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A Comparison of 1850 (50 mCi) and 3700 MBq (100 mCi) 131-Iodine Administered Doses for Recombinant Thyrotropin-Stimulated Postoperative Thyroid Remnant Ablation in Differentiated Thyroid Cancer

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Objective: Recently, a multicenter study in differentiated thyroid cancer (DTC) patients showed that 3700 MBq 131-iodine (^{131}I) after recombinant human TSH (rhTSH) had a successful thyroid ablation rate similar to that obtained after thyroid hormone withdrawal. We investigated whether 1850 MBq ^{131}I had a similar successful rate to 3700 MBq in patients prepared with rhTSH.

Design: A total of 72 patients with DTC were randomly assigned to receive 1850 (group A, n = 36) or 3700 MBq (group B, n = 36) ^{131}I after rhTSH. One injection of 0.9 mg rhTSH was administered for 2 consecutive days; ^{131}I therapy was delivered 24 h after the last injection, followed by a posttherapy whole-body scan. Successful ablation was assessed 6–8 months later.

Results: Successful ablation (no visible uptake in the diagnostic whole-body scan after rhTSH stimulation) was achieved in 88.9% of group A and B patients. Basal and rhTSH-stimulated serum thyroglobulin was undetectable (<1 ng/ml) in 78.9% of group A and 66.6% of group B patients ($P = 0.46$). Similar rates of ablation were obtained in both groups also in patients with node metastases.

Conclusion: Therapeutic ^{131}I activities of 1850 MBq are equally effective as 3700 MBq for thyroid ablation in DTC patients prepared with rhTSH, even in the presence of node metastases. (***J Clin Endocrinol Metab* 92: 3542–3546, 2007**)

MOST PATIENTS WITH differentiated thyroid cancer (DTC) are treated with therapeutic doses of radioiodine (^{131}I) after initial surgery (total or near total thyroidectomy), aimed to destroy microscopic residual normal or tumoral thyroid cells, and to facilitate the early detection of tumor recurrence based on serum thyroglobulin (Tg) measurement and ^{131}I whole-body scan (WBS) (1–5). Recently, preparation of patients for thyroid ablation with recombinant human TSH (rhTSH) and 3700 MBq ^{131}I on L-T_4 therapy has been approved in Europe by the European Medicines Agency as an alternative to thyroid hormone withdrawal (6), after a randomized, controlled, multicenter study demonstrated that both methods of preparation are equally effective (with 100% rate of successful ablation) and that patients prepared with rhTSH received lower total body irradiation and experienced a better quality of life compared with those rendered hypothyroid (7).

The present study was aimed to compare the efficacy of fixed activities of 1850 *vs.* 3700 MBq ^{131}I for postsurgical thyroid ablation in DTC patients prepared with rhTSH (TSHα, Thyrogen; Genzyme Therapeutics, Cambridge, MA) on L-T_4 therapy.

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Abbreviations: DTC, Differentiated thyroid cancer; rhTSH, recombinant human TSH; Tg, thyroglobulin; TgAb, Tg antibody; TNM, Tumor-Node-Metastasis; WBS, whole-body scan.

Patients and Methods

Newly diagnosed DTC patients, more than 18 yr old, recently treated by near total thyroidectomy were eligible for the study. Exclusion criteria were evidence of distant metastases and/or significant extrathyroidal invasion [T_4 of the latest Tumor-Node-Metastasis (TNM) classification]. A total of 72 patients with DTC (66 papillary, six follicular) were enrolled and randomly assigned to receive either 1850 or 3700 MBq ^{131}I. After randomization, 36 patients received 1850 MBq (group A), and 36 received 3700 MBq (group B) ^{131}I. The two groups did not differ with regard to age, sex, body mass index, histology, and TNM classification (Table 1).

Study design

All patients were started with suppressive doses of L-T_4 soon after thyroidectomy, which was continued throughout the entire study. In both groups, rhTSH was administered as previously described (7), and consisted of one injection of 0.9 mg rhTSH im for 2 consecutive days, followed by the therapeutic dose of ^{131}I 24 h after the last injection, and by a posttherapy WBS 72 h after ^{131}I treatment. To assess the effect of this therapy, patients were scheduled for a control phase 6–8 months after ablation. This protocol consisted of the injection of 0.9 mg rhTSH for 2 consecutive days, followed by a WBS, and spot views of the neck 48 h after administration of a tracer dose of 150 MBq radioiodine. Serum Tg determinations were performed 3 d after the last injection of rhTSH. Moreover, all patients underwent neck ultrasound. The procedure was performed on L-T_4 therapy (8).

TABLE 1. Epidemiological and clinical features of patients in groups A and B

Parameter	Group A (1850 MBq; n = 36)	Group B (3700 MBq; n = 36)	*P* value
Age (yr)			
Mean (SD)	47.9 (13.9)	50.5 (15.6)	0.45[a]
Median	44.5	49.5	
Sex			
No. of females (%)	29 (80.5)	31 (86.1)	0.75[b]
No. of males (%)	7 (19.5)	5 (13.9)	
Body mass index (kg/m^2)			
Mean (SD)	25.7 (5.41)	26 (5.8)	0.79[a]
Median	24.7	24.5	
No. of papillary (%)	34 (94.4)	32 (98.7)	0.67[b]
No. of follicular (%)	2 (5.6)	4 (1.28)	
No. of T1–T3 NX (%)	27 (75.0)	25 (69.4)	
No. of T1–T3 N0 (%)	5 (13.9)	2 (5.5)	0.20[c]
No. of T1–T3 N1 (%)	4 (11.1)	9 (25.1)	

[a] Unpaired *t* test.
[b] Fisher's exact test.
[c] χ^2 test.

Measurement of circulating thyroid hormones, TSH, anti-Tg antibodies (TgAbs), and Tg were performed at ablation, and at the control phase before and after rhTSH administration. Serum Tg, TSH, free T_4, and TgAbs were measured by chemiluminescent assay (Immulite 2000; Diagnostic Products Corp., Los Angeles, CA). Tg assay had a functional sensitivity of 0.9 ng/ml. TgAbs were considered negative when less than 20 IU/ml.

Serum free triiodothyronine was measured by enzyme-linked fluorescent assay (VIDAS; bioMerieux Italia SpA, Roma, Italy). Urinary iodine excretion was measured to exclude contamination from stable iodine, using a colorimetric method (AutoAnalyzer 3; Bran+Luebe, Gallarate, VA, Italy).

The study was approved by the ethical committee of our hospital. All patients provided written informed consent to participate in the study, and all of them completed the study.

Kinetic evaluation and dosimetric studies

For imaging of thyroid remnants, a tracer activity of ^{131}I (3.7 MBq) was administered to all patients on the same day of the second rhTSH injection (d 2), and the neck uptake was measured after 24 h (d 3) using a dedicated scintillation detector counter (Captus 300; Capintec, Inc., Ramsey, NJ).

For dosimetric purposes, the following procedures were performed. On d 4 (30 h after administration of the therapeutic activity), a WBS and planar acquisition, using a calibrated double-head γ-camera (E.CAM-variable geometry; Siemens, Berlin, Germany), were obtained in those patients with total retained activity less than 555 MBq to avoid γ-camera saturation. Body scans were performed with high-energy collimators and 15% no shift energy window on radioiodine photopick. Scan speed was 10 cm/min, and acquisition matrix was 256 × 1024 pixels, with zoom 1 and autocontour function. For planar acquisition, we used a 256 × 256 pixels matrix with zoom 1 and an acquisition time of 5 min.

On d 6 (72 h after the therapeutic activity), WBS was performed in all 72 patients to obtain the posttherapy scan for staging purpose.

In addition, we performed pinhole scans by a single-head γ-camera (DIACAM; Siemens, Berlin, Germany) for individual evaluation of each thyroid remnant. This procedure was performed in 47 patients (nine men and 38 women), 24 belonging to group A and 23 belonging to group B. Pinhole scans were performed at a neck-collimator distance of about 10 cm for 10 min. These scans were preceded by a scan of a "reperi" phantom, positioned on the patient's neck. The energy window was 15% on radioiodine photopick as well, and acquisition matrix was 256 × 256 pixels wide with zoom 3.2. In these 47 patients studied at 30 and 72 h, for each single scintigraphic scan, the γ-camera was calibrated using a known activity source in a neck phantom. The data extraction was performed by drawing regions of interest on the planar images of each thyroid residue. The corresponding counts were registered, and the remnant's uptake, at 30 h after therapy, was assessed for each residue (86 residues in total).

Statistical analysis

Publications of a recent series of patients undergoing thyroid ablation with radioiodine found that rates of successful ablation ranged from 88–100% (7, 9, 10). Based on these publications, we estimated for patients receiving 3700 MBq, an ablation rate of 93%. According to a standard noninferiority framework (11), the sample size required to detect clinical differences of 20% in ablation rate, under the aforementioned assumption of 93% successful ablation, was of at least 25 patients in each arm. The probability that the one-sided 97.5% confidence interval of the difference between the ablation rate in the two treatment groups did not include the clinically relevant difference is 79%. Our study included 36 patients in each group and, thus, meets the required sample size.

The nonparametric Mann-Whitney *U* test was used to compare quantitative data, not normally distributed (as defined by the Kolmogorov-Smirnov test), otherwise the *t* test was performed for unpaired data. There were 2 × 2 contingency tables analyzed using the Fisher exact test or by χ^2 for a 2 × 3 contingency table to evaluate significant frequency differences.

Results

At ablation, basal serum TSH was similar in the two groups: mean (±SD) 3.1 ± 4.1 μIU/ml (median 1.6) in group A and 5.3 ± 8.6 μIU/ml (median 1.9) in group B. In addition, mean (±SD) peak serum TSH after rhTSH was not different in the two groups: 166.4 ± 47.6 μIU/ml (median 162.7) in group A and 167.9 ± 59.3 μIU/ml (median 167.9) in group B.

When successful ablation of the thyroid residue was defined as "no visible uptake in the thyroid bed" in the 6–8 month control WBS, 32 of 36 (88.9%) patients of group A and 32 of 36 (88.9%) patients of group B were successfully ablated (Fig. 1). In group A, three patients with persistent thyroid bed uptake (not ablated) had undetectable basal serum Tg levels (<1 ng/ml) that converted to detectable after rhTSH stimulation in two cases (1.0 and 9.4 ng/ml) and remained undetectable in the third case. One additional patient with persistent thyroid bed uptake had detectable basal serum Tg levels (1.3 ng/ml) that reached a peak of 2.9 ng/ml after rhTSH stimulation. Neck ultrasound showed no evidence of lymph node metastases in all of them.

In group B, all four patients with persistence of thyroid bed uptake (not ablated) had undetectable basal serum Tg that converted to detectable levels after rhTSH stimulation in two patients (5.1 and 22.6 ng/ml) and remained undetectable in the other two patients. Neck ultrasound demonstrated a lymph node metastasis in the patient in whom undetectable serum Tg converted to 5.1 ng/ml and was negative in the others.

Of the 32 patients of group A with no thyroid bed uptake (ablated), 31 had also undetectable stimulated-serum Tg levels, whereas rhTSH-stimulated Tg increased to 3.7 ng/ml in one patient who had evidence of lymph node metastasis at neck ultrasound.

Of the 32 patients of group B with no thyroid bed uptake (ablated), two had evidence of lymph node at neck ultrasound and detectable stimulated-serum Tg levels (1.6 and 6.3 ng/ml); one patient had evidence of a single lung metastasis (not present at initial treatment and diameter of 7 mm at computed tomography scan) and detectable stimulated-serum Tg levels of 2.2 ng/ml, whereas the other 29 patients

had undetectable serum Tg levels both basally and after rhTSH stimulation.

We next analyzed the results of thyroid ablation under the definition of undetectable rhTSH-stimulated Tg at the control phase after excluding patients with detectable anti-TgAbs (one patient of group A and three of group B). It is worth noting that this definition of ablation has no meaning in patients (34 patients in our study) who have undetectable stimulated (at d 3) Tg before ablation. Consequently, these patients were excluded from the analysis. Of the remaining valuable patients (Fig. 2), 15 of 19 of group A (78.9%) and 10 of 15 of group B (66.6%) had undetectable stimulated-serum Tg with no statistical difference ($P = 0.46$ by Fisher's exact test). In group A, detectable serum Tg was associated with persistent thyroid residue in three patients (peak rhTSH serum Tg: 2.9, 9.4, and 1 ng/ml) and to one lymph node metastasis detected by diagnostic WBS and neck ultrasound in one patient (peak rhTSH serum Tg: 3.7 ng/ml). In group B, detectable serum Tg was associated with persistent thyroid residue in two patients (peak rhTSH serum Tg: 22.6 and 5.1 ng/ml), to lymph node metastases detected by neck ultrasound but missed by diagnostic WBS in two patients (peak rhTSH serum Tg: 1.6 ng/ml and 6.3 ng/ml) and to a single lung metastasis (diameter 7 mm), not seen at initial treatment, detected by diagnostic WBS and confirmed by computed tomography scan (peak rhTSH serum Tg: 2.2 ng/ml).

Lymph node metastases were present at surgery in 13 patients. Additional lymph node metastases were discovered on the posttherapy scan in five patients. Integrating the scintigraphic results of these five patients with the 13 pathological N1 patients, a total of 18 patients (six in group A and 12 in group B) may be classified as N1 at initial treatment (Table 2). rhTSH-aided radioiodine ablation was not impaired in these 18 patients. The thyroid remnant was successfully ablated in 16 of 18 patients (88.9%) and persisted only in two, one for each group. As far as the lymph node metastases are concerned, four patients, two in each group, had no evidence of disease after surgery, as demonstrated by no uptake in the posttherapy WBS and by negative neck ultrasound at ablation; these patients continued to have negative diagnostic WBS, negative neck ultrasound, and undetectable rhTSH-stimulated serum Tg at the control phase. In 11 patients (three in group A and eight in group B), lymph node metastases (persistent after surgery) disappeared after the ablative dose of radioiodine, as demonstrated by negative diagnostic WBS, negative neck ultrasound, and undetectable rhTSH-stimulated serum Tg at the control phase. Persistent lymph node metastases were limited to one patient in group A (detected in the diagnostic control WBS and by detectable rhTSH-stimulated serum Tg measurement), and in two patients of group B missed by diagnostic WBS but detected by rhTSH-stimulated serum Tg (1.6 and 5.1 ng/ml) and neck ultrasound (confirmed by fine-needle aspiration cytology).

When treating N1 patients after surgery with ^{131}I, a more extensive definition of successful ablation should be the disappearance of both the thyroid bed uptake and lymph node metastases. Under such definition, successful ablation at the control phase must include negative diagnostic WBS, no evidence of lymph node metastases at neck ultrasound, and undetectable rhTSH-stimulated serum Tg. Using this criterion, 86.1% of group A patients and 80.5% of group B patients were successfully ablated ($P = 0.75$ by Fisher's exact test) or, in other words, were probably in complete remission.

Dosimetric results

Mean (±SD) neck uptake of ^{131}I calculated 24 h after administration of a tracer activity of ^{131}I (3.7 MBq) was 2.0 ± 1.5% (range 0.4–7.2) in group A and 1.8 ± 1.6% (range 0.2–8.0) in group B, which was not statistically different ($P = 0.52$ by Mann-Whitney *U* test). All patients had detectable uptake. Mean (±SD) 30-h neck uptake after the therapeutic activity in the 86 residues studied (38 in group A and 48 in group B) was 2.5 ± 5.4% (range 0.2–29.9) in group A and 2.3 ± 3.4% (range 0.2–19.1) in group B, again without statistical difference ($P = 0.24$ by Mann-Whitney *U* test).

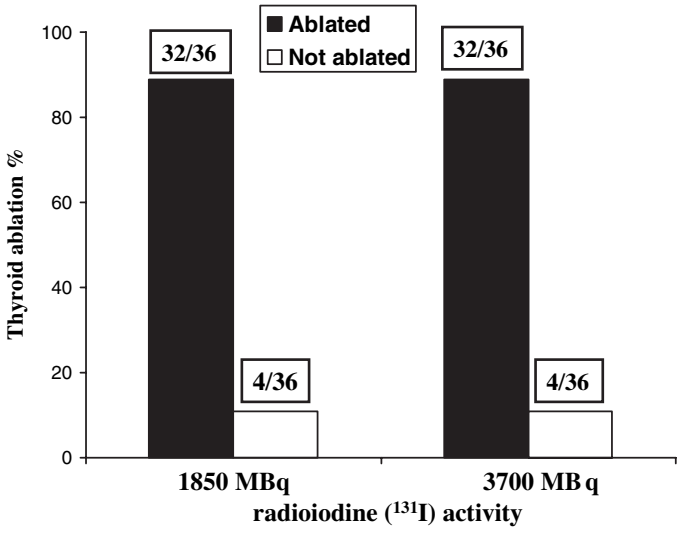

FIG. 1. Results of thyroid ablation at the 6- to 8-month control phase. Successful ablation was defined as no visible uptake at ^{131}I WBS.

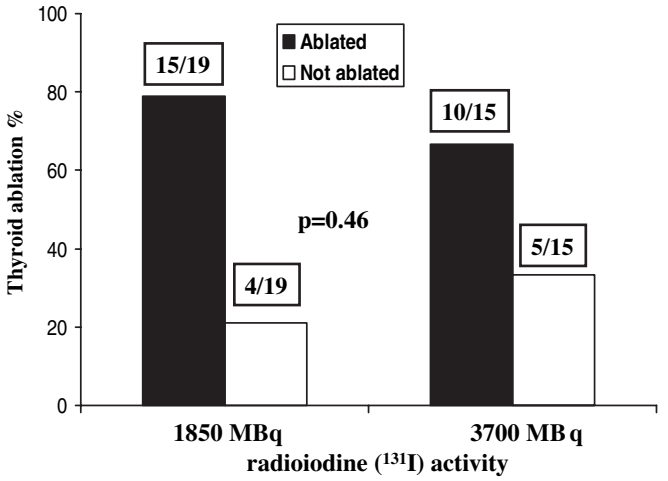

FIG. 2. Results of thyroid ablation at the 6- to 8-month control phase under the definition of undetectable serum Tg after rhTSH stimulation in patients with no AbTg and after excluding patients who had undetectable stimulated-serum Tg before ablation.

TABLE 2. Outcome of patients with lymph node metastases diagnosed at initial treatment by pTNM, posttherapy WBS, or neck ultrasound

	At initial treatment node mets diagnosed by			Outcome of node mets at 6–8 month control			
	pTNM	Posttherapy scan	Neck ultrasound	Diagnostic scan	Neck ultrasound	Peak rhTSH serum Tg	Outcome
1850 MBq	Not	Yes	Not	Negative	Negative	<1	NED after I^{131}
	Not	Yes	Not	Negative	Negative	<1	NED after I^{13}
	Yes	Yes	Yes	Negative	Negative	<1	NED after I^{13}
	Yes	Not	Not	Negative	Negative	<1	NED after surgery
	Yes	Not	Not	Negative	Negative	<1	NED after surgery
	Yes	Yes	Yes	Positive	Positive	3.7	Persistent
3700 MBq	Yes	Not	Not	Negative	Negative	<1	NED after surgery
	Yes	Not	Not	Negative	Negative	<1 (TgAb pos)	NED after surgery
	Not	Yes	Not	Negative	Negative	<1	NED after I^{13}
	Not	Yes	Not	Negative	Negative	<1	NED after I^{13}
	Not	Yes	Yes	Negative	Negative	<1	NED after I^{13}
	Yes	Yes	Yes	Negative	Negative	<1 (TgAb pos)	NED after I^{13}
	Yes	Yes	Yes	Negative	Negative	<1	NED after I^{13}
	Yes	Not	Not	Negative	Negative	<1	NED after I^{13}
	Yes	Not	Not	Negative	Negative	<1	NED after I^{13}
	Yes	Yes	Not	Negative	Negative	<1	NED after I^{13}
	Yes	Not	Yes	Negative	Positive	5.1	Persistent
	Yes	Yes	Yes	Negative	Positive	1.6	Persistent

mets, Metastases; NED, no evidence of disease; pos, positive.

Factors affecting successful ablation of thyroid residues

Considering group A and B patients together, a total of 64 (88.8%) patients were ablated, and eight (11.2%) were not. When correlating the ablation outcome with potential determining factors (Table 3), we found that failure to ablate was not dependent upon peak serum TSH values after rhTSH stimulation, radioactive activity administered, N status, neck uptake, and urinary iodine excretion.

Discussion

Recently, a prospective, randomized, multicenter study performed in low-risk patients with differentiated thyroid carcinoma demonstrated that rhTSH-aided postsurgical thyroid ablation is highly effective (100% successful ablation rate) and not inferior to preparation by thyroid hormone withdrawal when using a fixed activity of 3700 MBq ^{131}I (7). Based on this report, rhTSH has been approved in Europe by the European Medicines Agency (6, 7) for the preparation of low-risk DTC patients undergoing postsurgical radioiodine thyroid ablation with 3700 MBq activity, and this procedure is becoming the standard of care in many European centers (2). The present prospective, randomized study confirms that 3700 MBq ^{131}I activity is associated with high rates of successful thyroid ablation after rhTSH preparation and shows in addition that similar ablation rates (88.9%) are obtained also when using lower radioiodine activity (1850 MBq). These results were obtained when the criterion of successful ablation was defined as no visible uptake in the 6- to 8-month control diagnostic ^{131}I WBS after rhTSH stimulation but also when selecting the criterion of undetectable (<1 ng/ml) rhTSH-stimulated serum Tg. However, in the latter case, the analysis had the limitation of excluding 34 patients who had undetectable stimulated (at d 3) Tg before ablation, in whom an undetectable stimulated-serum Tg at the control phase cannot be assumed to have evidence of therapeutic effect.

TABLE 3. Factors affecting successful ablation of thyroid residues (cumulating patients of groups A and B)

Patients (n = 72)	Ablated (n = 64)	Not ablated (n = 8)	*P* value
Mean peak serum TSH SD (μIU/ml)	164.8 ± 53	185.4 ± 53	0.26[a]
TNM			
T1–T3 N0	48	6	
T1–T3 N1	16	2	1.0[b]
Thyroid bed uptake (%)	1.96 ± 1.5	2.16 ± 2.1	0.66[a]
Mean urinary iodine excretion ± SD (μg/liter)	140 ± 104	143 ± 87	0.81[a]
^{131}I activity[a]			
1850 MBq	32	4	
3700 MBq	32	4	1.0[b]

[a] Mann-Whitney *U* test.
[b] Fisher's exact test.

Several patients in our study had evidence of lymph node metastases on the posttherapy scan performed at ablation. In most of these cases, rhTSH-aided ablation with 1850 MBq treated not only the thyroid remnant, but also the lymph node metastases, without difference in comparison with the results obtained with 3700 MBq activity of ^{131}I. The dosimetric study showed that thyroid uptake was similar in patients treated with 1850 or 3700 MBq.

Peak serum TSH, tumor stage, percent thyroid uptake, urinary iodine excretion, as well as the administered activity of ^{131}I were not significant factors for ablation. As demonstrated in a previous study (7, 12), using rhTSH in euthyroid patients reduces total body irradiation. Although total body irradiation was not evaluated in the present study, it is highly likely that reducing the activity from 3700 to 1850 MBq will result in a further reduction of total body irradiation.

Our study lacks long-term follow-up. Thus, our definition of no evidence of disease according to negative serum Tg, negative diagnostic WBS, and negative neck ultrasound cannot be interpreted as definitive cure but just as an indication of apparent remission. The possibility that some disease is still present, although not visible, has been reported in a minority of patients (13, 14) and should always be considered, stressing the concept that follow-up of thyroid cancer

patients should go on throughout their entire life. Another concept that should be stressed is that, even reducing the radiation dose, thyroid ablation is still a procedure exposing the patient to some hazard and should not be used when a beneficial effect is not proven, like in patients with a very low-risk category (2, 3).

In conclusion, our study demonstrates that patients undergoing rhTSH-aided postsurgical thyroid ablation with 1850 MBq achieved a very high rate of successful ablation, not inferior to that obtained with higher activities, even in the presence of lymph node metastases, and also not inferior to that reported in the literature after preparation by thyroid hormone withdrawal (15–17). The use of our approach will facilitate the procedure of postsurgical thyroid ablation both in terms of preservation of quality of life (avoiding hypothyroidism) (18), and by lowering the side effects and potential hazards linked to radiation (by lowering the administered activity) (19). Although we were able to demonstrate the efficacy of 1850-MBq doses compared with 3700 MBq, we were not able to demonstrate satisfactory effects with 1110 MBq in a previous study that had the limitation of using a different protocol of thyroid ablation (20). Using the same low dose and a different protocol, other authors (21) have found a high rate of successful ablation. Thus, the issue of the minimal effective activity to use for thyroid ablation in low-risk differentiated thyroid carcinoma remains open. Further clinical trials using the same protocol used in the present study are needed to define the lowest effective activity of radioiodine.

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