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Editorial: Evaluation and Treatment of Sporadic Nontoxic Goiter—Some Answers and More Questions

Sporadic nontoxic goiter (SNG) is defined as a benign enlargement of the thyroid gland in a euthyroid subject living in an iodine-sufficient area. Such goiters can be diffuse, uninodular, or multinodular and can vary greatly in size at presentation, growth rate, and symptomatology. The causes of SNG are incompletely understood, but include autoimmune, genetic, and extrinsic factors. SNG is a common entity in clinical practice, because patients often present with a small, diffuse goiter or a solitary palpable nodule. In addition, recent studies using high resolution ultrasound report that ~50% of people with a solitary palpable nodule or a diffusely enlarged gland actually have multiple nodules (1–4). In addition, up to 50% of the general population have thyroid nodules by ultrasound, even when the gland is normal to palpation. Although SNG is common, there are a number of unresolved issues regarding its natural history, recommended evaluation, and optimal treatment that will be summarized here.

What are the natural history and risks of SNG?

It is often stated that the natural history of SNG is that of gradually increasing size, with eventual development of multiple nodules, local compressive symptoms, and/or cosmetic issues. An oft-quoted statistic for SNG is an average growth rate of 4.5% per year (5). However, this growth rate was calculated based on cross-sectional data in patients of different ages in one geographic area, and there are no long-term longitudinal studies of SNG growth in individual subjects. It is the clinical impression of endocrinologists who care for these patients that the growth rate is variable, and patients may have stable goiter size for many years. This clinical variability makes it difficult to predict whether an individual patient can be monitored safely without treatment, or should have treatment before the goiter grows any further.

Over time, there is a tendency for SNGs to form nodules, which can become autonomous and eventually cause subclinical or overt hyperthyroidism. It is stated that hyperthyroidism develops in ~10% of patients with SNG after 10 yr of follow-up, but most of those subjects had suppressed TSH levels and subclinical hyperthyroidism on presentation (6). The true rate of progression from normal thyroid function to subclinical and finally overt hyperthyroidism in SNG is unknown. It is undoubtedly variable, depending on intrinsic factors such as somatic mutations in individual nodules, as well as extrinsic factors such as iodine intake. Fortunately, with the use of sensitive TSH assays, this complication can be easily monitored, and treatment initiated at an appropriate point.

Another question is the risk of thyroid cancer in a SNG. Initial concerns that patients with multinodular glands might have increased rates of thyroid cancer have proven unfounded, and studies agree that the incidence of cancer in SNG is ~5%, regardless of whether the gland contains a single or multiple nodules (1–4). These reassuring data allow the endocrinologist to evaluate a dominant or suspicious nodule in a multinodular gland in the same fashion as a solitary nodule (with the exception of patients who have a history of external radiation to the head and neck, who have an increased risk of thyroid cancer).

How should a patient with a SNG be evaluated?

The evaluation of a patient with a SNG should begin with a TSH measurement, because many patients who are clinically euthyroid have biochemical evidence of hypo- or hyperthyroidism. The degree of thyroid dysfunction is often mild or subclinical, evidenced by an isolated TSH abnormality. Subclinical or overt hypothyroidism should be treated, to reverse or prevent symptoms as well as prevent further goiter growth. Overt hyperthyroidism should also be treated, especially because many subjects with SNG and hyperthyroidism are older and have increased cardiac risks. It is more difficult to decide whether to treat subclinical hyperthyroidism, which is the most common thyroid function abnormality in SNG. An increasing body of evidence suggests that subclinical hyperthyroidism is detrimental to the heart, bone, and cognitive function, and treatment decisions should take into account these risks in an individual patient.

What about the patient with normal thyroid function and a SNG? There is no consensus on how such a patient should be evaluated. Some authors recommend ultrasound in all patients, because ~50% have multiple nodules that are not detected on physical examination, and because repeated ultrasound measurements are very sensitive in detecting nodule growth (1, 7). Once nonpalpable nodules are discovered, published recommendations include fine-needle aspiration biopsy of any nodule that is at least 1–1.5 cm in diameter, to exclude the presence of thyroid cancer. Recent studies report that 4–6% of nonpalpable nodules biopsied under ultrasound guidance harbored cancer, a rate similar to that in palpable nodules (1, 3, 8). However, there are no longitudinal or cost-effectiveness studies that show this approach, which leads to high rates of biopsy and significant numbers of surgical referrals, affects long-term outcomes.

What is the optimal treatment for SNG?

The treatment goals for a patient with a benign SNG include relief of local compressive symptoms or cosmetic de-

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formity, prevention of progressive thyroid enlargement, and treatment of associated thyroid dysfunction. These symptoms vary widely among patients, from those with no symptoms and an incidentally discovered goiter to those with tracheal compression and stridor. Thus, there is no one optimal treatment for SNG, and treatment decisions must be individualized. There are four main treatment options for SNG: monitoring without treatment, thyroidectomy, levothyroxine (L-thyroxine) suppression, and radioactive iodine.

Monitoring without treatment. This option is not often discussed in the literature, possibly because of the cited natural history of goiter growth in SNG and the desire to treat before the goiter size reduces efficacy and increases risks. However, SNG growth can be quite variable, and some patients have stable goiters for many years. Given the risks of intervention (discussed below), I believe that a period of watchful waiting in patients without local symptoms or thyroid dysfunction is often the best option. If this option is chosen, it is not clear whether these patients are adequately followed by clinical examination alone, or whether they should have periodic ultrasound measurements of overall thyroid and nodule size.

Thyroidectomy. For many years, the recommended standard treatment for SNG was thyroidectomy. The long-term recurrence rate after thyroidectomy depends on the extent of surgery, ranging from 0% for total thyroidectomy to 60% for unilateral thyroidectomy (9). The average time to recurrence is many years, and many patients with recurrence do not require reoperation. Recurrence rates are not affected by postoperative treatment with L-thyroxine (except in patients with a past history of external radiation). Based on recurrence rates, one would recommend a total thyroidectomy for patients with SNG, except that complication rates also increase with extent of surgery. These include recurrent laryngeal nerve injury and hypoparathyroidism, which are, fortunately, uncommon in expert surgical hands. Thus, I believe that thyroidectomy is a suitable option in SNG, tailored to the patient's general health, size of goiter, symptoms, and available surgical expertise.

L-thyroxine suppression. The use of L-thyroxine in doses designed to suppress TSH levels has been extensively studied in SNG. The theory underlying this treatment is that TSH is a growth factor for SNG and suppressing TSH levels will remove this growth stimulus and cause goiter shrinkage or stabilization. Initial studies suggested that this approach is effective in SNG; however, many of these studies were short term, had no placebo group to control for spontaneous changes in goiter size, and/or were conducted in iodine-deficient areas. Placebo-controlled studies have, in general, been disappointing in terms of goiter shrinkage (see Refs. 2–4 for recent reviews), although one study did document prevention of nodule growth with L-thyroxine over 5 yr (10).

In all studies, SNGs regrow when L-thyroxine is discontinued, necessitating indefinite treatment. This means that the patient may have subclinical hyperthyroidism for many years. Increasing evidence now suggests that subclinical hyperthyroidism leads to bone loss, increased risk of atrial fibrillation and other cardiac problems, and neuropsychiatric and cognitive effects. The questionable long-term effectiveness of TSH suppression, combined with these risks, has led to a decline in enthusiasm for this treatment option.

Radioactive iodine. The first reports of the use of radioactive iodine to treat large multinodular goiters appeared in the 1960s and were followed by a number of uncontrolled studies. The seven published studies that document changes in goiter size following radioactive iodine are summarized in Table 1 (11–17). There are a number of caveats regarding these studies: in most cases, patients were selected who had large, symptomatic goiters and were either poor surgical candidates or refused surgery. Some of the studies were done in areas of low to borderline iodine intake, which might increase the effectiveness of radioiodine. Some of the subjects had suppressed TSH levels, and a few of them had outright hyperthyroidism. The doses of iodine-131 (^{131}I) varied widely, although in most cases an attempt was made to deliver 100 μCi per gram of thyroid tissue, corrected for the 24-h uptake. Follow-up was relatively short term in most studies, although two studies were 8 and 10 yr in duration. Despite these caveats, an encouraging uniformity of results emerges from these studies. Goiter size decreased in all cases by 40% or more, and most patients had significant relief of compressive symptoms. Side effects were mild, with the exception that high rates of eventual hypothyroidism were seen.

Given these encouraging preliminary studies, the time was right for a controlled, prospective study of radioiodine treatment of SNG. Such a study has now been reported by Wesche *et al.* (18) in this issue of the journal. Sixty-four patients with

TABLE 1. Summary of seven published studies regarding efficacy and side effects of radioactive iodine therapy for SNG

Reference	No. of patients	^{131}I dose	Follow-up	Results	Side effects
11	14	20–100 mCi	1–2 yr	Decreased goiter size by exam in 79%	1 thyroiditis, 1 hyperthyroid, 3 hypothyroid (2 subclinical)
12	25	7–28 mCi	1 yr	41% decrease in mean thyroid volume	2 hypothyroid, 1 transient hyperthyroid
13	15	20–50 mCi	Up to 8 yr	39% decrease in mean thyroid volume	100% hypothyroid at 8 yr
14	69	4–30 mCi	Up to 10 yr	55% decrease in mean thyroid volume	2 mild neck pain, 3 hyperthyroid, 22% hypothyroid
15	17	37–150 mCi	1 yr	40% decrease in mean thyroid volume	2 sore throat, 1 hyperthyroid
16	10	14–65 mCi	1–6 yr	48% decrease in mean thyroid volume	2 mild thyroiditis, 4 subclinical hypothyroid
17	38	60 mCi (fractionated over 4 months)	Up to 4 yr	Decreased goiter size by exam in 92%	3 neck pain, 66% hypothyroid at 18 months

SNG underwent appropriate initial evaluation, including an assessment of goiter size and nodularity by ultrasound and fine-needle aspiration of suspicious nodules to exclude malignancy. Fifty-nine of the subjects had multinodular goiters (of which five had substernal components), and five subjects had single nodules. The goiters varied widely in size, from 17–260 mL. Seventeen of the subjects had subclinical hyperthyroidism with suppressed TSH levels.

Subjects were stratified by gender and menopausal status and were randomized to receive suppressive doses of L-thyroxine (n = 32) or radioactive iodine (n = 32). Initial L-thyroxine doses were 2.5 μg/kg body weight·day, which is high, as shown by symptoms of mild thyrotoxicosis in 10 subjects and development of atrial fibrillation in 1 subject. L-thyroxine doses were titrated downward to the minimum dose needed to maintain TSH suppression, leading to a mean final dose of 1.9 μg/kg·day. The main adverse effect noted in the L-thyroxine-treated group was an increase in markers of bone turnover and a significant decrement in spine bone mineral density of 3.6% at 2 yr, which was not seen in the ^{131}I group.

Therapeutic ^{131}I doses were calculated at 120 μCi (4.44 MBq) per milliliter of thyroid tissue, with a range of 12–90 mCi administered. These doses are comparable with those reported in the literature summarized above. The initial side effects observed with ^{131}I treatment were neck tenderness and slight thyrotoxic symptoms in four patients. At 2 yr, 35% of the patients treated with ^{131}I were hypothyroid and 10% had subclinical hyperthyroidism.

The difference in outcomes between the two treatment groups was impressive: 97% of ^{131}I-treated patients had a significant decrease in goiter size (defined as 13% or more decrease in size, which corresponds to 2 SD of the ultrasound measurement variability). The mean decrease was 39% at 1 yr and 46% at 2 yr. These data are remarkably similar to those previously reported in the uncontrolled studies cited above. Of note, pretreatment goiter size was inversely related to goiter reduction. In contrast, the results from the L-thyroxine group are disappointing. Forty-three percent responded, with a mean decrease of 23% at 1 yr and 22% at 2 yr. Fifty-seven percent did not respond, with a mean decrease of 1% at 1 yr and a mean increase of 22% at 2 yr. The degree of goiter reduction was directly related to the baseline TSH, with especially poor responses among subjects who presented with subclinical hyperthyroidism.

One could quibble with some of the details of this study: the relative overtreatment with L-thyroxine probably led to higher rates of adverse effects and bone loss than would have been seen with more conservative doses. However, these doses also probably maximized efficacy rates for this group, and we are unlikely to see better responses with more modest L-thyroxine doses. The inclusion of subjects with suppressed TSH levels on presentation may have increased side effects and lowered efficacy rates for the L-thyroxine-treated group, while increasing efficacy rates for the ^{131}I-treated group. However, the authors performed a subanalysis of patients with normal TSH levels that did not change the results. Patients with small goiters were included in the study, and one could argue that such patients could be followed without treatment for a number of years. Goiter shrinkage with ^{131}I was inversely related to initial goiter size, which means that patients with larger goiters had less shrinkage. This is a bit disappointing, because it is exactly that group of patients who would benefit most from reduction in goiter size.

There is one long-term concern regarding the use of radioactive iodine in patients with SNG that cannot be addressed in a small-scale, short-term study like the one reported by Wesche *et al.* (18): the risk of radioiodine-induced carcinogenesis. The risk for thyroid carcinoma is not increased in patients given ^{131}I for therapy of hyperthyroidism or thyroid cancer (19, 20). Most of the published epidemiologic data on the development of nonthyroid secondary cancers following radioactive iodine treatment for Graves' disease are also reassuring. However, some studies suggest slight increases in rates of kidney, stomach, bladder, breast, or brain cancers. In addition, ^{131}I doses for Graves' disease are typically lower than those proposed for treatment of SNG, and, therefore, the extrathyroidal tissue exposure is much lower than that obtained when treating SNG. Other data in patients who receive high-dose ^{131}I treatment for thyroid cancer suggest that relative risks of secondary carcinoma or leukemia are increased only with high cumulative doses of ^{131}I (19, 20). Dosimetric measurements and calculations of risk estimates in patients given ^{131}I for large multinodular goiters are also reassuring, but are based on data modeling rather than patient follow-up (21). Therefore, this remains a concern, especially for younger patients, and needs to be discussed with them in the context of whether to choose surgery or radioactive iodine therapy for SNG.

If the administered dose of ^{131}I is a concern, then strategies to improve treatment efficacy of SNG while minimizing ^{131}I doses make sense. Such a strategy exists in the use of recombinant human TSH (rhTSH; Thyrogen, Genzyme Transgenics Corp., Boston, MA) in SNGs. rhTSH stimulates iodine uptake into normal and abnormal thyroid tissue and is in clinical use for the follow-up of patients with thyroid cancer. Huysmans *et al.* (22) recently published results of a Phase I study investigating whether radioactive iodine uptake can be enhanced in nontoxic multinodular goiters using rhTSH. Very low doses of rhTSH (0.01 and 0.03 mg, compared with 1.8 mg used for thyroid cancer) significantly increased 24-h radioactive iodine uptake in patients with multinodular goiters that were between 60 and 300 g in size. The higher dose also led to significant increases in thyroid hormone levels that lasted a week, and further dose-response studies are obviously needed to optimally define the best rhTSH dose and timing for this promising treatment. Additional studies of the use of rhTSH in the treatment of SNG are currently in progress, and their results are awaited with great interest.

In summary, the study reported by Wesche *et al.* (18) represents an important advance in our approach to treatment of SNG. Taken together with previous studies, I believe that these data conclusively put to rest the notion that L-thyroxine is a safe and effective treatment for SNG. In my opinion, patients with smaller, asymptomatic goiters can be followed expectantly, whereas patients with larger or symptomatic goiters have a choice between surgery and radioactive iodine treatment. This decision can be individualized based on clinical issues and patient preference. Further answers to our questions regarding optimal evaluation and

treatment for patients with SNG will hopefully be available from the results of studies now in progress.

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