	4.1 (2.3 to 6.7)	16	4.4 (2.5 to 7.0)	
Functional event					
Foci of radioiodine uptake outside thyroid bed resulting in further treatment	3‡		NA		
Structural event					
Abnormal results on neck ultrasonography with abnormal cytologic or elevated thyroglobulin findings in aspirate fluid					
Abnormal lymph node	2§		3¶		
Abnormal thyroid mass	0		0		
Biologic event					
Thyroglobulin level after recombinant human thyrotropin					
>5 ng per ml	3‖		NA		
>1 ng to ≤5 ng per ml on 2 consecutive measurements	6‖		NA		
Thyroglobulin level during THT					
>5 ng per ml	0		3**		
>1 ng to ≤5 ng per ml on 2 consecutive measurements	0		NA		
>2 ng to ≤5 ng per ml on 2 consecutive measurements	NA		4**		
Thyroglobulin antibodies					
Appearance of elevated levels	2		5		
Increase in titer during trial	0		2		

* The primary objective was to assess noninferiority in the no-radioiodine group as compared with the radioiodine group with respect to the absence of a 3-year composite end point, which was defined as the presence of abnormal foci of radioiodine uptake on whole-body scanning that required subsequent treatment (in the radioiodine group), abnormal findings on neck ultrasonography, or elevated levels of thyroglobulin or thyroglobulin antibodies. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes. NA denotes not applicable, and THT thyroid hormone treatment.

† A two-sided 90% confidence interval (equivalent to a 95% one-sided confidence interval) is reported for the between-group difference in the primary end point because the trial was designed to use one-sided hypothesis testing at an alpha level of 0.05.

‡ The 3 patients in this category had postoperative thyroglobulin levels of 0.2 ng, 0.3 ng, and 1.33 ng per milliliter while receiving THT.

§ The 2 patients in this category had postoperative thyroglobulin levels of 0.15 ng and 0.04 ng per milliliter while receiving THT.

¶ The 3 patients in this category had postoperative thyroglobulin levels of 0.7 ng, 0.9 ng, and 1.7 ng per milliliter while receiving THT.

‖ This category includes 1 patient who had two events at different time points: an elevated thyroglobulin level after the administration of human recombinant thyrotropin (>1 ng to ≤5 ng per milliliter) on two consecutive measurements, which was followed by an increased level (>5 ng per milliliter).

** This category includes 1 patient who had two events at different time points: an elevated thyroglobulin level during THT (>2 ng to ≤5 ng per milliliter) on two consecutive measurements, which was followed by an increased level (>5 ng per milliliter).

level that was higher than the two cutoff values we evaluated (0.5 ng and 1 ng per milliliter) while receiving thyroid hormone therapy in the absence of an elevated level of thyroglobulin antibodies (Table 3 and Table S9).

MOLECULAR DATA

In the nested case–control study (in which cases were patients with an event and controls were patients without an event), we performed molecular analysis on 100 tumor samples obtained from 96 patients, among which 90 samples could be analyzed (Table S10). Overall, 50 tumors had a *BRAF* mutation, 14 had a *RAS* mutation, and 6 had an oncogenic fusion (Table S11). The frequency of *BRAF* mutations was not materially different between cases (61.5%) and controls (53.1%). A total of 17 tumors did not have any genetic abnormalities, including 4 samples with noncontributive ribonucleic acid sequencing. No *TERT* promoter mutations were detected.

MEASURES OF EXCELLENT RESPONSE

Patients in the two groups had similar rates of excellent response, as defined by the American Thyroid Association, with respect to thyroglobulin levels that were measured at a central laboratory at both 10 months and 3 years (Table 4). Results regarding thyroglobublin levels as determined by local laboratories are provided in Table S12.

Table 3. Prognostic Factors Associated with a Primary Event in 730 Patients Who Could Be Evaluated during 3 Years (Univariate Analysis).*

Variable	Patients with Event	Odds Ratio (95% CI)†
	no./total no. (%)	
Age		
≤55 yr	14/402 (3.5)	Reference
>55 yr	17/328 (5.2)	1.5 (0.7–3.1)
Sex		
Female	27/604 (4.5)	Reference
Male	4/126 (3.2)	0.7 (0.2–2.0)
Histologic analysis		
Papillary	30/698 (4.3)	Reference
Follicular	1/24 (4.2)	1.0 (0.1–7.4)
Oncocytic: Hürthle cell	0/8	NE
Largest median tumor size		
≤14 mm	23/407 (5.7)	Reference
>14 mm	8/322 (2.5)	0.4 (0.2–0.96)
Nodal status		
N0	9/320 (2.8)	Reference
Nx	22/410 (5.4)	2.0 (0.9–2.8)
Multifocality		
No	15/411 (3.6)	Reference
Yes	16/319 (5.0)	1.4 (0.7–2.8)
Thyroglobulin level‡		
Higher cutoff value		
≤1 ng/ml	16/507 (3.2)	Reference
>1 ng/ml	7/48 (14.6)	5.2 (2.0–13.5)
Lower cutoff value		
≤0.5 ng/ml	12/426 (2.8)	Reference
>0.5 ng/ml	11/129 (8.5)	3.2 (1.4–7.5)

* NE denotes not evaluated.
† The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects within subgroups. No multivariate analysis was performed.
‡ The listed thyroglobulin level was evaluated during THT in 555 patients without an elevated level of thyroglobulin antibodies at randomization. Two thresholds of thyroglobulin level were tested.

DISCUSSION

Our randomized trial addressed the usefulness of follow-up without postoperative administration of radioiodine in patients with low-risk thyroid cancer undergoing thyroidectomy. We observed that less than 5% of the patients in the two groups had events that included abnormal findings on whole-body scanning or neck ultrasonography or elevated levels of thyroglobulin or thyroglobulin antibodies during the first 3 years of follow-up. This rate is concordant with the definition of low-risk thyroid cancer, and our trial showed that the risk of events was not higher in the absence of postoperative administration of radioiodine.[4] The patients in our trial were representative of patients with a pT1 thyroid tumor measuring 20 mm or less, a category that constitutes 50 to 70% of all thyroid cancers and 65 to 75% of those with a nodal status of N0 or Nx.[3,18-20]

Radioiodine is administered postoperatively to destroy remaining normal thyroid tissue, to facilitate follow-up, and to diagnose and eventually treat microscopic disease and therefore increase recurrence-free survival. In accordance with these goals, we defined events as structural

Table 4. Response to Treatment at 10 Months and 3 Years.

Response	Radioiodine	No Radioiodine
Evaluation at 10 mo		
No. of patients	325	342
Distribution of response — no. (%)		
Excellent*	282 (86.8)	295 (86.3)
Structurally incomplete: abnormal imaging	4 (1.2)	1 (0.3)
Biochemically incomplete†	8 (2.5)	13 (3.8)
Indeterminate‡	31 (9.5)	33 (9.6)
Evaluation at 3 yr		
No. of patients	363	367
Distribution of response — no. (%)		
Excellent§	265 (73.0)	272 (74.1)
Structurally incomplete: abnormal imaging	4 (1.1)	3 (0.8)
Biochemically incomplete¶	2 (0.6)	12 (3.3)
Indeterminate‖	40 (11.0)	37 (10.1)
Missing data for central laboratory assessment	52 (14.6)	43 (11.7)

* Listed are the results of a post hoc analysis comparing the percentages of patients with an excellent response (as defined by the 2015 guidelines of the American Thyroid Association) according to central laboratory measurements. The definition of an excellent response to treatment at 10 months was normal findings on neck ultrasonography and a thyroglobulin level of less than 1 ng per milliliter after the administration of recombinant human thyrotropin in the radioiodine group or while patients were receiving THT in the no-radioiodine group in the absence of an elevated level of thyroglobulin antibodies.

† A biochemically incomplete response at 10 months was defined as normal results on neck ultrasonography and a thyroglobulin level of 10 ng per milliliter or more after the administration of recombinant human thyrotropin in the radioiodine group or a level of 2 ng per milliliter or more during THT in the no-radioiodine group in the absence of an elevated level of thyroglobulin antibodies or an increasing level over time.

‡ The criteria for an indeterminate response at 10 months were the same as those for a biochemically incomplete response except that the thyroglobulin cutoff was 1 ng to less than 10 ng per milliliter in the radioiodine group and 1 ng to less than 2 ng per milliliter in the no-radiodine group; or the presence of elevated thyroglobulin antibodies with a decreasing level over time.

§ An excellent response at 3 years was defined as normal findings on neck ultrasonography and a thyroglobulin level of less than 0.2 ng per milliliter in the radioiodine group and a level of less than 1 ng per milliliter in the no-radioiodine group during THT in the absence of an elevated level of thyroglobulin antibodies.

¶ A biochemically incomplete response at 3 years was defined as normal findings on neck ultrasonography and a thyroglobulin level of 1 ng per milliliter in the radioiodine group and a level of 2 ng per milliliter in the no-radioiodine group during THT in the absence of an elevated level of thyroglobulin antibodies; or the presence of an elevated level of thyroglobulin antibodies with an increasing level over time.

‖ The criteria for an indeterminate response at 3 years were the same as those for an indeterminate response at 10 months except that the thyroglobulin cutoff was 0.2 ng to less than 1 ng per milliliter in the radioiodine group and a level of 1 ng to less than 2 ng per milliliter in the no-radioiodine group.

or functional, with the need for further treatments (surgery or radioiodine administration), or biologic, defined as an elevated level of thyroglobulin or thyroglobulin antibodies. The measurement of thyroglobulin antibodies was included in this composite definition of events, even though the clinical relevance is questionable. The appearance of elevated levels of thyroglobulin antibodies or an increase in the titer over time is not always related to structural recurrence but frequently leads to further diagnostic examination or administration of radioiodine.

Thresholds for abnormal thyroglobulin levels were more than 5 ng per milliliter after the administration of recombinant human thyrotropin or more than 1 ng per milliliter in the radioiodine group and more than 2 ng per milliliter in the no-radioiodine group while the patients were receiving thyroid hormone therapy. These levels are consonant with the standard of care at the initiation of the trial, with 5% of patients having a thyroglobulin level between 1 ng and 2 ng per milliliter while receiving thyroid hormone therapy in the absence of recurrence after total thy-

roidectomy without radioiodine.[17,21] A post hoc analysis that we performed using thyroglobulin thresholds recommended by the 2015 American Thyroid Association guidelines (0.2 ng per milliliter in patients treated with radioiodine and 1 ng per milliliter in the absence of radioiodine) showed a similar percentage of patients with an excellent response in the two trial groups.

In addition, the patients in the two groups had similar scores with respect to quality of life, anxiety, distress, and fear of recurrence, findings that reflect the absence of consequences in patients who did not receive postoperative radioiodine. Also, lacrimal discomfort was more frequent at 2 months in the radioiodine group.[6]

Among the trial patients, genomic abnormalities were similar to those listed in the thyroid data set of the Cancer Genome Atlas, with the *BRAF* V600E mutation present in more than half the patients.[22] Although the presence of the tall-cell variant of papillary thyroid cancer was an exclusion criterion, this variant was detected in 25% of the samples that underwent central laboratory review, which explains the high incidence of *BRAF* mutations and underlines the importance of central histologic review to detect these pathological subtypes.[23] We did not find any *TERT* promoter mutations.[24] The presence of the *BRAF* V600E mutation is correlated with a more advanced pTNM stage.[25,26] In retrospective studies, the presence of this mutation has been associated with a poor outcome, but this was not the case in a study involving patients with N1 microcarcinoma.[26] On the basis of our findings, it appears that in patients with low-risk disease, the presence of a *BRAF* mutation would not be an indication for radioiodine administration.

In our trial, a postoperative thyroglobulin level that was higher than the two cutoff values we evaluated (0.5 ng and 1 ng per milliliter) in patients who were undergoing thyroid hormone therapy was associated with an increased risk of an event, which suggests that elevated postoperative levels should be an indication for closer follow-up. In our trial, a tumor size of less than 14 mm was predictive of an event; this unexpected finding could be related to multifocality, which was present at a high rate in the trial patients.

Our trial has certain limitations. Our results should be confirmed with longer follow-up. However, in previous retrospective studies involving patients with low-risk thyroid cancer, most recurrences occurred during the first 5 years of follow-up.[27,28] The 3-year period in our trial allowed for control of indeterminate findings over time while limiting loss to follow-up.

In this randomized trial involving patients with low-risk differentiated thyroid cancer, we found that follow-up without the use of radioiodine after thyroidectomy was noninferior to the administration of 1.1 GBq of radioiodine after the administration of recombinant human thyrotropin.

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APPENDIX

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