# Prestimulation with Recombinant Human Thyrotropin (rhTSH) Improves the Long-Term Outcome of Radioiodine Therapy for Multinodular Nontoxic Goiter

Søren Fast, Viveque Egsgaard Nielsen, Peter Grupe, Henrik Boel-Jørgensen, Lars Bastholt, Peter Bøgeskov Andersen, Steen Joop Bonnema, and Laszlo Hegedüs

Departments of Endocrinology (S.F., V.E.N., S.J.B., L.H.), Ear, Nose, and Throat (S.F.), Nuclear Medicine (P.G., H.B.-J.), Radiology (P.B.A.), and Oncology (L.B.), Odense University Hospital, DK-5000 Odense, Denmark

**Objective:** The objective of the study was to evaluate the long-term outcome of recombinant human TSH (rhTSH)-augmented radioiodine ($^{131}$I) therapy for benign multinodular nontoxic goiter.

**Patients and Methods:** Between 2002 and 2005, 86 patients with a multinodular nontoxic goiter were treated with $^{131}$I in two randomized, double-blind, placebo-controlled trials. $^{131}$I-therapy was preceded by 0.3 mg rhTSH (n = 42) or placebo (n = 44). In 2009, 80 patients completed a follow-up (FU) visit, including determination of thyroid volume, thyroid function, and patient satisfaction by a visual analog scale.

**Results:** In both groups, thyroid volume was further reduced from 1 yr to final FU (71 months). The mean goiter volume reductions obtained at 1 yr and final FU [59.2 ± 2.4% (SEM) and 69.7 ± 3.1%, respectively] in the rhTSH group were significantly greater than those obtained in the $^{131}$I-alone group (43.2 ± 3.7 and 56.2 ± 3.6%, respectively, $P = 0.001$ and $P = 0.006$), corresponding to a gain of 24% at final FU. At last FU the mean reduction in compression visual analog scale score was significantly greater in patients receiving rhTSH ($P = 0.049$). Additional therapy (thyroid surgery or $^{131}$I) was required more often in the placebo group (nine of 44) compared with the rhTSH group (two of 42) ($P = 0.05$). The prevalence of hypothyroidism at 1 yr [9 and 43% in the placebo and rhTSH groups, respectively ($P < 0.0001$)] increased to 16 and 52%, respectively, at final FU ($P = 0.001$).

**Conclusion:** Enhanced goiter volume reduction with rhTSH-augmented $^{131}$I therapy improves the long-term reduction in goiter-related symptoms and reduces the need for additional therapy compared with plain $^{131}$I therapy. Overall patient satisfaction is benefited, despite a higher rate of permanent hypothyroidism. (**J Clin Endocrinol Metab 97: 2653–2660, 2012**)

In some countries, radioiodine ($^{131}$I) therapy has been used for more than 3 decades as an alternative to thyroid surgery to reduce the size of symptomatic benign multinodular nontoxic goiter (MNG) (1, 2). On average, goiter volume is reduced by 40% 1 yr after treatment (3–7) and 50–60% at 3–5 yr (5, 6). Low and/or inhomogeneous $^{131}$I uptakes (RAIU) constitute major limitations for $^{131}$I therapy. Furthermore, considerable variation in goiter

volume reduction (GVR) (15–70%) is seen, and up to 20% of patients have very limited response (6). Finally, GVR declines with increasing goiter size (8), which, together with the need for relatively high $^{131}$I activities, questions its use in large goiters. Thus, $^{131}$I therapy is far from an ideal treatment in this context.

Recombinant human TSH (rhTSH) doubles or increases even more the thyroid RAIU (4, 9–12), depending

Abbreviations: FU, Follow-up; GVR, goiter volume reduction; $^{131}$I, radioiodine; MNG, multinodular nontoxic goiter; MRI, magnetic resonance imaging; RAIU, $^{131}$I uptake; rhTSH, recombinant human TSH; TV, thyroid volume; US, ultrasound; VAS, visual analog scale.

**TABLE 1.** Baseline TV and therapeutic ^{131}I activities in our two previous studies in goiters less than [trial A (16)] and greater than [trial B (17)] 100 ml

| | Trial A | | Trial B | |
| --- | --- | --- | --- | --- |
| | Placebo+[131]I (n = 29) | rhTSH+[131]I (n = 28) | Placebo+[131]I (n = 15) | rhTSH+[131]I (n = 14) |
| Goiter size (ml) | 51 (20–99) | 59 (25–92) | 170 (99–440) | 151 (112–395) |
| Therapeutic ^{131}I activity (MBq) | 519 (173–658) | 581 (241–666) | 1550 (633–3198) | 1400 (819–3700) |

Medians with range in *parentheses* is provided.

on the baseline RAIU, and results in a more homogeneous distribution of ^{131}I in multinodular goiters (13). During the last decade, and based on the above observations, rhTSH has been evaluated as an adjuvant to ^{131}I therapy, in an attempt to improve the eligibility for and the efficacy of this treatment for MNG (4, 14, 15).

In terms of GVR, the superiority of rhTSH-augmented ^{131}I therapy over ^{131}I alone has been demonstrated in five randomized, placebo-controlled studies (16–20). In our previous double-blind superiority studies (*i.e.* aiming at increased GVR) (16, 17), GVR was enhanced by 35–56% 1 yr after therapy, the gain being most pronounced in large goiters (17). Despite improved GVR and evidence of superior reduction of tracheal compression (21), it has proved difficult to demonstrate a better outcome in terms of reduction of goiter related symptoms and quality of life (16–19). Although this should not withhold clinicians from using rhTSH, this issue deserves further attention, especially because the use of rhTSH is related to an up to 5-fold increase in the rate of permanent hypothyroidism (16) and is used off label in this context. In theory, the augmented GVR, when rhTSH is used, could translate into a reduced need for additional therapy due to sustained

goiter reduction and persistent relief of goiter related symptoms. In fact, little is known about the long-term risk of goiter recurrence after ^{131}I therapy, whether with or without rhTSH stimulation. The only available study using ^{131}I alone demonstrated recurrent goiter growth in 8% of patients after 5 yr (6). In the only long-term study of the impact of rhTSH on the outcome of ^{131}I therapy for benign nodular goiter (22), the difference in GVR seen at 1 yr was maintained at 4 yr.

In the following text, we present long-term follow-up (FU) data from our two prospective, randomized, double-blind superiority studies (16, 17), which comprises the largest number of individuals and the longest FU.

## Patients and Methods

### Study population and design

Between 2002 and 2005, we treated, with ^{131}I, in two randomized and double-blind, placebo-controlled trials 86 patients with benign MNG (16, 17). Radioiodine therapy was preceded by either 0.3 mg rhTSH (n = 42) or placebo (n = 44) in two separate protocols, including goiters less than (16) or greater than 100 ml (17) (Table 1). From late 2009 all patients were offered a FU visit. Six patients were lost to FU: four patients had died (cause of death: cerebral insult, congestive heart failure, myocardial infarction, and unknown at age 89, 91, 81, and 81 yr, respectively). Another two patients did not wish to participate (Fig. 1). The FU visit included thyroid volume (TV) estimation, thyroid function tests, assessment of additional therapy, and evaluation of patient satisfaction by a visual analog scale (VAS). The study was approved by the local ethics committee of the county of Funen, Denmark. Along with the invitation to participate in the FU study, patients were asked to return a questionnaire containing information on additional therapy (*i.e.* thyroid surgery or additional ^{131}I) and the indication for such therapy. Furthermore, patients were asked whether they had normal thyroid function and whether they received levothyroxine or antithyroid medication.

### Study Population



**FIG. 1.** Outline of the study population including our two previous studies A (16) and B (17).

### [131]I therapy

Based on a baseline (nonstimulated) RAIU, the therapeutic ^{131}I activity was calculated to deliver a thyroid dose of 100 Gy in both groups (Table 1). In
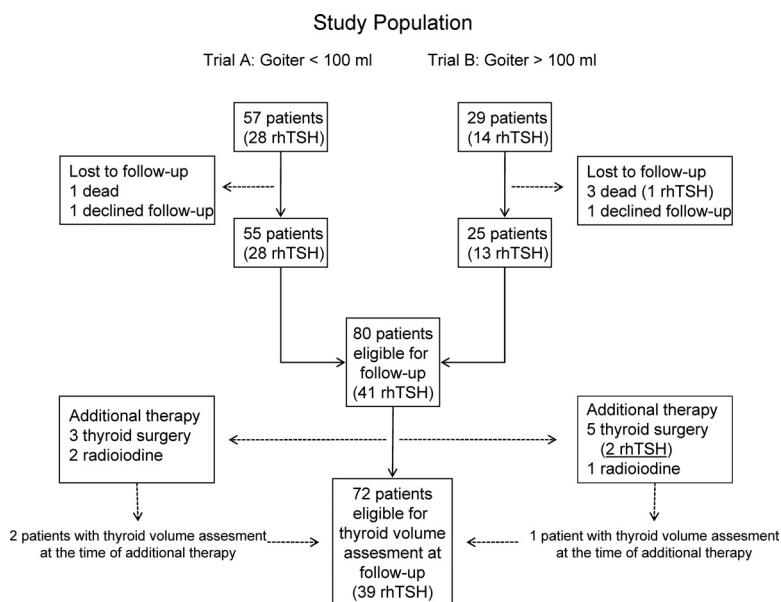
accordance with the official Danish radiation regulatory agency, the administered $^{131}$I activity was limited in seven patients in both the $^{131}$I-alone and the rhTSH+$^{131}$I groups.

## Thyroid size estimation

Goiter size was estimated by three-dimensional planimetric ultrasound (US) or magnetic resonance imaging (MRI), using, in each patient, the same image modality as in the original protocol (*i.e.* US in goiters initially < 100 ml and MRI in goiters initially > 100 ml). To ensure a high validity of the primary outcome measure, TV was calculated by an investigator blinded toward randomization. Details on the precision of the MRI and US procedures can be found in previous publications (23, 24). In patients who had received additional therapy before the FU visit, the patient files were checked to obtain the last valid TV (*i.e.* before additional therapy).

## Thyroid function

Thyroid function tests included serum TSH, serum total $T_3$, and serum total $T_4$. Serum free $T_4$ index and free $T_3$ index were calculated by multiplying the total values by the percentage of $T_3$ resin uptake. In addition, TSH receptor antibodies and thyroid peroxidase antibodies were measured. Reference intervals and characteristics of these routine assays are available in our previous publication (25). In patients lost to FU, the patient files were checked to obtain information on thyroid function status. In patients who had received thyroid surgery or additional $^{131}$I therapy, the patient files were checked to obtain information on thyroid function at the time of additional therapy.

## Patient satisfaction and need for additional therapy

To evaluate the subjective benefit of $^{131}$I therapy, goiter-related symptoms were registered by a VAS. In contrast to the original protocols, patients were unblinded toward randomization at the FU visit. In a similar setup as that used in the original protocols, each individual was asked to indicate on the VAS ranging from 0 to 10 (arbitrary units), the degree of cervical compression, and cosmetic discomfort. A score of 0 represented no complaints and 10 the worst possible degree of compression/ discomfort. Furthermore, patients were asked (questionnaire) whether they were satisfied overall with the result of the initial therapy (dichotomized as yes or no). Finally, patients were asked whether they had received any additional therapy for their MNG (questionnaire) and, importantly, the indication for such therapy was established from the patient files. In patients lost to FU, the indication for additional therapy (if administered) was obtained from the patient files.

## Statistical analyses

Statistical analyses were performed using the SPSS statistical software program, version 16.0 (SPSS Inc., Chicago, IL). Depending on the normality of the data, parametric or nonparametric tests were used for analysis. Within-group change in absolute TV was assessed by Friedman's test. Between-group differences in the relative change in TV were analyzed using an independent-samples $t$ test. Multiple linear regression analysis using a mixed model was used to evaluate the effect of randomization on GVR. To compare frequencies, the $\chi^2$ and Fisher's exact tests were used. Kaplan-Meier survival curves, a log-rank

test, and Cox-regression were used to evaluate factors influencing the rate of therapeutic failure. The level of statistical significance was chosen as $P < 0.05$.

# Results

## Therapeutic failure resulting in additional therapy

Based on the patient files and questionnaire answers, none of the six patients lost to FU had received additional therapy. Nine of 44 patients in the $^{131}$I-alone group (20%) had received additional therapy (thyroid surgery in six and additional $^{131}$I therapy in three), compared with two (thyroid surgery in both) of 42 patients (5%) receiving rhTSH + $^{131}$I therapy ($P = 0.05$). Because more patients had received additional therapy in the $^{131}$I-alone group, the median time of FU was shorter compared with the rhTSH+$^{131}$I group [62 months (13–82 months) *vs.* 73 months (16–84 months) ($P = 0.001$)]. In all 11 patients who required additional therapy, the cause was established as failure of the initial therapy to relieve goiter-related symptoms/signs. Histology reports were benign in all eight patients undergoing thyroid surgery. The proportion of dose-limited patients experiencing therapeutic failure (two of 14, both in the placebo group) did not differ from that of the patients receiving the intended $^{131}$I activity (nine of 72, $P = 1.00$). A survival analysis (log rank test) confirmed that pretreatment with rhTSH was associated with a lower risk of requiring additional therapy (Fig. 2). Although not statistically significant ($P = 0.17$), the majority of therapeutic failures occurred in goiters initially greater than 100 ml (six of 29, or 21%) compared with five of 57 (9%) in goiters less than 100 ml. In a Cox regression, including baseline TV, baseline compression VAS score, and GVR at 1 yr as covariates, the rate of therapeutic failure increased with increasing TV and compression
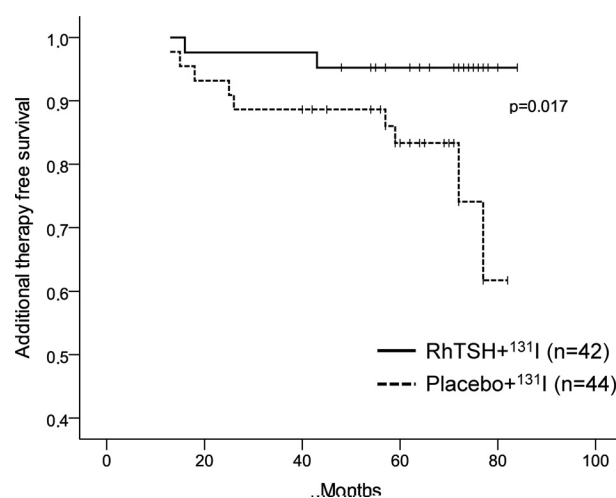
**FIG. 2.** Additional therapy-free survival rate by randomization group (Kaplan-Meier plot). Each *tick* (|) denotes a censored patient.

**TABLE 2.** Cox regression estimating the rate of therapeutic failure (requiring additional therapy), including baseline TV, baseline compression VAS score, and GVR at 1 yr as covariates

| Variable | Exp(B) | P value | 95% CI for Exp(B) | |
| --- | --- | --- | --- | --- |
| | | | Lower | Upper |
| Baseline TV (ml) | 1.007 | 0.026 | 1.001 | 1.013 |
| Baseline compression VAS score (arbitrary units) | 1.524 | 0.01 | 1.105 | 2.101 |
| GVR at 1 yr (%) | 0.961 | 0.01 | 0.932 | 0.99 |

Exp(B), Hazard ratio (*i.e.* the ratio of the hazard rate given a 1 U increase in the covariate to the hazard rate without such an increase); CI, confidence interval.

VAS score at baseline, whereas the rate decreased with increasing GVR at 1 yr (Table 2). The hazard ratio was 1.007 for baseline TV, indicating that a 50-ml increase in TV corresponds to a 42% increase in the rate of therapeutic failure (*i.e.* $1.007^{50} = 1.42$). In contrast, the estimated rate of therapeutic failure decreased by 33% with a 10% absolute increase in the 1-yr GVR [*i.e.* $(1-0.961^{10})100$]. None of the 22 patients who had developed permanent hypothyroidism at the 1-yr FU required additional $^{131}$I or surgery in the FU period, compared with 11 of the 64 patients who had remained euthyroid (17%) ($P = 0.03$).

## Goiter volume reduction

In the 11 patients who had received additional therapy, TV was not assessed at FU. However, a valid TV estimate, obtained at the time of additional therapy, was available in three of these individuals. Thus, long-term GVR could be compared in 72 patients (n = 80−11 + 3), of whom 39 were pretreated with rhTSH. In the $^{131}$I-alone group (n = 33) the median time of FU [65 months (45−82 months)] was slightly shorter compared with that of the rhTSH group (n = 39) [73 months (54−84 months) ($P = 0.01$ between groups)].

In the $^{131}$I-alone group, GVR continued after the first year. The median baseline TV of 61 ml (20−183 ml) was reduced to 37 ml (5−125 ml) at the 1-yr FU and to 33 ml (1−85 ml) at 65 months of FU. A Friedman's test revealed an overall difference between the three time points ($P < 0.0001$), and the difference between 1 yr and 65 months of FU also reached statistical significance ($P = 0.001$). In the rhTSH group, a similar pattern was seen. The median baseline TV of 67 ml (25−395 ml) was reduced to 27 ml (6−207 ml) at 1 yr of FU and to 20 ml (2−200 ml) at 73 months of FU, with an overall difference between the groups ($P < 0.0001$) and a statistically significant difference between the 1 yr and the 73 months of FU data ($P < 0.0001$).
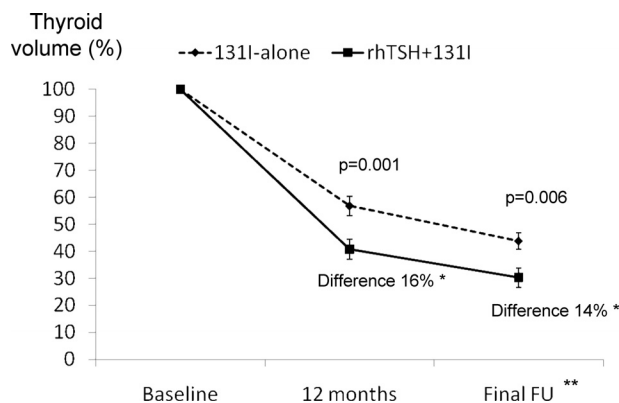


**FIG. 3.** Relative GVR (mean ± SEM) at 1 yr and at final FU in the $^{131}$I-alone group (n = 33) and in the rhTSH+$^{131}$I group (n = 39), respectively. Of the 80 patients completing the FU visit, some individuals receiving additional therapy were excluded from this analysis (Fig. 1). *, Difference represents the absolute difference between the two curves at 1 yr (16%, $P = 0.001$) and final FU (14%, $P = 0.006$), respectively; **, because more patients had received additional therapy in the $^{131}$I-alone group, the median time of the final FU was slightly shorter compared with that of the rhTSH+$^{131}$I group (65 and 73 months, respectively).

The mean relative GVR obtained at 1 yr and after 73 months of FU [GVR 59.2 ± 2.4% (SEM) and 69.7 ± 3.1%, respectively] in the rhTSH group were both significantly greater than those obtained at 1 yr and at 65 months in the $^{131}$I-alone group (GVR 43.2 ± 3.7 and 56.2 ± 3.6%, respectively, $P = 0.001$ and $P = 0.006$, respectively) (Figs. 3 and 4). To adjust for the difference in the length of the FU period between the groups, a multiple linear regression analysis (using a mixed model) including randomization, time of FU, and baseline TV was performed. This analysis revealed that only randomization contributed to the ab-
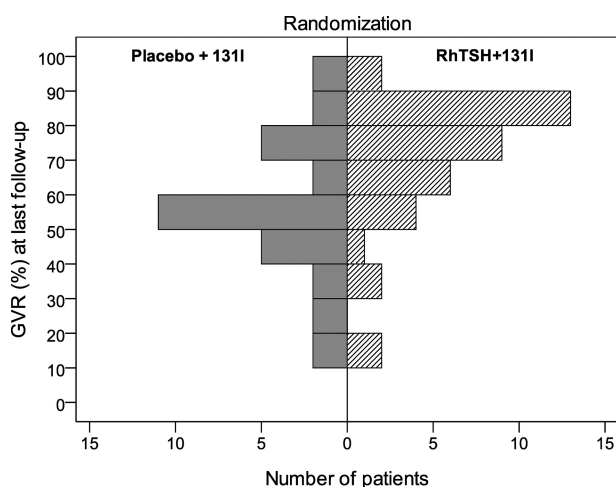


**FIG. 4.** Distribution of GVR (percentage) at final FU in the placebo+$^{131}$I (n = 33) and rhTSH+$^{131}$I (n = 39) groups, respectively. Of the 80 patients completing the FU visit, some individuals receiving additional therapy were excluded from this analysis (see Fig. 1). Because more patients had received additional therapy in the $^{131}$I-alone group, the median time of final FU was slightly shorter compared with that of the rhTSH+$^{131}$I group (65 and 73 months, respectively).

solute difference in GVR, estimated to be 14.4% (95% confidence interval 5.8–23.1%) greater in the rhTSH group. At 71 months patients who had developed permanent hypothyroidism (27 of 72) also achieved a more pronounced mean GVR compared with those who remained euthyroid (GVR 76.7 ± 3.0 and 55.5 ± 3.0%, respectively, $P < 0.0001$). When all patients were combined, a negative correlation between the initial TV and subsequent GVR (at 1 yr) could be demonstrated (r = −0.24, $P = 0.03$).

### Thyroid function

At 1 yr, permanent hypothyroidism, requiring levothyroxine replacement therapy, had developed in four of 44 patients in the ^{131}I-alone group (9%), compared with 18 of 42 in the rhTSH group (43%) ($P < 0.0001$). We were able to collect information about thyroid function and levothyroxine replacement therapy, beyond 1 yr, in five of the six subjects lost to FU. In all 11 patients receiving additional therapy, thyroid function status at the time of additional therapy was used for analysis. Thus, with a median FU time of 62 months, the prevalence of permanent hypothyroidism had increased to 16% (seven of 43) in the ^{131}I-alone group, compared with 52% (22 of 42) in the rhTSH group after 73 months of FU ($P = 0.001$ between groups). In a binary logistic regression including randomization, baseline TV, and 1-yr GVR as covariates, the risk of permanent hypothyroidism increased with the use of rhTSH and increasing GVR, whereas the risk decreased with increasing baseline TV (data not shown). At final FU, the TSH receptor antibody was not detected in any patients (compared with two at 1 yr). Likewise, the number of individuals with positive thyroid peroxidase antibodies decreased between 1 yr (n = 15) and the final FU (n = 6).

### Patient satisfaction

Overall patient satisfaction could be evaluated in 80 subjects. Thirty-seven of 41 patients pretreated with rhTSH (90%), compared with 27 of 39 treated with ^{131}I alone (69%) ($P = 0.025$) were satisfied overall with the initial treatment. At 1 yr and at the final FU, the GVR was more pronounced in the subjects who ended up being overall satisfied, compared with those who were not satisfied [mean GVR 54 *vs.* 36% at 1 yr ($P = 0.002$) and 65 *vs.* 42% at the final FU ($P = 0.001$)].

For analyses of the compression-related VAS scores, only individuals who initially reported compression symptoms (n = 72) and individuals who subsequently reported symptoms (not present at baseline) on the VAS scale (one patient) were included in the analyses. Consequently, a total of 73 patients were included in the analyses. Of the

11 patients receiving additional therapy, a valid VAS score (registered when the decision to undertake additional therapy was made) was recorded in only two subjects. However, based on information in the patient files, all 11 patients did require additional therapy due to either goiter regrowth or persistent symptoms. For the final FU analysis, the baseline VAS score was assigned for the FU evaluation in these nine patients. Using these data, the baseline (mean ± SD) compression symptom VAS score was 4.7 ± 2.5 and 4.5 ± 2.1 in the rhTSH and the ^{131}I-alone group, respectively ($P = 0.67$). At the final FU, the reduction in the VAS score was more pronounced in the rhTSH group (3.5 arbitrary units) compared with the ^{131}I-alone group (2.6 arbitrary units, $P = 0.049$ by Mann-Whitney test). At the 1-yr FU, the reduction in pressure VAS score was positively correlated to the obtained GVR (r = 0.30, $P = 0.01$, Fig. 5).

## Discussion

With the largest number of individuals and the longest FU time, we demonstrate that the enhanced GVR achieved by prestimulation with rhTSH is maintained for at least 71 months. Importantly, the absolute gain in GVR at 71 months (14%) was maintained, although we had to exclude subjects with therapy failure (indicating low GVR), which occurred more often in the ^{131}I-alone group. Therefore, any difference in GVR at the final examination represents an underestimation of the difference between the two groups. Of clinical importance we, for the first time, demonstrate that pretreatment with rhTSH not only improves GVR but also results in a superior outcome in terms of increased patient satisfaction and reduced need for additional therapy. In the group receiving plain ^{131}I therapy,
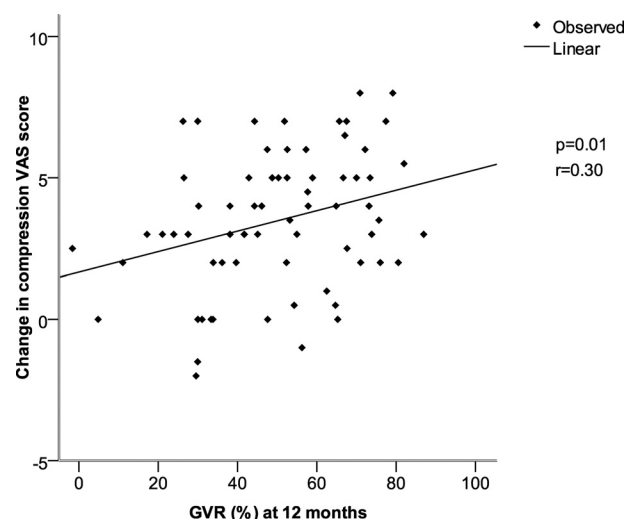


**FIG. 5.** At the 1-yr FU, there was a positive correlation between the obtained GVR and the reduction in compression VAS score (n = 73).

20% of patients required additional therapy, whereas the corresponding number was 5% in the rhTSH group. With the reservation that our sample size is small with regard to the number of end point events (*i.e.* additional therapy), our results suggest that the risk of therapeutic failure decreases with increasing GVR, whereas it increases with increasing goiter size and compression symptoms (VAS score) before therapy. This observation is in accordance with our finding that GVR tends to be inversely correlated to the initial thyroid volume, an observation also made previously (6, 16). These observations underline the recommendations in international guidelines that thyroid surgery is the treatment of choice for very large goiters and/or patients with extensive compressive symptoms/signs (1, 26).

The enhanced GVR, obtained by using rhTSH, mainly occurred within the first year after $^{131}$I therapy, whereas GVR beyond 1 yr continued with a similar rate independent of rhTSH stimulation. TV was reduced by approximately 10% from 1 to 6 yr after therapy in both groups. In the only other randomized, controlled, long-term (4 yr) study, Cardia *et al.* (22) demonstrated a similar long-term GVR of 73% in patients pretreated with rhTSH *vs.* 57% in patients receiving $^{131}$I alone. Patient satisfaction was not evaluated, but two of 13 patients in the $^{131}$I-alone group, compared with none of 17 patients receiving rhTSH, experienced goiter growth (22). Recently, similar results were reported in the controlled but nonrandomized study by Giusti *et al.* (27) comparing the effect of $2 \times 0.1$ mg rhTSH in combination with an adjusted thyroid dose *vs.* matched controls treated with $^{131}$I alone (obtained GVR 60 and 44% at 3 yr, respectively). Although the achieved GVR at the 3-yr FU was significantly greater in subjects receiving rhTSH, a VAS score could not detect any differences in the reduction of subjective complaints. In that study, four of 21 patients treated with $^{131}$I alone required additional treatment compared with none of the patients pretreated with rhTSH. On the other hand, a slight increase in TV after 2 yr has been reported in four of 30 patients treated with rhTSH-augmented $^{131}$I therapy (uncontrolled design) (28).

The prevalence of permanent hypothyroidism increased in both groups over time. At 5.5 yr, the prevalence of hypothyroidism was 52 and 16% in the rhTSH and $^{131}$I-alone group, respectively, which is comparable with that in other studies (6, 22, 27). The risk of hypothyroidism decreased with increasing goiter size, as reported by others (6). Importantly, the development of hypothyroidism was associated with enhanced GVR, which in turn reduced the need for additional therapy. Neither we nor others (22, 27) have observed an increased rhTSH-related incidence of thyroid autoantibodies.

Our study has some limitations. Thus, we have only TV estimation in the FU period in three of the 11 patients referred for additional therapy. Despite the fact that these patients experienced persistent goiter-related symptoms (suggesting low GVR), this introduces some inaccuracy in the evaluation of long-term GVR. With regard to the need for the additional therapy end point, it is a weakness that there were no predefined criteria to determine whether the patient should be offered additional therapy. This decision was based on a combination of patient dissatisfaction and the obtained GVR after the initial therapy. Moreover, the time of FU was 8 months shorter in the $^{131}$I-alone group compared with the rhTSH group because more patients in the $^{131}$I-alone group had received additional therapy. Considering that GVR continues with time, this slightly disfavored the $^{131}$I-alone group in the evaluation of GVR at final FU. However, the mixed-model regression analysis, taking time of FU into consideration, demonstrated that the difference in GVR between the two randomization arms was very robust. Dose limitation did not have a major impact on the rate of therapeutic failure in our study, underlining that the factors determining the outcome of $^{131}$I therapy are complex and not dependent only on the absorbed thyroid dose. Nonetheless, it is reassuring that dose limitation occurred in a similar proportion of patients in the two groups and is thus not likely to have influenced the overall result of the present study.

All previous attempts to demonstrate that patient satisfaction is augmented by the increased GVR obtained with rhTSH prestimulation have failed (16–19). A number of factors may explain this. First, the required GVR to reduce symptoms may be heavily influenced by the degree of symptoms in the population studied. Second, it is likely that VAS scores and/or reported quality-of-life items are boosted at study inclusion (*i.e.* fear of malignancy), and as a consequence the majority of patients are likely to report improvement in quality of life, regardless of the extent of GVR because adherence to the protocol and time is a reassuring factor. Third, a low sensitivity of the VAS score for quality-of-life evaluation may contribute to the difficulty in measuring differences in quality of life. Although we, in line with another study (29), were able to demonstrate that the decrease in pressure symptom VAS score was positively correlated with the obtained GVR, the correlation coefficient was relatively low, indicating large variation in the individual responses. Future studies evaluating quality of life should thus include patients with pronounced and preferably longstanding symptoms related to the goiter.

As an alternative to the superiority strategy (aiming at increased GVR), evaluated in this study, we have recently demonstrated that prestimulation with rhTSH allows up

to 80% reduction of the therapeutic $^{131}$I activity while maintaining goiter reduction comparable with that of $^{131}$I therapy alone (*i.e.* approximately 35%) as well as high patient satisfaction at the 1-yr FU (29). With the reservation that long-term FU is not yet available, the dose-reduction strategy is attractive in terms of minimizing post-therapeutic restrictions and in reducing the potential risk of radiation-induced malignancy. The optimal strategy in a given patient depends on goiter size, the degree of symptoms, the wish to maintain normal thyroid function, the risks associated with radiation exposure, and the therapeutic alternatives. Subjects with a large compressive goiter, in whom the only therapeutic alternative is near-total thyroidectomy, are obvious candidates for the superiority strategy. In these patients destroying enough goiter tissue to cause hypothyroidism may be seen as analogous to near-total thyroidectomy, which also leaves the patient with life-long levothyroxine replacement therapy. On the other hand, patients with small to moderate sized oligo-symptomatic goiters may not require extensive GVR. Such patients could possibly benefit from remaining euthyroid, especially considering the increasing awareness of some patients experiencing decreased quality of life, albeit on levothyroxine replacement therapy (30, 31).

In conclusion, the increased GVR, when radioiodine therapy is preceded by rhTSH, is maintained after 6 yr of FU. Importantly, our results indicate that the increased GVR, when rhTSH is used, is beneficial in the long run because the need for additional therapy is reduced and the overall patient satisfaction is improved. Nonetheless, the factors determining the subjective patient outcome are complex. Hopefully the application of the recently developed thyroid disease-specific quality-of-life questionnaire, ThyPRO (32), can provide a more sensitive method for evaluating patient outcomes in future studies.

## Acknowledgments

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