J Clin Endocrin Metab. First published ahead of print April 26, 2013 as doi:10.1210/jc.2012-4137

Patients with differentiated thyroid cancer who underwent radioiodine thyroid remnant ablation with low-activity ^{131}I after either recombinant human TSH or thyroid hormone therapy withdrawal showed the same outcome after a 10-year follow-up

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Background: No long-term follow-up data are available for differentiated thyroid carcinoma (DTC) patients prepared with either exogenous or endogenous TSH and treated with low-activity (1.1 GBq [30 mCi]) radioiodine (^{131}I).

Aim: The aim of this study was to evaluate the 10-year follow-up of DTC patients who underwent remnant ablation with 1.1 GBq of ^{131}I after levothyroxine (LT4) withdrawal, or following recombinant human TSH (rhTSH) administration, or both.

Patients: 159 DTC patients treated with total thyroidectomy and 1.1 GBq (30 mCi) of ^{131}I for remnant ablation and stimulated with rhTSH and/or endogenous TSH were separated into ablated (n=115) and not ablated (n=44) patients and prospectively followed-up for at least 10 years. Besides, we evaluated several features that could correlate with the final status of patients.

Results: During the follow-up, 4/115 (3.5%) ablated patients showed a recurrence and one was successfully cured. Among not ablated patients, 16/44 (36.4%) had a persistent disease. At the end of the 10-year follow-up, 140/159 (88.1%) patients were disease-free while 19/159 (11.9%) remained affected. No correlation was found with the type of TSH stimulation and no other clinical and pathological features showed any correlation with the final status. However, low levels of stimulated serum thyroglobulin (<5.4 ng/ml) at first control after remnant ablation identified a subgroup of not ablated patients who became spontaneously cured.

Conclusions: Long-term outcomes are similar in DTC patients treated with 1.1 GBq (30 mCi) of ^{131}I and prepared either with rhTSH or endogenous TSH. It is of interest that serum thyroglobulin at first control after ablation can have a prognostic role.

Patients with differentiated thyroid carcinoma (DTC), both papillary and follicular, are typically treated with total thyroidectomy followed by ^{131}I ablation of the postsurgical thyroid remnant whenever needed (1). The rationale for ^{131}I ablation is that it decreases the risk of locoregional recurrence (2–3) and facilitates long-term surveillance (4).

To be effective, ^{131}I thyroid remnant ablation requires

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received December 7, 2012. Accepted April 15, 2013.

Abbreviations:

TSH stimulation, which can be performed after either thyroid hormone therapy (HT) withdrawal (THW) or, as recently demonstrated, after the administration of recombinant human (rh) TSH (rhTSH) (5–8). Several studies have attempted to establish whether the rate of thyroid remnant ablation after rhTSH stimulation is similar to that obtained after THW (5–8). However, the use of rhTSH stimulation for thyroid remnant ablation was accepted worldwide in clinical practice only after a report of a multicentric, international and randomized study showed comparable success in the thyroid ablation of patients prepared with rhTSH and those prepared after THW (5).

Conversely, the amount of ^{131}I activity to be used for remnant ablation (i.e., low vs high activities) is still a matter of debate (9–14) and only recently two large randomized studies (Estimabl study in France and Hilo study in United Kingdom) demonstrated comparable rates of ablation in patients treated with high (i.e., 3.7 GBq corresponding to 100 mCi) or low activities (i.e., 1.1 GBq corresponding to 30 mCi) ^{131}I and stimulated either with rhTSH or after THW (15–16). We and others have demonstrated that the follow-up of patients prepared for ^{131}I ablation either after THW or rhTSH is comparable (17–19). Because DTC can relapse 20–30 y after initial treatment (20–22), these three studies were limited by their relatively short-term follow-up (i.e., 3.7, 2.5 and 5 y, respectively).

To our knowledge, no studies have compared DTC patients ablated after THW or rhTSH with a long-term follow-up. Therefore, the aim of this study was to evaluate the 10-y follow-up of the 162 patients enrolled in our previous study (23) who underwent ^{131}I postsurgical thyroid remnant ablation with a fixed low activity of ^{131}I either after THW, rhTSH or THW and rhTSH. A secondary objective of the study was to evaluate several clinical and pathological features that could be correlated with the final status of our patients.

Patients and Methods

Patient Population

After the previous study (23), we continued to prospectively follow-up the 162 enrolled patients with yearly clinical and biochemical controls. The follow-up period was at least 10 y. At the time of publication, 3/162 (1.8%) patients were lost to follow-up and therefore, this study included 159 patients.

The patients were classified into the original 3 groups according to the TSH stimulation performed at the time of ablation: Hypo Group, treated after THW (n = 50); Eu+rhTSH Group, treated after rhTSH (n = 70); and Hypo+rhTSH Group, treated after THW+rhTSH (n = 39).

All patients signed an informed consent to participate in both the previous ablation study and in the present follow-up study. The study obtained the approval of the Institutional Review Board (IRB).

The clinical and pathological features at the time of ablation were previously reported and were statistically comparable in the 3 groups of patients (23). For the current study, we further classified the 159 patients into 4 classes according to De Groot's classification (24) and into 3 levels of risk according to the ATA classification (25): also the distribution of the classes and levels of risk were similar in the three groups (Table 1).

Because the criteria to define the success of ablation have changed after the publication of the previous paper, we recalculated the prevalence of ablated and not ablated patients in the 3 groups according to the new criteria (25–26) which are: a) serum thyroglobulin (Tg) level after TSH stimulation < 1.0 ng/ml; b) the absence of interfering circulating antithyroglobulin antibodies (Tg-Abs); c) negative neck ultrasound. Ablated patients were followed with 12- to 18-mo follow-up visits, and at every visit, they underwent neck ultrasonography and a clinical examination. A blood sample was taken to measure basal Tg, circulating Tg-Abs, free thyroid hormones (FT3 and FT4) and TSH. Whenever indicated (e.g., detectable levels of basal Tg or evidence of neck node recurrence), patients were treated either with ^{131}I therapy or surgery.

Patients who were not ablated at the time of the first study were followed with 6–12-mo follow-up visits as described above. Following our standard protocol, when basal serum Tg was > 1.0 ng/ml, ^{131}I therapy or surgical treatment was performed taking into account the clinical evidence of the disease, the ability to take or not to take up ^{131}I, the size and location of the disease (unique or multiple) and, last but not least, the patients' preference. When basal serum Tg was < 1.0 ng/ml, patients underwent an rhTSH stimulation test for Tg, and only cases with stimulated Tg > 2 ng/ml were treated with ^{131}I empiric therapy followed by a post-therapy whole body scan (ptWBS).

Measurement of serum thyroglobulin (Tg) and antithyroglobulin antibodies (Tg-Abs)

Serum Tg was measured using an immunometric assay introduced at our department in 1998 (ICMA test) (Immulite 2000 Thyroglobulin, Diagnostic Product Corporation, Los Angeles, CA) with a functional sensitivity of 0.9 ng/ml. However, over time, the functional sensitivity of the assay fell to 0.5 ng/ml ac-

Table 1. distribution of patients according to the ATA risk level and De Groot's Class in the 3 groups[b].

	EU+rhTSH	HYPO	HYPO+rhTSH	p
ATA Level Risk				**0.75**
Low	**48**	**30**	**26**	
Intermediate	**11**	**9**	**8**	
High	**11**	**11**	**5**	
De Groot's Class				**0.87**
1	**46**	**33**	**28**	
2	**7**	**3**	**3**	
3	**17**	**14**	**8**	
4	**0**	**0**	**0**	

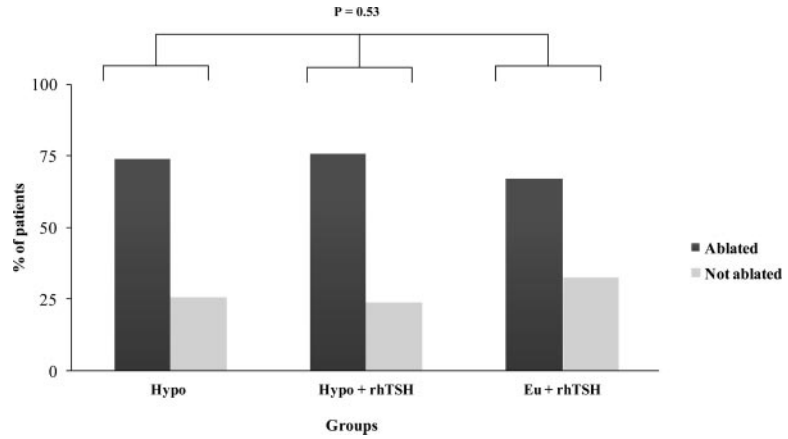

Figure 1. Ablation success (%) in the Hypo, Hypo+rhTSH and Eu+rhTSH groups was similar when the rate of ablation was recalculated using the most recent ablation criteria.

cording to the results of the CV controls obtained in our laboratory.

Due to their potential interference in the determination of serum Tg, Tg-Abs were measured with an immunoenzymometric assay (AIA-Pack TgAb system; Tosoh Corporation, Tokyo, Japan) introduced in the year 2000 (normal range: 0–50 U/ml). Because a Tg-Abs titer of < 50 U/ml was demonstrated to not interfere with the serum Tg determination in our laboratory (unpublished data), it was considered as "negative" for the present study.

rhTSH -stimulated Tg (rhTSH-Tg) test and diagnostic whole body scan (d-WBS)

The rhTSH-Tg test was performed by administering one injection of rhTSH (0.9 mg, i.m., Thyrogen, Genzyme Corp., Cambridge, MA) on 2 consecutive days. Serum Tg was measured before the first rhTSH injection and 24 h, 48 h and 72 h after administration of the second. Patients with a potentially interfering level of Tg-Abs also underwent a d-WBS that was performed after the administration of a tracer dose of ^{131}I (4 mCi). Until 2004 the apparatus used for ^{131}I imaging was a one-head gamma camera (Aspex SPX 4000, Elscint, Italy) with a high-energy collimator and a sensitivity of 160 cpm/μCi. The scan speed was 10 cm/min with total counts of at least 140,000 cpm. After 2004 a dual head large field-of-view gamma camera (Axis, Philips) with a 6/8" thick crystal equipped with high-energy collimators (HEHR) was used.

Neck ultrasonography

Neck ultrasonography was performed using a color Doppler apparatus (AU 590 Asynchronous, Esaote Biomedica, Genova, Italy) until 2004 and then with an updated apparatus (MyLab50, Esaote Biomedica, Firenze, Italy) that is still in use. In both cases we used a 7.5 MHz linear transducer. Neck ultrasonography was used to inspect the central and bilateral neck lymph node compartments and the superior mediastinum.

Statistical analysis

The χ^2 test was used to compare the outcome of patients in the three different groups. The Mann-Whitney U and the Kruskal-Wallis tests were used to assess differences in the median Tg concentration between two or more groups of patients, respectively. Post hoc analyses were conducted using the Bonferroni correction of statistical significance. Logistic regression analyses were performed to predict the outcomes of not ablated patients according to their clinical and pathological features. The Receiver Operating Characteristic (ROC) curve (27) was calculated in order to identify the value of Tg that better classified subjects who spontaneously became disease-free compared to those who received further treatment. The best cutoff value in terms of both sensitivity and specificity in the ROC curve analysis was selected as that with the highest Youden index (28).

For both ablated and not ablated DTC patients, survival curves were calculated and compared using the Kaplan-Meier method. Statistical significance between survival curves belonging to different groups was assessed using the log-rank test. A p-value less than 0.05 was considered statistically significant. Statistical analyses were performed in StatView 4.5 software (Abacus Concept Inc., Berkeley, CA).

Results

Reclassification of ablation rate

Based on the new criteria (25–26), at a normal Tg-Ab titer < 50 U/ml, the rate of successful ablation in the three groups of patients changed from 84% (42/50) to 74% (37/50) in the HYPO group, from 78.5% (33/42) to 76.2% (32/42) in the Hypo+rhTSH group and from 54% (38/70) to 67.1% (47/70) in the Eu+rhTSH group. As shown in Figure 1, although a slightly lower percentage of ablation was still evident in the Eu+rhTSH group, no statistically significant differences were found among groups when using the most recent criteria of ablation ($P = .53$).

Follow-up of ablated and not ablated patients, defined using the most recent criteria

The 10-y follow-up of ablated DTC patients showed that 4/115 (3.5%) patients had a recurrence, with one biochemical recurrence (detectable Tg but no evidence of disease) and three lymph node metastases. The details of these recurrences are shown in Table 2. No epidemiological or pathological features, staging or risk levels suggesting the possibility of a recurrence were present at the time of ablation (Table 2, panel A). Additionally, as shown in Figure 2 panel A, the four recurrences were distributed across the three groups (e.g., Hypo vs Hypo+rhTSH vs Eu+rhTSH), with no statistically significant differences between them ($P = .73$).

The follow-up of not ablated DTC patients showed that 28/44 (63.6%) became cured during the follow-up period

Table 2. patients with recurrence after complete ablation: panel A) epidemiological, clinical and pathological features at the time of ablation; panel B) biochemical and/or imaging detection of recurrence.

	A			ABLATION TIME			B				RECURRENCE TIME		
Pt.	Group	Age at ablation	Sex	Hystotype	TNM	Stage	De Groot's class	Risk stratification	Basal Tg (ng/ml)	rhTSH-Tg (ng/ml)	Neck US#	Post-therapy WBS	CT scan
1*	Hypo	59	F	PVF	T2N0M0	II	1	L	3.18	-	Negative	Negative	Negative
2**	Hypo	29	F	PVC	T2bN1M0	I	2	I	<0.5	<0.5	LFN	Negative	LFN
3***	Hypo + rhTSH	25	F	PVC	T2bN0M0	I	1	L	<0.5	<0.5	LFN	-	LFN
4****	Eu + rhTSH	52	M	F	T3aN0M0	III	3	I	49.9	-	LFN	-	Lung

LFN metastases were always confirmed by cytology and/or Tg measurement in the wash out of the needle used for aspiration

* Follow-up, no treatments.

** Submitted to lymphadenectomy with a histology positive for lymph node metastasis of papillary thyroid cancer.

*** Submitted to lymphadenectomy: now cured

**** Submitted to lymphadenectomy with a histology positive for poorly differentiated metastasis. He is still alive with a progressive disease treated with TKI.

M: male; F: female; PVC: papillary classic variant; PVF: papillary follicular variant; F: follicular; L: low; I: intermediate; H: high; LFN: lymph node metastasis.

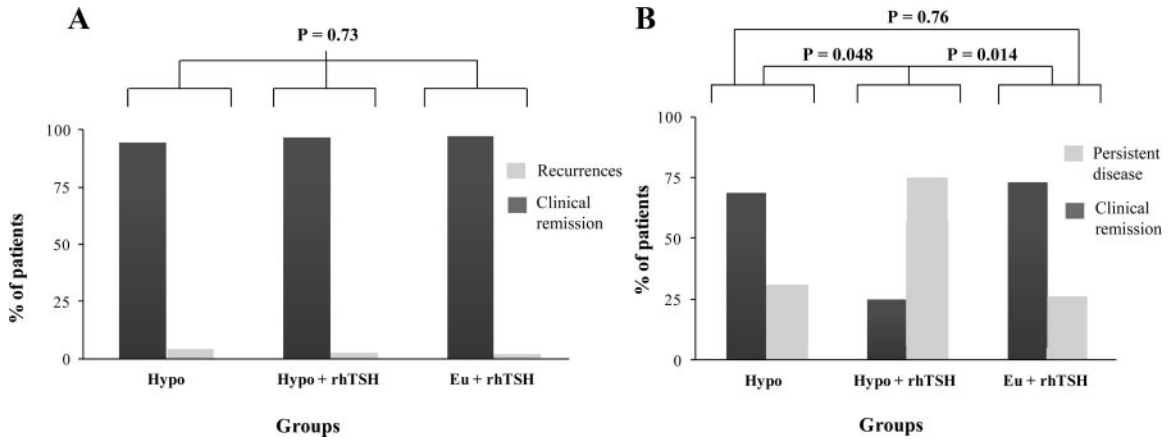

Figure 2. Panel A: The percentage of ablated patients with recurrences during the 10-y follow-up according to the type of TSH stimulation performed at the time of ablation (HYPO, Hypo+rhTSH; Eu+rhTSH). Panel B: The percentage of not ablated patients with persistent disease at the end of the 10-y follow-up according to the type of TSH stimulation performed at the time of ablation (HYPO, Hypo+rhTSH; Eu+rhTSH). No significant difference was found in the recurrence rate (panel A) in the three groups of patients. Similarly, the persistent disease rate (panel B) was similar in HYPO and Eu+rhTSH groups. An unexplained difference of the persistent disease rate, discussed in the text, was observed in the Hypo+rhTSH group when compared with the other two.

without any additional therapy; all these patients remained in remission throughout the present study. However, 16/44 (36.4%) continued to have persistent disease, either biochemical (8/16, 50%) or structural (8/16, 50%) disease after 10 y. As shown in Figure 2 panel B, the outcome of the Hypo and Eu+rhTSH groups did not significantly differ, whereas a statistically significant difference was observed between the Hypo+rhTSH and Hypo groups and the Hypo+rhTSH and Eu+rhTSH groups.

When we analyzed the follow-up of not ablated patients who were in remission at the end of the follow-up period, we found that 9/28 (32%) became spontaneously negative for both serum Tg and neck ultrasonography, while 19/28 (68%) received further ^{131}I courses to reach a definitive cure.

The details of the 16 patients with persistent disease at the end of the follow-up period are reported in Table 3. No pathological or epidemiological features suggesting that this group would not be cured, were present at the time of ablation (Table 3, panel A).

Finally, when considering the overall disease status of all our patients at the end of the follow-up period, we observed that they had the same likelihood of cure (90%, 85% and 90% in the HYPO, HYPO+rhTSH and Eu+rhTSH groups, respectively) regardless of the treatment they received (Figure 3, panel A for ablated patients and panel B for not ablated patients).

Clinical and pathological features of not ablated patients and their outcomes

We evaluated correlations between age, sex, stage of disease, ATA risk level (25), De Groot's class (24), serum TSH and Tg after THW at the first control after ^{131}I thyroid ablation (supplemental Table 1) to identify features

Table 3. patients with persistent disease at the end of follow-up: panel A) epidemiological, clinical and pathological features at the time of ablation; panel B) biochemical and imaging data at the end of follow-up.

	A				ABLATION TIME				B		END OF FOLLOW-UP			
Pt	**Group**	**Age at diagnosis**	**Sex**	**Histo type**	**TNM**	**Stage**	**De Groot's class**	**Risk stratification**	**Basal Tg (ng/ml)**	**rhTSH-Tg (ng/ml)**	**Neck US#**	**Post-therapy WBS**	**CT Scan**	**Outcome**
1	Hypo	55	M	PV F	T3N1M0	III	3	I	<0.5	2.3	Negative	-	nd	BD
2*	Hypo	63	M	PVC	T4bN1bM0	IV B	3	H	17.5	-	LFN	R + LC-LFN	LC-LFN	SD
3	Hypo	35	M	PVC	T4aN1bM0	II	3	H	<0.5	4.15	Negative	Negative	Nd	BD
4	Hypo	38	F	PVC	T4bN1aM0	II	3	H	<0.5	1.6	Negative	R	Negative	BD
5	Hypo + rhTSH	57	M	PVF	TxN1M1	IV C	4	H	1.22	2.25	LFN	LC-LFN + Md/LFN	Lung LSSx	SD
6**	Hypo + rhTSH	57	F	PVF	T4aN0M0	IV A	3	H	0.952	4.88	Negative	Lung	Lung LSDx+LMDx	SD
7	Hypo + rhTSH	35	F	PVC	T3N1aM0	I	3	I	<0.5	8.27	Negative	Negative	LC-LFN and lung	SD
8	Hypo + rhTSH	35	F	PVTC	T4N0M0	I	3	H	<0.5	1.84	Negative	Md-LFN	Negative	BD
9	Hypo + rhTSH	59	F	PVC	TxN0M0	-	-	-	-	-	LFN	Negative	LC-LFN + Md-LFN	SD
10	Hypo + rhTSH	37	F	PVC	T3N0M0	I	3	I	<0.5	24.4	LFN	Negative	Nd	BD
11	Eu + rhTSH	27	F	PVC	T2N0M0	I	1	L	1.18	11.8	LFN	Negative	LFN	SD
12***	Eu + rhTSH	26	F	PVS	T1aN0M0	I	1	L	2.05	33.4	LFN	R + LC-LFN	Nd	SD
13****	Eu + rhTSH	56	F	PVF	T3N1aM0	III	3	I	25.3	-	LFN	Negative	LC-LFN	SD
14	Eu + rhTSH	17	F	PVC	T1bN0M0	I	1	L	<0.5	2.9	Negative	Negative	Nd	BD
15	Eu + rhTSH	41	F	PVC	T1aN0M0	I	1	L	<0.5	2.46	Negative	R	Nd	BD
16	Eu + rhTSH	39	F	PVC	T2N0M0	I	1	L	<0.5	1.2	Negative	Negative	Negative	BD

LFN were always confirmed by cytology and/or Tg measurement in the wash out of the needle used for aspiration

* Submitted to lymphadenectomy with a histology positive for poorly differentiated thyroid cancer metastasis.

** Submitted to external neck radiotherapy (62 Gy).

***Submitted to lymphadenectomy with a histology positive for lymph node metastasis of papillary thyroid cancer.

**** Submitted to lymphadenectomy with a histology positive for recurrence of papillary thyroid cancer infiltrating fibro muscular tissues.

M: male; F: female; PVC: papillary classic variant; PVF: papillary follicular variant; PVTC: papillary tall cell variant; PVS: papillary sclerosant variant; L: low; I: intermediate; H: high; R: remnant/recurrence; LFN: lymph node metastasis; LC: latero-cervical; Md: mediastinum; LSSx: left superior lobe; LSDx: right superior lobe; LMDx: right medium lobe; BD: biochemical disease; SD: structural disease.

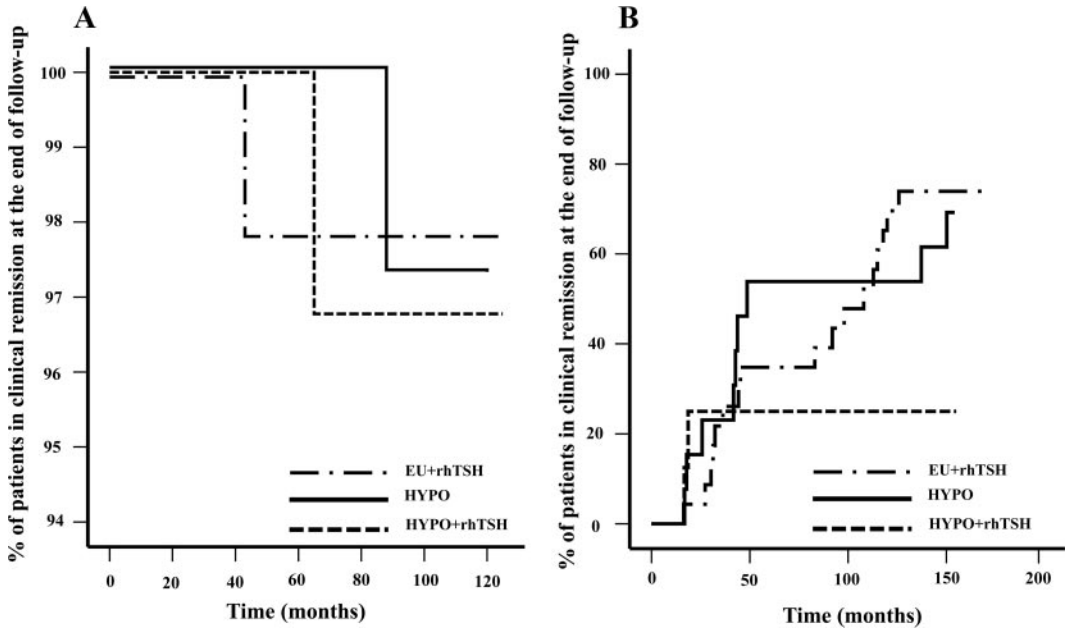

Figure 3. Outcomes of ablated (panel A) and not ablated (panel B) patients at the end of the 10-y follow-up. The patient outcome was similar regardless of the type of TSH stimulation at the time of ablation.

that could distinguish patients who became disease-free without any further treatment(s) (n = 9, group A) and those who received other treatment(s), independent of whether they were cured (n = 19, group B) or remained affected by the disease (n = 16, group C). No epidemiological, biochemical or pathological features could predict the different outcomes of these 3 groups of patients. However, according to the ROC curve analysis, we found that a serum Tg cutoff of 5.4 ng/ml off L-T4 therapy at the time of first control after remnant ablation showed 89% sensitivity and 71.5% specificity in distinguishing patients who become disease-free without any further treatment (group A) from those who received other treatment(s) (groups B + C) (AUC = 0.79, $P < .01$) (supplemental

Figure 1). In fact serum Tg at the time of first control after remnant ablation was significantly lower in patients who spontaneously became disease-free (group A) compared to those who received further treatment(s) (groups B and C) but, unfortunately, the serum Tg values could not distinguish those who would be cured from those who remained affected despite additional ^{131}I or surgical treatment(s) (supplemental Figure 2).

Discussion

Several studies have demonstrated the efficacy of rhTSH in preparing PTC patients for the ^{131}I ablation of postsurgical thyroid remnants using high-activity (3.7 GBq corresponding to 100 mCi) ^{131}I (5–6). In particular, a prospective, randomized, multicentric study demonstrated a comparable efficacy of ^{131}I remnant ablation when thyroid cancer patients were prepared by either administering rhTSH in the euthyroid state or withdrawing thyroid HT for endogenous TSH stimulation (5). Based on this report, rhTSH was approved in Europe in 2005 by the European Medicines Agency (29) and later by the Food and Drug Administration (FDA) in 2007 for the preparation of low-risk DTC patients undergoing postsurgical ^{131}I remnant ablation with 3.7 GBq, and this procedure is becoming the standard of care in many centers worldwide.

Controversial studies have demonstrated that thyroid remnant ablation can also be obtained with low-activity ^{131}I (8–9, 12–14, 23). Lower activity ^{131}I is preferable due to the lower exposure to radiation, lower probability of developing a second primary tumor (30) and fewer side effects (31–32). However, clinicians are hesitant to use low-activity ^{131}I for remnant ablation because there are no long term follow-up studies and they are very much afraid to reduce the effectiveness of the cure by using less ^{131}I. Moreover, a previous study performed in our institution demonstrated a lower percentage of ablation in patients treated with 1.1 GBq after rhTSH stimulation compared to a control group prepared with thyroid hormone withdrawal (THW) (23). It is conceivable that this hesitancy will soon disappear because of the evidences provided by the results of the two large randomized studies (Estimabl study in France and Hilo study in United Kingdom) recently published (15–16). Both studies clearly demonstrated a similar rate of ablation in 4 randomized groups of DTC patients prepared with either rhTSH or Hypo and treated with either 1.1 GBq or 3.7 GBq of ^{131}I.

It is still not completely clear why we found a statistically significant difference in the previous study between the successful ablation of the 3 groups of patients, which was unfavorable for those prepared with rhTSH (23). This is even more difficult to explain currently in light of the results of the Estimabl and Hilo studies (15–16), which showed no differences in very large series of DTC patients. Several explanations can be provided, including the relatively low number of patients that we enrolled, the fact that we analyzed the rate of ablation after LT4 therapy withdrawal while all other studies did so during LT4 therapy, the later administration of ^{131}I (48 h vs 24 h after the second injection of rhTSH) and/or the different criteria used currently to define ablation. In this regard, it is also worth noting that even 10 y ago, at the time of the previous study, the rate of ablation in the rhTSH study group could increase up to 74% if we considered only the undetectable levels of serum Tg regardless of visible thyroid bed uptake in the scintiscan, as discussed in our previous paper, and would therefore not differ from the other groups (23). As a matter of fact, after reviewing our previous ablation data according to the new criteria for defining remnant ablation (25–26), in agreement with the recent French and English data, we found no statistically significant differences between patients prepared with either rhTSH or THW and 1.1 GBq of ^{131}I.

Of concern in using rhTSH to prepare DTC patients for ablation are the unknown follow-up and final outcome of patients. Three follow-up studies of patients prepared with rhTSH or hypo for ^{131}I ablation have been reported, but the longest follow-up was 5 y (19), and no study included patients treated with low-activity ^{131}I. In the present study, during a long-term follow-up (i.e., at least 10 y), we demonstrated that the outcome of patients prepared with either rhTSH or THW and 1.1 GBq of ^{131}I was similar. In particular, when the three groups were compared, there was no difference in the number of patients who recurred after evidence of a clinical remission obtained at the time of ablation or the number of patients who went into clinical remission after further treatment (either ^{131}I treatment or surgical treatment) or the number of those who never reached clinical remission. The only significant difference observed between the Hypo+rhTSH and Hypo groups and the Hypo+rhTSH and Eu+rhTSH groups had no simple explanation. We can only hypothesize that despite a similar rate of ablation, those cases that were not ablated at first treatment and exposed to such a strong TSH stimulation derived by the sum of THW and rhTSH might have becoming "resistant" to 131-I.

The level of risk of the patients with DTC to be treated is also concerning. Both the randomized multicentric international study (5) and the Estimabl study (15) included only low-risk patients, while the Hilo study (16) included intermediate-risk patients. In our study (23), we included patients belonging to any risk class with the exception of metastatic patients, but we did not observe any difference

in the follow-up course of low-, intermediate- and high-risk patients. Moreover, the stage of the disease, regardless of the classification used, and several other clinical and pathological features did not correlate with the outcomes of not ablated patients; only serum Tg value at the time of the first control after remnant ablation, which was performed after LT4 therapy withdrawal, could predict patient outcome and indicate the need of further treatments. This correlation was observed in all groups, and was independent of the type of preparation for ablation. Although in the past it was reported that the serum Tg level at the time of ablation could predict the success of radioiodine treatment (33–35), to our knowledge, it was never reported as a factor predictive of the outcome of not ablated patients.

In conclusion, to our knowledge, this is the first paper comparing the long-term follow-up and final outcomes of patients ablated with rhTSH stimulation or THW and low-activity ^{131}I (i.e., 1.1 GBq of ^{131}I). We demonstrated that DTC patients in any class of risk treated with low-activity ^{131}I and prepared with rhTSH have the same rate of ablation success and the same outcome compared to those treated with low-activity ^{131}I and stimulated with endogenous TSH. As secondary objective of this study, an important prognostic role of serum Tg at the first control after ablation was also identified. However, it is worth noting that these Tg measurements were done after LT4 withdrawal and making patients hypothyroid which was still a common practice at that time. Further studies are warranted to confirm a similar role of stimulated Tg in patients submitted to a rhTSH-Tg test that nowadays represents the standard of care to control serum Tg levels during the follow up of DTC patients.

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This work was supported by Grant: grants from the Ministero della Istruzione Universitaria e Ricerca Scientifica (MIUR), the Associazione Italiana per la Ricerca sul Cancro (AIRC), the Istituto Toscano Tumori (ITT) and the Ministero della Salute, Progetto Ricerca Oncologica RF-CAM 2006353005.

Author disclosure: The authors have nothing to disclose.

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