After a median follow-up of 3.7 years, patients with low-risk thyroid cancer prepared for postoperative remnant ablation with either L-T_4 withdrawal or rhTSH stimulation have comparable rates of thyroid remnant ablation and tumor recurrence or persistent disease.

Elisei R, Schlumberger M, Driedger A, Reiners C, Kloos RT, Sherman SI, Haugen B, Corone C, Molinaro E, Grasso L, Leboulleux S, Rachinsky I, Luster M, Lassmann M, Busaidy NL, Wahl RL, Pacini F, Cho SY, Magner J, Pinchera A, Ladenson PW. 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(11):4171-9.

SUMMARY

BACKGROUND

This international group previously demonstrated in a prospective, randomized study that thyroid remnant ablation rates with 100 mCi of ^{131}I were comparable after patients with low-risk tumors were prepared with either thyroid hormone withdrawal (THW) or recombinant human thyrotropin-α (rhTSH). A posttherapy evaluation of the efficacy of thyroid remnant ablation was performed at a mean (±SD) of 8±1 months after the treatment, at which time patients were studied with rhTSH-stimulated ^{131}I whole-body diagnostic scans (DxWBS) and measurement of serum thyroglobulin (Tg) levels. The aim of the current study was to compare outcomes of the original patients 3.7 years later.

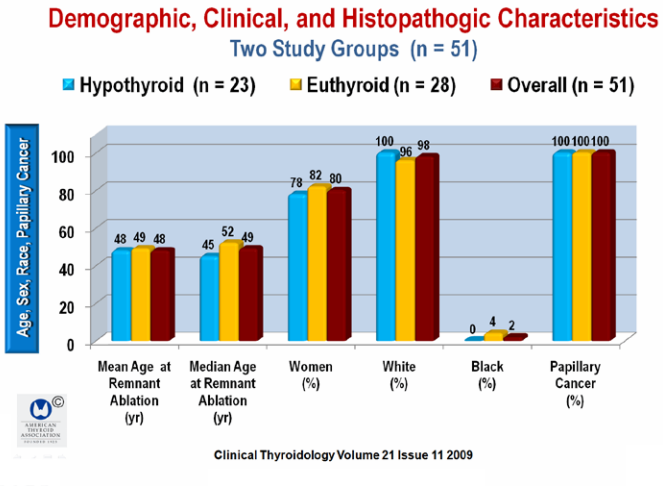
Patients and Methods

In the original study, 63 patients—61 with papillary thyroid cancer and 2 with follicular thyroid cancer—were randomly assigned postoperatively to either thyroid hormone withdrawal (hypothyroid group) or rhTSH stimulation (euthyroid group) in preparation for thyroid remnant ablation with 100 mCi of ^{131}I. Ten of the 61 patients were ineligible for the current follow-up study for several reasons, such as the inconvenience of further testing or recent extensive diagnostic evaluation during follow-up. The current study cohort thus comprised 51 (81%) of the original 63 patients, 28 of whom were in the euthyroid group (55%) and 23 in the hypothyroid group (45%). An ^{131}I DxWBS was performed in 43 of the 51 patients (84%). Successful remnant ablation was defined by the same criteria used in the previous study, which was no visible uptake in the thyroid bed, or if uptake was visible, then radioiodine uptake <0.1%. The secondary criterion was an rhTSH-stimulated serum Tg <2 ng/ml. The current study compared the rhTSH-stimulated serum Tg levels and the neck ^{131}I uptake at the 8-month evaluation in the first study, with the 3-to 4-year testing results in the present study. Here and elsewhere percentages have been rounded to an integer.

RESULTS

The Demographic Characteristics of the Study Patients (Figures 1 and 2)

The demographic characteristics, clinical and histopathologic features of the study group are summarized in Figures 1A and 1B. The mean (±SD) ages of the cohort were 48±13, 49±12, and 48±12 years in the hypothyroid, euthyroid, and combined groups, respectively. The tumor–node–metastasis (TNM) status of the patients ranged from T1 through Mx and was approximately the same in the hypothyroid and euthyroid groups (Figure 1B) The characteristics of the patients in the first trial who were not enrolled and those in the current follow-up study were comparable (Figure 2).



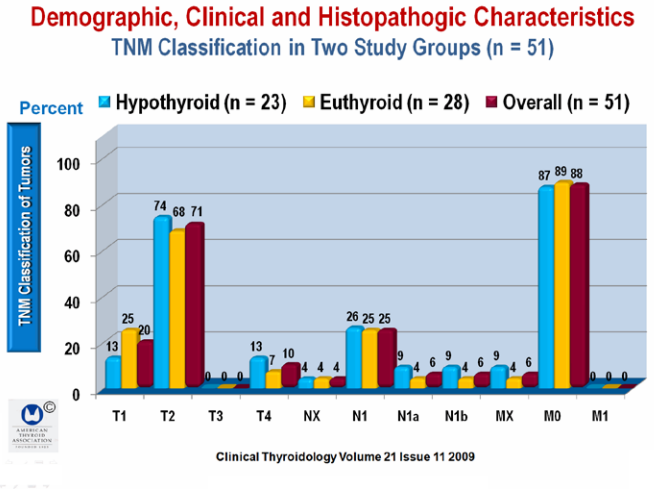


Figure 1. (a) This figure shows the comparison of patient and tumor characteristics in the current follow-up study of 51 patients prepared for remnant ablation with either thyroid hormone withdrawal or recombinant human TSHα (rhTSH), **(b)** This figure shows the TNM stage in this group. Figures are derived from data in Table 1 of Elisei et al. THW = thyroid hormone withdrawal.

Characteristics of the Nine Study Patients Requiring Further Therapy (Figure 3)

None of the 63 patients who participated in the first trial had died by the time of the second follow-up study; however, 9 of the 51 patients (18%) in the second study group (5 hypothyroid and 4 euthyroid) had received additional ^{131}I therapy, 2 of the 9 (1 hypothyroid and 1 euthyroid) also had further surgery, and 1 (euthyroid) had surgery without further ^{131}I treatment; none of them had iodine-avid disease. These data are summarized in Figure 3.

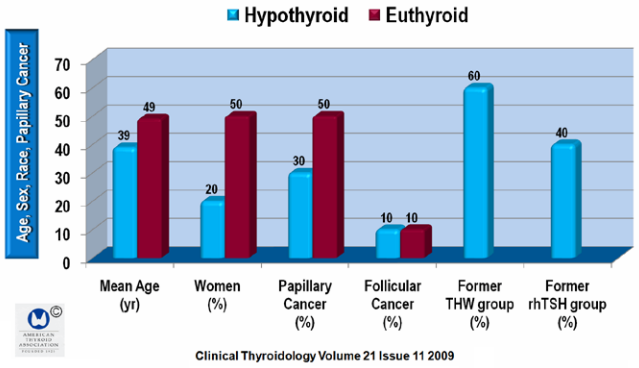


Figure 2. This figure shows the patient and tumor characteristics of those from the original study cohort who were not enrolled in the current follow-up study. There are no significant differences between the two groups. rhTSH = recombinant human thyrotropin-α; THW = thyroid hormone withdrawal. Figures are derived from data in Table 2 of Elisei et al.

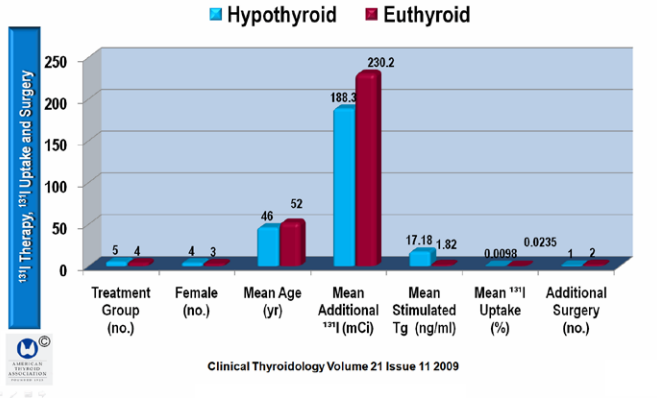


Figure 3. This figure shows the details of the nine patients in the current cohort who were treated with ^{131}I and surgery after the 8-month evaluation of outcome in the original study group. Mean values are shown for serum recombinant human thyrotropin-α (rhTSH)-stimulated serum thyroglobulin, the amount of ^{131}I used for therapy for the patients with recurrences, and the mean ^{131}I uptake. *P <0.004 and †P = 0.015 comparing mean ^{131}I uptake in the two study groups. The mean values were calculated and figures derived from Table 3 by Elisei et al.

The nine patients who required further therapy were judged to have had successful remnant ablation based on the absence of ^{131}I uptake in the neck, but none had unequivocal serum Tg evidence of being free of disease or without thyroid tissue, but instead had persistent elevation of the TSH-stimulated serum Tg levels (n = 4) or uninterpretable Tg measurements because of serum anti-Tg antibodies (TgAb). One patient had a small thyroid remnant found

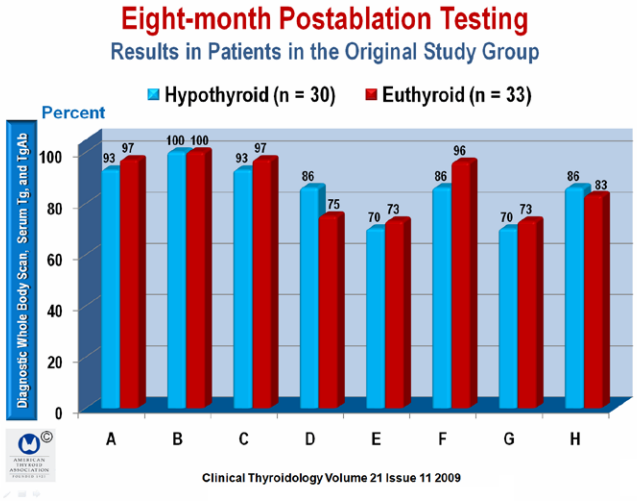


Figure 4A. This figure shows the 8-month postablation testing in the evaluable patients in the original study group, comparing hypothyroid and euthyroid groups. A = patients included in scan analysis divided by all original patients; B = patients with no visible uptake or <0.1% divided by patients in scan analysis; C = patients included in DxWBS analysis divided by all original patients; D = patients with no visible ^{131}I uptake divided by patients in DxWBS analysis; E = patients with serum Tg measurement and no interfering TgAb divided by all original patients; F = patients with serum Tg <2 ng/ml divided by all patients with Tg analysis; G = patients with serum Tg measured and no interfering TgAb divided by all original patients; H = patients with serum Tg <1 ng/ml divided by all patients with Tg analysis. TgAb = thyroglobulin antibody. Figures 4A and B are derived from data in Table 4 of Elisei et al.

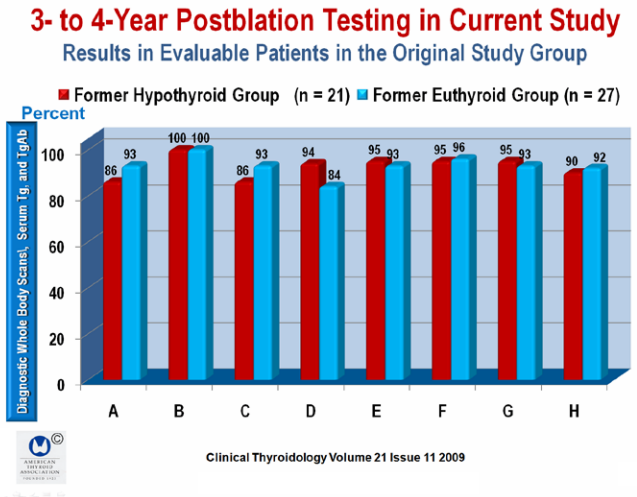


Figure 4B. This figure shows the 3-to 4-year postablation testing in the current study group comparing the former hypothyroid group with the former euthyroid group. See Figure 4A legend for definitions of A through H.

by neck ultrasonography, and 4 others had persistent thyroid-bed ^{131}I uptake or cervical lymph-node metastases detected on the initial posttherapy whole-body scan. All three of the patients who required additional surgery had a negative DxWBS, but all had elevated serum Tg values or serum TgAb levels and ultrasound evidence of suspicious cervical lymph nodes. Seven of the 9 study patients who required further therapy (78%) had a negative rhTSH-stimulated DxWBS but 2 (1 hypothyroid and 1 euthyroid) still had an rhTSH-stimulated serum Tg >2 ng/ml reflecting persistent cervical lymph-node metastases. None of the 51 patients in the follow-up study who had been thought to be free of disease on the basis of undetectable rhTSH-stimulated serum Tg levels subsequently had tumor recurrence.

Comparison of 8-Month and Current Study Results for Evaluable Patients (Figures 4A, 4B, and 5)

Because 3 of the 51 patients enrolled in the second study could not be given rhTSH for various reasons, diagnostic testing was done in 48 patients (21 hypothyroid and 27 euthyroid). Among the 48 patients, 43 agreed to receive 4 mCi for a DxWBS. Serum Tg measurements were completed in 47 of the 48 patients, but were uninterpretable in 3 because of serum anti-Tg TgAb levels >30 U/ml, reducing the number of patients from 48 to 45 with reliable serum Tg measurements.

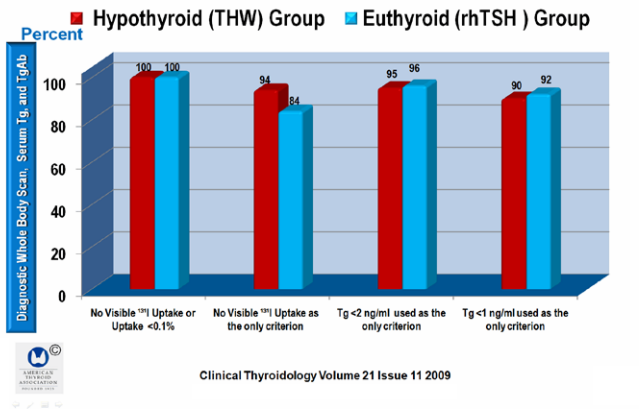


Figure 5. This figure compares the rate of successful ablation using the criteria in the original study with only the criterion of <0.1% ^{131}I uptake in the thyroid bed, in which case 100% of the hypothyroid and euthyroid groups had an ablation rate of 100%. When no visible uptake was used instead of <0.1% ^{131}I uptake, fewer patients were regarded as having successful ablation. When TSH-stimulated Tg <2 ng/ml levels were compared with <1 ng/ml as the only criterion for remnant ablation, there was little difference in the rates of successful ablation between the two Tg cutoffs.

Thus, the long-term efficacy of the original ^{131}I ablation procedure was evaluated in 43 patients who completed both an rhTSH-stimulated WBS and rhTSH-stimulated Tg measurement in the current follow-up study. Also, this group included 9 patients who had received further therapy after the original study, thus confounding the evaluation of efficacy in the original ablation study. As a consequence, 100% of the patients in both the hypothyroid and euthyroid groups continued to meet the initial criteria of no visible ^{131}I uptake or less than 0.1% uptake in the thyroid bed, which interfered with calculation of the confidence intervals (Figure 4A). When no visible ^{131}I uptake was used as the only criterion, five patients (one hypothyroid and four euthyroid) had minimally visible ^{131}I activity, making the successful ablation rates 94% and 84% in the two groups, respectively (Figure 4B).

When TSH-stimulated Tg was used to evaluate outcome, 45 patients could be assessed, and all but two (one hypothyroid and one euthyroid) had an rhTSH-stimulated serum Tg <2 ng/ml, making the ablation rates 95% and 96% (95% confidence interval [CI], –11.3 to 13.3) in the two groups, respectively. Using the even more stringent criterion of an rhTSH-stimulated Tg <1 ng/ml, all but four patients (two hypothyroid and two euthyroid) were considered to have had successful ablation, thus making the ablation rates 90% and 92%, respectively (95% CI, –14.9 to 18.9. in the two groups, respectively) (Figure 5).

After a median of 3.7 years, patients prepared with thyroid hormone withdrawal or recombinant human TSHα, have similar rates of remnant ablation, tumor recurrence, and persistent disease.

Two patients with serum TgAb >30 U/ml were excluded from the main Tg follow-up analysis (one hypothyroid and one euthyroid), and nine were excluded (four hypothyroid and five euthyroid) when the more stringent criterion of TgAb <5 U/ml was used. When the rhTSH-stimulated serum Tg levels were <1 ng/ml 8 months after the original ^{131}I ablation study, the Tg values remained at this level in the current follow-up study.

In the eight cases (four hypothyroid and four euthyroid) in which the rhTSH-stimulated serum Tg levels were >1 ng/ml 8 months after the original ^{131}I ablation (five >2 ng/ml and three >1 ng/ml), three had elevated Tg levels, but also had high anti-TgAb levels that potentially interfered with the Tg results. As a result, comparison of ^{131}I efficacy for remnant ablation in the two study groups could not be assessed because six of the patients had been retreated after the initial therapy. Only one patient had not been treated with ^{131}I during the interim and had no interfering anti-TgAb. However, this did not change the Tg evidence for ablation with rhTSH and THW.

CONCLUSION

After a median follow-up of 3.7 years, patients with low-risk thyroid cancer prepared for postoperative remnant ablation with either L-T_4 withdrawal or rhTSH stimulation have comparable rates of thyroid remnant ablation and tumor recurrence or persistent disease.

COMMENTARY

The study by Elisei et al. strengthens our understanding of how patients can be prepared for ^{131}I remnant ablation. It is a follow-up of an important study reported in 2006, by Pacini et al. (1), who published the results of a randomized, controlled, international, multicenter trial aimed at assessing the efficacy and safety of rhTSH in a cohort of patients with low-risk thyroid cancers, 97% of which were papillary thyroid carcinoma, with the others being follicular thyroid cancers. In the clinical trial, patients

receiving levothyroxine therapy were prepared for thyroid remnant ablation with 100 mCi (3.7 GBq) of ^{131}I using rhTSH (euthyroid) or levothyroxine withdrawal (hypothyroid) to stimulate uptake of ^{131}I by postoperative thyroid remnants. The study was also designed to assess the quality of life and the rate of ^{131}I clearance from blood and thyroid remnants and to evaluate the extent of whole-body irradiation in patients prepared with rhTSH as compared with those using thyroid hormone withdrawal. The study protocol defined the primary criterion for successful ablation as "no visible uptake in the thyroid bed, or if visible, ^{131}I uptake <0.1%" on a diagnostic neck scan performed 8 months after therapy. The goal of remnant ablation was achieved in 100% of both groups. A secondary criterion for assessment of ^{131}I remnant ablation in the two groups was an rhTSH-stimulated serum Tg <2 ng/ml, which was fulfilled in 23 of 24 (96%) euthyroid patients and 18 of 21 (86%) hypothyroid patients (P = 0.2). The study also found that patients prepared with rhTSH maintained a substantially better quality of life and received significantly less radiation exposure to the blood as compared with hypothyroid patients.

At the time of the current follow-up study, none of the 63 patients who had participated in the 2006 trial had died. Moreover, the current study found that patients prepared with rhTSH and THW continue to have comparable rates of successful remnant ablation after approximately 4 years of follow-up. This is of considerable importance since it is within the first year after surgery that recurrence rates are highest (2) and typically have the worst outcomes (3). Nine of the patients in the original trial (five hypothyroid and four euthyroid) received additional ^{131}I therapy and two, along with another patient who did not receive ^{131}I therapy, were surgically treated for cervical lymph-node metastases. The patients treated with ^{131}I were all found to have non–iodine-avid tumors. The patients considered to have successful remnant ablations at 8 months after ^{131}I therapy all were confirmed to have an absence of visual ^{131}I uptake in the neck or <0.1% ^{131}I uptake, and were subsequently found to have a negative rhTSH-stimulated DxWBS a median of 3.7 years later. This confirms that repeat diagnostic scanning is not necessary in most patients who have a negative postoperative scan.

All the patients in this study had low-risk tumors of stage T2 or T4 with minor invasion of the thyroid capsule, N0 to N1, and M0, or T0 to T1, N1, and M0. The authors provide the caveat that T4 tumors were considered ineligible later in the initial study, because certain centers routinely treated such patients with more than 100 mCi of ^{131}I or were treated with external-beam radiotherapy, which might apply to patients with higher stages of disease.

The other important finding in this study relates to the diagnostic differences of serum Tg levels and visible uptake of ^{131}I on a DxWBS. An rhTSH-stimulated serum Tg measurement in the absence of anti-TgAb has a greater sensitivity, in the range of 80%, when the Tg is rising (4, 5). In contrast, an rhTSH-stimulated DxWBS has a much lower sensitivity in detecting tumor recurrence (6), which is best done with neck ultrasonography and rhTSH-stimulated serum Tg measurements (7).

Tuttle et al. (8) retrospectively assessed tumor recurrence a median of 2.5 years after ^{131}I remnant ablation in 394 consecutive patients with thyroid cancer (93% papillary) treated with a median of 108 mCi ^{131}I for remnant ablation (3996 MBq). The study found similar ablation and tumor recurrence rates after preparation with rhTSH and thyroid hormone withdrawal (4% and 7%, respectively; P = not statistically significant for both tumor and remnant ablation) in 320 patients prepared with rhTSH and 74 by THW. When the definition of no clinical evidence of disease included a suppressed Tg <1 ng/mL and a stimulated thyroglobulin level <2 ng/mL, rhTSH-assisted remnant ablation was found to be associated with significantly higher rates of no clinical evidence of disease (74% rhTSH vs. 55% THW, P = 0.02) and significantly lower rates of persistent disease (19% rhTSH vs. 32% THW, P = 0.02) than was remnant ablation after THW. The conclusion of the study was that rhTSH-assisted remnant ablation is associated with rates of clinically evident disease recurrence and persistent uptake in the thyroid bed that are similar to those for traditional THW.

Elisei et al., in an even longer follow-up study, confirm that ^{131}I remnant ablation performed with rhTSH stimulation, over a median of nearly 4 years of follow-up, is a safe and effective means of preparing for remnant ablation as compared with THW in patients with low-risk tumors and is superior to ^{131}I DxWBS.

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