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Review

Radioiodine – an attractive alternative to surgery in large non-toxic multinodular goitres

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Abstract

Sporadic non-toxic goitre (SNG) is defined as thyroid enlargement in a euthyroid patient living in an area without endemic goitre. Because thyroid hormone function is within the reference range, the main problems are the signs of thyroid enlargement, thus reducing the size of the goitre is undoubtedly the primary goal of therapy. Although SNG is a common disease, there is no single optimal management of treatment strategy. L-thyroxine treatment, although only moderately effective and with reported reductions in goitre volume of less than 30%, is still used. Moreover, in patients over 60 years of age, long-term TSH-suppression treatment may cause iatrogenic hyperthyroidism and is associated with a significant risk of paroxysmal atrial fibrillation as well as osteoporosis, especially in postmenopausal women. In patients with huge goitres, the surgical removal of a gland is made most frequently. The great advantage of thyroid surgery is its immediate effect. Unfortunately, surgery carries a risk of goitre recurrence and complications, both surgical and anaesthesia-related. For those patients who do not want to be operated on, or have contraindications for invasive treatment, and taking into consideration the low efficacy of L-thyroxine treatment, the best option is radioiodine. Despite encouraging reports of the high efficacy of radioiodine in the treatment of SNG this method is still not commonly used by many clinicians. In our work we would like to point out the efficacy, adverse effects, and contraindications of using iodine-131. Going through the advantages and disadvantages of all accessible methods of treatment of SNG, we would like to focus on using radioiodine as an attractive alternative to surgery.

Key words: sporadic non-toxic goitre, multinodular goitre, radioiodine treatment

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Goitre

A goitre, defined as the enlargement of the thyroid gland, is a common disorder, with women four times more likely to be affected than men [1]. The prevalence of goitres is estimated at 4 to 7% in regions where iodine supplementation is routinely practiced and probably more in iodine-deficient areas [2]. Goitres are said to be endemic when the prevalence in a population is more than 10%, otherwise they are termed sporadic goitres [3]. Based on hormone activity, goitres can be classified as hypothyroid, euthyroid (non-toxic), or hyperthyroid (toxic). Other classifications are based on the morphology of the thyroid. Homogenous hypertrophy of the entire gland is called a diffuse goitre, whereas focal hypertrophy with the formation of single or multiple nodules is termed a uninodular or multinodular goitre, respectively. Ultrasonography (US) shows multiple nodules in nearly 50% of persons with a solitary palpable nodule or diffuse gland enlargement [4–6]. Even in the absence of any findings on palpation, up to 50% of the general population are found to have thyroid nodules on ultrasound [7]. Similar results have been obtained in autopsy studies where the prevalence of nodules was estimated at 50%, with most cases being those in a multinodular goitre [2].

It is estimated that nodular goitres affect 5% of the general population [2]. Thyroid enlargement without hormonal abnormalities is usually considered to be due to a nodular goitre, but there are several other causes like diffuse goitre, thyroiditis, or thyroid neoplasia [8].

Sporadic non-toxic goitre

Sporadic non-toxic goitre (SNG) is defined as thyroid enlargement in a euthyroid patient living in an area without endemic goitre [9]. The usual clinical course of a non-toxic goitre is that of a gradual increase in gland size with the formation of nodules which then become autonomic and cause at first subclinical and subsequently clinically evident hyperthyroidism [7, 10]. The exact pathomechanism of the non-toxic goitre is still insufficiently understood, but complex metabolic disturbances caused by environmental or genetic factors are being considered [11].

The usual goitre growth ratio is estimated at 10–20% per year [12]. High individual variability in the clinical course makes it difficult to predict whether the goitre size remains stable and the patient can only be observed and monitored, or whether dynamic thyroid growth will require invasive treatment.

It has been demonstrated that hyperthyroidism develops in 10% of patients with SNG after, on average, 10 years from the disease onset [13]. Thus, even in the case of small goitres which do not require invasive treatment the possibility of future hyperthyroidism should be considered and regular monitoring of thyroid hormones should be performed.

Another problem in this group of patients is the risk of malignant transformation. Contrary to previous reports, the likelihood of developing thyroid malignancy is the same in patients with solitary nodules and multinodular goitres and is estimated at 5–10% [4–6, 14–16]. For this reason, every dominant nodule in a multinodular goitre should be worked up in the same way as a single thyroid nodule [8].

Symptoms

In SNG the concentration of thyroid hormones remains normal so that symptoms caused by gland enlargement predominate. The degree of gland enlargement is variable, from a slightly enlarged thyroid to a massive goitre, and determines the severity of symptoms. Patients most commonly (70%) consult their physician because of symptoms due to the compression of the trachea and other neighbouring structures, and for cosmetic reasons [17]. Patients experience shortness of breath or difficulty in swallowing (caused by the compression of the oesophagus). A huge goitre may obstruct venous return from the neck, causing distension of the veins, or compress the recurrent laryngeal nerve leading to coarseness [11].

Diagnostic work-up and management

Although SNG is widely prevalent, uniform guidelines regarding diagnostic workup and treatment are still lacking. Thus Bonnema et al. [18] created a questionnaire examining the management strategy employed by members of the European Thyroid Association. An index case report was presented: a 42-year-old woman with an irregular, bilaterally enlarged thyroid. The aim of the questionnaire was to assess the approach to the diagnosis and therapy depending on the hospital, region, or country. All of the respondents chose to determine the concentration of thyroid stimulating hormone (TSH). There was no agreement as to other laboratory tests performed. The median number of blood tests ordered was four, with one third of the respondents selecting six or more tests. The majority (90%) chose US and/or scintigraphy as the initial imaging study. US was recommended by 84%, scintigraphy by 75%, and both modalities were employed by 69% of the respondents. The greatest discrepancies concerned the management strategy. Surgery was recommended by only 10%, treatment with L-thyroxine by 50%, with radioactive iodine by 4%, and no treatment at all, despite the patient having reported "moderate discomfort", was recommended by 28% of the respondents [18].

In 2006, the American Association of Clinical Endocrinology issued guidelines for the diagnosis and management of thyroid nodules. According to these, all patients with palpable thyroid nodules should undergo an ultrasound examination. An ultrasound-guided fine needle aspiration (FNA) is indicated for nodules > 10 mm, but also for nodules < 10 mm if there are clinical or ultrasonographic features suggesting malignancy. The determination of serum TSH concentration is the best initial laboratory test for the assessment of thyroid function. In the case of low TSH values, the concentration of free thyroxine (fT4) should be checked as well. If TSH concentration is high, thyroid peroxidase antibodies (TPO) should be tested. Finally, a large, symptomatic goitre should be treated surgically or with radioiodine [19].

Therapy

Reducing the size of the goitre is undoubtedly the primary goal of therapy. Therapy should be aimed at reducing symptoms of compression, achieving a good cosmetic effect, preventing progression of gland enlargement, and controlling hormonal disturbances which might occur as a result of gland dysfunction [7]. As discussed above, there is no single optimal management strategy. Each case should be evaluated individually. When choosing therapeutic options, all available methods should be taken into consideration (observation only, thyroidectomy, L-thyroxine suppression therapy, and radioiodine therapy) along with their individual advantages, disadvantages, and potential adverse effects.

Some factors influencing the choice of therapy are:

- the patient's subjective feeling of disease, their perception of symptoms and their willingness to undergo treatment;
- the rate of goitre growth - in stable disease, observation without intervention may be considered;
- the patient's age and concomitant diseases;
- the size of the goitre and severity of compression symptoms;
- hormonal function of the gland;
- features suggesting malignancy - compelling careful diagnostic workup and surgical treatment;
- contraindications to any of the treatment methods;
- estimated risk of a given complication with each type of treatment;
- patient's consent to, and acceptance of, the proposed management strategy.

Monitoring without treatment

In the questionnaire by Bonnema et al. [18], observation only was recommended by 28% of respondents, and by as many as 90% of respondents from the UK. This choice is controversial, considering that the natural course of disease is characterized by constant growth of the gland. On the other hand, active therapy does

not seem justified in cases with stable disease, without local symptoms or hormonal abnormalities. However, the possibility of further gland enlargement, development of hyperthyroidism, or malignant transformation makes constant observation necessary. It is still unclear, though, whether patient follow-up should consist of physical examination only, or whether regular ultrasound exams are necessary and if so, in what intervals. Another question is what laboratory tests to perform and how often to repeat them [7]. Some researchers recommend yearly imaging studies combined with measurement of serum TSH [20].

Thyroidectomy

The most important advantage of thyroid surgery is its immediate effect: surgical treatment leads immediately post-operation to almost complete resolution of compressive symptoms [21, 22]. Concerns about possible malignancy are another argument in favour of this strategy [23]. Unfortunately, surgery carries a risk of complications, both surgical and anaesthesia-related [24, 25]. Of note, the risk of complications increases with increasing goitre size and the number of re-operations [26, 27]. The risk of permanent damage to the recurrent laryngeal nerve and parathyroid glands does not exceed 1% for an experienced surgeon [26–28]. The more thyroid tissue is removed, the lesser the risk of goitre recurrence but the greater the risk of surgical complications [21, 22]. The rate of recurrence depends on the extent of surgery and varies from 0% with total thyroidectomy to 60% with hemilobectomy [29]. The rate of recurrence does not depend on the postoperative administration of L-thyroxine [30–32].

Despite the indisputable advantages of surgical treatment, some patients refuse surgery or are not surgical candidates because of concomitant maladies. Nevertheless, some authors conclude that surgery is the best management strategy in generally healthy patients with large goitres that are surgically accessible [7].

L-thyroxine suppression

L-thyroxine decreases pituitary release of TSH, the hormone directly responsible for thyreocyte growth. Supplementation with L-thyroxine removes this influence, and thus leads to a decrease in goitre size or at least stabilization of goitre growth [7]. Wesche et al. [33] demonstrated a 22% reduction in thyroid volume with a positive response to treatment in 46% of patients. In the placebo-controlled randomized trial of Breghout et al. [12] the mean decrease in goitre size was only 25% in 59% of treated patients. Other authors report that treatment reduces the volume of diffuse goitre by 30% and question whether a similar effect can be achieved with multinodular goitres [12, 32, 34]. In order to achieve maximum benefit, TSH concentration should be maintained below the lower limit of the reference range, possibly for several years, until the time when discontinuation of L-thyroxine does not cause regrowth of the goitre to pre-treatment size in the course of 3 months [12, 34]. Long-term L-thyroxine treatment causing iatrogenic hyperthyroidism is associated with a significant risk of paroxysmal atrial fibrillation in patients over 60 years of age [35, 36], as well as osteoporosis, especially in postmenopausal women [36–39]. It should be noted that it is in this age group that large multinodular goitres causing compressive symptoms are most common [40]. The questionable efficacy of long-term TSH suppression and the associated adverse effects have largely diminished interest in this treatment method [7]. Some authors even maintain that in case of a symptomatic goitre, L-thyroxine, although still used, should not be recommended [36, 39, 41].

Radioiodine

Radioiodine has been used successfully for the control of hypertrophy and hyperthyroidism for more than 50 years [42]. The first reports on the treatment of non-toxic goitres with radioiodine were published in 1960, which, incidentally, does not exclude the possibility of earlier use and many previous uncontrolled studies [7].

Radioiodine acts by emission of beta rays, which interfere with cell division and function, leading to their destruction [42].

The effectiveness of radioiodine therapy depends on delivering iodine inside the thyroid, as radiation energy, coming almost entirely from beta rays, is absorbed within 2 mm of the source. Functional and "warm" areas which absorb iodine are destroyed, whereas in "cold" areas this effect is reduced. For this reason, knowing the distribution of radioiodine within the gland is important for therapy [42, 43]. The results of 6 studies regarding the efficacy of radio-iodine therapy are summarized in Table 1 [10, 33, 40, 44–46].

The candidates for radioiodine therapy were elderly patients with goitre causing compressive symptoms who did not consent to surgery or had important medical contraindications for surgery. The activity of radioiodine was calculated based on thyroid volume determined by US, scintigraphy, or MRI, as well as on the results of 24-hour iodine uptake. One of the studies used fractionated doses of radioiodine. The pre-treatment goitre size was different in different studies and varied from 41 to 311 ml. However, the differences did not affect the rate of goitre size reduction expressed as a percentage of the pre-treatment volume. Most patients experienced a significant reduction in compressive symptoms [10, 33, 40, 44–46].

Radioiodine treatment is known to reduce goitre size by 40 to 60% within 1–2 years from administration, with maximal reduction of gland volume during the first 3 months of therapy [45, 46]. The results presented above indicate 34 to 56% reduction in thyroid size. A study by Wesche et al. assessed the success of therapy as judged by the percentage of patients with a positive response to radioiodine and L-thyroxine [33]. A randomized clinical trial showed that radioiodine is much more effective in reducing the size of SNG than suppression with L-thyroxine. In the radioiodine group, 97% of patients showed response to treatment (defined as a reduction in gland size of more than 13%) with goitre size reduction of 46% compared with 43% and 22%, respectively, in the L-thyroxine group [33]. The study [33], while questioning the usefulness of L-thyroxine therapy, confirmed the high efficacy of radioiodine previously estimated to be 80–100%. The studies summarized above showed similar results, with 86–100% response rates [10, 33, 40, 44–46]. In patients with insufficient response, another dose of radioiodine can be administered. In such cases, the possibility of thyroid stunning should be considered. Thyroid stunning is defined as temporarily impaired thyroid tissue function with inhibition of iodine ^{131}I uptake by thyroid cells caused by a previous administration of radioiodine. The degree of uptake inhibition and delay depends on the dose of iodine previously absorbed by the thyroid [47]. If fractionated doses are used in therapy, maintaining an interval of one month between doses seems sufficient to prevent thyroid stunning [48].

Table 1. Summary of studies regarding the efficacy and side effects of radioiodine therapy for sporadic non-toxic goitre (SNG)

Ref.	N	Age (median)	Goitre size [ml] (median)	Response to treatment	Reduction of gland size	Duration of follow-up	Dose of I 131	Complications
[46]	7	62–82	145	100%	56%*	1 year	4 × 22 mCi	Hypothyroidism (28%) Transient hyperthyroidism (28%)
[33]	29	49 ± 14	56	97% 44%	38% 44%	1 year 2 years	4.44 MBq/ml Thyroid volume	Overt hypothyroidism (35%) Subclinical hypothyroidism (10%) Transient hyperthyroidism (14%)
[10]	10	33–55 (44)	41	100%	47% **	1 year	3.7 MBq/g Thyroid mass	Hypothyroidism: transient — without treatment (10%) permanent — requiring treatment (10%)
[40]	50	30–82 (53)	82	86%	49%	2 years	4.4 MBq/g Thyroid mass	Overt hypothyroidism (22%) Subclinical hypothyroidism (26%)
[45]	69	30–83 (57)	74	98%	34%** 55%**	1 year 2 years	3.7 MBq/g Thyroid mass	Hypothyroidism (16%) Hyperthyroidism: transient — without treatment (2.8%) permanent — requiring treatment (4.3%)
[44]	23	42–86 (67)	311	Not reported	34%***	1 year	5.55 MBq/g Thyroid mass	Hypothyroidism (22%)

*fractionated dose, 4 doses of 22 mCi each in 3-month intervals, to a total dose 88 mCi; **some patients received more than one dose; ***the study included patients with a large both toxic and non-toxic goitre; N — number of patients

Repetitive administration of radioiodine is particularly beneficial in patients with large goitres [48]. Large goitres that have been present for many years are often characterized by marked inhomogeneity. When using fractionated doses, "warm" areas are destroyed initially, allowing increased uptake by primarily "cold" areas with the next administration [46]. Fractionated dosing is also used if the calculated dose of radioiodine exceeds the maximum permitted outpatient value [10] or if there is no satisfactory response to treatment [45]. The use of fractionated dosing helps to avoid problems with calculating exact doses, which would require estimating goitre size and predicting sensitivity of thyroid cells to radiation [42]. Most importantly, comparison of fractionated-dose and single-dose radioiodine therapy (in the range between 60 and 150 mCi ^{131}I) has not thus far revealed significant differences with regard to efficacy [46].

An interesting question, from the endocrinologist's point of view, is what influences the individual differences in response to treatment. Le Moli et al. [40] list the dose of the isotope and the size of goitre as the factors directly responsible for treatment effect. In their view, reduction in thyroid size is proportional to the administered activity of ^{131}I and inversely proportional to the size of goitre. Other factors such as the age of the patient and duration of goitre as well as values directly associated with initial goitre size, although significantly influencing treatment efficacy, have been excluded from the group of independent prognostic factors. The study did not demonstrate a correlation between the final results and initial concentration of TSH. Comparison of the listed parameters between responders and non-responders has shown that treatment failure may be attributed to insufficient activity administered, or to large goitre size [40].

Similar conclusions with regard to the relationship between pre-treatment goitre size and treatment effect were reached by other authors [10, 49]. Some authors stress that treatment effect is better in diffuse goitre before it becomes nodular [10], which seems consistent with the natural course of disease.

As with any kind of therapy, radioiodine treatment is not free from adverse effects. The most common side effect of radioiodine therapy resulting from the damage to thyroid cells is hypothyroidism. Because of natural aging processes occurring in the thyroid, the risk of hypothyroidism increases over time. The incidence of hypothyroidism after radioiodine therapy varies from 22 to 58% over 5 to 8 years [40, 45, 50]. Increased risk of post-treatment hypothyroidism is found in patients with TPO antibodies, a positive family history of thyroid disorders, and smaller pre-treatment size of thyroid [10, 33, 40, 51]. Patients with large, long-standing goitres and more often subclinically hyperthyroid (lower TSH level and higher radioiodine uptake probably have a protective role) become hypothyroid significantly less often compared to patients with smaller goitres [40]. Surprisingly, no correlation has been found between radioiodine activity and the risk of hypothyroidism [40, 45]. Many researchers are of the opinion that hypothyroidism should not be considered a complication but as a less-desired effect of therapy [46], especially as it is easily managed with L-thyroxine [33].

Initially, there was great concern about the possibility of acute post-radiation oedema of the thyroid and, in consequence, increased compression of the upper airways after radioiodine administration in non-toxic and toxic goitres. Today we know that radioiodine treatment for nodular goitres does not increase the volume of the thyroid. In patients with non-toxic multinodular goitres, maximal increase in thyroid size (median) was observed on the 7th day after radioiodine administration and was estimated to be 4% of pre-treatment size. In toxic goitres, this increase was even smaller (2%). Increased compressive symptoms were not seen in any of the patients [52, 53].

Another complication of radioiodine therapy is radiation thyroiditis. Symptoms such as fever, neck pain, difficulty in swallowing, thyroid tenderness, and hyperthyroidism usually occur a few days after treatment with ^{131}I [41, 52]. The symptoms are transient and self-limiting and last no longer than a few weeks. Symptomatic treatment with anti-inflammatory medications is usually sufficient [41]. The risk of radiation thyroiditis is estimated to be 3% [52].

Another cause of hyperthyroidism occurring after radioiodine therapy (53) is induction of antibodies against the TSH receptor (TRAb) and the resulting Graves-like disease. In a small subset of patients (5%), an autoimmune process develops within 3 months after treatment, leading to de novo occurrence of, or increase in, TR antibodies, probably resulting from the release of thyroglobulin (Tg) and other antigens from damaged thyroid cells [41, 46, 52]. It seems that patients with already-present anti-TPO antibodies have an increased risk of such complications [52]. This complication is rare (5%) and usually resolves spontaneously within a few months. However, sometimes persistent symptoms with worsening ophtalmopathy are observed [41, 46, 52].

With radioiodine therapy, a certain risk of carcinogenesis should be kept in mind. In contrast to the other complications, the evaluation of this risk requires long-term analysis. Huysmans et al. [54] estimated the lifetime risk of non-thyroid malignancy after radioiodine therapy at 1.6%. For patients over the age of 65 years, the calculated risk is lower at 0.5%, comparable with the risk of death after thyroidectomy. By way of comparison, the average lifetime risk of malignancy for persons not exposed to radioiodine (all ages) is about 20% [23, 55].

An interesting solution is the use of recombinant human TSH (rhTSH) to increase thyroid iodine uptake. This increases iodine absorption by the thyroid to an average of 75% and makes for a more homogenous distribution of radioiodine in thyroid tissue [56–59]. The use of rhTSH makes it possible to reduce the given account of radioiodine without diminishing its efficacy (40% decrease in goitre size). This approach also reduces radiation exposure of non-thyroid tissue.

With unchanged activity of radioiodine, the use of rhTSH increases the absorbed dose, resulting in increased reduction in goitre size (to 30–50%). Unfortunately, more homogenous distribution of radioiodine in the thyroid causes damage to a greater number of active cells, leading to an increased rate of hypothyroidism, estimated at approximately 65% [58]. Additionally, treatment may cause neck pain and transient thyrotoxicosis. A study conducted in a group of healthy persons showed that the administration of rhTSH causes a transient increase in thyroid size by an average of 35%. Therefore, we have to take into consideration similar goitre swelling in patients during rhTSH-augmented ^{131}I therapy [57]. In patients with SNG, a mean increase in thyroid size of more than 24% was observed [60]. The results of the above studies should be kept in mind especially when discussing treatment of patients with large goitres, in whom increasing thyroid volume and tracheal compression can be dangerous.

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