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REVIEW

Non-surgical approach to the benign nodular goiter: new opportunities by recombinant human TSH-stimulated ^{131}I-therapy

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Abstract The optimal treatment strategy in a goiter patient depends—among other factors—on goiter size, the degree of cosmetic or compressive symptoms, the age of the patient, the impact on the upper airways, the wish to maintain normal thyroid function, the ability of the thyroid gland to take up ^{131}I, and the possibility of thyroid malignancy. When treatment is warranted in a patient with benign goiter, the choice usually stands between surgery and ^{131}I-therapy. Focal destructive treatment, by ethanol sclerotherapy or interstitial laser photocoagulation, may be considered in patients with a solitary benign nodule. If thyroid hyperfunction due to nodular autonomy is the dominant problem, life-long anti-thyroid drug treatment may be relevant in elderly individuals. With the advent of recombinant human TSH (rhTSH) stimulation the goiter reduction following ^{131}I-therapy is significantly enhanced and this treatment is of particular benefit, as compared with conventional ^{131}I-therapy, in patients with a low baseline thyroid ^{131}I uptake and a large goiter. If the rhTSH dose does not exceed 0.1 mg the risk of temporary hyperthyroidism and acute thyroid swelling is low. Since patient satisfaction seemingly is not improved by the greater goiter reduction obtained by rhTSH-stimulated ^{131}I-therapy, and permanent hypothyroidism is more frequent, it may be more relevant to reduce the administered radioactivity equivalent to the rhTSH-induced increase in the thyroid ^{131}I uptake. Future large-scale well-controlled studies should explore this strategy, with focus on cost-benefit and quality of life. A major hindrance of widespread and routine use of rhTSH-stimulated ^{131}I-therapy is its present status as an off-label treatment.

Keywords Nodular goiter · Levothyroxine · Radioiodine therapy · Recombinant human thyrotropin

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Introduction

Iodine deficiency, still prevalent in many areas of the world, is—particularly in genetically predisposed individuals [1]—a major etiological factor for the development of nodular thyroid diseases. Despite iodine fortification programs in many countries, nodular goiter remains a diagnostic and therapeutic challenge for years to come [2, 3]. The clinical evaluation of goiter is imprecise and inaccurate [4], even by experienced clinicians. Only thyroid nodules bigger than 10 mm can be identified reliably by palpation [5], and since 70% of nodules are smaller than 10 mm in diameter [2, 5], it follows that application of ultrasound is necessary to achieve a reliable examination of the thyroid gland. A core issue, when facing a patient with nodular goiter, is to rule out thyroid malignancy—primarily based on fine needle biopsy of large or suspicious nodules guided by ultrasound [6, 7]. In fact, we consider thyroid ultrasound to be mandatory in the evaluation of goiter. In elderly people, the goiter often descends into the mediastinum, necessitating thyroid imaging by use of computed tomography or magnetic resonance imaging (MRI) [8]. In addition to an exact determination of the goiter volume, these methods can also more precisely assess whether the goiter causes compression or deviation of the trachea [9].

Obviously, determination of the thyroid function, primarily by serum TSH, is part of the initial investigations

[2]. Many patients with multinodular goiter have a low-normal or suppressed serum TSH, reflecting some degree of nodular autonomy. There is no reason to make any firm distinction between the toxic and the nontoxic multinodular goiter, since the two conditions should be regarded as the same disease but at different evolutionary stages. The choice of treatment may, however, to some extent be influenced by the functional state of the thyroid.

This review will discuss therapeutic options for patients with benign nodular goiter, with particular focus on ^{131}I-therapy and recombinant human TSH (rhTSH)-stimulated ^{131}I-therapy, the latter being a relatively novel principle, which amplifies the effect of ^{131}I-therapy.

Therapeutic options for goiter

Due to the normally slow growth of a goiter many patients have no or only few symptoms [10, 11] and furthermore, there is a poor correlation between goiter size and symptoms [12]. As a consequence, the decision to treat must be based on the preference of the patient and a range of other factors, listed in Table 1. An individualized approach is further supported by the fact that there is no consensus among experts on the treatment of either the solitary thyroid nodule [13–15] or the multinodular nontoxic goiter [16–19]. There are several options in case treatment of goiter is indicated. Unfortunately, elimination of the nodule(s) and normalization of the thyroid size, with preservation of an intact thyroid gland, is not possible. Thyroid surgery, used for many years, has the clear advantage of complete and rapid removal of the goiter. In addition, it allows a thorough histological examination of the thyroid gland. There are certain situations (listed in Table 2) that favor operation, unless there are strong contraindications to thyroid surgery. As for the toxic or nontoxic benign solitary thyroid nodules, ethanol sclerotherapy or interstitial laser photocoagulation may be an option in selected cases. Neither these two focal treatments nor thyroid surgery will be further discussed in the present review, but literature covering these treatments can be found elsewhere [7, 20, 21]. In addition, diagnostic and therapeutic aspects of nodular goiter are discussed thoroughly in recent guidelines [22].

Table 1 The decision to treat a patient with goiter must be based on a range of factors, as listed below

Large goiter or progressive growth (independent of presence of symptoms)
Marked neck disfigurement
Cosmetic complaints
Local cervical symptoms
Impact on the upper airways (clinically or detected by lung function testing or imaging)
Overt or subclinical hyperthyroidism due to nodular autonomy
Cancrophobia (favors surgery)
Preference of the patient

Table 2 In patients with nodular goiter some situations, listed below, favor treatment by either thyroid surgery or ^{131}I-therapy

Surgery
Suspicion of thyroid malignancy
Symptomatic scintigraphically 'cold' solitary/dominant nodule
Very large goiter and/or disfiguration of the head/neck
Severe tracheal compression causing compromised respiration
Need of rapid relief of goiter symptoms
Goiter in pregnancy (treatment can usually be postponed to after delivery)
Inadequate previous ^{131}I-therapy
^{131}I-therapy
Small or moderate goiter volume
Previous thyroidectomy
Co-existing hyperthyroidism due to nodular autonomy
Advanced physiological age and/or co-morbidity associated with an increased surgical risk

The recommendations are supported by recent European and American guidelines [22]. Patients with large goiter or a low thyroid ^{131}I-uptake may in particular benefit from rhTSH-stimulated ^{131}I-therapy, as compared with conventional ^{131}I-therapy

Levothyroxine (LT4) suppressive treatment, and to some extent iodine supplementation, or both treatments combined, are still used by some clinicians for treatment of nodular goiter [13–19]. The aim of LT4 treatment is to partly suppress the serum TSH level with the intention to inhibit thyroid growth. In patients with multinodular goiter, LT4 and ^{131}I-therapy were compared in a randomized trial, which showed no significant effect of LT4 on goiter shrinkage during a 2-year follow-up [23]. The effect of LT4 suppressive therapy on the solitary thyroid nodule volume has been evaluated in several studies [24, 25], mostly showing a limited efficacy and only in a fraction of patients. In a recent large, double-blind, randomized trial [26] in patients with either one or more thyroid nodules, a combination of iodine and LT4, aiming at a serum TSH in the range of 0.2–0.8 mU/l, reduced the thyroid nodule volume by 17.3% after 1 year, which was more than either component alone or placebo. The thyroid volume reduction was merely 7.9%, and was even less if the treatment included either LT4 or iodine alone [26]. Besides the very modest effect (if any) of iodine supplementation, a major hindrance for the use of this treatment is the induction of thyrotoxicosis commonly seen by a sudden increase of iodine intake [27, 28].

If LT4 suppressive therapy is instituted this probably needs to be life-long to avoid goiter growth [29]. The consequence is iatrogenic subclinical hyperthyroidism

affecting adversely the skeleton and the cardiovascular system [30]. Progression of nodular autonomy is a further hindrance for this treatment [31], and many goiter patients are already at diagnosis ineligible for LT4 therapy due to pre-existing autonomously functioning nodules [32]. Due to these obstacles and the poor efficacy, we do not include LT4 suppressive therapy and iodine supplementation in the treatment armamentarium for patients with nodular goiter. Importantly, the major thyroid associations advocate against the routine use of LT4 for this indication [6, 22]. This leaves ^{131}I-therapy as the only alternative to surgery if goiter treatment is warranted.

^{131}I-therapy is the treatment of choice in most patients with *toxic* nodular goiter, whether uninodular or multinodular [33]. Since the hyperthyroidism due to nodular autonomy usually is moderate and oligo-symptomatic, most patients can be given ^{131}I-therapy without being pre-treated with anti-thyroid drugs, particularly if cardiovascular co-morbidity is absent. Anti-thyroid drugs may potentially attenuate the efficacy of ^{131}I-therapy. This concerns both the cure rate for hyperthyroidism [34] and the goiter volume reduction [35]. In elderly individuals with modest thyroid hyperfunction and no goiter symptoms, life-long anti-thyroid drug treatment may be considered instead of ^{131}I-therapy. However, it is important to emphasize that goiter growth probably continues, or is even aggravated during anti-thyroid drug treatment.

^{131}I-therapy

Besides being able to cure the hyperthyroidism, it has long been recognized that ^{131}I also leads to shrinkage of the thyroid gland. During the latest 25 years, ^{131}I-therapy for symptomatic nontoxic goiter has therefore been used in a number of centers as a non-surgical option [2, 16]. In fact, ^{131}I-therapy has replaced surgery as the treatment of choice in most patients in some European countries. This shift toward ^{131}I-therapy probably has several reasons, although both treatments are effective for goiter reduction. ^{131}I-therapy is an out-patient treatment in most countries, and it is probably superior to surgery as regards cost-effectiveness [36]. Many clinicians and patients argue against the use of ^{131}I-therapy in patients with multinodular goiter due to the risk of permanent hypothyroidism. However, this is also the consequence of surgery in such patients, since total thyroidectomy is necessary, as well as recommended, in order to hinder recurrence [37]. No trial has yet compared ^{131}I-therapy and surgery head-to-head and the optimum treatment remains to be established by future randomized studies, including data on effect, side-effects, cost, and quality of life [38].

The final choice among observation, surgery, and ^{131}I-therapy should be based on a dialog with the patient. In our experience most eligible patients prefer non-surgical treatment if offered. There are evidently some situations, listed in Table 2, that favor the choice of ^{131}I-therapy. Since re-operation is associated with increased risk of complications [39], patients with previous thyroidectomy are obvious candidates for ^{131}I-therapy in case of goiter recurrence. ^{131}I-therapy should also be preferred if a small or moderate sized goiter and few cervical symptoms coexists with hyperthyroidism due to thyroid autonomy. Finally, surgery is relatively contraindicated in goiter patients with advanced physiological age and/or severe co-morbidity.

A range of studies [23, 40–44], most of them lacking a control group, have demonstrated the efficacy of ^{131}I-therapy in patients with multinodular nontoxic goiter. On average, ^{131}I-therapy reduces the goiter volume by ~40% after 1 year and 50–60% after 2 years, without further significant reduction. Also substernal goiters have been treated with beneficial results [45]. The effect of ^{131}I-therapy on the goiter volume is to some extent related to the absorbed thyroid dose [42, 46]. Generally, ^{131}I doses of 3.7 MBq per gram of thyroid tissue corrected for the thyroid ^{131}I uptake (RAIU), have been given [23, 40–43]. Although the response to ^{131}I varies considerably and is difficult to predict, symptoms most often improve and patient satisfaction is high [12, 41, 42, 47]. The treatment can be repeated if further goiter reduction is required [43]. While long-term risk of goiter recurrence following ^{131}I-therapy remains to be evaluated, secondary goiter growth following ^{131}I-therapy should always raise suspicion of malignancy and lead to re-evaluation.

^{131}I-therapy amplification by rhTSH stimulation

Undoubtedly effective in many patients with multinodular goiter, there are some limitations with conventional (without rhTSH stimulation) ^{131}I-therapy. This treatment is unlikely to succeed if the thyroid RAIU is low (less than 15% at 24 hour), and/or the dominant nodule(s)—which causes the compressive symptoms—is scintigraphically 'cold'. Furthermore, the relative goiter reduction is inversely correlated with the initial goiter size [40, 42], probably because large goiters harbor a higher amount of degenerated and fibrous tissue which has lost the ability to take up ^{131}I. Thus, the reduction is less, around 35%, in goiters above 100 ml, despite the application of equivalent thyroid ^{131}I doses [40].

Declining efficacy with increasing goiter size is one of the major challenges in conventional ^{131}I-therapy [40]. This problem could be overcome by increasing the administered ^{131}I activity and thereby the absorbed thyroid dose, but the concomitant increase in the whole-body radiation burden is a clear disadvantage [48]. The limitations inherent with conventional ^{131}I-therapy can to some

extent be overcome by rhTSH stimulation prior to the ^{131}I administration. RhTSH is a very potent stimulator of the thyroid RAIU, as demonstrated more than 10 years ago [49, 50]. Thus, rhTSH increases the thyroid 24-h RAIU by 100% or even more [50–54], without compromising the ^{131}I half-life to any greater extent. Furthermore, it causes a more homogeneous distribution of ^{131}I within the goiter [53, 55]. With rhTSH doses between 0.03 and 0.1 mg, the dose–response curve, in terms of enhancing the thyroid RAIU, is relatively flat [53]. With lower doses the effect seems to decline but data are conflicting [50]. Importantly, the increase in the thyroid RAIU is inversely correlated to the initial RAIU [50–52, 56], as shown in Fig. 1, and this implies that rhTSH stimulation is most beneficial in patients with multinodular nontoxic goiter, in whom conventional ^{131}I-therapy would not be an option due to a low thyroid RAIU. Considering these beneficial properties of rhTSH, ^{131}I-therapy augmented by rhTSH seems very attractive, at least when compared with conventional ^{131}I-therapy. However, it is important to emphasize that the use of rhTSH is restricted to thyroid cancer patients, and that offering this drug to patients with benign thyroid diseases is at present off-label. Also, the long-term effect of rhTSH-stimulated ^{131}I-therapy, as compared to conventional ^{131}I-therapy, is largely unknown and needs further evaluation.

The concept of rhTSH-stimulated ^{131}I-therapy of multinodular nontoxic goiter has been thoroughly evaluated in clinical trials during the last decade [46, 47, 52, 57–68], listed in Table 3, and the topic has been discussed in previous reviews [54, 69–73]. Four trials were double-blinded and compared pre-stimulation with either rhTSH or placebo [46, 47, 66, 67]. Most studies explored whether an rhTSH-mediated increase of the absorbed thyroid dose can improve the goiter reduction. In contrast, a few studies [57, 67, 68] used rhTSH stimulation to reduce the amount of radioactivity according to the increase in the thyroid RAIU, while preserving a goiter reduction of the same magnitude as with conventional ^{131}I-therapy. These two different approaches can be characterized as a 'superiority strategy' and an 'equality strategy', respectively.

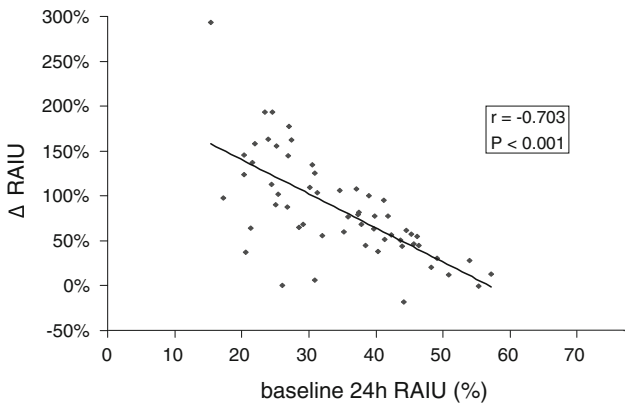

Fig. 1 The thyroid ^{131}I uptake (RAIU) in patients with multinodular nontoxic goiter following 0.1 mg rhTSH. The increase is inversely correlated to the baseline RAIU, and patients with a high baseline value benefit very little from rhTSH stimulation. From Ref. [56], with permission

With a 'superiority strategy' the goiter reduction is on average enhanced by 35–56% 1 year after ^{131}I-therapy [46, 47]. Interestingly, the gain is most pronounced in large goiters, and the negative correlation between initial goiter size and goiter reduction, seen with conventional ^{131}I-therapy, is much attenuated when rhTSH is used [46, 47]. Although rhTSH amplifies the goiter reduction considerably, randomized trials [46, 47] have failed to demonstrate a positive impact on patient satisfaction and quality of life (assessed by a visual analog scale), when compared with conventional ^{131}I-therapy. Although subjective benefit has been difficult to demonstrate, there are some clear advantages by rhTSH-stimulated ^{131}I-therapy, in addition to the improved goiter reduction. Thus, we have shown in a randomized trial [74] that rhTSH-stimulated ^{131}I-therapy is more effective in relieving upper airway obstruction. A 31% increase in the smallest cross-sectional area of the trachea and a 25% increase in the inspiratory flow were observed 1 year after rhTSH-stimulated ^{131}I-therapy, whereas no significant change was found in either parameter in the control group, which was given conventional ^{131}I-therapy [74].

Many multinodular goiters harbour autonomously functioning nodules. In such patients, the thyroid RAIU is heterogeneous and typically confined to a few hot spots, while the non-autonomous part of the thyroid has a low RAIU [75]. rhTSH stimulation reverses this, since the increase in the RAIU in relatively cold areas has been observed to be significantly higher [55]. Accordingly, patients with subclinical hyperthyroidism seem to obtain a more pronounced increase in the RAIU than goiter patients without nodular autonomy [56]. Theoretically, the goiter reduction following rhTSH-stimulated ^{131}I-therapy should therefore be most effective in patients with subclinical hyperthyroidism, reflected by a low-serum TSH at baseline. At present, this possibility remains speculative and needs to be confirmed in future trials.

The goal of ^{131}I-therapy should be pursued with the lowest possible radiation burden to the patient as well as to the environment. As long as the long-term risk of thyroidal and particularly extra-thyroidal malignancy is not clarified, an 'equality strategy', by which the radiation burden is reduced, may be more attractive. In an uncontrolled study, Nieuwlaat et al. [55] were the first to demonstrate that the administered ^{131}I activity could be reduced by a factor corresponding to the increase in RAIU without compromising the goiter reduction. Pre-treatment with 0.01 and 0.03 mg rhTSH allowed a 50% reduction of administered

Table 3 Studies on the effect of rhTSH-stimulated ^{131}I-therapy in patients with benign multinodular goiter

Author (year)	*n*	Dose of rhTSH (mg)	^{131}I activity or intended dose	Goiter reduction
Nieuwlaat [57]§	12	0.01	100 Gy	35% at 1 year
	10	0.03		41% at 1 year
Duick [58]	6	0.3	Fixed 1110 MBq	30–40% at 7 months
	10	0.9		30–40% at 7 months
Silva [59]**	17	0.45	Fixed arbitrary levels	58 and 73% at 1 and 4 years
	17	Placebo		40 and 57% at 1 and 4 years
Albino [52]	18	2 × 0.1	Fixed 1110 MBq	39% at 6 months
Cohen [60]	17	0.03	Fixed 1110 MBq	34% at 6 months
Giusti [61]	12	2 × 0.2	Fixed	44% at 20 months
	8	Controls	370–555 MBq	25% at 22 months
Nielsen [47]*	28	0.3	Above 100 Gy	62% at 1 year
	29	Placebo	100 Gy	46% at 1 year
Bonnema [46]*	14	0.3	Above 100 Gy	53% at 1 year
	15	Placebo	100 Gy	34% at 1 year
Paz-Filho [62]	17	0.1	Fixed 1110 MBq	46 and 53% at 1 and 2 years
Cubas [63]	9	0.1	Fixed 1110 MBq	33 and 37% at 1 and 2 year
	9	0.005		33 and 39% at 1 and 2 year
	10	Placebo		13 and 15% at 1 and 2 year
Romão [64]	42	0.1	Fixed 1110 MBq	From 153 mL to 32 mL at 3 years
Giusti [65]	19	2 × 0.1	Restricted to 600 MBq	60% at 3 years
	21	Controls		44% at 3 years
Albino [66]*	8	0.1	Fixed 1110 MBq	37% at 1 year
	6	0.01		37% at 1 year
	8	Placebo		19% at 1 year
Fast [67]§*	60	0.1	50 Gy	35% at 1 year
	30	Placebo	100 Gy	35% at 1 year
Ceccarelli [68]§	11	0.03	100 Gy	47% at 1 year
	7	Controls		35% at 1 year

The three studies marked with '§' follow the 'equality approach', by which the amount of radioactivity is reduced according to the rhTSH-induced increase in the thyroid ^{131}I uptake. In other studies, the amount of radioactivity is unchanged resulting in a greater goiter irradiation according to the increase in the thyroid ^{131}I uptake ('superiority approach'). * Randomized double-blind trials. ** Randomized (not blinded) controlled trial. Other studies were non-randomized, with or without a control group

^{131}I activity, while still achieving a goiter reduction of ~40% after 1 year [55]. The same authors also showed that pre-stimulation with rhTSH resulted in a two to threefold lower absorbed dose in the bladder and the stomach compared to conventional ^{131}I-therapy [76]. Recently, we published the results of a large randomized, double-blinded, placebo-controlled trial, demonstrating that the therapeutic ^{131}I activity can be reduced beyond what is accounted for by increased thyroid RAIU [67]. The combination of 0.1 mg rhTSH and a target thyroid dose of 50 Gy resulted in a goiter reduction (35% at 1 year), identical to that of placebo-stimulated ^{131}I-therapy aiming at an absorbed dose of 100 Gy. Cervical compression symptoms, as determined by a VAS-score, were equally reduced in both groups. The combination of a lower target thyroid dose (50 Gy) and rhTSH stimulation allowed an up to 80% reduction of the required ^{131}I activity compared to ^{131}I alone (aiming at 100 Gy) [67]. As a direct consequence, the need for hospitalization and post-therapeutic restrictions was profoundly reduced. That study supports the view that the goiter reduction following ^{131}I-therapy is less dependent on the absorbed thyroid dose when rhTSH is used for pre-stimulation. This raises the possibility that rhTSH preconditions the nodular goiter beyond increasing the thyroid RAIU, thereby allowing reduction of the absorbed thyroid dose without compromising the effect on goiter reduction. The mechanisms behind this intriguing feature of rhTSH may be a qualitative improvement in the thyroid

RAIU [55], and/or an increased radiosensitivity of the thyrocyte. Results from our trials employing the 'superiority strategy' [46, 47], delivering higher absorbed thyroid doses, make it apparent that the absorbed thyroid dose is a major determinant of goiter reduction, also when rhTSH is used. These results imply that the preconditioning effect of rhTSH might result in a parallel shift of the dose–response curve.

Adverse effects of ^{131}I-therapy, with and without rhTSH stimulation

As regards adverse effects, experience has accumulated during 25 years use of ^{131}I-therapy for nontoxic goiter. In accordance with its use in hyperthyroid diseases, ^{131}I-therapy of nontoxic goiter also carries a risk of permanent hypothyroidism, which occurs in 11–58% of patients within 1–8 years of therapy [42, 43, 47]. The development of hypothyroidism is positively correlated with decreasing goiter size and presence of anti-TPO antibodies [77]. In the early phase after ^{131}I-therapy, a slight and temporary release of thyroid hormones into the circulation may occur, and an acute thyroid swelling may also be seen [40, 78]. Since tracheal compression and airway obstruction may be present in patients with a large goiter, despite absence of symptoms [10, 11, 79], ^{131}I-therapy may potentially cause respiratory distress. Nevertheless, this treatment is generally well tolerated with few clinically relevant adverse effects. Radiation thyroiditis is rarely seen [77], and is easily treated with short-term mild analgesics or glucocorticoids. A Graves'-like autoimmune hyperthyroidism (1–5% of patients), associated with the appearance of TSH receptor antibodies is occasionally seen, typically 3–6 months after ^{131}I-therapy [77, 80]. The hyperthyroidism can be controlled by anti-thyroid drugs until the condition resolves spontaneously, which usually happens within 12 months. There are yet no data on the risk of ^{131}I-induced malignancy, in the thyroid or in other organs, when this treatment is used for nontoxic goiter. However, studies in hyperthyroid patients have shown that the risk is negligible [81–86].

When ^{131}I-therapy is preceded by rhTSH stimulation the risk of thyroid hyperfunction and acute thyroid swelling is, at least in theory, increased. The dose of rhTSH used for augmenting ^{131}I-therapy of multinodular nontoxic goiter is much lower than that used for thyroid cancer patients (which is 0.9 mg given twice). Usually, a single injection is given 24–48 h before ^{131}I administration, but repetitive injections of rhTSH have been evaluated in a few uncontrolled trials [52, 61]. In some of the early studies in multinodular nontoxic goiter, the dose of rhTSH was 0.3–0.45 mg and symptoms of hyperthyroidism and cervical compression were frequently observed following the ^{131}I-therapy [59]. In subsequent studies, it has become apparent that lower doses of rhTSH can be used with fewer side-effects [54], while still achieving a significant rise in the thyroid RAIU and thereby an increased absorbed thyroid radiation dose. In both healthy individuals [49, 87] and subjects with multinodular nontoxic goiter [53, 88], rhTSH injection results in an increase in the thyroid hormone levels. This peaks around 24–48 h after injection, followed by normalization within 3 weeks. The response is positively correlated with the rhTSH dose, but with 0.1 mg or less the impact on the thyroid hormone levels is insignificant [87], as shown in Fig. 2. Interestingly, subjects with subclinical hyperthyroidism at baseline experience a higher increase in thyroid hormones during rhTSH-stimulated ^{131}I-therapy [67], as compared with euthyroid goiter patients. This observation is in line with another study [64], showing that side-effects related to thyroid hyperfunction are more common in subjects with nodular autonomy at baseline, when stimulating with rhTSH. It follows that rhTSH-stimulated ^{131}I-therapy is not feasible in goiter patients with overt hyperthyroidism.

Recombinant human TSH per se has the potential to cause temporary thyroid swelling by 30–45%, peaking around 72 h after injection [87, 88]. In line with the impact on thyroid function, thyroid swelling is less likely to occur with rhTSH doses at or below 0.1 mg [87]. However, the combined effect of rhTSH and ^{131}I on thyroid volume may act in a synergistic way and lead to a temporary but critical tracheal compression, and such a complication has indeed been reported [46]. A few studies have investigated the acute effect of rhTSH-stimulated ^{131}I-therapy on the goiter volume utilizing MRI. An uncontrolled study [57] reported a 5% increase in thyroid volume, 1 week after 0.03 mg rhTSH and ^{131}I-therapy, while our randomized double-blinded placebo-controlled trial [74], using 0.3 mg rhTSH, found the average thyroid volume unchanged in both

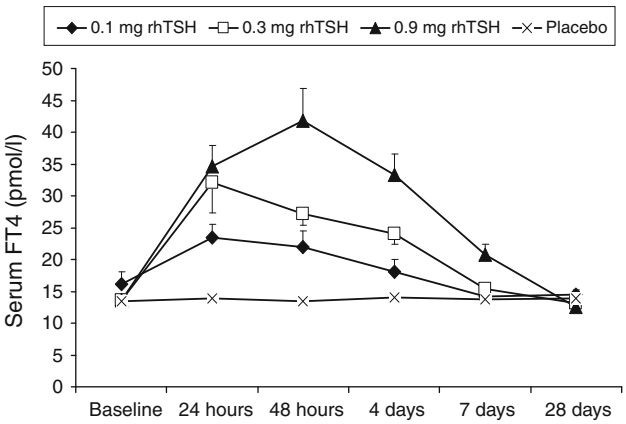

Fig. 2 Serum thyroxine in healthy subjects after one injection of rhTSH (0.1, 0.3, or 0.9 mg). The thyroid hormone secretion was very modest following 0.1 mg rhTSH and caused no symptoms. From Ref. [87], with permission

groups at 1 week. In the latter study, pulmonary function tests and MRI, 1 week after ^{131}I-therapy, detected no major change in the respiratory function or the tracheal dimension in either the placebo group or the rhTSH group [74]. These results were confirmed in another placebo-controlled study [66], demonstrating that the goiter volume and the tracheal dimensions were unaltered on days 2 and 7 after ^{131}I-therapy. A recent large phase II trial [89], evaluating the safety of 'modified release' (MR)rhTSH-stimulated ^{131}I-therapy, also provides some reassurance. On average, the thyroid volume was not altered to any greater extent 96 h after ^{131}I-therapy preceded by 0.01 or 0.03 mg of MRrhTSH. Neither did thyroid hormone alterations differ significantly from the control group, offered conventional ^{131}I-therapy [89].

Thus, using rhTSH doses at or below 0.1 mg (which still has significant impact on the thyroid RAIU) in combination with ^{131}I-therapy does not lead to clinically significant acute side-effects. This applies to the goiter volume and respiratory function, as well as to the thyroid hormone serum levels. However, variation in the inter-individual sensitivity to rhTSH, as well as the ^{131}I-therapy, is likely. Particular attention should be given patients with tracheal compression due to a very large goiter. In such cases, although not based on randomized studies, we recommend considering prophylactic glucocorticoids in order to avoid thyroid swelling and potential worsening of the tracheal compression [2, 40].

While serious acute side-effects seem of little concern when using low rhTSH doses, the more pronounced goiter reduction, seen with rhTSH-stimulated ^{131}I-therapy, is unfortunately achieved at the expense of an up to fivefold increase in the rate of permanent hypothyroidism [47, 59]. It is unclear whether this is solely caused by the increased absorbed thyroid dose or if the use of rhTSH has an independent role in the development of hypothyroidism. In our 'equality study', 0.1 mg rhTSH (and applying a thyroid dose of 50 Gy) was not associated with an increased prevalence of hypothyroidism compared to conventional ^{131}I alone (applying a thyroid dose of 100 Gy) [67]. Thus, it seems that the risk of hypothyroidism is related to the goiter reduction, which was similar in the two groups, and not to the use of rhTSH per se.

Conclusions regarding rhTSH-stimulated ^{131}I-therapy

Some conclusions can be drawn regarding the benefit and future use of rhTSH-stimulated ^{131}I-therapy of benign nontoxic goiter. Most importantly, rhTSH increases the number of individuals eligible for ^{131}I-therapy, since subjects with a low thyroid RAIU may also be treated. Applying the 'superiority strategy' the goiter reduction can be enhanced by more than 50% 1 year after therapy [46]. This gain is most pronounced in large goiters, where it is most needed. Consequently, rhTSH-stimulated ^{131}I-therapy more effectively relieves tracheal compression [74], often seen in these patients. However, a positive impact on patient satisfaction and quality of life by the 'superiority strategy' remains to be demonstrated. In view of the higher rate of hypothyroidism [47], the question of whether a 'superiority strategy' is worth while needs to be addressed. Long-term follow-up data indicate that the difference in obtained goiter reduction is maintained [90], but large and well-controlled studies are needed in order to clarify whether rhTSH-stimulated ^{131}I-therapy confers any long-term benefit, compared with conventional ^{131}I-therapy. Based on the present knowledge, patients with a nontoxic nodular goiter who are most obvious candidates for rhTSH-stimulated ^{131}I-therapy are those with a low thyroid RAIU (<15% at 24 h) and/or those with a moderate to large goiter. Until more data on safety issues are available, patients with a very large goiter should still be encouraged to surgery, particularly if the upper airways are critically compromised.

Some patients are reluctant to receive ^{131}I-therapy because of fear of developing radiation-induced cancer, a concern also shared by some clinicians, although not supported by the current literature. Employing the 'equality strategy', rhTSH allows up to 80% reduction of the therapeutic ^{131}I activity without compromising goiter reduction compared to that obtained with conventional ^{131}I-therapy [67]. An important clinical implication of this strategy is that the substantial reduction of the necessary ^{131}I activity reduces the need for hospitalization in many countries. In addition, patient restrictions are less rigorous with lower ^{131}I activities. These results imply that the 'equality strategy' may prove cost-effective compared with the 'superiority strategy' as well as to conventional ^{131}I-therapy. This and other relevant issues should be addressed in future studies.

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References

1. T.H. Brix, K.O. Kyvik, L. Hegedüs, Major role of genes in the etiology of simple goiter in females: a population-based twin study. J. Clin. Endocrinol. Metab. **84**, 3071–3075 (1999)
2. L. Hegedüs, S.J. Bonnema, F.N. Bennedbæk, Management of simple nodular goiter: current status and future perspectives. Endocr. Rev. **24**, 102–132 (2003)
3. P. Vejbjerg, N. Knudsen, H. Perrild et al., Effect of a mandatory iodization program on thyroid gland volume based on individuals' age, gender, and preceding severity of dietary iodine deficiency: a prospective, population-based study. J. Clin. Endocrinol. Metab. **92**, 1397–1401 (2007)
4. A.E. Jarløv, L. Hegedüs, T. Gjørup, J.E. Hansen, Accuracy of the clinical assessment of thyroid size. Dan. Med. Bull. **38**, 87–89 (1991)
5. G.H. Tan, H. Gharib, C.C. Reading, Solitary thyroid nodule. Comparison between palpation and ultrasonography. Arch. Intern. Med. **155**, 2418–2423 (1995)
6. R. Paschke, L. Hegedus, E. Alexander, R. Valcavi, E. Papini, H. Gharib, Thyroid nodule guidelines: agreement, disagreement and need for future research. Nat. Rev. Endocrinol. **7**, 354–361 (2011)
7. L. Hegedüs, Clinical practice. The thyroid nodule. N. Engl. J. Med. **351**, 1764–1771 (2004)
8. L. Hegedus, S.J. Bonnema, Approach to management of the patient with primary or secondary intrathoracic goiter. J. Clin. Endocrinol. Metab. **95**, 5155–5162 (2010)
9. S.J. Bonnema, P.B. Andersen, D.U. Knudsen, L. Hegedüs, MR imaging of large multinodular goiters: observer agreement on volume versus observer disagreement on dimensions of the involved trachea. AJR Am. J. Roentgenol. **179**, 259–266 (2002)
10. N.J. Gittoes, M.R. Miller, J. Daykin, M.C. Sheppard, J.A. Franklyn, Upper airways obstruction in 153 consecutive patients presenting with thyroid enlargement. Br. Med. J. **312**, 484 (1996)
11. P.V. Pradeep, P. Tiwari, A. Mishra et al., Pulmonary function profile in patients with benign goiters without symptoms of respiratory compromise and the early effect of thyroidectomy. J. Postgrad. Med. **54**, 98–101 (2008)
12. S.J. Bonnema, V.E. Nielsen, L. Hegedüs, Long-term effects of radioiodine on thyroid function, size and patient satisfaction in non-toxic diffuse goitre. Eur. J. Endocrinol. **150**, 439–445 (2004)
13. F.N. Bennedbæk, H. Perrild, L. Hegedüs, Diagnosis and treatment of the solitary thyroid nodule. Results of a European survey. Clin. Endocrinol. (Oxf). **50**, 357–363 (1999)
14. F.N. Bennedbæk, L. Hegedüs, Management of the solitary thyroid nodule: results of a North American survey. J. Clin. Endocrinol. Metab. **85**, 2493–2498 (2000)
15. J.P. Walsh, S.A. Ryan, D. Lisewski et al., Differences between endocrinologists and endocrine surgeons in management of the solitary thyroid nodule. Clin. Endocrinol. (Oxf). **66**, 844–853 (2007)
16. S.J. Bonnema, F.N. Bennedbæk, W.M. Wiersinga, L. Hegedüs, Management of the nontoxic multinodular goitre: a European questionnaire study. Clin. Endocrinol. (Oxf). **53**, 5–12 (2000)
17. S.J. Bonnema, F.N. Bennedbaek, P.W. Ladenson, L. Hegedus, Management of the nontoxic multinodular goiter: a North American survey. J. Clin. Endocrinol. Metab. **87**, 112–117 (2002)
18. M.C. Bhagat, S.S. Dhaliwal, S.J. Bonnema, L. Hegedüs, J.P. Walsh, Differences between endocrine surgeons and endocrinologists in the management of non-toxic multinodular goitre. Br. J. Surg. **90**, 1103–1112 (2003)
19. L.A. Diehl, V. Garcia, S.J. Bonnema, L. Hegedüs, C.C. Albino, H. Graf, Management of the nontoxic multinodular goiter in Latin America: comparison with North America and Europe, an electronic survey. J. Clin. Endocrinol. Metab. **90**, 117–123 (2005)
20. F.N. Bennedbæk, S. Karstrup, L. Hegedüs, Percutaneous ethanol injection therapy in the treatment of thyroid and parathyroid diseases. Eur. J. Endocrinol. **136**, 240–250 (1997)
21. H. Dossing, F.N. Bennedbaek, L. Hegedus, Long-term outcome following interstitial laser photocoagulation of benign cold thyroid nodules. Eur. J. Endocrinol. **165**, 123–128 (2011)
22. H. Gharib, E. Papini, R. Paschke et al., American association of clinical endocrinologists, Associazione Medici Endocrinologi, and european thyroid association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. J. Endocrinol. Invest. **33**, 287–291 (2010)
23. M.F. Wesche, M.M. Tiel-Van Buul, P. Lips, N.J. Smits, W.M. Wiersinga, A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goiter. J. Clin. Endocrinol. Metab. **86**, 998–1005 (2001)
24. F.N. Bennedbæk, L.K. Nielsen, L. Hegedüs, Effect of percutaneous ethanol injection therapy versus suppressive doses of L-thyroxine on benign solitary solid cold thyroid nodules: a randomized trial. J. Clin. Endocrinol. Metab. **83**, 830–835 (1998)
25. F. Zelmanovitz, S. Genro, J.L. Gross, Suppressive therapy with levothyroxine for solitary thyroid nodules: a double-blind controlled clinical study and cumulative meta-analyses. J. Clin. Endocrinol. Metab. **83**, 3881–3885 (1998)
26. Grussendorf M, Reiners C, Paschke R, Wegscheider K: Reduction of thyroid nodule volume by levothyroxine and iodine alone and in combination: a randomized, placebo-controlled trial. J Clin Endocrinol Metab doi:10.1210/jc.2011-0356 (2011)
27. J.B. Stanbury, A.E. Ermans, P. Bourdoux et al., Iodine-induced hyperthyroidism: occurrence and epidemiology. Thyroid **8**, 83–100 (1998)
28. D.P. Livadas, D.A. Koutras, A. Souvatzoglou, C. Beckers, The toxic effect of small iodine supplements in patients with autonomous thyroid nodules. Clin. Endocrinol. (Oxf). **7**, 121–127 (1977)
29. A. Berghout, W.M. Wiersinga, H.A. Drexhage, N.J. Smits, J.L. Touber, Comparison of placebo with L-thyroxine alone or with carbimazole for treatment of sporadic non-toxic goitre. Lancet **336**, 193–197 (1990)
30. M.I. Surks, E. Ortiz, G.H. Daniels et al., Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA **291**, 228–238 (2004)
31. J.J. Diez, P. Iglesias, An analysis of the natural course of subclinical hyperthyroidism. Am. J. Med. Sci. **337**, 225–232 (2009)
32. S. Fast, S.J. Bonnema, L. Hegedus, The majority of Danish nontoxic goitre patients are ineligible for Levothyroxine suppressive therapy. Clin. Endocrinol. (Oxf). **69**, 653–658 (2008)
33. R.S. Bahn, H.B. Burch, D.S. Cooper et al., Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American thyroid association and American association of clinical endocrinologists. Thyroid **21**, 593–646 (2011)
34. M.A. Walter, M. Briel, M. Christ-Crain et al., Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials. Br. Med. J. **334**, 514 (2007)
35. S.J. Bonnema, F.N. Bennedbæk, J. Gram, A. Veje, J. Marving, L. Hegedüs, Resumption of methimazole after ^{131}I therapy of hyperthyroid diseases: effect on thyroid function and volume evaluated by a randomized clinical trial. Eur. J. Endocrinol. **149**, 485–492 (2003)
36. M. Dietlein, K.W. Lauterbach, H. Schicha, Treatment of toxic nodular goitres: comparative costing of radioiodine therapy and surgery. Exp. Clin. Endocrinol. Diabetes **106**(Suppl 4), S66–S70 (1998)

37. L. Hegedüs, B. Nygaard, J.M. Hansen, Is routine thyroxine treatment to hinder postoperative recurrence of nontoxic goiter justified? J. Clin. Endocrinol. Metab. **84**, 756–760 (1999)
38. T. Watt, M. Grønvold, A.K. Rasmussen et al., Quality of life in patients with benign thyroid disorders. A review. Eur. J. Endocrinol. **154**, 501–510 (2006)
39. N.N. al Suliman, N.F. Ryttov, N. Qvist, M. Blichert-Toft, H.P. Graversen, Experience in a specialist thyroid surgery unit: a demographic study, surgical complications, and outcome. Eur. J. Surg. **163**, 13–20 (1997)
40. S.J. Bonnema, H. Bertelsen, J. Mortensen et al., The feasibility of high dose iodine ^{131} treatment as an alternative to surgery in patients with a very large goiter: effect on thyroid function and size and pulmonary function. J. Clin. Endocrinol. Metab. **84**, 3636–3641 (1999)
41. D.A. Huysmans, A.R. Hermus, F.H. Corstens, J.O. Barentsz, P.W. Kloppenborg, Large, compressive goiters treated with radioiodine. Ann. Intern. Med. **121**, 757–762 (1994)
42. R. Le Moli, M.F. Wesche, M.M. Tiel-Van Buul, W.M. Wiersinga, Determinants of longterm outcome of radioiodine therapy of sporadic non- toxic goitre. Clin. Endocrinol. (Oxf). **50**, 783–789 (1999)
43. B. Nygaard, L. Hegedüs, M. Gervil, H. Hjalgrim, P. Søe-Jensen, J.M. Hansen, Radioiodine treatment of multinodular non-toxic goitre. Br. Med. J. **307**, 828–832 (1993)
44. J. Bachmann, C. Kobe, S. Bor et al., Radioiodine therapy for thyroid volume reduction of large goitres. Nucl. Med. Commun. **30**, 466–471 (2009)
45. S.J. Bonnema, D.U. Knudsen, H. Bertelsen et al., Does radioiodine therapy have an equal effect on substernal and cervical goiter volumes? Evaluation by magnetic resonance imaging. Thyroid **12**, 313–317 (2002)
46. S.J. Bonnema, V.E. Nielsen, H. Boel-Jørgensen et al., Improvement of goiter volume reduction after 0.3 mg recombinant human thyrotropin-stimulated radioiodine therapy in patients with a very large goiter: a double-blinded, randomized trial. J. Clin. Endocrinol. Metab. **92**, 3424–3428 (2007)
47. V.E. Nielsen, S.J. Bonnema, H. Boel-Jørgensen, P. Grupe, L. Hegedüs, Stimulation with 0.3-mg recombinant human thyrotropin prior to iodine ^{131} therapy to improve the size reduction of benign nontoxic nodular goiter: a prospective randomized double-blind trial. Arch. Intern. Med. **166**, 1476–1482 (2006)
48. D.A. Huysmans, W.C. Buijs, M.T. van de Ven et al., Dosimetry and risk estimates of radioiodine therapy for large, multinodular goiters. J. Nucl. Med. **37**, 2072–2079 (1996)
49. M.S. Torres, L. Ramirez, P.H. Simkin, L.E. Braverman, C.H. Emerson, Effect of various doses of recombinant human thyrotropin on the thyroid radioactive iodine uptake and serum levels of thyroid hormones and thyroglobulin in normal subjects. J. Clin. Endocrinol. Metab. **86**, 1660–1664 (2001)
50. D.A. Huysmans, W.A. Nieuwlaat, R.J. Erdtsieck et al., Administration of a single low dose of recombinant human thyrotropin significantly enhances thyroid radioiodide uptake in nontoxic nodular goiter. J. Clin. Endocrinol. Metab. **85**, 3592–3596 (2000)
51. V.E. Nielsen, S.J. Bonnema, H. Boel-Jørgensen, A. Veje, L. Hegedüs, Recombinant human thyrotropin markedly changes the ^{131}I kinetics during ^{131}I therapy of patients with nodular goiter: an evaluation by a randomized double-blinded trial. J. Clin. Endocrinol. Metab. **90**, 79–83 (2005)
52. C.C. Albino, C.O. Mesa Jr., M. Olandoski et al., Recombinant human thyrotropin as adjuvant in the treatment of multinodular goiters with radioiodine. J. Clin. Endocrinol. Metab. **90**, 2775–2780 (2005)
53. L. Braverman, R.T. Kloos, B. Law Jr., M. Kipnes, M. Dionne, J. Magner, Evaluation of various doses of recombinant human thyrotropin in patients with multinodular goiters. Endocr. Pract. **14**, 832–839 (2008)
54. S. Fast, V.E. Nielsen, S.J. Bonnema, L. Hegedus, Time to reconsider nonsurgical therapy of benign non-toxic multinodular goitre: focus on recombinant human TSH augmented radioiodine therapy. Eur. J. Endocrinol. **160**, 517–528 (2009)
55. W.A. Nieuwlaat, A.R. Hermus, F. Sivro-Prndelj, F.H. Corstens, D.A. Huysmans, Pretreatment with recombinant human TSH changes the regional distribution of radioiodine on thyroid scintigrams of nodular goiters. J. Clin. Endocrinol. Metab. **86**, 5330–5336 (2001)
56. S. Fast, V.E. Nielsen, P. Grupe, S.J. Bonnema, L. Hegedus, Optimizing ^{131}I uptake after rhTSH stimulation in patients with nontoxic multinodular goiter: evidence from a prospective, randomized, double-blind study. J. Nucl. Med. **50**, 732–737 (2009)
57. W.A. Nieuwlaat, D.A. Huysmans, H.C. Van Den Bosch et al., Pretreatment with a single, low dose of recombinant human thyrotropin allows dose reduction of radioiodine therapy in patients with nodular goiter. J. Clin. Endocrinol. Metab. **88**, 3121–3129 (2003)
58. D.S. Duick, H.J. Baskin, Utility of recombinant human thyrotropin for augmentation of radioiodine uptake and treatment of nontoxic and toxic multinodular goiters. Endocr. Prac. **9**, 204–209 (2003)
59. M.N. Silva, I.G. Rubio, R. Romao et al., Administration of a single dose of recombinant human thyrotrophin enhances the efficacy of radioiodine treatment of large compressive multinodular goitres. Clin. Endocrinol. (Oxf). **60**, 300–308 (2004)
60. O. Cohen, J. Ilany, C. Hoffman et al., Low-dose recombinant human thyrotropin-aided radioiodine treatment of large, multinodular goiters in elderly patients. Eur. J. Endocrinol. **154**, 243–252 (2006)
61. M. Giusti, C. Cappi, B. Santaniello et al., Safety and efficacy of administering 0.2 mg of recombinant human TSH for two consecutive days as an adjuvant to therapy with low radioiodine doses in elderly out-patients with large nontoxic multinodular goiter. Minerva Endocrinol. **31**, 191–209 (2006)
62. G.J. Paz-Filho, C.O. Mesa-Junior, M. Olandoski et al., Effect of 30 mCi radioiodine on multinodular goiter previously treated with recombinant human thyroid-stimulating hormone. Braz. J. Med. Biol. Res. **40**, 1661–1670 (2007)
63. E.R. Cubas, G.J. Paz-Filho, M. Olandoski et al., Recombinant human TSH increases the efficacy of a fixed activity of radioiodine for treatment of multinodular goitre. Int. J. Clin. Pract. **63**, 583–590 (2009)
64. R. Romao, I.G. Rubio, E.K. Tomimori, R.Y. Camargo, M. Knobel, G. Medeiros-Neto, High prevalence of side effects after recombinant human thyrotropin-stimulated radioiodine treatment with 30 mCi in patients with multinodular goiter and subclinical/clinical hyperthyroidism. Thyroid **19**, 945–951 (2009)
65. Giusti M, Caputo M, Calamia I et al.: Long-term outcome of low-activity radioiodine administration proceeded by adjuvant recombinant human TSH pretreatment in elderly subjects with multinodular goiter. Thyroid Res. 2, 6 (2009)
66. C.C. Albino, H. Graf, G. Paz-Filho et al., Radioiodine plus recombinant human thyrotropin do not cause acute airway compression and are effective in reducing multinodular goiter. Braz. J. Med. Biol. Res. **43**, 303–309 (2010)
67. S. Fast, L. Hegedus, P. Grupe et al., Recombinant human thyrotropin-stimulated radioiodine therapy of nodular goiter allows major reduction of the radiation burden with retained efficacy. J. Clin. Endocrinol. Metab. **95**, 3719–3725 (2010)
68. C. Ceccarelli, L. Antonangeli, F. Brozzi et al., Radioiodine (131)I treatment for large nodular goiter: recombinant human thyrotropin allows the reduction of radioiodine (131)I activity to be

administered in patients with low uptake. Thyroid **21**, 759–764 (2011)
69. M. Dietlein, B. Dederichs, C. Kobe, P. Theissen, M. Schmidt, H. Schicha, Therapy for non-toxic multinodular goiter: radioiodine therapy as attractive alternative to surgery. Nuklearmedizin **45**, 21–34 (2006)
70. G. Medeiros-Neto, S. Marui, M. Knobel, An outline concerning the potential use of recombinant human thyrotropin for improving radioiodine therapy of multinodular goiter. Endocrine **33**, 109–117 (2008)
71. G.J. Paz-Filho, H. Graf, Recombinant human thyrotropin in the management of thyroid disorders. Expert. Opin. Biol. Ther. **8**, 1721–1732 (2008)
72. S.J. Bonnema, V.E. Nielsen, L. Hegedüs, Radioiodine therapy in non-toxic multinodular goitre. The possibility of effect-amplification with recombinant human TSH (rhTSH). Acta Oncol. **45**, 1051–1058 (2006)
73. V.E. Nielsen, S.J. Bonnema, L. Hegedüs, The effects of recombinant human thyrotropin, in normal subjects and patients with goitre. Clin. Endocrinol. (Oxf). **61**, 655–663 (2004)
74. S.J. Bonnema, V.E. Nielsen, H. Boel-Jorgensen et al., Recombinant human thyrotropin-stimulated radioiodine therapy of large nodular goiters facilitates tracheal decompression and improves inspiration. J. Clin. Endocrinol. Metab. **93**, 3981–3984 (2008)
75. S.J. Bonnema, S. Fast, V.E. Nielsen et al., Serum thyroxine and age: rather than thyroid volume and serum TSH: are determinants of the thyroid radioiodine uptake in patients with nodular goiter. J. Endocrinol. Invest. **34**, e52–e57 (2011)
76. W.A. Nieuwlaat, A.R. Hermus, H.A. Ross et al., Dosimetry of radioiodine therapy in patients with nodular goiter after pretreatment with a single, low dose of recombinant human thyroid-stimulating hormone. J. Nucl. Med. **45**, 626–633 (2004)
77. B. Nygaard, J.H. Knudsen, L. Hegedüs, A. Veje, J.E. Hansen, Thyrotropin receptor antibodies and Graves' disease, a side-effect of ^{131}I treatment in patients with nontoxic goiter. J. Clin. Endocrinol. Metab. **82**, 2926–2930 (1997)
78. B. Nygaard, J. Faber, L. Hegedüs, Acute changes in thyroid volume and function following ^{131}I therapy of multinodular goitre. Clin. Endocrinol. (Oxf). **41**, 715–718 (1994)
79. S.J. Bonnema, Upper airway obstruction due to goiter: an overlooked problem. J. Postgrad. Med. **54**, 82–83 (2008)
80. B. Nygaard, R.A. Metcalfe, J. Phipps, A.P. Weetman, L. Hegedüs, Graves' disease and thyroid associated ophthalmopathy triggered by ^{131}I treatment of non-toxic goiter. J. Endocrinol. Invest. **22**, 481–485 (1999)
81. T. Angusti, A. Codegone, R. Pellerito, A. Favero, Thyroid cancer prevalence after radioiodine treatment of hyperthyroidism. J. Nucl. Med. **41**, 1006–1009 (2000)
82. J.A. Franklyn, P. Maisonneuve, M. Sheppard, J. Betteridge, P. Boyle, Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. Lancet **353**, 2111–2115 (1999)
83. J.A. Franklyn, M.C. Sheppard, P. Maisonneuve, Thyroid function and mortality in patients treated for hyperthyroidism. JAMA **294**, 71–80 (2005)
84. P. Hall, G. Berg, G. Bjelkengren et al., Cancer mortality after iodine-131 therapy for hyperthyroidism. Int. J. Cancer **50**, 886–890 (1992)
85. S. Metso, A. Auvinen, H. Huhtala, J. Salmi, H. Oksala, P. Jaatinen, Increased cancer incidence after radioiodine treatment for hyperthyroidism. Cancer **109**, 1972–1979 (2007)
86. E. Ron, M.M. Doody, D.V. Becker et al., Cancer mortality following treatment for adult hyperthyroidism. Cooperative thyrotoxicosis therapy follow-up study group. JAMA **280**, 347–355 (1998)
87. S. Fast, V.E. Nielsen, S.J. Bonnema, L. Hegedus, Dose-dependent acute effects of recombinant human TSH (rhTSH) on thyroid size and function: comparison of 0.1, 0.3 and 0.9 mg of rhTSH. Clin. Endocrinol. (Oxf). **72**, 411–416 (2010)
88. V.E. Nielsen, S.J. Bonnema, L. Hegedüs, Transient goiter enlargement after administration of 0.3 mg of recombinant human thyrotropin in patients with benign nontoxic nodular goiter: a randomized, double-blind, crossover trial. J. Clin. Endocrinol. Metab. **91**, 1317–1322 (2006)
89. H. Graf, S. Fast, F. Pacini et al., Modified-release recombinant human TSH (MRrhTSH) augments the effect of ^{131}I therapy in benign multinodular goiter. Results from a multicenter international, randomized, placebo-controlled study. J. Clin. Endocrinol. Metab. **96**, 1368–1376 (2011)
90. M.S. Cardia, I.G. Rubio, G. Medeiros-Neto, Prolonged follow-up of multinodular goitre patients treated with radioiodine preceded or not by human recombinant TSH. Clin. Endocrinol. (Oxf).**64**, 474 (2006)