Radioiodine treatment for non-toxic goitre
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Abstract
There is no ideal treatment for benign multinodular goitre. Besides surgery, which is recommended for large goitres or when malignancy cannot be excluded, the non-surgical treatment options are levothyroxine therapy and radioiodine (\textsuperscript{131}I) therapy. Conventional \textsuperscript{131}I therapy [without recombinant human thyroid-stimulating hormone (rhTSH)] has been used for more than a decade in symptomatic non-toxic multinodular goitre, and although it does lead to significant thyroid volume reduction, relatively high activities of radioiodine are needed because of a frequent finding of a low thyroid radioiodine uptake. rhTSH, even when used in very small doses in combination with \textsuperscript{131}I therapy, enhances the thyroid volume reduction at lower \textsuperscript{131}I activities by doubling the thyroid radioiodine uptake. However, before rhTSH stimulation can be routinely used by clinicians to optimise the \textsuperscript{131}I therapy in multinodular goitre, aspects of this association, such as the cost-benefit and optimum rhTSH dose and safety, will have to be sufficiently clarified.

Introduction and context
Radioactive iodine has been used extensively for treatment of hyperthyroidism for more than 60 years. As it was noticed that the treatment not only alleviated the hyperthyroid state but also caused goitres to shrink, this therapy was introduced more than 20 years ago as a possible treatment modality in the management of non-toxic goitre [1-6]. The first reports described patients with large multinodular goitres who for other reasons were not eligible for surgery (for example, patients with cardiac or respiratory failure). In one study, it was stated that the use of radioactive iodine therapy constitutes an alternative to surgery in selected patients with large compressive goitres in whom surgery was contraindicated because of age or other medical conditions [7]. Later, treatment was given to patients with diffuse non-toxic goitre, all of whom had serious symptoms but refused surgery [8].

The general treatment modalities for non-toxic goitre are medical treatment with levothyroxine, surgery, and radioactive iodine. Thyroxine treatment for diffuse non-toxic goitre is a well-established modality in some countries, especially in iodine-deficient regions where often the disease affects more than 10% of the population. A reduction in thyroid volume of 20-30% within 3 months can be achieved but requires a thyroxine dose that can lead to suppression of serum thyrotropin, tissue thyrotoxicosis, and risk of osteoporosis [9,10]. Life-long treatment is necessary, yet most patients will develop nodular thyroid disease, for which thyroxine is much less effective.

Non-toxic multinodular goitres are more prevalent in populations with low or borderline iodine intake. The disease most often starts at a young age with a diffuse enlargement that gradually becomes more nodular with time and with increasing numbers of autonomously functioning nodules [11,12]. At the nodular stage, thyroxine therapy is inefficient in reducing thyroid volume since thyrotropin starts to be suppressed by the autonomous nodules, and therefore in most countries surgery has been the only option for therapy [12,13]. A fear of increasing the thyroid gland through radiation...
thyroiditis was allayed by a study by Nygaard and colleagues [14], which demonstrated that the inspiratory flow curve was not negatively affected after treatment and that, on the contrary, there was a beneficial effect. Another aspect has been the occurrence of thyroid autoimmunity with a Graves’ disease-like reaction after radioiodine therapy [15], in some cases accompanied by thyroid-associated ophthalmopathy [16]. It has not yet been resolved as to whether this is a de novo autoimmunity; instead, it might be existing asymptomatic Graves’ disease within a nodular goitre with a transitory deterioration of the autoimmune process due to antigen release after the destructive radiation. Finally, the possibility of a thyroid tumour harboured in a nodular goitre, though rare, must be kept in mind.

The introduction of radioiodine as a treatment modality has advanced the management of these patients on the one hand but has posed some problems on the other hand since many of the populations who were initially low in iodine have now started iodine salt addition programmes, which notoriously lower the uptake of radioiodine. The treatment success therefore is limited and requires much greater amounts of radioiodine to overcome this problem, thus creating a potential environmental problem due to surplus radioiodine excreted in the urine [17].

Recent advances
The problem of low iodine uptake has recently been overcome by introducing recombinant human thyroid-stimulating hormone (rhTSH) as a stimulator before the radioiodine therapy [18-20]. In one of the studies, it was shown that, followed by 1.11 GBq, a very low dose of 0.005 mg rhTSH was as safe and effective as 0.1 mg of rhTSH. Both doses increased the efficacy of radioiodine. Adverse events were mild, transient, and readily treatable [19]. Other studies have verified that the uptake was dramatically increased, even by low doses of rhTSH [21,22], and the regional distribution of the uptake can change substantially, thus providing the possibility for efficient shrinkage of previous large cold nodules by even a single low dose of rhTSH [23]. Subsequent studies have investigated issues such as the amount of rhTSH to be used, the timing, and the effect, even in persons with normal thyroid glands [24-26]. As in radioiodine treatment without pre-stimulation, there have been several reports of thyroid enlargements after rhTSH, and some of these enlargements have been very serious [27-29]. However, the general picture shows a safe procedure with a tendency to relieve local tracheal symptoms [30]. An alternative to this treatment has been presented as repeated doses of radioiodine rather than pre-stimulation [31]. When used together, these two modalities may prove to be beneficial in some very difficult cases.

Implications for clinical practice
Although surgeons still advocate surgery as the treatment of choice in non-toxic goitres [12,13], it seems clear to most clinicians that radioactive iodine therapy is an attractive alternative with few side effects and is easy for the patient as it does not require hospitalisation. The limitation of the therapy of having to use either very high or repeated doses of radioiodine due to many large goitres with low iodine uptake has been overcome by pre-treatment with rhTSH [18-26]. Although this treatment at present is rather expensive, it appears that much smaller doses of the drug have sufficient efficacy, and the price therefore should be adjusted by the production of appropriate ampoule sizes. To further document a more widespread use of rhTSH as a pre-treatment, additional randomised clinical trials comparing doses of rhTSH and comparing radioiodine therapy with surgery in terms of outcome measures such as efficacy of goitre control, thyroid function, health care costs, and health-related quality of life are needed [32,33]. Only then can the treatment continue based on solid evidence, which is very likely to change treatment algorithms for non-toxic goitre in the future [34].

Abbreviation
rhTSH, recombinant human thyroid-stimulating hormone.

Competing interests
The author has received unrestricted research grants from Genzyme (Cambridge, MA, USA) and has served on one of the advisory boards of the same company.

References


