Management of Simple Nodular Goiter: Current Status and Future Perspectives

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The simple nodular goiter, the etiology of which is multifactorial, encompasses the spectrum from the incidental asymptomatic small solitary nodule to the large intrathoracic goiter, causing pressure symptoms as well as cosmetic complaints. Its management is still the cause of considerable controversy.

The mainstay in the diagnostic evaluation is related to functional and morphological characterization with serum TSH and (some kind of) imaging. Because malignancy is just as common in patients with a multinodular goiter as patients with a solitary nodule, we support the increasing use of fine-needle aspiration biopsy (cytology).

Most patients need no treatment after malignancy is ruled out. In case of cosmetic or pressure symptoms, the choice in multinodular goiter stands between surgery, which is still the first choice, and radioiodine if uptake is adequate. In addition to surgery, the solitary nodule, whether hot or cold, can be treated with percutaneous ethanol injection therapy. If hot, radioiodine is the therapy of choice. Randomized studies are scarce, and the side effects of nonsurgical therapy are coming into focus. Therefore, the use of the optimum option in the individual patient cannot at present be based on evidence. However, we are of the view that levothyroxine, although widely used, should no longer be recommended routinely for this condition.

Within a few years, the introduction of recombinant human TSH and laser therapy may profoundly alter the nonsurgical treatment of simple nodular goiter. (*Endocrine Reviews* 24: 102–132, 2003)

I. Introduction

NODULAR GOITERS ARE clinically recognizable enlargements of the thyroid gland characterized by excessive growth and structural and/or functional transformation of one or several areas within the normal thyroid tissue. In the absence of thyroid dysfunction, autoimmune thyroid disease, thyroiditis, and thyroid malignancy, they constitute an entity described as simple nodular goiter (SNG; Ref. 1).

Simple goiter occurs both endemically, mainly related to iodine deficiency when goiter prevalence in children 6–12 yr of age within a population is more than 5%, and sporadically, when this number is 5% or less. The clinical evaluation of size, morphology, and function is highly inaccurate (2) as illustrated, for example, by up to 50% of subjects with a solitary palpable nodule or a diffusely enlarged gland actually having multiple nodules when investigated by sonography (3–5). Additionally, up to 50% of the general population has thyroid nodules by sonography, even when the gland is normal to palpation (3–5). This may be one of the explanations for the increasing tendency, at least for thyroidologists, to use diagnostic imaging in the evaluation of such patients, in addition to functional characterization with serum TSH (6–9).

SNG covers a spectrum from the clinically normal gland to diffuse, uninodular, or multinodular and cystic enlargement of the thyroid, using the most sensitive of imaging techniques (4, 10). The clinical manifestations are related to those of growth and functional autonomy, unpredictable in the individual patient, leading to cosmetic and pressure symptoms on the one hand and that of hypersecretion of thyroid hormone on the other (1). The latter is increasingly recognized as a health hazard (11, 12). Another question is the risk of thyroid cancer in SNG. Although concern of an increased prevalence in SNG seems unfounded (3, 5), accumulating evidence suggests that the risk of cancer in SNG, approximately 3–5%, is no different whether the gland contains a single nodule or multiple nodules (3, 5).

Pathogenesis of SNG, excellently reviewed in recent publications (1, 13–17), is considered beyond the scope of this article. We will, however, in brief, comment on etiological aspects of this condition (1, 13–18), because consideration of possible preventive measures is a prerequisite for cost-effective management. Consequently, the discussion will emphasize management aspects, *i.e.*, diagnostic and thera-

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Abbreviations: ATA, American Thyroid Association; CI, confidence interval; ETA, European Thyroid Association; FNAB, fine-needle aspiration biopsy; ^{131}I, radioiodine; ILP, interstitial laser photocoagulation; L-T$_4$, levothyroxine; MNG-1, multinodular goiter 1; MR, magnetic resonance; MTC, medullary thyroid carcinoma; NIS, sodium iodide symporter; PEIT, percutaneous ethanol injection therapy; PET, positron emission tomography; SNG, simple nodular goiter; Tg, thyroglobulin; TPO, thyroid peroxidase; TSHR, TSH receptor; US, ultrasonography.

peutic aspects. For this, we rely heavily on our recent questionnaire studies among clinician members of the European Thyroid Association (ETA) and the American Thyroid Association (ATA). A number of issues are unresolved, and it should be evident from the following that major controversies exist (6–9, 19, 20). Despite this, we aim at providing a balanced recommendation and point at future therapeutic perspectives whenever this is at all possible. Although a distinction between the solitary nontoxic nodule and the multinodular nontoxic goiter is not always straightforward, we have in the following, whenever appropriate, tried to separate the two.

II. Etiology

Familial clustering of simple goiter has long been recognized, but classical genetic analysis based on Mendelian principles has shown no simple mode of transmission. In recent years, it has become clear that both endemic and sporadic simple goiter belong to the group of diseases referred to as complex diseases (18, 21) along with, for example, autoimmune thyroid disease (Graves' disease and Hashimoto's thyroiditis; Refs. 22 and 23). These conditions are common, vary in their severity, and are multifactorial, with the clinical phenotype representing the net effect of all the contributing genetic and environmental factors. In these conditions, it has been difficult to separate environmental influences from genetic susceptibility (Fig. 1).

It is generally accepted that iodine deficiency is a major environmental factor contributing to both endemic and sporadic simple goiter (24). In fact, thyroid size is negatively correlated to urinary iodine excretion (25). Constitutional factors such as gender are clearly implicated in the etiology, because the ratio of females to males in nonendemic goiter regions may exceed from 5:1 to 10:1. Other suggested risk factors include cigarette smoking (26, 27), naturally occurring goitrogens (28), emotional stress (29), certain drugs (30, 31),

and infections (32). Interestingly, alcohol seems to have the opposite effect. It is associated with a decrease in thyroid volume, possibly related to a direct toxic effect of alcohol (33, 34).

Although familial aggregation of simple goiter has repeatedly been demonstrated (35–37), family studies cannot determine whether this results from shared genes or shared environment. However, because concordance rates for simple goiter in female monozygotic twins have been reported higher in endemic (80%; Refs. 38 and 39) as well as nonendemic areas (42%; Ref. 21) as compared with female dizygotic twins [40–50% (Refs. 38 and 39) and 13% (Ref. 21), respectively], evidence of a genetic component in the etiology of simple goiter is provided. In an endemic goiter area, the heritability of the liability to goiter development in females has been calculated to 39% [95% confidence interval (CI), 0–79%; Ref. 39]. On the basis of path analysis (structural equation modeling), Brix *et al.* (21) estimated this heritability to be 82% (95% CI, 67–92%) in a nonendemic goiter area. The remaining 18% (95% CI, 8–33%) of the phenotypic variance resulted from individual-specific environmental factors not shared by the twins (21). Although the twin data cannot uncritically be interpreted as the relative importance of heredity and environment, in any population, both endemic and sporadic simple goiter seems to develop on the basis of genetic susceptibility interacting with environmental factors, the two most important being level of iodine intake and cigarette smoking. Consequently, possible susceptibility genes or genetic markers will be recognized more easily in nonendemic than endemic goiter areas.

Studies assessing the role of specific candidate genes in the etiology of simple goiter have given conflicting results. Corral *et al.* (40) demonstrated a thyroglobulin (Tg) gene point mutation in chromosome 8 associated with nonendemic goiter, which could, however, not be confirmed by others (41). Using classic linkage analysis in combination with a genome-wide screening in a large French-Canadian pedigree, Bignell
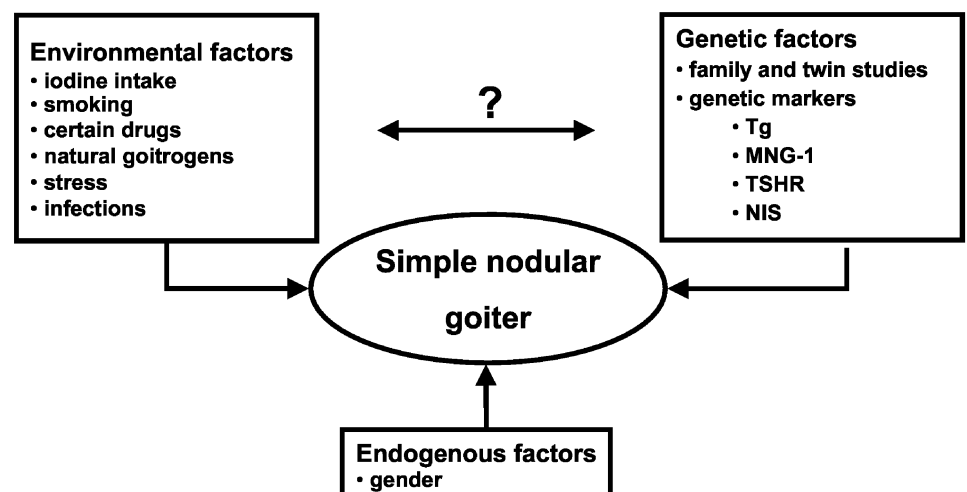
Etiology of simple nodular goiter

FIG. 1. The development of simple nodular goiter seems to involve complex interactions between environmental, genetic, and endogenous factors. At present, it is not clear how and to what degree the susceptibility genes interact with the environmental risk factors.

et al. (42) identified a region of interest on chromosome 14, multinodular goiter 1 (MNG-1). Two other studies (41, 43) have examined the role of MNG-1 and other possible candidate genes/markers, including Tg, TSH receptor (TSHR), and sodium iodide symporter (NIS), in the etiology of simple goiter, with conflicting results. Recently, Capon *et al.* (44) mapped a dominant form of multinodular goiter to chromosome Xp22. This finding awaits confirmation. It follows that genetic heterogeneity, *i.e.*, no single gene being either necessary or sufficient for disease development, is highly likely. The results of these studies, all in single or small groups of families, cannot at present be extrapolated to the general population. It is likely that single genes play a role in certain families. However, studies in larger numbers of pedigrees, taking gene-environment interaction into consideration, are necessary.

In light of the observed linkage between MNG-1 and goiter (41, 42), it is intriguing that Tomer *et al.* (45) have found linkage of Graves' disease to another locus on chromosome 14, Graves' disease 1. If confirmed, this could indicate the presence of a gene complex on chromosome 14, etiologically related to thyroid disease in general. However, as pointed out in *Section I*, simple goiter certainly comprises a number of phenotypes, complicating any comparison between available studies. This, in addition to the small number of families studied, hinders any firm conclusion on possible candidate genes in SNG.

III. Epidemiology

Epidemiological studies of nodular goiter are hampered by problems such as selection criteria (*e.g.*, age, sex), influence of environmental factors (*e.g.*, iodine and drug intake, smoking and drinking habits), evaluation of size and morphology (palpation, sonography, scintigraphy), and determination of thyroid function and whether subjects with subclinical thyroid dysfunction are included (46). Most studies have focused on middle-aged women and the elderly, whereas only a few have documented the prevalence of nodular thyroid disease in a population-based manner. Large-scale population-based longitudinal studies using diagnostic imaging allowing distinction between uninodular and multinodular disease and morphological as well as functional characterization do not exist. Therefore, adequate data on prevalence, incidence, etiological risk factors, and the natural history are lacking. These limitations should be born in mind when considering the available data. Despite these shortcomings, a pattern of increased thyroid volume and nodularity in areas with iodine deficiency is the rule (46–50). Furthermore, it has been suggested that relatively small differences in the iodine intake of a population may lead to notable differences in median thyroid volume, goiter prevalence, and nodule size (51). There are insufficient data allowing estimation of the optimum level of iodine intake to minimize goiter occurrence. Additionally, it is emphasized that goiter and thyroid nodules also exist in the face of iodine sufficiency, and even in the case of iodine excess (52, 53).

In the Whickham survey of a representative sample of the adult population from a geographic area of the United King-

dom, 15.5% of the participants had a palpable goiter (8.6% had a small goiter), with a female to male ratio of 4.5:1 (54). There was a weak association between goiter and thyroid autoantibodies and no relation to urinary iodine excretion. In Framingham, Massachusetts, where iodine intake was also sufficient, 1% of persons between 30 and 59 yr of age had multinodular goiter by palpation (55). In Connecticut, 2% of adults were reported to have nodular glands (56, 57). In Denmark, palpable goiter was demonstrated in 9.8% of a mildly iodine-deficient population and 14.6% of a moderately iodine-deficient population (49). This frequency increased to 15.0% and 22.6%, respectively, when goiter was defined by sonographic determination of thyroid volume (49). There are a vast number of such studies underscoring the inaccuracy of and also the large observer variation in the determination of goiter and thyroid size by clinical examination (2, 58, 59).

In the Whickham survey (54), solitary thyroid nodules were estimated to be present in 5.3% of women and 0.8% of men (ratio, 6.6:1). No details were given about nodule size, function, or their association with goiter. In Framingham, this frequency was 4.6% in all (6.4% in women and 1.6% in men; Ref. 55). However, these numbers are markedly changed if sonography is used. Then, the prevalence of thyroid nodules, even if defined as more than 10 mm in diameter, is usually 20–30% in unselected populations (46, 49, 60, 61) and even higher in older age groups and in areas with insufficient iodine intake (46, 62). These findings are substantiated by autopsy studies demonstrating that half the population had either single or multiple thyroid nodules (46, 63).

Little is known of the functionality of these solitary nodules. Although not systematically investigated, available data suggest that approximately 5% are toxic, 10% are warm, and 85% are cold (49, 64).

IV. Natural History

It is often stated that the natural history of nodular goiter is that of gradually increasing size with development of multiple nodules, local compression symptoms, and/or cosmetic complaints. However, the natural history with respect to growth and function varies and is difficult to predict in a given patient because no specific growth parameters exist. Therefore, it is difficult to decide whether an individual patient can be monitored without treatment or should have treatment before the goiter grows any further and possibly affects treatment outcome adversely (65). This dilemma is clearly illustrated by recent European and North American questionnaire surveys dealing with the solitary (6, 7) as well as the multinodular goiter (8, 9), disclosing profound differences within and between countries in the proneness to offer treatment, once malignancy has been ruled out.

In the Whickham survey (66), 20% of the women and 5% of the men who had goiters in the initial survey had no goiter in the follow-up survey, whereas only 4% of the women and none of the men acquired a goiter between the two surveys. In a 20-yr follow-up study of 11- to 18-yr-old subjects in the southwestern United States, 60% of the 92 subjects who had

diffuse goiters initially had spontaneous regression by the age of 30 yr (67). In a large epidemiological study, Knudsen *et al.* (51) only found an increase of thyroid volume up to the age of 40 yr. On the basis of cross-sectional data and ultrasonic scanning, an average annual growth rate of 4.5% in multinodular goiter has been reported (68). In patients referred because of SNG and who qualified for treatment, it has been estimated to be up to 20% yearly in a noniodine-deficient region (69) but is usually much lower. The suggested decreasing frequency of goiter with age could possibly be explained by a fall in lean body mass with age, known to be related to thyroid volume (70). A fall with age in IGF-I and GH, which is associated in the elderly (71), in patients with anorexia nervosa (72), and in pygmies (73) with a decrease in goiter frequency and thyroid volume, is another possibility. At least in women, the loss of estradiol-mediated increase in proliferation and down-regulation of the NIS gene may be of importance (74).

The natural history of thyroid nodules is poorly understood. In the Framingham survey, new nodules appeared with an incidence of 1 per 1000 per year (57), leading to an estimated lifetime risk for developing a nodule to between 5 and 10%. In a study of 140 selected Japanese patients who had not been treated and were reexamined 15 yr later (75), 13% had an increase in nodule size, 34% were unchanged, 23% had decreased, and in 30% the nodule was no longer palpable. The nodules that increased were originally predominantly solid, whereas those that disappeared were predominantly cystic. With the same reservations, that is the patients with rapid growth, for example, symptoms and clinical suspicion of malignancy were offered treatment, others have found that nodules on average do not change significantly over time (49).

Patients with nontoxic nodular goiter can become hyperthyroid or, less commonly, hypothyroid. However, thyroid dysfunction usually develops only after the nontoxic goiter has existed for many years. Hyperthyroidism often develops insidiously, in contrast to that of Graves' disease. It often begins with a prolonged period of subclinical hyperthyroidism characterized by low serum TSH and normal serum free T_4 and free T_3 concentrations (76). Increasing nodularity and size are related to a decrease in serum TSH (68). The true rate of progression from normal thyroid function to subclinical and finally overt hyperthyroidism is poorly described. However, two studies suggest an incidence of 9–10% of overt hyperthyroidism during a 7- to 12-yr follow-up period (77, 78). In part, this progression depends on genetic predisposition (21), somatic mutations in individual nodules (17), and extrinsic factors such as iodine intake (52). The latter may be alimental or related to iodine-containing drugs such as disinfectants and amiodarone or from radiographic contrast agents, which, in a goiter with increasing autonomous iodine metabolism, leads to the production of excessive amounts of thyroid hormone. In autonomously functioning solitary nodules (hot nodules), the evolution into a toxic nodule has been estimated at annual rates of 0–6% (79, 80). In one study, 67 of 375 patients developed hyperthyroidism over a mean follow-up of 53 months, corresponding to 4.1% per year (80). Size of the nodule seems crucial because Hamburger (81), during a 6-yr follow-up, demonstrated that nodules greater

than 3 cm in size at diagnosis carried a 20% risk of developing hyperthyroidism, whereas nodules less than 2.5 cm in size had only a 2–5% risk of developing hyperthyroidism within the same time frame.

V. Diagnosis

A. Clinical evaluation

1. Manifestations. There is no clear-cut relation between thyroid size, morphology, and function of the thyroid gland on one hand and the complaints of the individual patient on the other hand. The majority of patients with SNG have few or no clinical symptoms (Table 1). Therefore, given euthyroidism and exclusion of malignancy, many need no treatment. A simple management algorithm for the majority of patients with a solitary or a dominant nodule (index nodule, *i.e.*, the palpable nodule in a thyroid gland with other nodules found incidentally by imaging or a growing nodule in a preexisting multinodular gland) is given in Fig. 2.

When present, the most important symptoms and signs of SNG are caused by compression of vital structures in the neck or upper thoracic cavity. Besides various degrees of neck disfigurement, which in itself can merit treatment, the symptoms are related to compression of the trachea or esophagus. These compression symptoms are more often seen when there is an intrathoracic extension of the goiter. Such a goiter develops insidiously often in the elderly with long-standing goiter. When there is substantial growth into the thorax, usually into the anterior mediastinum, the thoracic inlet may become occluded. This is known as "the thyroid cork phe-

TABLE 1. Clinical symptoms, signs, and investigations in the diagnosis of SNG

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| Symptoms and signs |
| Often family history of benign thyroid disease |
| Slowly growing anterior neck mass |
| Uni- or multinodularity on examination |
| Enlargement during pregnancy |
| Cosmetic complaints |
| Asymmetry, tracheal deviation, and/or compression |
| Occasionally upper airway obstruction, dyspnea, cough, and dysphagia |
| Sudden transient pain or enlargement secondary to hemorrhage |
| Gradually developing hyperthyroidism |
| Superior vena cava obstruction syndrome (rare) |
| Recurrent nerve palsy (rare) |
| Horner's syndrome (rare) |
| No adenopathy |
| Investigations |
| TSH normal or decreased, free T_4 and free T_3 normal |
| Tg usually elevated |
| Calcitonin normal |
| Thyroid autoantibodies (TPO and Tg) negative in approximately 90% |
| Scintigraphy with solitary or multiple hot and/or cold areas |
| Ultrasound finding of solitary or multiple nodules with varying echogenicity (nonhomogeneity) |
| Computed tomography and MR imaging demonstrating solitary or multiple nodules with varying echogenicity (nonhomogeneity) |
| Lung function testing may demonstrate impaired inspiratory capacity |
| Fine-needle aspiration of solitary or dominant nodules—benign cytology |
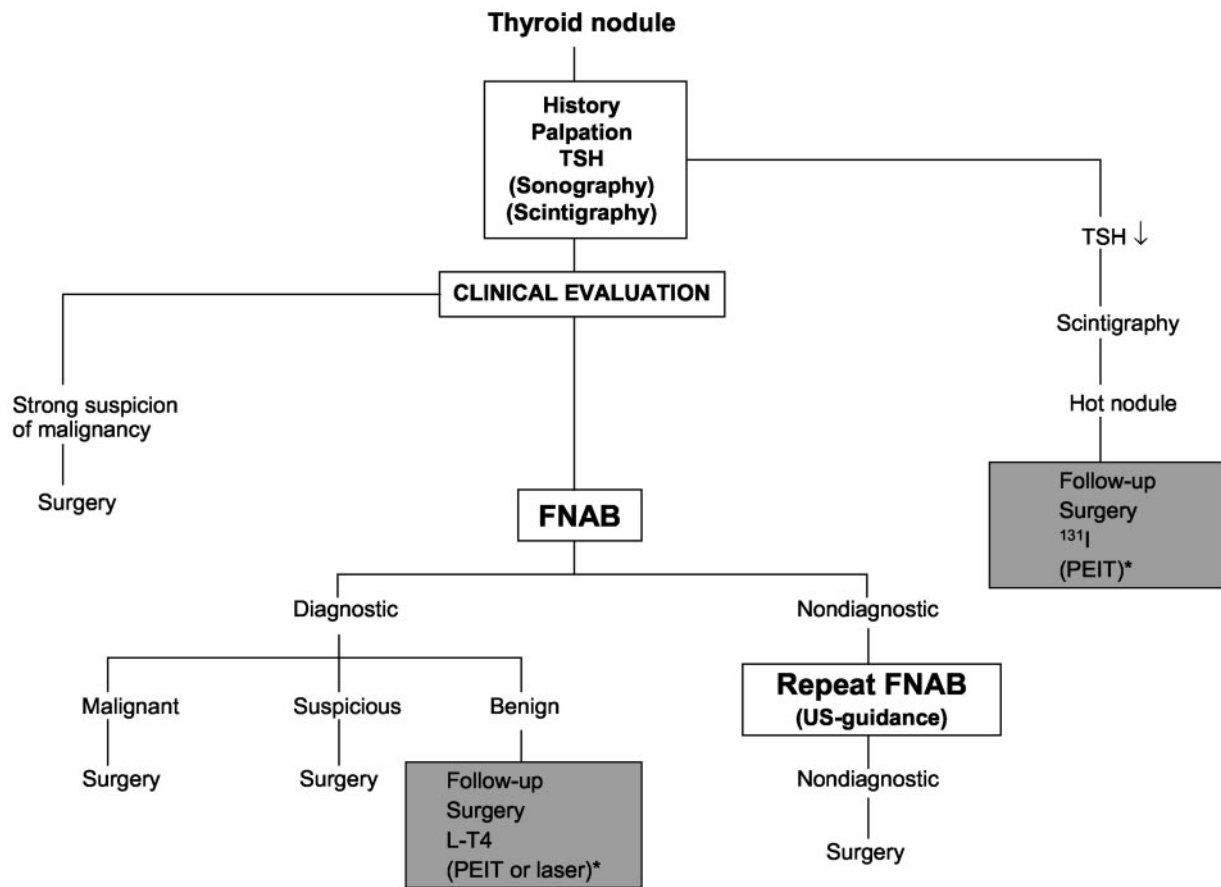
FIG. 2. Algorithm outlining a cost-effective evaluation and treatment of the solitary or dominant thyroid nodule. In case of strong suspicion of malignancy, surgery is advised irrespective of FNAB results. In case of a nondiagnostic result, repeat FNAB yields a satisfactory aspirate in 50%. FNAB guided by US (US-guidance) allows sampling from the periphery of a solid nodule or solid part of a mixed solid-cystic nodule, increasing the sufficiency rate. The options in case of a diagnostic FNAB cover both solid and cystic nodules. In case of recurrent cysts, the possibilities are reaspiration, surgery, or ethanol injection. The *shaded boxes* indicate treatment options. *, PEIT or ILP.

nomenon" (82). Evidence of venous outflow obstruction, *i.e.*, compression or thrombosis of the jugular or subclavian veins or the superior vena cava, can be provided by Pemberton's sign (83). Extending the arms over the head (Pemberton's maneuver) raises the goiter into the thoracic inlet, resulting in shortness of breath, stridor, distension of neck veins, or facial plethora.

The symptoms of tracheal compression are dyspnea, stridor, cough, and choking sensation. With an intrathoracic localization, respiratory distress is present in 30–85% of patients referred to surgery (84–87). However, such goiters are often very large, and it is unsettled whether the tracheal compression is related to the goiter size or the substernal localization *per se*. The detrimental influence by the goiter on the respiration is amplified in the recumbent position (88). Concomitant with tracheal narrowing, dyspnea and stridor develop initially only on exertion, but later also at rest. An acute exacerbation in upper airway obstruction may have a benign origin like hemorrhage into a nodule or cyst or upper respiratory infections causing endotracheal swelling. In patients with severe or acute airway distress, often requiring acute intubation, 20–50% may be caused by thyroid malignancy (89, 90). Even in asymptomatic individuals, attention should be paid to the trachea. Thus, Gittoes *et al.* (91) found

that in patients referred with a moderately enlarged goiter, flow-volume loops revealed upper airway obstruction among a third, and correlated poorly with symptoms. Complaints due to esophageal compression are less common and most prevalent in patients with large and partly intrathoracic goiters (86, 87). Even rarer is vocal cord paralysis, which can be transient or permanent, caused by stretching or compression of one or both recurrent laryngeal nerves (86, 87, 92). Phrenic nerve paralysis (93) and Horner's syndrome (94), due to compression of the cervical sympathetic chain, have been described but are extremely rare. If present, malignancy should always be suspected.

Toxic nodular goiter is beyond the scope of SNG; therefore, symptoms and signs of thyrotoxicosis have not been included. However, a number of patients with SNG certainly have subclinical hyperthyroidism biochemically (17% in one study; Ref. 95), and some of these patients have symptoms compatible with thyroid hyperfunction. Treatment aspects of these conditions will be dealt with subsequently.

2. Clinical examination. The evaluation of a patient with SNG comprises initially a careful history and physical examination focusing on inspection of the neck (including regional lymph nodes) and the upper thorax and palpation of the

goiter to determine its size and nodularity. This clinical evaluation, preferably done with the patient swallowing gulps of water and the head tilted slightly backward, essential for deciding on subsequent investigations and treatment, seems to be a lost or unlearned art for many physicians, as demonstrated by the considerable inter- and intraobserver variation regarding size and morphology of the thyroid (2, 59, 96). Recognition of this may well be one of the reasons for the increasing use of diagnostic imaging by European as well as North American thyroidologists in the evaluation of SNG (6–9).

With practice, the thyroid gland can also be palpated when of normal size, but to most the thyroid gland does not become palpable until the volume has doubled. A visibly diffusely enlarged goiter has often reached a volume of 30–40 ml. In general, the size of smaller goiters is overestimated, and the size of larger goiters is underestimated (2). Detection of nodules depends on their size, morphology, location within the thyroid parenchyma, anatomy of the patient's neck, and most of all the training of the physician. The patient is usually unaware of the presence of a nodule smaller than 1.5–2 cm in diameter. Awareness may, however, depend on localization, speed of growth, and the possible pain or discomfort related to, for example, hemorrhage into a nodule. Most goiters remain stable or increase in size slowly. Disregarding the possibility of malignancy, rapid increases may also be due to menstrual cycle-related alterations (97) or release of norepinephrine from a pheochromocytoma (98).

3. Assessment of risk of malignancy. SNG does not include thyroid cancer, but one of the main aims of the clinical evaluation is to exclude or at least minimize the risk of overlooking thyroid cancer. Table 2 lists the most important factors suggesting thyroid malignancy.

A family history of benign goiter usually suggests a benign disorder but is no proof thereof. Familial medullary thyroid cancer, with or without multiple endocrine neoplasia, should lead to exclusion of this possibility. The occurrence of familial papillary thyroid tumors occurring independently or in

Cowden's disease, Gardner's syndrome, or familial polyposis coli (99) is important in risk assessment.

The risk of harboring thyroid cancer is highest in the young and the old, and therefore the diagnostic approach should be more aggressive in these age groups. Nodular thyroid disease is 5–10 times more common in females, whereas the rates of thyroid carcinoma are nearly equal in men and women. Therefore, nodular goiter in a man is more likely to be a carcinoma. Head and neck irradiation in infancy or childhood, for a number of benign conditions, is strongly associated with a subsequent occurrence of carcinoma (100). The possibility that many naturally occurring thyroid carcinomas may be due to fallout radiation from various radiation sources or natural background is strengthened by the observed epidemic of childhood papillary thyroid cancer seen in Belarus and Ukraine after the Chernobyl nuclear accident (101).

Rate of growth is of the essence. Thyroid carcinomas usually grow slowly over a period of weeks or, more often, months. Growth during thyroid hormone therapy is particularly worrisome. Sudden growth is most likely a thyroid cyst or a previously undetected nodule into which a hemorrhage has occurred. Rapid enlargement is also encountered in cases of anaplastic carcinoma or the development of lymphoma in a patient with previous chronic autoimmune thyroiditis.

The presence of discomfort in the neck, jaw, or ear and dysphagia, hoarseness, or dyspnea can occur in patients with benign thyroid nodules, particularly in those with large multinodular goiters, but may also indicate thyroid carcinoma. A hard and fixed nodule is suggestive of thyroid carcinoma, as is paralysis of the vocal cords and ipsilateral lymphadenopathy. Although virtually all patients with thyroid carcinoma are euthyroid (as are most patients with benign thyroid nodules), a suppressed serum TSH suggests subclinical hyperthyroidism. Usually, this rules out clinically significant malignancy, but it should be noted that coexisting hyperthyroidism does not exclude malignancy in the multinodular goiter. Thus, in one large series of operated hyperthyroid patients, thyroid cancer was found in 1.6% of patients with a toxic multinodular goiter, contrasting with none among those with Graves' disease (102).

It should be remembered that glands that harbor malignancy are in many cases indistinguishable from those that do not. In case of a high clinical suspicion of malignancy (Table 2), thyroidectomy should be advocated irrespective of a benign cytology because the likelihood of malignancy is very high (Ref. 103; Fig. 2). When two factors suggesting high suspicion are present, the likelihood of thyroid malignancy approaches 100% (103).

B. Laboratory investigations

Serum TSH is by far the most used test in the initial evaluation of SNG (6–9). This approach is indeed justifiable, because present TSH assays are very sensitive in detecting thyroid dysfunction. Although preferred by more than half of clinicians (Table 3), it can be strongly questioned whether an initial measurement of thyroid hormones adds further information in this setting, provided the serum TSH is within

TABLE 2. Factors suggesting the diagnosis of thyroid carcinoma in patients with nodular thyroid disease, according to degree of suspicion

High suspicion
Family history of MTC or multiple endocrine neoplasia
Rapid tumor growth (especially during L-T$_4$ therapy)
Very firm nodule(s)
Fixation to adjacent structures
Vocal cord paralysis (laryngoscopy)
Regional lymphadenopathy
Distant metastasis (lungs or bones)
Moderate suspicion
Age <20 yr or >60 yr
Male sex
Solitary nodule
History of head and neck irradiation
Firm texture, possible fixation
Nodule >4 cm in diameter and partially cystic
Compression symptoms: dysphagia, dysphonia, hoarseness, dyspnea, cough
Low suspicion
All others

the normal range. When it comes to the use of other biochemical tests than TSH, North American clinicians are clearly more restrictive than are Europeans (Table 3; Refs. 6–9).

Antithyroid peroxidase (anti-TPO) antibodies are measured by more than half of clinicians (6–9). This seems relevant because thyroid antibodies are found in approximately 10% of the population (104, 105), and consequently, autoimmunity may well coexist within a goiter. On the other hand, diffuse or focal lymphocytic infiltrates in an enlarged gland may represent chronic autoimmune thyroiditis and not merely simple goiter (4). This can be confirmed by fine-needle aspiration biopsy (FNAB), and subsequently, L-T$_4$ therapy may be considered in these cases, particularly if the serum TSH level is located in the upper normal range. Additionally, knowledge of the anti-TPO status is relevant for therapy with radioiodine (^{131}I), because these antibodies constitute a risk factor for thyroiditis, hypothyroidism, and transition into Graves' disease (106).

Although serum Tg correlates with the iodine status and/or the size of the thyroid gland, this marker is too inaccurate at the individual level to have any independent value in the diagnosis of goiter (107, 108). This is reflected by less than 10% of clinicians measuring serum Tg (6–9).

A test giving rise to much discussion during recent years is serum calcitonin. This hormone is a marker of medullary thyroid carcinoma (MTC), and the serum levels correlate with the tumor burden (109). MTC accounts for less than 10% of all thyroid cancers and is supposed to be present in less

than 0.5% of all thyroid nodules (16). Of particular interest is its use in the early diagnosis of MTC. A two-site immunometric calcitonin assay should be used (110), but presence of heterophilic antibodies may still cause falsely elevated values (111). With modern assays, serum calcitonin is below 10 pg/ml in 99% of healthy subjects (112) and is slightly higher in men than in women (113). Raised levels of calcitonin not related to thyroid diseases are seen in conditions such as impaired renal function (114), pseudohypoparathyroidism (115), or treatment with proton pump inhibitors (116). Pentagastrin-stimulated calcitonin was much used in the past to test family members for MTC associated to the multiple endocrine neoplasia 2 syndrome, but this can now easily be done by genetic test for mutations in the RET protooncogene (117). Pentagastrin stimulation may still have a role in sporadic cases in which basal calcitonin exceeds 10 pg/ml (118). In the United States, where pentagastrin is no longer available, the calcium-calcitonin test may be used instead (119). The normal upper limit of serum calcitonin after stimulation with pentagastrin is approximately 40 pg/ml (113). If the level exceeds 100 pg/ml, this strongly indicates the presence of MTC or C cell hyperplasia (120). In case of familial disposition, C cell hyperplasia is considered as carcinoma *in situ*. In other cases, the significance of C cell hyperplasia is unclear, because it is a common finding in the elderly, present in 20% at autopsy (121). The results of six large-scale studies (112, 118, 122–125) of the routine use of serum calcitonin in patients with nodular thyroid disease are summarized in Table 4. The studies vary with regard to the diagnostic set-up and the fraction of patients with histological verification. The prevalence of MTC was up to 1.4% in a large French study (123) in which 41% of 34 patients with an elevated basal calcitonin had MTC, but also included two false-negative cases. In the study of Hahm *et al.* (112), 56 of 1448 patients (3.9%) with nodular thyroid diseases had a serum calcitonin level above 10 pg/ml. Ten patients (0.7%) proved to have MTC. Half of these subjects had a basal serum calcitonin level above 100 pg/ml. Vierhapper *et al.* (118) found 3 of 1062 patients having a basal calcitonin level exceeding 100 pg/ml. More important, in 10 of 31 patients with basal calcitonin ranging from 10–100 pg/ml, a pentagastrin-stimulation increased calcitonin above 100 pg/ml (118). MTC was found in three patients, and another six had C cell hyperplasia. Basal or stimulated calcitonin levels were generally more sensitive than FNAB in detecting MTC, and the routine use of serum calcitonin was recommended by all authors of these studies (112, 118, 122–125). However, a clear conclusion is not easy to draw from the existing data. Cost-benefit must be taken into consideration, and a high false-

TABLE 3. Routine biochemical tests used by ATA and ETA members, according to questionnaire surveys (6–9), in the diagnostic evaluation of a patient with a nontoxic solitary nodule or a nontoxic multinodular goiter and no suspicion of malignancy

	Solitary nodule		Multinodular goiter	
	ATA (n = 142)	ETA (n = 110)	ATA (n = 140)	ETA (n = 120)
TSH	99	99	100	100
Total T$_4$	12	20	21	17
Total T$_3$	9	25	23	23
Free T$_4$/index	49	53	54	74
Free T$_3$/index	6	31	11	43
TPO antibodies	30	41	61	65
Microsomal antibodies	6	11	17	10
Tg antibodies	18	26	34	49
TSHR antibodies	0	6	0	8
Calcitonin	5	43	4	32
Tg	4	14	2	8
Sedimentation rate	6	16	9	13

Numbers are percentage of clinicians in the two organizations.

TABLE 4. Studies of the routine use of serum calcitonin (CT) in patients with nodular goiter

Author	No. of patients	Use of pentagastrin test	Prevalence of MTC (%)
Pacini *et al.* (124)	1385	Yes, if elevated basal CT	0.57
Rieu *et al.* (122)	469	Yes, if elevated basal CT	0.84[a]
Niccoli *et al.* (123)	1167	Yes, in 121 patients with normal basal CT	1.37
Vierhapper *et al.* (118)	1062	Yes, if elevated basal CT	1.13[b]
Özgen *et al.* (125)	773	No	0.52
Hahm *et al.* (112)	1448	Yes, in 39 patients with elevated basal CT or disposing factors	0.69

[a] Demonstrated histologically or by immunostaining with anti-CT antibodies.
[b] Including C cell hyperplasia.

positive rate of 60–80% (112, 123) will result in many unnecessary thyroidectomies. It is also evident from our surveys (6–9) that there is no consensus on this issue (Table 3). Thus, more than 30% of Europeans measure basal serum calcitonin routinely (6, 8), perhaps reflecting that five of the six large studies mentioned (118, 122–125) were performed in Europe. In contrast, only very few clinicians in North America routinely use basal calcitonin measurement, except in the case of a family history of thyroid cancer (7, 9). This approach is in accordance with existing ATA guidelines (126) as well as guidelines published by the American Association of Clinical Endocrinologists (127).

In agreement with the attitudes of most ETA and ATA clinicians (6–9), we conclude that serum TSH and anti-TPO are mandatory in the evaluation of SNG. If TSH is found outside the normal range, assays for T_4 and T_3 are also justified. In contrast, the routine use of calcitonin in all patients with a nodular thyroid gland is controversial (6–9) and can be questioned, but it seems clear that if a basal plasma calcitonin level above 10 pg/ml is found, this must elicit further investigations. We find no place for the routine assessment of serum Tg and only rarely for Tg antibodies.

C. Diagnostic imaging

Although simple and cheap, neck palpation is notoriously imprecise with regard to both thyroid gland morphology (2,

58, 128) and size determination (2, 96, 129). For this purpose, several imaging methods are available: sonography, scintigraphy, computed tomography scan, magnetic resonance (MR) imaging, and perhaps positron emission tomography (PET). Table 5 lists characteristics, advantages, and disadvantages of these imaging modalities. Of these, sonography clearly has first priority among clinicians (6–9).

1. Sonography. Introduction of thyroid sonography has had a dramatic impact on clinical practice. It was shown by Marqusee *et al.* (5) that in patients referred to a thyroid clinic due to palpable thyroid abnormalities, sonography altered the clinical management in two thirds of the cases. The main reasons for the widespread use of thyroid sonography are availability, low cost, limited discomfort to the patient, and the nonionizing nature. Some years ago, the routine use of sonography was not recommended in the management of nodular goiters (126, 130), but today this attitude is rapidly changing (6–9). Also, sonography has many favorable features, such as detection of nonpalpable nodules, estimation of nodule size/goiter volume (*e.g.*, monitoring the effect of therapy), and guidance for FNAB (Table 5). However, the high sensitivity can also lead to detection of clinically insignificant nodules and to unnecessary work-up and anxiety for the patient. Some of the above advantages have led more than 80% of ETA members and 60% of ATA members to

TABLE 5. Characteristics of imaging procedures in relation to nodular thyroid disease

	Advantages	Disadvantages
Sonography	High availability High morphologic resolution No ionizing irradiation Dynamic picture Blood flow visualization (Doppler) Biopsy guidance, also of lymph nodes Moderate precision in volume estimation Low patient discomfort "Bed-side" investigation	Operator dependency No information of functionality Not feasible in substernal goiter Poor prediction of malignancy
Scintigraphy	Information of functionality Differentiates between destructive and hyperthyroid conditions Measurement of thyroid iodine uptake Predictive of feasibility of ^{131}I therapy Detects ectopic thyroid tissue	Requires nuclear medicine units Ionizing irradiation Poor resolution Poor differentiation between solid and cystic cold nodules Volume estimation inaccurate ^{99m}Tc may falsely show nodular uptake Invalidated by iodine contamination
CT scan	Good availability High morphologic resolution Visualization of adjacent structures Ideal for substernal goiter Planimetric volume estimation Volume estimation probably accurate	Ionizing irradiation No information of functionality Poor prediction of malignancy
MR imaging	No ionizing irradiation High morphologic resolution Visualization of adjacent structures Ideal for substernal goiter Planimetric volume estimation Volume estimation with high precision, probably with high accuracy	Moderate availability Long procedure time Not usable with metallic objects inside patient No information of functionality Poor prediction of malignancy Claustrophobia
PET	Information of functionality Metabolic investigations Good prediction of malignancy	Low availability Requires specialized units Ionizing irradiation Poorly evaluated

CT, Computed tomography.

include sonography routinely in the initial management of the patient with nodular goiter (6–9). Thyroid sonography has recently been comprehensively reviewed (4). First of all, high-resolution sonography with great certainty distinguishes solid from cystic lesions. Furthermore, it is very sensitive in the detection of thyroid nodules, for which purpose the interobserver variation is low (131). Sonography detects five times as many nodules as thyroid palpation and twice as many when only nodules larger than 2 cm are considered (132). Thus, after the introduction of sonography, it has become clear that nodules in the thyroid gland are very prevalent, ranging from 17% to as much as 67% in a given population (51, 133–135). As a consequence, the term "thyroid incidentaloma" has emerged. Some authors recommend regular sonographic follow-up of such incidentalomas (61, 126), although the growth rate does not seem useful in distinguishing malignant from benign nodules (136). Sonographic characteristics like hypoechogenicity, microcalcifications, and increased nodular flow visualized by Doppler are all to some extent predictive of malignancy (Table 6). However, the low accuracy in most studies disqualifies sonography in the differentiation between benign and cancerous lesions (4), and it is clearly inferior to FNAB in this setting.

The possibility of measuring thyroid volume is another highly useful feature of sonography, particularly where diagnosis and monitoring of goiter size are of crucial importance. The validity of sonographic volume measurement depends on the principle used. The ellipsoid method (length ∗ width ∗ depth ∗ $\pi/6$) has an interobserver coefficient of variation of 10% (131), and the measurement error is 10–16% compared with postmortem specimens (131, 137). When compared with MR planimetry, the ellipsoid method underestimates the thyroid volume by 22.7%, independent of the thyroid size. This difference is halved, however, if the MR estimates are also based on the ellipsoid formula (138). The problem with an irregularly shaped goiter, increasing with size and invalidating the ellipsoid method, can be overcome by a planimetric method. Precision and accuracy of this principle are sufficiently high for most purposes. The interobserver coefficient of variation is 5% (47, 139), and the measurement error is 7% (139). In a comparison between the planimetric and the ellipsoid methods, Nygaard *et al.* (140) recently revealed that the latter technique underestimates the thyroid volume by a median of 9% and also has a lower reproducibility (median variation, 10% *vs.* 5.5% for the planimetric method). Sonographic planimetry for thyroid volume estimation has been compared with computed tomography [small to moderate enlarged goiters (140)] as well as MR imaging [very large goiters (141)]. In these cases, sonography clearly underestimates the goiter size by 17% (140) and 19.5% (141), respectively. In the latter study (141), the difference between the estimates was found to expand with increasing volumes. Also, use of sonography is hampered by the substernal extension frequently encountered with large goiters. A new three-dimensional sonographic technique introduced recently for thyroid volume estimation has a significantly higher accuracy than conventional sonographic methods (142). Additional studies are needed to evaluate this promising technology.

2. Scintigraphy. Thyroid isotope imaging has been used for many years. Although the scintigraphic resolution can be enhanced to 6–7 mm by tomography (SPECT; Ref. 143), this is still far below that of sonography. Therefore, scintigraphy at present has little place in the anatomotopographic evaluation of the nodular goiter (Table 5). However, scintigraphy is very helpful in the determination of the functionality of the thyroid nodules. TSH suppression by levothyroxine (L-T_4) administration emphasizes autonomous nodular function (144), but is not routinely used (6–9). Nodules with a high uptake by scintigraphy almost never harbor clinically significant malignancy, although exceptions have been reported (145). ^{99m}Tc used as a tracer may result in falsely positive uptake in 3–8% of thyroid nodules (146), whereas iodine isotopes are devoid of this problem. This may explain why the use of ^{123}I is favored by 63% (solitary nodule) and 49% (multinodular goiter) of ATA members (7, 9). The fact that ^{99m}Tc is inexpensive and easier to use, in addition to several studies being unable to demonstrate any significant dissimilarities between the two tracers (147–149), may explain why this isotope is recommended by 85% of ETA members (6, 8).

The fraction of inactive or "cold" lesions constitutes 77–94% of nodules in consecutive series of thyroid scintigrams (150–152). The *a priori* risk of malignancy among cold nodules is reported to be 8–25% or even higher (151, 153–155). However, such risk estimates are without a doubt heavily influenced by selection bias, because cold scintigraphic nodules greater than 10 mm are found in 2.4% of the subjects living in a borderline iodine deficient area (49). Tracers like ^{201}Thallium and ^{99m}Tc-MIBI have an increased uptake in differentiated malignant thyroid nodules, but the sensitivity and specificity do not support their general use (156–159). Thyroid scintigrams have been used through the decades for measurement of the thyroid volume. However, in comparison with modern imaging techniques, it is very inaccurate (160–162) and cannot be recommended for this purpose.

Many disregard thyroid scintigraphy in the initial evaluation of patients with nontoxic nodular goiter (16, 126). Nevertheless, more than two thirds of ETA members (6, 8) rou-

TABLE 6. Ultrasonographic features in subjects with nodular thyroid disease suggestive of malignancy

Benign	Malignant
Normal echogenicity or hyperechogenicity	Hypoechogenicity
Coarse calcifications	Microcalcifications
Thin, well defined halo	Thick, irregular, or absent halo
Regular margin	Irregular margin
Lack of invasive growth	Invasive growth
No regional lymphadenopathy	Regional lymphadenopathy
Low intranodular flow by Doppler	High intranodular flow by Doppler

tinely use scintigraphy, whereas less than 25% of ATA members prefer such a strategy in this condition (7, 9). Indisputable indications for scintigraphy in the setting of a nodular goiter are hyperthyroidism (to visualize hot nodules suitable for ^{131}I therapy) and a follicular neoplasm shown by FNAB, because warm nodules with great certainty are benign (163).

3. Computed tomography and MR imaging. Computed tomography and MR provide high-resolution three-dimensional visualization of the thyroid gland. Some aspects of MR and computed tomography for thyroid imaging have recently been reviewed (164). None of these methods have any advantages over sonography when it comes to detailed visualization of the intrathyroidal structure (Table 5). The major strength of computed tomography and MR is their ability to diagnose and assess the extent of substernal goiters much more precisely than any other method (Fig. 3). However, in this situation, only 15–20% of clinicians use these techniques (8, 9). The only comparative study done so far showed that MR is more precise than computed tomography in the anatomotopographic evaluation of the substernal goiter (165). However, whether computed tomography or MR is preferred probably depends on cost and availability. Another advantage of computed tomography and MR is the possibility for planimetric volume estimations, especially useful in

FIG. 3. Coronal MR image of a large goiter, demonstrating narrowing of the trachea (*white arrow*) and left-sided substernal extension (*black arrows*).

irregularly enlarged goiters. For this purpose, the observer variation of MR imaging is 2–4% (141, 161). Interestingly, MR measurements based on the ellipsoid principle underestimate the thyroid volume by approximately 12% in comparison with MR planimetry (138). With regard to computed tomography planimetric estimates, the median intra- and interobserver variations are 5% and 11%, respectively (140), and compared with surgical specimens, computed tomography overestimates the volume by up to 57% (mean, 12%; Ref. 166). The volume of surgical and postmortem thyroid specimens may, however, be dissimilar to *in vivo* determinations due to the influence of thyroid perfusion. The agreement between computed tomography and MR estimates is unknown, and little is known about the accuracies of the methods, because no gold standard is attainable.

All of the methods described above have little value in the differentiation between malignant and benign thyroid lesions, but new techniques are promising in this respect. An increased glucose metabolism as measured by [18F]-2-deoxy-2-fluoro-D-glucose PET (FDG-PET) can with high precision differentiate malignant from benign thyroid nodules (167, 168). A recent study showed that nearly 50% of thyroid nodules detected incidentally by FDG-PET harbor cancer (169). Although this technique seems promising in the diagnosis of thyroid malignancy, its use is hampered by cost and limited accessibility to most clinicians.
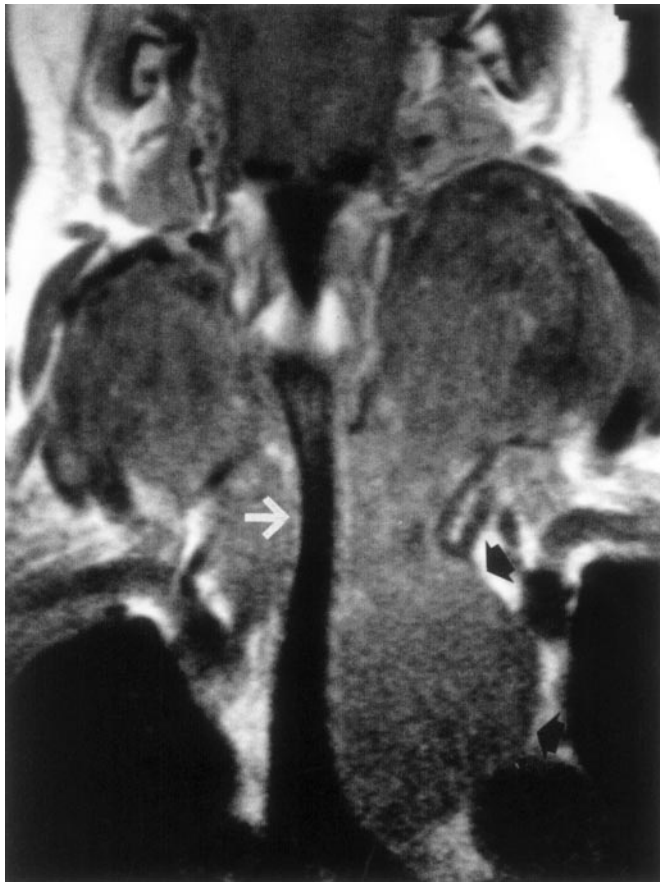
4. Tracheal imaging and relation to goiter size and lung function. The air flow rate, particularly in the inspiratory phase, will obviously be critically compromised if the lumen of the trachea is reduced beyond a certain point. Imaging of the trachea can be done by plain x-ray, computed tomography, or MR imaging. Plain x-ray has a poor sensitivity with regard to detection of airway obstruction and shows poor correlation with air flow rate (91, 170–173). However, the tracheal area, which can be measured by computed tomography or MR imaging, is a more relevant variable. Melissant *et al.* (173) found that computed tomography estimates of the smallest cross-sectional tracheal area, as well as plain tracheal radiograms, were unrelated to the lung function. In contrast, a relationship between the corresponding MR estimates and the inspiratory capacity has been demonstrated in large goiters (65). Changes in goiter volume and the tracheal area resulting from ^{131}I therapy also correlated well in the study by Huysmans *et al.* (174). However, results have been inconsistent, maybe due to the low precision of the imaging of the small tracheal dimensions (141). Other sources of error may be changes of the tracheal lumen caused by the respiration itself, the applied intrathoracic pressure, and the position of the patient (175–177). Furthermore, even with a small increase of the tracheal area, the flow rate becomes much less dependent of the luminal space. Thus, tracheal imaging cannot stand alone in the evaluation of respiration in the patient with a goiter. Because asymptomatic tracheal compression is prevalent (91), a flow volume loop should be considered, in particular if the goiter is very large, but in this case less than 15% of ATA members and even fewer of ETA members include a lung function test in the diagnostic setup (8, 9).

D. Fine-needle aspiration biopsy

FNAB provides the most direct and specific information about a thyroid nodule, and it is used by the majority of thyroidologists given a solitary nodule or a dominant nodule in a multinodular goiter (Table 7; Refs. 6–9). As the cornerstone in the evaluation, it is virtually without complications, inexpensive, and easy to learn. Figure 2 depicts the central role of FNAB in the investigation of nodular thyroid disease, with special emphasis on the solitary or the dominant nodule. The use of FNAB reduces the number of thyroidectomies by approximately 50% (178), roughly doubles the surgical yield of carcinoma, and reduces the overall cost of medical care in these patients by 25% (163).

The technique involves the use of a 5- to 20-ml plastic syringe with a 21- to 27-gauge needle. The skin is cleaned with alcohol and may be infiltrated with 1–2 ml of 1% lidocaine. The needle, attached to the syringe, is inserted perpendicular to the anterior surface of the neck. Negative pressure is applied, and as soon as bloody fluid in the hub of the needle appears, pressure is released and the needle withdrawn. No fluid should enter the syringe. If the nodule is a cyst or partly cystic, the aspiration should be followed by FNAB of any residual solid component. Investigation of the cyst sediment rarely gives useful information. After withdrawal, the needle is detached, and the specimen is evacuated onto a slide.

Diagnostically useful FNAB specimens are obtained in approximately 80% of the cases (Table 8; Refs. 130 and 179). The number of insufficient samples depends on operator experience, number of aspirations, the character of the nodule (cystic or solid), the experience of the cytopathologist, and especially the criteria used for adequacy of a sample. The number of sufficient samples increases if FNAB is guided by ultrasonography (US; Refs. 180 and 181). Rebiopsy will typically halve the number of insufficient FNABs (130, 182). Needle-steering devices and pistol-grip equipment are used by some. The specimens should be smeared immediately (pull-apart technique); most use air drying and staining with May-Giemsa-Grünwald stain, good for cytoplasmic details, or alternatively Papanicolaou's stain, good for nuclear details (183).

Diagnostic accuracy of FNAB depends on the handling of suspicious lesions. If considered negative, sensitivity will decrease, and specificity will increase. If suspicious results are regarded as positive, the converse is true. In our opinion, patients with suspicious, malignant, and nondiagnostic cytology (after reaspiration) should be operated (Fig. 2). The relevant question is what the false-negative rate is in the

TABLE 8. Causes of thyroid nodules and the relative distribution of FNAB results

	Frequency (range)
Benign (no evidence of malignancy)	69% (53–90%)
Colloid nodule	
Thyroiditis (chronic, acute, or subacute)	
Cyst	
Suspicious	10% (5–23%)
Follicular neoplasm	
Normofollicular (simple)	
Macrofollicular	
Microfollicular (fetal)	
Trabecular and solid (embryonal)	
Oxyphilic cell type (Hürtle cell)	
Malignant	4% (1–10%)
Follicular carcinoma	
Papillary carcinoma	
Medullary carcinoma (C cell carcinoma)	
Undifferentiated (anaplastic) carcinoma	
Lymphoma	
Metastasis (rare)	
Nondiagnostic (insufficient)	17% (15–20%)[a]

Adapted from Gharib and Goellner (130) and Burch (179).
[a] This amount can be halved by rebiopsy.

remaining 70–80% of the cases in which nonsurgical treatment is an option. This has generally been estimated at 1% (184). Repeated FNAB during follow-up, to decrease the false-negative rate, will virtually eliminate the risk of overlooking thyroid malignancy (185). At worst, the diagnosis of low-grade thyroid malignancy (papillary or follicular thyroid carcinoma) is postponed.

Most cytopathologists agree that it is nearly impossible to distinguish benign from malignant follicular neoplasms on the basis of fine-needle aspiration cytology. In a large 3-yr prospective study from The Mayo Clinic comprising nearly 2000 patients, 17% had suspicious cytological findings, and in 24% of these patients malignancy was found (186). If scintigraphy of the cytologically suspicious nodule suggests that it is hyperfunctioning, also indicated by a suppressed TSH in case of the solitary nodule, such a lesion almost never harbors malignancy. In this situation, as also supported by others (16, 163), surgery can be avoided. In fact, clinicians should refrain from FNAB in scintigraphically hot nodules. Figure 2 shows our suggestion for the role of FNAB in the diagnostic setup. The application of a more complex cytological classification system to follicular lesions has been suggested by one group, but they were unable to demonstrate improved cancer yield with this cumbersome system (187). Large-needle biopsy does not have a higher diagnostic accuracy, *i.e.*, correctly identifying follicular carcinomas, than FNAB; furthermore, large-needle biopsy is more likely to yield an insufficient specimen, and more often hematomas are seen due to this procedure (188). In a smaller prospective study, a smaller needle size seemed to provide more cellular specimens, but diagnostic accuracy was unrelated to needle size (189).

Sonography has the advantage of providing multiple axial, longitudinal, and oblique planes of section and, most importantly continuous real-time needle localization. The maneuver can be performed by freehand, with the needle being inserted through the skin directly into the plane of view of the transducer without a guide or by the use of

TABLE 7. Frequency of use (%) of FNAB in nodular thyroid disease

	ATA	ETA
Solitary nodule: using FNAB	100	99
Guided only by palpation[a]	87	58
Guided by sonography[a]	13	42
Multinodular goiter: using FNAB	74	94
Guided only by palpation[a]	64	33
Guided by sonography[a]	36	67

Results are from ATA and ETA questionnaire surveys (6–9).
[a] Percentage of clinicians performing biopsy.

built-in or attachable needle slots. US guidance is reliable because it allows the maneuver to be performed quickly, with no exposure to x-rays and under permanent visual surveillance. US-guided FNAB dramatically reduces the risk of sampling error, and the rate of adequate material aspirated during the procedure greatly increases (180, 190). In a retrospective Italian study by Danese *et al.* (181) comparing conventional FNAB with US-guided FNAB in 4697 and 9683 patients, respectively, sensitivity, specificity, and overall diagnostic accuracy were significantly improved when using US guidance. In another retrospective study from California, sensitivity and specificity improved to 100%, and adequacy rate improved from 84% to 93% when compared with conventional FNAB (191).

The true risk of malignancy in the cystic or mixed cystic/solid thyroid lesion is enigmatic to many clinicians. The usefulness of FNAB in thyroid cysts is hampered by the fact that specimens suitable for cytological examination cannot be collected from all cystic lesions. Attempts to add biochemical analysis of thyroid cyst fluid obtained by FNAB to analyze various enzyme concentrations, Tg, and other components has not given clear evidence of any simple test that distinguishes benign from malignant lesions (192, 193). Given clinical factors (Table 2) or cytological findings increasing the likelihood of thyroid malignancy in a euthyroid patient with a cystic hypofunctioning nodule, the risk of neoplasia and cancer is the same as in solid hypofunctioning nodules, and surgery should be recommended (Fig. 2; Refs. 194 and 195). Certain sonographic features (Table 6) are at best suggestive but are no proof of malignancy (4, 10, 196), and the macroscopic appearance of the cyst fluid, cyst resolution after one aspiration, or other characteristics of the cyst provide no additional information in the context of ruling out malignancy (195, 197, 198). Some report of a low rate of accurate diagnosis for the cystic malignant lesion (199) with a high false-negative rate (200), whereas others have been able to obtain diagnostic FNAB in 71% of patients with cystic nodules with no false-negative results (198). If the solid portion of a cystic mass is aspirated under US guidance and cytology is performed after centrifugation of the aspirated fluid, diagnostic accuracy may be improved (199).

The risk of malignancy in thyroid nodules occurring within a multinodular goiter has not been completely clarified, but some authors find a similar frequency in uni- and multinodular goiters (62, 201). This is consistent with the low accuracy of physical examination in detecting thyroid nodules. When diagnostic errors occur in identifying the number of nodules, the results are biased toward classifying multiple nodules as single because the sensitivity of the physical examination is rather low, in the range of 30% (202). The single nodule, if identified by palpation, will often be reclassified as a dominant (or prominent) nodule within a multinodular thyroid gland if sonography is used. Additional nodule(s) identified by sonography will not decrease the *a priori* risk of malignancy in the index nodule. For example, in nodules larger than 10 mm, the prevalence of cancer is unrelated to whether they can be detected by palpation (203). The possibility of thyroid malignancy should be considered in all patients with multinodular goiters, and the use of US guidance has been shown to enhance the diagnostic efficacy of FNAB (204). It has been recommended that nodules less than 10 mm, detected incidentally, do not require a FNAB (61, 126). However, in the recent study by Papini *et al.* (205), thyroid malignancy was found in 6% of nonpalpable lesions of 8–15 mm in size in multinodular goiters (9% in solitary thyroid nodules). The risk was similar in nodules smaller or greater than 10 mm. A similar independency of size with regard to malignancy in nonpalpable nodules was found in an earlier study (190). However, whether carcinomas found in nodules other than the index nodule constitute clinically significant cancers or just incidental microcarcinomas remains an unsolved issue, leaving the clinician with no clear-cut guidelines for management. Sonographic features (205) may guide the clinician to include FNAB in nodules other than the index nodule. If scintigraphy is performed, we recommend FNAB in up to two nodules, provided these are scintigraphically cold. This strategy is based purely on pragmatism and not evidence.

So far, results clearly indicate that FNAB remains superior to other diagnostic tests. Further improvement of diagnostic sensitivity could arise from TPO immunodetection as a tool to assist diagnosis of thyroid nodules by FNAB (206, 207). Immunodetection of other candidate molecules, such as the lectin-related molecules, as markers of malignantly transformed thyrocytes may add valuable information in the selection of those nodules that need to be surgically resected, but confirmatory studies are needed (208). At present, telomerase assays do not add significant information to that of FNAB alone (209, 210).

VI. Treatment

A. Multinodular nontoxic goiter

There is no ideal treatment for the simple goiter. This is reflected by the fact that one third of clinicians would refrain from treatment facing a patient with moderate discomfort due to a multinodular nontoxic goiter of 50–80 g in which malignancy has been ruled out (Refs. 8 and 9; Fig. 4).

At first glance, iodine supplementation seems to be an adequate approach, because goiter development is strongly associated with even mild iodine insufficiency (24). The efficacy of iodine supplementation, once a nodular goiter has developed, has only very scarcely been evaluated. In a controlled trial, performed in an iodine-deficient area, a daily dose of 400 μg iodine during 8 months was as effective as 150 μg L-T$_4$ in reducing the size of diffuse goiter (211). A major hindrance in the use of iodine supplementation, however, is the fact that a sudden increase of the iodine intake may induce thyrotoxicosis in predisposed individuals (212, 213). Of further concern is that iodine supplementation appears to increase the incidence of papillary thyroid cancers and lymphoid thyroiditis (214). Due to these drawbacks, iodine supplementation in the context of nodular goiters is disregarded as an option, both in Europe (except in Germany) and in North America (8, 9). This leaves in essence three kinds of therapy: L-T$_4$ suppressive therapy, surgery, and ^{131}I therapy. These options are quite dissimilar as to their mode of action and adverse effects. In Table 9, we have tried to list advan-
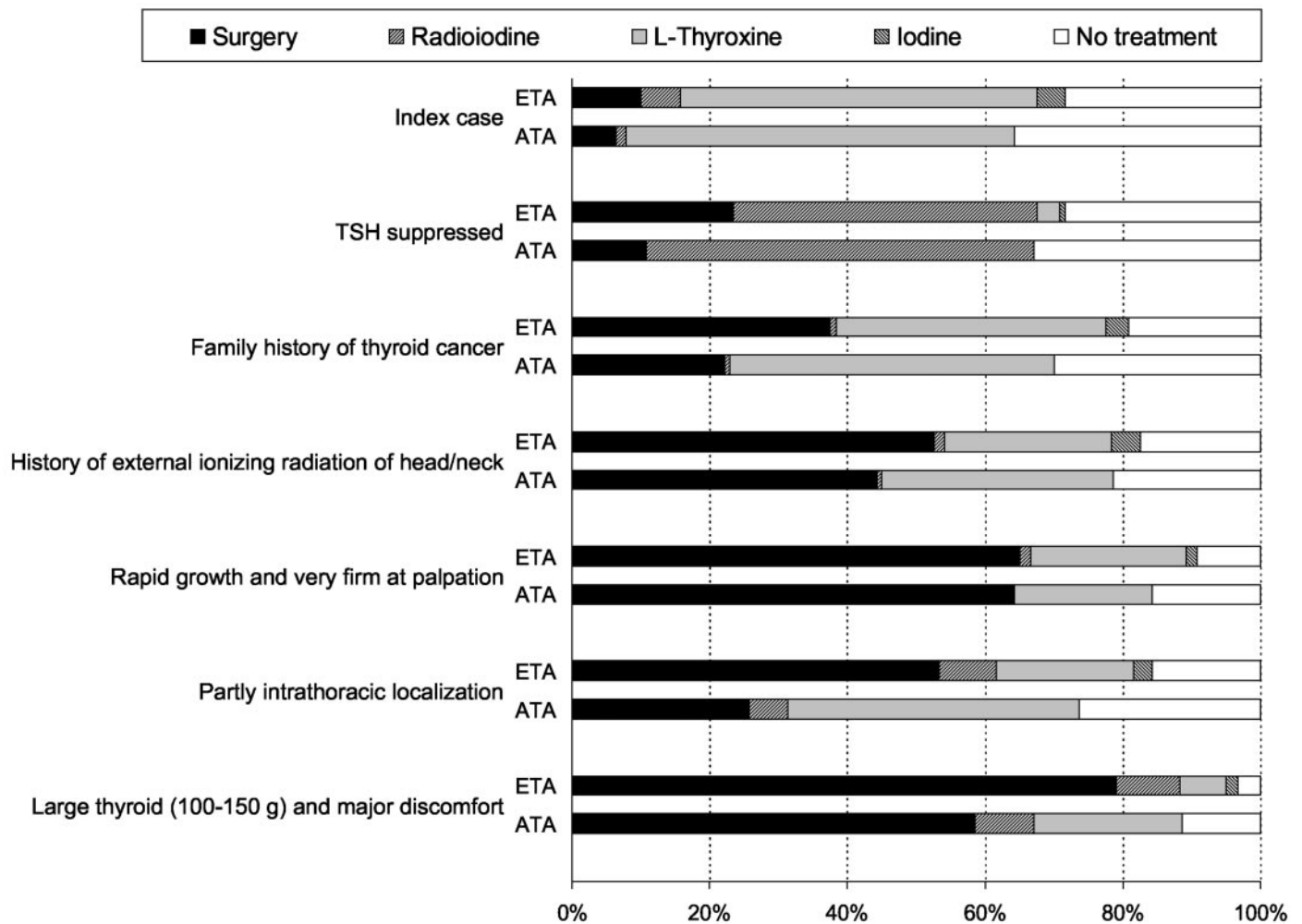
FIG. 4. Treatment options in nontoxic multinodular goiter and preferences among ATA and ETA members according to questionnaire surveys (8, 9). Index case: "A 42-yr-old premenopausal Caucasian woman admitted to your hospital/clinic due to an irregular nontender bilaterally enlarged thyroid. Clinically judged to be 50–80 g, absence of lymphadenopathy. No family history of thyroid disease. No previous external irradiation. No symptoms of thyroid dysfunction or anterior neck pain. The goiter has been present for 3–5 yr, and the patient reports of moderate local neck discomfort. Your investigations, whatever these have been, have demonstrated a benign condition." In the six listed variations, only one variable has been changed.

tages and disadvantages of the treatment options in benign nontoxic multinodular goiter.

1. T₄ therapy. In thyroid tissue that has not undergone autonomous degeneration, TSH suppression during treatment with thyroid hormones is supposed to slow or even revert growth of the thyroid gland. Indeed, a beneficial effect of thyroid hormones in diffuse goiters has been demonstrated in several controlled trials (211, 215–221). In general, a goiter reduction of 15–40% can be expected within 3 months, but the gland returns to the pretreatment size just as soon after withdrawal (215, 216). Treatment effect with T_3 or in combination with L-T_4 does not differ from that of L-T_4 alone (216, 217), but the effect may be more sustained after cessation of T_3 therapy (216). The efficacy of thyroid hormones is shown to depend on the degree of TSH suppression (216, 217), although results have been conflicting (218). In some of the studies in which L-T_4 was compared (211, 218, 220) or combined (211, 220, 221) with iodine supplementation, no substantial differences were found between the regimens, but

L-T_4 resulted in a more pronounced depression of serum TSH than did iodine (211, 218, 221). It has been recommended that diffuse euthyroid endemic goiters are treated with 200 μg iodine combined with 100 μg L-T_4 for at least 6 months, followed by iodine alone (222). Comparing nodular and diffuse goiters, the effect of L-T_4 is clearly more convincing in diffuse glands (219).

When it comes to the nontoxic multinodular goiter, there are only three controlled studies (69, 223, 224) in which sonography was used for objective size monitoring (Table 10). In the nonrandomized study of Lima *et al.* (223), the control group only comprised 15 patients. Thirty per cent of patients were regarded as responders (>50% reduction of the total nodular volume), whereas partial responders (20–50% reduction) constituted 23%. In the control group, 87% showed no change or an increase in goiter size. Berghout *et al.* (69), in a randomized double-blind trial, showed that the goiter volume was only reduced by 25% within a period of 9 months in the subgroup comprising 58% of the patients,

TABLE 9. Advantages and disadvantages of the treatment options in nontoxic multinodular goiter

	Advantages	Disadvantages
Surgery	Significant goiter reduction Rapid decompression of trachea Prompt relief of symptoms Definite histological diagnosis	Inpatient High cost Surgical risk Vocal cord paralysis: ~1% Hypoparathyroidism: ~1% Risk of hypothyroidism dependent of resection Risk of recurrence dependent of resection
^{131}I	Most often outpatient If outpatient: low cost Few subjective side effects Goiter reduction: 50% within 1 yr Improves inspiratory capacity in long term Can be repeated successfully	Limitation of administrated radioactivity Restricted proximity to other persons Contraceptives needed in fertile women Gradual reduction of the goiter Decreasing effect with increasing size Small risk of acute goiter enlargement Risk of thyroiditis: 3% Risk of transition into Graves' disease: 5% 1 yr risk of hypothyroidism: 15–20% Long-term cancer risk unknown
L-T$_4$	Outpatient Low cost May prevent new nodule formation	Low efficacy Lifelong treatment Adverse effects (bone, heart) Not feasible when TSH is suppressed

TABLE 10. Controlled studies of L-T$_4$ therapy in nontoxic multinodular goiter using an objective thyroid size determination

Author	Randomized	n	Duration of therapy (months)	Dose of L-T$_4$	Outcome: L-T$_4$	Treatment in control group	Outcome: control group
Berghout *et al.* (69)	Yes	55	9	2.5 μg/kg (adjusted)	25% reduction among responders (58% of patients)[a]	Placebo (double blind)	20% increase[a]
Lima *et al.* (223)	No	62	12	200 μg	30% responders[b]	No treatment	0% responders[b]
Wesche *et al.* (224)	Yes	57	24	2.5 μg/kg (adjusted)	22% reduction among responders (43% of patients)[a, c]	^{131}I	44% reduction

[a] Responders were patients achieving a goiter reduction more than 13% (>2 SD of the coefficient of variation).

[b] Responders defined as goiter reduction >50%.

[c] Reduction by 1% including nonresponders.

who responded significantly to L-T$_4$ therapy (>13% decrease of volume). In the placebo group, the goiter continued to increase in size by more than 20% on average after 9 months. If this rather high growth rate in the placebo group was taken into account, L-T$_4$ therapy caused a 45% size reduction. In the L-T$_4$ group, the goiter volume returned to baseline values 9 months after discontinuation of the therapy. Finally, Wesche *et al.* (224) compared L-T$_4$ with ^{131}I therapy in a randomized trial (Fig. 5). Among ^{131}I-treated patients, L-T$_4$ was commenced in 45% in the follow-up period due to increasing serum TSH levels. The median reduction of goiter volume in the ^{131}I-treated group was 38% and 44% after 1 and 2 yr, respectively, whereas the corresponding values in the L-T$_4$-treated group were 7% and 1%, respectively. The difference in number of responders, 97% (^{131}I) *vs.* 43% (L-T$_4$), was highly significant (224). Disfavoring L-T$_4$ therapy, more than one third developed symptoms of thyrotoxicosis, and a significant bone mineral loss as evaluated by dual-energy x-ray absorptiometry scanning was also noticed in that group (224). The above-mentioned trials (69, 223, 224) show that the effect of L-T$_4$ is at best very modest and that a sufficient goiter reduction can only be expected in a minority of the patients.

Other problems also raise concern. L-T$_4$ dose is often targeted toward a partly suppressed serum TSH level (8, 9). The
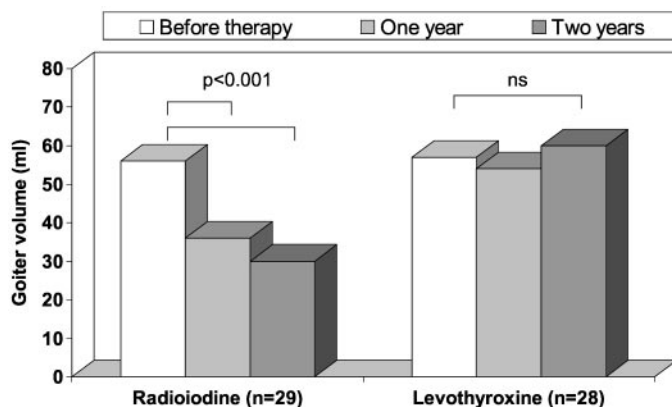

FIG. 5. Comparison of ^{131}I therapy and L-T$_4$ in the treatment of nontoxic multinodular goiter. *Bars* represent median goiter volumes. Adapted from Wesche *et al.* (224).

consequence is subclinical hyperthyroidism. This condition affects the skeleton and the cardiovascular system adversely, and abnormalities in other organ systems have also been reported (11, 12). There is no evidence that patients with subclinical hyperthyroidism have an increase in fractures (225, 226), but a significant reduction in bone density in

postmenopausal women is seen (227, 228). In addition, there is a documented risk of atrial fibrillation in patients with subclinical hyperthyroidism, and the cumulative incidence is inversely related to the TSH concentration (229, 230). Low serum TSH in individuals aged 60 yr or older is associated with increased mortality from all causes, and in particular mortality due to circulatory and cardiovascular diseases (11, 12). Because lifelong therapy is probably needed to avoid goiter recurrence (69) and the natural history of the disease is progression toward hyperthyroidism due to autonomous function of the thyroid nodules (77, 78), L-T$_4$ treatment is unfeasible in many patients.

With these considerations in mind, it must be strongly questioned whether L-T$_4$ suppressive therapy has any role in the treatment of the nontoxic multinodular goiter. Although L-T$_4$ seems to be the prime therapy according to recent surveys (8, 9), this therapy cannot be recommended, except in small diffuse goiters in the young where it is least necessary. In our own country (Denmark), this therapy has been abandoned (231).

2. Surgery. Although L-T$_4$ appears to be the main treatment for small to moderately enlarged nontoxic goiters, several complicating factors, in particular a large goiter and suspicion of thyroid malignancy, cause most clinicians to recommend surgery (Refs. 8 and 9; Fig. 4). The advantage of surgery is the significant goiter reduction with prompt relief of symptoms and definite tissue diagnosis, but problems have to be taken into account (Table 9). Numerous reports, of which many include various kinds of thyroid diseases, have described the short- and long-term results of surgery. Specific complications related to thyroid surgery are injury to the recurrent laryngeal nerve and injury to the parathyroid glands. Permanent lesions of these structures occur in less than 1% of the patients in specialized units (232). Complications are related to the goiter size and extent of the resection (232, 233).

Surgical removal of large goiters may be followed by postoperative respiratory complications in up to 30% of cases (234). Furthermore, large goiters often exhibit a substernal extension, found among 5–17% of patients referred for thyroidectomy (232, 235). Although removal of substernal goiters is mostly accomplished through a collar incision, resection of substernal goiters is nevertheless followed by a higher complication rate (232, 235, 236). Postoperative tracheomalacia, necessitating intubation, may ensue in 5–10% of patients operated for large, substernal goiters (234, 237). A matter of concern is the apparently high prevalence (7–17%) of thyroid carcinomas in substernal goiters (86, 236, 238). However, this seemingly high frequency may be heavily influenced by selection bias. It thus remains to be confirmed whether a substernal goiter localization *per se* is associated with a higher risk of malignancy.

Recurrence of the nontoxic multinodular goiter is seen in 15–40% of patients with long-term follow-up (239–241). The risk is inversely correlated with the volume of the postoperative remnant (239), whereas possible factors such as age, duration of goiter, and serum TSH level during follow-up do not seem to be of importance (241). With this high probability of goiter recurrence, prophylactic measures clearly are jus-

tified. Postoperative use of L-T$_4$ is preferred by more than 50% of clinicians (8, 9). However, of four randomized trials (239, 242–244), only one (244) demonstrated a beneficial effect of L-T$_4$. Hence, in concert with the treatment issue discussed above, the postoperative use of L-T$_4$ can generally not be recommended. Iodine prophylaxis has also been tested in iodine-deficient areas, but the effect on goiter recurrence after surgery does not differ from that of L-T$_4$ (245).

A reoperation for the recurrent goiter accounts for approximately 10% of thyroidectomies (232, 246) and results in a 3- to 10-fold increase in risk of permanent vocal cord paralysis or hypoparathyroidism (232, 233, 246). Although the absolute risk still may be relatively low, ^{131}I therapy seems to be a favorable alternative in these cases. Goiter recurrence can be completely avoided if a total thyroidectomy is performed initially. Such an approach is now the standard procedure for the multinodular goiter at some centers, apparently with the same low rate of complications as with subtotal thyroidectomy (247–250).

The long-term risk of hypothyroidism after subtotal resection of nontoxic multinodular goiters is insufficiently described, but it is probably not significantly different from the 10–20% reported for toxic multinodular goiters (251).

3. ^{131}I therapy. During more than half a century, ^{131}I therapy has been used to treat hyperthyroid disorders, primarily Graves' disease. It became evident early that ^{131}I therapy also results in shrinkage of the thyroid gland, even if hyperthyroidism persists. Due to this effect on gland volume, ^{131}I has been used during the last two decades in the treatment of compressive nontoxic nodular goiters, but in most countries, ^{131}I is restricted to hyperthyroid patients (8, 9). With one exception (224), all studies dealing with the effect of ^{131}I therapy on goiter reduction lack a control group. Nevertheless, the results have been very consistent. In 1988, Hegedüs *et al.* (252), using sonography, demonstrated a mean thyroid volume reduction from 73–43 ml 1 yr after ^{131}I treatment of nontoxic multinodular goiters. Similar results have been obtained in subsequent studies (253–255), showing a goiter size reduction ranging from 40% to 60% within 1–2 yr of ^{131}I therapy (Table 11). Half of the effect appears within the first 3 months (253). A second ^{131}I dose may cause thyroid volume reduction similar to that obtained by the first dose (253, 254). The superiority of ^{131}I over L-T$_4$ has been demonstrated recently in the earlier mentioned study by Wesche *et al.* (Ref. 224; Fig. 5). Only a few studies have been performed in large goiters beyond 100 ml (Table 11). In such large goiters, a considerable amount of ^{131}I is needed, which in most cases requires hospitalization and isolation. Although the treatment with 100–150 mCi (3700–5550 MBq) ^{131}I in an outpatient setting may be accepted by various states in the United States, this is certainly not the rule. In the three studies in which a valid goiter monitoring was applied (*i.e.*, computed tomography or MR imaging; Refs. 65, 162, and 174), the mean thyroid volume reduction was 30–40% with considerable individual variations. Fractionated therapy can be given to outpatients and might be an option in large goiters (256). However, the doses should probably be given with wide intervals to rule out thyroid stunning (257), which makes this treatment modality even more cumbersome. It has recently

TABLE 11. Studies of ^{131}I therapy in nontoxic multinodular goiter

Author	n	Age (yr)	Goiter size (ml)	[131]I dose (per gram thyroid) (MBq)	Follow-up (yr)	Evaluation	Goiter reduction (%)[a]
Hegedüs *et al.* (252)	25	56 (41–79)	73 ± 6 SEM	3.7	1	Sonography	41[b]
Verelst *et al.* (262)	15	67 (62–86)	175 ± 13 SEM	2.8–3.7	2.5	Scintigraphy	39
Nygaard *et al.* (253)	69	57 (30–81)	74 (21–296)	3.7	2	Sonography	55[b]
Huysmans *et al.* (174)	19	66 ± 14 SD	269 ± 153 SD	3.7	1	MRI	40
Wesche *et al.* (255)	10	48 (40–74)	88 ± 15 SEM	4.4	1	Sonography	48
de Klerk *et al.* (162)	27	60 (36–81)	194 ± 138 SD	1.1–4.8	1	CT	34
Le Moli *et al.* (254)	50	53 (30–82)	82 (17–325)	4.4	2	Sonography	49
Bonnema *et al.* (65)	23	67 (42–86)	311 ± 133 SD	3.7–5.5	1	MRI	34
Wesche *et al.* (224)[c]	29	50 ± 13 SD	56 (17–198)	4.4	2	Sonography	44

Values are given as mean ± SD/SEM or median (range). CT, Computed tomography; MRI, MR imaging.
[a] Mean or median values.
[b] Some patients were treated with more than a single ^{131}I dose.
[c] Randomized study including a control group treated with L-T$_4$.

been shown that patients with a substernal goiter may also benefit from ^{131}I therapy (258). Because thyroid malignancy may be more prevalent in goiters with a substernal component (86, 236, 238), some risk of overlooking a cancer must be taken with this approach. The benign nature should be confirmed by FNAB of accessible dominant nodules and interpreted in the light of relevant clinical factors (firmness of the gland, growth rate, presence of lymphadenopathy, *etc.*).

Two small uncontrolled studies of ^{131}I therapy of diffuse nontoxic goiter are available (259, 260). The median thyroid volume was reduced by 62% within 1 yr of therapy. Thus, it seems that the goiter reduction is more pronounced than in the multinodular goiter and comparable to what is seen in Graves' disease (261). Future long-term studies will clarify the role of ^{131}I in this disease.

In general, patients are satisfied with the outcome of ^{131}I therapy, but quantitative analyses of the improvement in symptoms are scarce (Table 12). Little is known of the rate of goiter recurrence after ^{131}I therapy. Le Moli *et al.* (254) found that 8% of the patients had recurrent goiter growth 3–5 yr after therapy, apparently due to large goiters and/or a lower ^{131}I dose administered. However, a controlled study comparing surgery and ^{131}I, including the aspect of persistent or recurrent disease, is indeed needed. Two studies (65, 254) have demonstrated that the relative goiter reduction after ^{131}I therapy is inversely correlated with initial goiter size, despite aiming at the same absorbed dose (Fig. 6). Such a relationship is plausible, because a larger fraction of the gland may become inert and subsequently less susceptible to [131]I. The goiter reduction might be augmented by increasing the amount of radioactivity, as suggested by data from Le Moli *et al.* (254), but no dose-response study has been performed to clarify this issue specifically. In most studies of nontoxic goiters (65, 162, 174, 224, 252–254, 262), the administered ^{131}I activity was 3.7–5.5 MBq/g thyroid tissue corrected for ^{131}I thyroid uptake, aiming at an absorbed dose of approximately 100 Gy. However, it should be noticed that dose calculation based on 24-h ^{131}I uptake and not half-life may strongly overestimate the intended dose to nodular goiters (263). In fact, an elaborated algorithm for dose calculation may not be worthwhile, as is also evident in the case of hyperthyroidism (264, 265). Besides a poorly defined individual susceptibility to ^{131}I, which remains to be identified, the thyroid ^{131}I uptake displays a considerable variation with time (266, 267). The

iodine biokinetics is probably also affected by the ^{131}I therapy itself (266). Finally, the absorbed dose may be influenced by shrinkage of the gland during therapy (268).

The efficacy of ^{131}I therapy on the whole gland is hampered by the irregular ^{131}I uptake in the multinodular goiter. The number of suppressed nodules and extent of degenerated tissue probably set an upper limit for the obtainable reduction with this treatment. The fact that so few thyroidologists routinely recommend ^{131}I therapy in the euthyroid patient is bewildering (Refs. 8 and 9; Fig. 4), especially when 40–55% of clinicians will turn to ^{131}I therapy facing a patient with a suppressed serum TSH level (Refs. 8 and 9; Fig. 4). In this situation, goiter volume reduction is no better than that observed in the euthyroid patient (269). However, the recent advent of recombinant human TSH having the potential of doubling the 24-h ^{131}I uptake (270) opens new avenues. In addition, pretreatment with recombinant human TSH causes a more homogeneous distribution of ^{131}I within the nodular gland by stimulating the ^{131}I uptake relatively more in cold areas than in hot areas (271). These potential benefits of recombinant human TSH are very intriguing in the context of an amplification of the ^{131}I therapy, but whether the goiter reduction can be improved and whether this leads to a change in attitude among clinicians remains to be proven.

Only in very few European countries, like Denmark and to some extent The Netherlands, is ^{131}I now the routine choice as treatment of the benign nontoxic multinodular goiter (8, 9). In North America, for example, the thyroid iodine uptake is rather low due to the high dietary iodine intake. Thus, if ^{131}I therapy is to be used, a relatively high amount of radioactivity is needed, and this may hinder outpatient treatment. Other reasons for the reluctance to use ^{131}I therapy in nontoxic goiters may be lack of experience and fear of side effects (Table 9). There has been concern of an early goiter enlargement caused by the radiation, thereby leading to a possible exacerbation of the tracheal compression. A general reservation is not justified because, on average, ^{131}I therapy is not followed by any significant acute thyroid enlargement (65, 272), either in moderate or in very large multinodular goiters. However, because a goiter increment of 15–25% occasionally may be seen (65, 272), caution should be taken if severe tracheal compression is present. [131]I therapy is generally well tolerated. A radiation-induced thyroiditis may be seen in a few percentage of cases (106), occurring within the first

TABLE 12. Goiter-related symptoms and signs before and after ^{131}I therapy in 50 patients with nontoxic goiter

	Baseline (% of patients)	2 yr after ^{131}I (% of patients)
Symptoms		
Cosmetic complaints	28	7
No obstructive symptoms	24	83
Globulus sensation	64	16
Shortness of breath	40	6
Difficulties in swallowing	24	5
Signs		
No obstructive signs	64	81
Deviation of trachea	36	5
Inspiratory stridor	12	0
Hoarseness	6	0

Adapted from Le Moli *et al.* (254).

FIG. 6. Relation between initial goiter size and effect of ^{131}I in nontoxic multinodular goiter. Adapted from Bonnema *et al.* (65).

month after therapy. This self-limiting condition is characterized by severe tenderness of the thyroid, elevated sedimentation rate, and fever. Antiphlogistics are helpful until the thyroiditis resolves, which usually happens within a few weeks. In addition, β-blockade for a short period of time may be indicated due to the concomitant hyperthyroidism caused by dumping of stored thyroid hormones into the circulation. The fact that ^{131}I therapy may trigger a transition into Graves' disease in 5% of patients (106, 273), occasionally associated with ophthalmopathy (274), is a matter of great concern. Presence of anti-TPO antibodies is a risk marker for this autoimmune response (106) and can thus to some extent be anticipated. This Graves'-like disease, occurring typically within 1–3 months after treatment, is associated with the *de novo* appearance of TSHR antibodies, probably triggered by the release of antigenic components from follicular cells during the ^{131}I therapy. This complication is mostly transitory but in the occasionally persistent cases, therapy of the hyperthyroidism and the ophthalmopathy can be troublesome.

^{131}I therapy of any thyroid disorder always includes a certain risk of thyroid hypofunction, increasing with time. In patients with diffuse nontoxic goiters treated with ^{131}I, permanent hypothyroidism occurs in 14% after 1 yr (259, 260), whereas long-term follow-up data are not available. The incidence of permanent hypothyroidism after ^{131}I therapy in moderately enlarged multinodular nontoxic goiters ranges from 22% to 58% within 5–8 yr (253, 254), occurring more commonly in those patients with an initially smaller goiter size and with the presence of anti-TPO antibodies (254). The cumulated risk of hypothyroidism after treating large goiters is theoretically the same as in smaller goiters, because the administered radioactivity is targeted at the same absorbed dose. Indeed, the 1-yr incidence of hypothyroidism of 14–22% is not particularly high (65, 162).

When giving therapeutical amounts of radioactivity, the cancer risk is of paramount concern. ^{131}I therapy, given for Graves' disease for decades, is not followed by any clinically significant increased risk of cancer deaths according to several long-term studies (275, 276). In a study from the United Kingdom (275), a slightly increased incidence of thyroid cancers was observed (nine *vs.* an expected three), but the overall cancer mortality was actually reduced. Data on the multinodular goiter are more sparse. In the study by Ron *et al.* (276), 1089 patients were treated for a toxic nodular goiter,
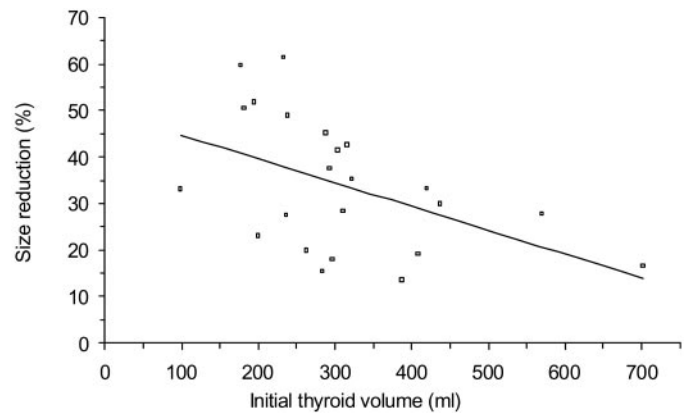
and these individuals had a 31% increase in overall cancer mortality, nearly exclusively attributable to thyroid malignancy. However, a similar pattern was seen in patients having the same disease but not treated with ^{131}I. In a Swedish study (277), the corresponding mortality rate was increased by more than 26% in 4,000 patients. Most of the increased mortality among patients with nodular thyroid diseases was due to thyroid cancer deaths, and this mortality diminished during prolonged follow-up (277). Hence, the disclosure of a thyroid cancer in a nodular goiter after ^{131}I therapy raises the question whether malignancy in a nodule was overlooked at the time of therapy. A recent study (278) including more than 5000 patients previously treated with ^{131}I for toxic nodular thyroid diseases is reassuring, because no significantly increased incidence of thyroid cancers was found during the 27 yr of follow-up. Nonetheless, the absolute number of cancers that may occur after ^{131}I is small in all studies and seems of minor clinical importance. The risk of thyroid cancer due to ^{131}I therapy should not be different when treating small or large thyroid glands. During high-dose ^{131}I therapy of large goiters, Huysmans *et al.* (279) calculated the theoretical lifetime risk of an extrathyroidal cancer to be 1.6% and a little lower (0.5%) when given to persons aged 65 yr (279).

For nontoxic goiter, we restrict the use of ^{131}I therapy to patients above 20 yr old. In case of a very large goiter, surgery clearly should be preferred to high-dose ^{131}I therapy, and until long-term data on the actual cancer risk are available, this latter therapy should not be given to patients younger than 40 yr, unless surgery is absolutely contraindicated.

4. Effect of treatment on tracheal compression and lung function. That treatment of the goiter has a favorable effect on the tracheal air flow was reported 25 yr ago (170) and has been verified in subsequent studies. Geraghty *et al.* (171) found a 25% increase in the maximal inspiratory flow rate after thyroidectomy, even in patients with a normal tracheal radiogram preoperatively. Similar results have been found in other studies (172, 280). Also, ^{131}I therapy has proven its efficacy (281). In the study of large goiters by Bonnema *et al.* (65), the smallest tracheal cross-sectional area was diminished by 9% 1 wk after therapy due to goiter enlargement in some patients, but no significant deterioration of the inspiratory capacity was observed in that study. If severe tracheal

compression is known to be present before therapy, in principal documented by a flow-volume curve, or clinical worsening of the cervical compression should occur post treatment, glucocorticoids (prednisone 25 mg/d for a few weeks) to reduce thyroid edema might be of benefit, although this strategy is not documented by any controlled trial. In the long term after ^{131}I therapy, the smallest cross-sectional tracheal area has been shown to increase by 17–36% (65, 174), and the tracheal deviation decreases by 20% (174). The individual changes of the inspiratory capacity may show wide variations, but on average a 20–25% increase of this variable can be expected (65, 174).

The possible effect of L-T_4 suppressive therapy on the respiratory function or the tracheal anatomy has not been evaluated in any large-scale study (170).

B. The solitary nontoxic nodule

Because the aspects of surgery, ^{131}I, and L-T_4 therapy bear much resemblance to what has been detailed regarding the

multinodular goiter, we will focus on the newest (experimental) modalities regarding treatment of the solitary nodule. Much of the evidence of current treatment preferences, as with multinodular nontoxic goiter (8, 9), stems from recent ATA and ETA questionnaire studies (Refs. 6 and 7; Fig. 7). Whenever applicable, we will refer to these studies. The solitary nontoxic nodule is also covered by the algorithm in Fig. 2. Table 13 summarizes advantages and disadvantages of the various treatment options in the patient with a solitary nontoxic benign nodule.

1. Incidentaloma. Nodules measuring 1–1.5 cm or larger are usually palpable when located superficially and should undergo FNAB. Therefore, it is reasonable to offer nonpalpable nodules of the same size US-guided FNAB (128, 190). The proportion of malignancies among incidentalomas smaller than 1.5 cm ranges from 3–6%, similar to the frequency for palpable nodules (181, 203), thus suggesting that incidentalomas cannot be left untreated with impunity. However, only 1 of 15 occult thyroid cancers will progress to a clinical stage,
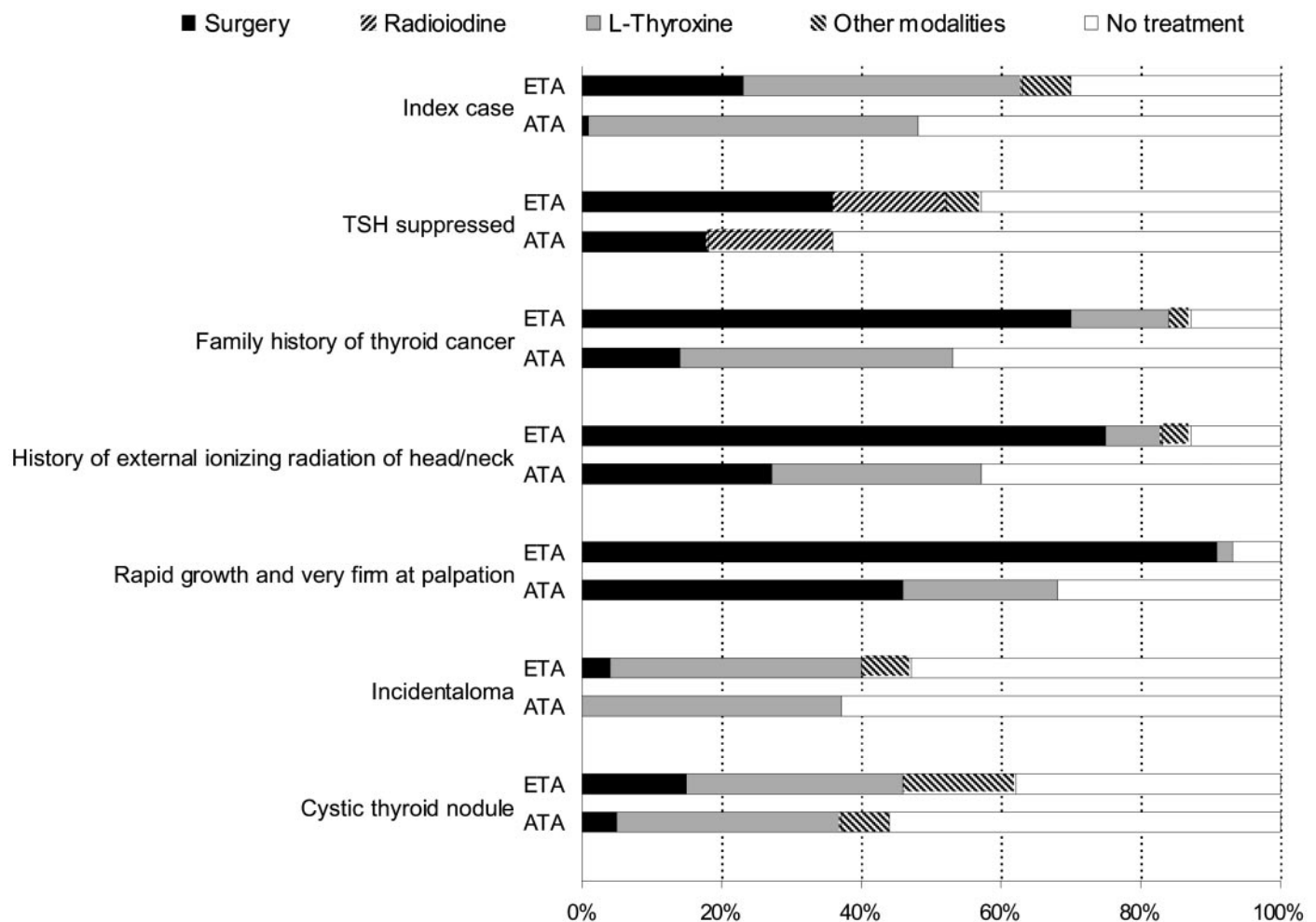

Fig. 7. Treatment options in nontoxic solitary thyroid nodules and preferences among ATA and ETA members according to questionnaire surveys (6, 7). Index case: "A 42-yr-old Caucasian woman is seen in your hospital/clinic due to a palpable mass in the left thyroid lobe. It is clinically judged to be a solitary 2 × 3-cm mobile nodule. There is no lymphadenopathy and no symptoms of thyroid dysfunction or anterior neck pain. The nodule has been present for 3 months, and the patient reports of moderate local neck discomfort. There is no family history of thyroid disease and no positive information of previous external irradiation. Your investigations, whatever these have been, have demonstrated a benign condition." In the six listed variations, only one variable has been changed. Other modalities: Iodine, iodine together with L-T_4, or PEIT.

TABLE 13. Advantages and disadvantages of the treatment options in nontoxic solitary thyroid nodules

	Advantages	Disadvantages
Surgery	Nodule ablation Complete relief of symptoms Definite histological diagnosis	Inpatient High cost Surgical risk Vocal cord paralysis: ~1% Hypoparathyroidism: <1% Hypothyroidism: 1%[a]
Ethanol injection	Outpatient Relatively low cost No hypothyroidism	Repeat injections needed Low efficacy in larger nodules (>15 ml) Operator dependency Painful, causing reduced patient compliance Transient dysphonia: 1–2% Thyrotoxicosis (autoimmune response): ~1% Seepage of ethanol[b] Cytological/histological interpretation impeded in treated nodules
^{131}I[c]	Outpatient Low cost Few subjective side effects Nodule reduction: 45% within 2 yr	Contraceptives needed in fertile women Gradual reduction of the nodule Hypothyroidism: 10% within 5 yr Radiation thyroiditis: 1–2% Autoimmune response: <1% Long-term cancer risk unknown
L-T$_4$	Outpatient Low cost Nodule growth slowed Prevents in part new nodule formation	Low efficacy Lifelong treatment Regrowth after cessation Adverse effects (bone, heart) Not feasible when TSH is suppressed

[a] Hemithyroidectomy.
[b] Side effects due to ethanol escaping outside the nodule or drainage of ethanol are rare (<1%) and comprise nerve damage, perinodular/periglandular fibrosis jeopardizing subsequent surgery, thrombosis of the jugular vein, and neck hematomas.
[c] Treatment of the autonomous thyroid nodule.

and the vast majority will remain occult throughout life (46). In the centimetric incidentaloma, sized 1×1 cm, and without clinical suspicion of malignancy, the majority of North American and European thyroidologists (63% and 53%, respectively) prefer the conservative strategy of surveillance, including FNAB in case of growth (6, 7). One third support the use of TSH suppressive therapy (Fig. 7). We do not routinely perform FNAB in the subcentimetric nodule.

2. Solitary hot nodule. In the clinically euthyroid patient, autonomous thyroid nodules may present as a hot lesion on scintigraphy with varying degrees of extranodular suppression. The majority of these patients have subnormal or suppressed serum TSH levels. Treatment may be indicated due to either nodule size, causing compression of the adjacent structures, or cosmetic complaints. Additionally, treatment may prevent hyperthyroidism [annual risk, 4% (80)], particularly in patients with heart disease or in the elderly (282). The prevalence of carcinoma in the autonomous nodules (with or without hyperthyroidism) is low (283–286). Therefore, risk of cancer does not enter into the choice of therapy (282). These patients with subclinical hyperthyroidism (subnormal serum TSH but normal serum T$_4$ and T$_3$) have few or no symptoms or signs of hyperthyroidism, but the natural history is progression to overt hyperthyroidism with an annual risk of 4% (80). Because subclinical hyperthyroidism also has a detrimental effect on particularly the skeleton and the cardiovascular system (11, 12, 227–229), as discussed earlier, there is no reason to postpone treatment when facing this condition. Still, the majority of clinicians would refrain

from therapy until biochemical hyperthyroidism ensues (Fig. 7; Refs. 6 and 7).

a. ^{131}I therapy. ^{131}I is a simple, cost-effective, and safe procedure. A cure rate (normalization of scintigraphy and serum TSH) of 75% and a thyroid volume reduction of 40% (total as well as nodule volume) after a single dose of ^{131}I can be anticipated (282). This is similar to that observed in toxic solitary thyroid nodules (287, 288). Side effects are few, consist of hypothyroidism in approximately 10% after 5 yr, and seem unrelated to any type of dose planning (282). The frequency of hypothyroidism is higher among patients who also have thyroid autoimmunity (289) or persistent uptake by extranodular thyroid tissue (290).

b. Surgery. Surgery and ^{131}I are both effective, and the choice among them depends largely on their availability, some clinical features, and the personal preference of the patient and the physician. Either can also result in hypothyroidism. Surgery is often preferred for younger patients and those with larger nodules or in case of clinical or cytological suspicion of malignancy (Figs. 2 and 7). ^{131}I is preferred for older patients and those with smaller nodules.

The preferred operation is a unilateral subtotal lobectomy. The frequency of complications due to surgery depends on several factors, and experience tends to reduce the rates with specialized training (232). Recurrence after surgery is rare, and the frequency of hypothyroidism is low, although up to 22% of patients with a toxic nodule develop hypothyroidism (291). Such a high frequency is probably explained by the fact

that one third of the patients in that study (291) had a bilateral subtotal thyroidectomy.

c. Other treatment. Reluctance to use radioactive tracers has been the incentive for numerous Italian centers to introduce percutaneous ethanol injection therapy (PEIT) during the last 12 yr, but none has compared PEIT with standard therapy (^{131}I or surgery), and the studies comprise only selected patients (292–311). The sclerosing properties of ethanol have been recognized for many years, and the mechanism of action is a coagulative necrosis and concomitant small vessel thrombosis. Disappearance of nodular hypervascularity is visualized during treatment and at follow-up by means of color or power Doppler sonography (displays the Doppler signal in color) and may improve the accuracy of the procedure (310). The procedure is performed under US guidance and on an outpatient basis. Markers of efficacy comprise thyroid function, thyroid scintigraphy, and sonography including changes in nodular volume. Complete cure, defined as normalization of serum TSH and scintigraphic reactivation of extranodular tissue, is achieved in 68–100% of solitary hot nodules (312). Partial cure, defined as detectable serum TSH and partial reactivation of extranodular tissue, is achieved in 0–39% (312). In the largest series comprising 429 patients from 5 Italian centers followed for 12 months, complete cure was achieved in 83% of the pretoxic nodules with a concomitant reduction in nodule volume of approximately 50% (301). The most important factors in predicting a clinically relevant response to PEIT are pretreatment nodule volume, thyroid hormone and TSH levels, and the experience of the operator. PEIT seems less effective in larger nodules (>15 ml; Refs. 294, 297, and 301).

One of the limitations is clearly the need of repeat ethanol injections to achieve complete cure, *e.g.*, a median of 4 sessions (range, 2–12), in the largest study (301). Side effects comprise radiating pain in 90% (and called for interruption of the treatment in 5%), hyperpyrexia in 8%, transient dysphonia in 5%, neck hematoma in 4%, and thrombosis of the ipsilateral jugular vein in one patient (301). Despite release of thyroid antigen after the injection procedure, formation of autoantibodies was seen in only 3% in one study with 5-yr follow-up (302). Hypothyroidism is rarely encountered (0–3%; Refs. 292–311), and appearance of Graves' disease has only been described in a case story (313). Long-term effects and side effects are reported scantily. The risk of fibrosis and adhesion to periglandular structures may seriously jeopardize subsequent surgery, a fact that has been given little attention (312, 314). One percent of ETA members recommend this treatment routinely, and it still remains to be introduced in North America (Fig. 7; Refs. 6 and 7). Although the complication rate seems low, the treatment is often uncomfortable, and its efficacy is operator dependent. PEIT seems most effective in small nodules and still requires multiple injections, and introduction into routine use cannot be recommended until comparative randomized studies testing PEIT against standard therapy have been undertaken.

Recently, a feasibility study from Rome described US-guided percutaneous interstitial laser photocoagulation (ILP) in two patients with huge autonomously functioning nodules, before thyroidectomy (315). Using low-energy output (2–5 W), a significant coagulative necrosis in well defined areas was caused in the treated nodule. This novel approach appears feasible but needs confirmation in additional studies.

3. Solitary solid cold nodule

a. T$_4$ therapy. It is still common practice to use thyroid suppression in the management of solid thyroid nodules in the euthyroid patient (Fig. 7; Refs. 6 and 7). This treatment is intended to shrink existing nodules, considered to be a favorable sign, indicating that the nodules are benign and therefore do not require surgery. The method is also used to prevent the occurrence of new nodules. Most evidence suggests that changes in nodule size are independent of serum TSH levels, and treatment seems at best beneficial in a subgroup of patients with smaller solid nodules (316). Twenty percent or less of solitary nodules will actually regress significantly as a result of L-T$_4$ treatment, and regrowth is seen after cessation of therapy (316, 317). A 5-yr follow-up study confirms that the nodule-reducing effect of L-T$_4$ is insignificant (318). Likewise, a recent review suggests that only a subset of patients have a clinically significant (≥50%) reduction of nodule size or arrest of nodule growth (319). It seems probable that a beneficial effect on pressure symptoms and/or cosmetic complaints in the responders is due also to the reduction in perinodular thyroid volume explained by a preserved TSH responsiveness of the tissue (320). In a recent meta-analysis of 6 randomized controlled trials comprising 346 patients, it was found that only 22% of patients treated with L-T$_4$, compared with 10% in the control groups, had a nodule volume decrease by more than 50% (321). Overall treatment response did not achieve statistical significance but was associated with a trend toward a reduction of more than 50% in nodule volume after 6–12 months of L-T$_4$ therapy.

Nodule growth may be suppressed or slowed, and the formation of new nodules may be prevented. Nodules grow less if serum TSH is suppressed below 0.1 mU/liter than if TSH is greater than 0.1 mU/liter (318). This degree of TSH suppression may, however, have adverse effects. Because suppressive therapy results (by definition) in subclinical hyperthyroidism, treated patients are at increased risk of atrial fibrillation, other cardiac abnormalities, and reduced bone density (11, 12, 228). These side effects, combined with the questionable efficacy, have led to recommendations that vary depending upon the age, sex, and menopausal status of the patient. L-T$_4$ suppressive therapy is least tempting in elderly patients and in postmenopausal women. If used at all, it should be reserved for small nodules (223) in which treatment is least necessary, *i.e.*, in younger patients. Although this treatment has been abandoned in our country (Denmark) (322), it is still the routine choice of nearly half of ATA and ETA members (Fig. 7). In view of the potential side effects and the questionable efficacy, it is surprising that 50–70% would aim at subnormal serum TSH levels and treat more than 1 yr (6, 7).

b. Surgery. The main indications for surgery are malignant or suspicious cytological features and symptoms due to the nodule itself, be it pressure related or cosmetic (Figs. 2 and

7). Certain clinical features raising the suspicion of thyroid malignancy (Table 2) are an indication for surgery, despite benign cytological features, as recommended by the majority of European and half of the American thyroidologists (Refs. 6 and 7; Fig. 7). In the clinically and cytologically benign thyroid nodule, surgery is recommended as the therapy of choice by 23% of European thyroidologists but hardly ever by North American thyroidologists (Refs. 6 and 7; Fig. 7).

Patients with a single thyroid nodule who are offered surgery will generally be managed with hemithyroidectomy (lobectomy; Ref. 179). The clinical recurrence rate is approximately 10% (323). Resident nodules, overlooked if imaging has been left out in the diagnostic approach, are a common cause of recurrence (178). Total thyroidectomy is not routinely indicated, although some authors choose this approach in case of a history of head and neck irradiation to avoid reoperation and to eliminate any subsequent risk of malignancy in irradiated thyroid glands (324). Postoperative thyroid suppression to avoid recurrence is questionable (239, 323, 325). The incidence of complications, particularly postoperative hypocalcemia and injuries to the recurrent laryngeal nerve, is low in the case of lobectomy (1% and 1–3%, respectively; Refs. 232, 326); correlates with the extent of the surgical procedure; and decreases with increasing experience and specialized training (327). Minimally invasive video-assisted thyroid lobectomy using endoscopic techniques may also affect the practice of thyroid surgery (328–330), but it is still implemented in only a few centers.

c. Other treatment. Absolute ethanol (70–100%) can cause permanent tissue ablation due to coagulative necrosis and local small vessel thrombosis. A single small dose of ethanol injected into benign cold solitary solid thyroid nodules results in relief of clinical symptoms in 50% of patients, based on a nodule volume reduction of approximately 50% (320, 331). Repeat (*i.e.*, seven or more) injections result in a reduction in nodule volume of 80% (332, 333). In one study, the total amount of ethanol administered per patient was on average 1.3 ml/ml nodular volume and never exceeded 20% of the nodule volume in each session (332). In this study, nodule reduction was unrelated to absolute or relative amount of ethanol injected but closely negatively related to pretreatment volume, although similar effects were obtained whether pretreatment nodule volume was larger or smaller than 15 ml. A limitation is the need of repeat ethanol injections to prevent renewed growth in solid cold nodules. Furthermore, the procedure is often painful despite local anesthesia, and complications such as periglandular adherence (impeding subsequent surgery in case of failure of the treatment), dysphonia, or mild fever must be anticipated in some (331). An autoimmune response with development of thyroid autoantibodies can be seen in up to 11% of treated patients (332). To minimize the risk of complications due to sudden increase in intranodular pressure and extranodular seepage of ethanol, each dose should probably not be higher than 20% of the pretreatment nodule volume. The special technical skill obtained at a center familiar with interventional sonography is required to reduce the risk of complications. The procedure should still be considered experimental and reserved for those who cannot or will not

undergo standard therapy. The experimental status is illustrated by only 1% of the ETA clinicians (6) and none of the ATA clinicians (7) advocating this therapy (Fig. 7).

Recently, we introduced US-guided ILP (Fig. 8; Ref. 334). In 16 patients treated with 1–3 W for a median of 8 min, one treatment resulted in an overall reduction in nodule volume of 46% and significant relief of pressure symptoms. This is surprisingly similar to results obtained with ethanol therapy (331). Apart from mild transient pain, the treatment was well tolerated. The advantage of thermal destruction is that the spread of energy, and thus the extent of tissue ablation, can be controlled as opposed to chemical destruction by injection of a fluid, *e.g.*, absolute ethanol. So far, therapy must be individualized on the basis of the patient's preference and risk of adverse effects. Additional data, including dose-response, preferably from prospective, randomized studies are needed before evaluating the possible future of this technique.

4. Solitary cyst. Evaluated by sonography, 15–25% of solitary thyroid nodules are cystic or predominantly cystic (163). The literature on thyroid cysts varies due to definitions depending on whether it is based on sonographic findings alone or addition of some descriptive cytological features, often indicating degenerative changes in a benign or neoplastic lesion (195). The main concern is the fear of malignancy. The inconsistency in malignancy rates is most likely due to the results being based on retrospective data in selected patients and different selection criteria for performing surgery (195). Although data indicate a lower frequency of malignancy in a cystic than in a solid thyroid lesion (195), it is certainly high enough to warrant considerable attention.

In an unselected population of patients with nodular thyroid disease, most cysts arise from benign thyroid tissue (335). In case of a benign lesion, simple aspiration is the treatment of choice, but the recurrence rate is 10–80% depending on the number of aspirations and the cyst volume (336, 337). That is, the greater the volume, the greater is the risk of recurrence (312). Still, the fact that a number of benign cystic nodules resolve spontaneously, given sufficient time (338), makes therapy superfluous in some. Indications for therapy are symptoms of compression or cosmetic complaints. Smaller cysts (<2–3 ml) are generally best left untreated (312). If larger, we always perform aspiration and FNAB of any residual nodule. Rarely (1–3%), supposed thyroid cysts do not originate from the follicular epithelium, but from the parathyroids. Such cysts often contain fluid that is transparent like water. Diagnosis is based on high concentrations of PTH and low or undetectable concentration of Tg in the aspirate (339).

a. T$_4$ therapy. In a prospective double-blind randomized study including only 20 patients, no effect on the recurrence of thyroid cysts after aspiration was seen in patients treated with L-T$_4$ when compared with patients receiving placebo (340). Thus, the use of L-T$_4$ by nearly one third of ATA and ETA thyroidologists is not based on evidence of its efficacy (Fig. 7; Refs. 6 and 7).

b. Surgery. Surgery should be considered, given certain clinical features (Table 2; Refs. 194 and 197). Some authors,
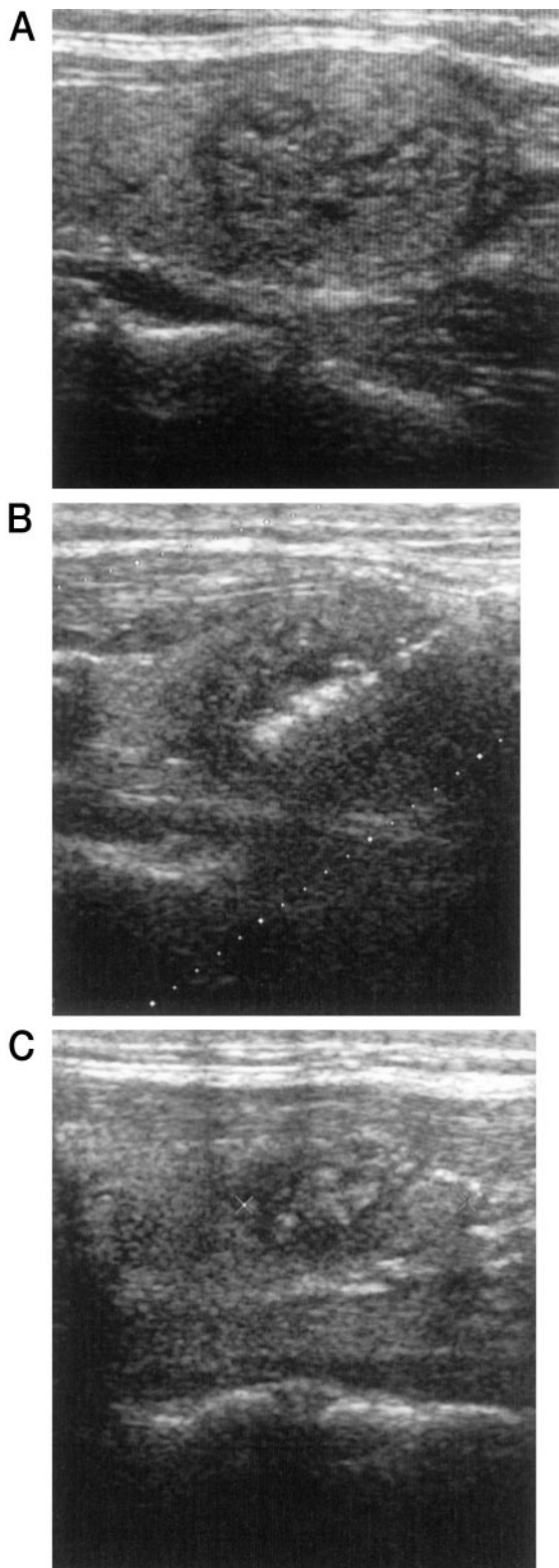
FIG. 8. Longitudinal ultrasonographic scan of the neck showing a solid nodule in the left thyroid lobe before ILP (A), during ILP (B), and at the follow-up 1 month after ILP (C). In B (60 sec after ILP has been initiated), a cylindrical echogenic area is seen centrally. In C, a hyperechogenic area representing scar tissue is seen in the center of the nodule. A small rim is untreated in the proximal and caudal part of the nodule.

as suggested by 5% and 15% of ATA and ETA thyroidologists, respectively (Fig. 7; Refs. 6 and 7), recommend thyroid lobectomy for histological verification even with benign cytology (341). Surgery is advisable in case of suspicious or persistently nondiagnostic cytology (198) after repeat aspiration, including a possible solid component and the wall of the lesion. It is evident that this is best obtained by US-guided FNAB (199). Surgical removal should indeed be considered if large cysts more than 3 cm recur after aspiration, because more than 10% of these lesions are reported to harbor thyroid cancer (342), despite a benign FNAB initially.

c. Other treatment. In 1981, Bean (343) suggested that renal cysts can be treated by PEIT. This success was the basis for introducing the new technique in the treatment of cystic lesions in other parenchymatous organs or soft tissues such as in the thyroid gland (312).

Various sclerosing agents, such as tetracycline, have been suggested, but results have been conflicting (344–352). In one nonrandomized study, instillation of tetracycline hydrochloride resulted in the cure of 91% of patients with recurrent thyroid cysts, but on the other hand, 86% were cured after aspiration alone (351). However, in the only randomized study, Hegedüs *et al.* (349) demonstrated that tetracycline treatment and isotonic saline were equally effective. Reported complications comprise local or radiating pain and transitory hyperpyrexia (349–352).

Seven studies using ethanol instillation in thyroid cysts have been published (306, 353–358), comprising 214 patients treated with PEIT. The success rate, defined as near disappearance or marked (>50%) size reduction, varies from 61–95%. In the only placebo-controlled study with just one treatment, the short-term (1 month) success rate was 80% in the group treated with ethanol and 30% in the group treated with simple aspiration (353). Long-term follow-up (12 months) in 32 consecutive patients treated once with ethanol confirms the preliminary results obtained in the smaller randomized study (353). Other studies lack an evaluation of success rate based on the number of ethanol instillations and an adequate control group (306, 354–358).

Side effects of ethanol instillation into cystic thyroid nodules seem to be few and are generally described as mild and transient, and pain is less pronounced than that described after injections into solid structures (312). However, serious side effects due to seepage outside the capsule causing considerable fibrosis and thrombosis of the jugular vein have been described (359). PEIT should still be regarded as an experimental treatment and be performed only by skilled operators. Five percent of ETA members have already introduced this option in a routine clinical setting (Fig. 7; Refs. 11 and 12).

Data from experimental treatment, whether in autonomously functioning nodules, solid cold nodules, or cystic nodules, are at large based on nonrandomized studies comprising selected patients. What is needed now is cost-benefit studies comparing a standardized ethanol regimen with standard treatment in properly conducted comparative randomized studies. The same certainly holds for future research into laser therapy.

Table 13 summarizes advantages and drawbacks of the

therapeutical options in the treatment of solitary hot, cold, and cystic thyroid nodules.

VII. Unresolved Issues and Future Perspectives

Although SNG affects millions of individuals, also in iodine-sufficient regions, many fundamental aspects pertaining to etiology, natural history, and diagnostic as well as therapeutic management of the disorder remain unclarified.

Although major environmental risk factors such as iodine deficiency and cigarette smoking are involved in the etiology, an increasing body of evidence suggests that heredity is equally, if not more, important. Current strategies, including whole genome scanning in multiply affected families, aim at clarifying the molecular basis of the genetic susceptibility and aspects of the gene-environment interaction, thereby possibly leading to more focused preventive actions in the future.

Until such strategies bear fruit, an intensified debate on cost-effective management of nodular thyroid disease is necessary. There is agreement on the central role of FNAB in addition to serum TSH determination in the initial evaluation of such individuals. Evidence suggests that US guidance increases adequacy of sampling. An increasing number of specialists use diagnostic imaging (mainly sonography and scintigraphy), which is pertinent when selecting patients for nonsurgical therapy. Although new isotopes, contrast media, Doppler technology, and three-dimensional investigations have increased sensitivity, specificity for detecting thyroid malignancy still needs to be improved. More promising, however, is the search for non-TSH related growth factors. The combination of new molecular genetic techniques applied on the easily attainable thyroid tissue, by FNAB, should lead to an increasing understanding of the pathogenesis of nodular thyroid disease and a better characterization of phenotypes.

Treatment still focuses very much on L-T_4, although at best this treatment slows growth for a limited time period in a minority of patients at the cost of significant side effects related to bone and the cardiovascular system. The available evidence suggests that L-T_4 should be abandoned in the euthyroid individual. Surgery should be recommended for younger patients, for those with a large goiter (especially if intrathoracic), and in case of clinical or cytological suspicion of malignancy. However, in our opinion, ^{131}I should have a higher priority in the treatment hierarchy. At present, this option is sparsely used. It needs to be clarified whether this is based on tradition, availability, fear of thyroid or nonthyroid malignancy, or regulations allowing a low outpatient ^{131}I-dose. The latter can to some extent be overcome by the recently available recombinant human TSH, which seems to be able to double the iodine uptake in multinodular nontoxic goiter. When it comes to the benign solitary nodule, the research focus is on ethanol injection and laser photocoagulation as nonsurgical alternatives to L-T_4 therapy, which should be abandoned.

Independent of phenotype, much of the discrepancy in treatment recommendations stems from the lack of adequately performed prospective randomized studies, taking effect, side effects, patient satisfaction, and cost into consideration. For such studies to have any impact, the development and use of disease-specific quality-of-life questionnaires are mandatory.

Finally, it should be emphasized that much of our knowledge is based on what experts advise. We have little idea of whether the large majority of patients, managed by family doctors and nonthyroid specialists, are treated according to this advice, which in this case, is not even very clear.

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