Radioiodine Treatment of Graves’ Hyperthyroidism

To the editor:

In a recent issue of JCEM, Leslie et al. (1) describe their randomized comparison of two fixed doses and two volume and uptake-adjusted doses of iodine-131 in the treatment of Graves’ hyperthyroidism. They found no difference in clinical outcome and conclude that dose adjustment does not confer any advantage over a fixed dose.

Although the randomized approach and careful and long-term follow-up are welcome, there may be important limitations to the study. The sample size was relatively small so that their negative results may reflect lack of power (and consequently a type 2 error). The authors appropriately considered persistent or recurrent hyperthyroidism as treatment failure, reporting the rates of failure below (Table 1):

These data suggest the absence of important differences between these treatment groups, however, 95% confidence intervals for these failure rates were wide (Table 2):

It is possible, therefore, that real and clinically significant differences in outcome exist between groups. Sample sizes required to detect (or rule out) such differences are considerably larger than those in the present study. For example, to detect at 5% significance level, a difference of 10%, e.g. a fall in treatment failure rate from 25 to 15%, with 80% power would require 270 patients in each group and for 90% power 354 patients (2).

Furthermore, the present study used relatively low doses of 131-I; low fixed 235 MBq, high fixed 350 MBq, low adjusted 2.96 MBq/g, and high adjusted 4.44 MBq/g, in contrast to other recently published series (3) and in contrast to the practice in our United Kingdom center (fixed dose of 375 or 600 MBq) (4). Also, from the recent randomized trials cited in the study (5, 6), the message would be to use higher doses. Jarlov et al. (5) used fixed doses of 185, 370, and 555 MBq for gland volumes below 30, 30 to 60, and above 60 ml, respectively, and an adjusted dose 3.7 MBq/g with a reported failure rate of 35 to 41%. As the mean thyroid gland volume in Leslie’s study (1) was relatively high at over 60 ml, many patients treated with fixed doses would fall into Jarlov’s 555-555 MBq group. Peters et al. (6) compared a fixed dose of 555 MBq with a lower adjusted dose calculated to deliver 100 Gy (roughly 4.7 MBq/g) and whereas they had somewhat better results with the fixed dose (failure rate, 29% vs. 42%), from the dose-response relationship they recommend individualization aimed at about 200 Gy (roughly 9.5 MBq/g). Also, preliminary data from our Czech center and dose-response analysis suggest a decrease in failure rate with doses over 6.2 MBq/g (7).

We therefore consider the randomized study of Leslie et al. (1) as an important advance in the investigation of optimal radioiodine dosing in Graves’ disease but not as the final step. We suggest that a randomized study comparing a fixed dose of 555 to 600 MBq with an adjusted dose of approximately 6.5 MBq/g and sample sizes of up to 300 patients in each treatment arm is desirable.

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A response to this letter was invited, but the authors of the original article chose not to provide one.
may arise when patients with an intact thyroid function and/or goiter are stimulated with this agent. Although 131I therapy is used routinely in some countries (e.g. Denmark and The Netherlands) for treatment of nontoxic goiter, this is clearly not the case in many parts of the world, as demonstrated by recent questionnaire surveys (4). Additionally, the evidence for this strategy almost exclusively relies on uncontrolled studies (4). Therefore, before introducing a novel principle in this setting, indisputable evidence based on well-designed controlled trials should be provided. Unfortunately, no control group was included in the study by Nieuwlaat et al. (1) which predisposes to overlook confounding factors. For example, the goiter-reducing effect obtained by the 131I therapy may have been blurred by a possible dependency on the pre-treatment goiter volume, as described in other studies (4).

An issue largely overlooked is the fact that upper airway obstruction is present in a large fraction of patients with goiter, despite absence of symptoms (4). Some reports have suggested that stimulation with rhTSH causes significant swelling of tumor tissue in patients with papillary thyroid carcinoma (5, 6). It is plausible, but not proved, that a similar situation can occur in patients with a benign goiter. Considering that 131I therapy in some cases causes a transient goiter growth (without prior rhTSH stimulation) of 15–25% within the first week (4), the combination with rhTSH may lead to severe tracheal compression resulting in acute airway obstruction in susceptible individuals. In the study by Nieuwlaat et al. (1), the goiter enlargement as well as the smallest tracheal cross-sectional area was estimated by magnetic resonance 1 wk after the 131I therapy. On average, both structures were insignificantly altered, although a goiter growth up to 17% and a tracheal area reduction by 15% were observed (1). These figures are very similar to previous findings by us (7). However, it is our experience that the thyroid gland in some individuals may respond profoundly to rhTSH stimulation per se by an acute enlargement of more than 100% (8). This appears within 48 h and is fortunately followed by a rapid reversion to normal size. Thus, it is possible that a transient but significant goiter increase in fact did occur immediately before or during the 131I therapy in the study by Nieuwlaat et al. (1) but was overlooked because patients were scanned at the earliest 1 wk after therapy. It is reassuring that rhTSH stimulation in the low doses that were used in that study seemingly was well tolerated, but the number of patients was small (n = 22) and only few suffered from a goiter larger than 150 ml (1). Should it be confirmed that rhTSH stimulation may give rise to a significant acute thyroid enlargement, it must be investigated in detail whether this can be prevented successfully by e.g. corticosteroids or nonsteroidal antiinflammatory drugs, as suggested by two recent reports (2, 8).

Besides this potential problem of goiter swelling and tracheal compression due to rhTSH stimulation, particularly in combination with 131I therapy, other issues also need to be clarified. The aim in the study by Nieuwlaat et al. (1) was to reduce the 131I activity through a higher rhTSH-induced radioiodine thyroid uptake. The average goiter reduction obtainable by 131I therapy is 35–50% (4), which still may leave some patients with compressive symptoms, particularly those with large goiters. Although some studies have indicated a dose-relationship between 131I and goiter reduction (4), this remains to be proven in a prospective controlled set-up. Because some areas in a goiter simply may not be susceptible to 131I therapy due to inactive and degenerated nodular tissue, it may well be that the thyroid irradiation usually employed (approximately 100 Gy) is sufficient to obtain the maximum goiter reduction. Thus, it is presently an open question whether the goiter reduction can be amplified by the use of rhTSH pre-stimulation. A previous study by Nieuwlaat et al. (9) demonstrating a more homogeneous distribution of 131I in the nodular goiter after rhTSH stimulation holds promise in this setting. To estimate the impact of rhTSH stimulation on the thyroid irradiation, it would have been highly interesting if Nieuwlaat et al. (1) had measured the 131I kinetics during the 131I therapy of the patients with nontoxic multinodular goiter and compared data with a control group. Although rhTSH preconditioning. Finally, the optimal dose of rhTSH remains to be determined. By using small amounts of rhTSH, thyrotoxicosis can be avoided in most individuals with an intact thyroid gland (1), but this must of course be balanced against the overall purpose of a sufficient increase of thyroid 131I uptake. Thus, evidence of a beneficial effect of rhTSH pre-stimulation awaits proper conducted randomized trials before routine use can be recommended. In addition, cost-benefit, optimum rhTSH dose, and most important, safety issues need to be clarified.

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References


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Authors’ Response: Pretreatment with a Single, Low Dose of Recombinant Human Thyrotropin Allows Dose Reduction of Radioiodine Therapy in Patients with Nodular Goiter

To the editor:

We thank Dr. Bonnema and colleagues for their comments. Indeed, our study (1) is an observational study, not a randomized trial, comparing the safety and efficacy of rhTSH (3) therapy after treatment with various doses of recombinant human TSH (rhTSH) with that of standard 131I therapy, i.e. without pretreatment with rhTSH. As Bonnema et al. emphasize, rhTSH administration in patients with nodular goiters might induce acute increases in serum thyroid hormone levels and thyroid size. At the start of our study, no data on this issue were available. Therefore, the principal aim of our study was to explore the short-term safety of the administration of a therapeutic dose of 131I after pretreatment with a single dose of rhTSH. For safety reasons, we used low doses of rhTSH (0.01 or 0.03 mg), and we adjusted the therapeutic dose of 131I to the rhTSH-induced increase in 24-h radioactive iodine uptake, as determined in a diagnostic study, using a tracer dose of 131I. We did not aim at doses higher than 100 μCi (3.7 MBq) 131I per gram of thyroid tissue retained at 24 h. We agree that thyroid volume measurements in the first few days after rhTSH administration would have been informative. However, because in our study a therapeutic dose of 131I was given 24 h after rhTSH administration, radiation safety regulations in our hospital precluded such early measurements. Anyhow, we did not observe symptoms and signs of (worsening of) tracheal compression in the first days after rhTSH administration.