DISEASES OF THE THYROID

Pathophysiology and management

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MULTINODULAR GOITER: DIAGNOSIS AND MANAGEMENT

6

C. Renate Pickardt and Peter C. Scriba

Multinodular thyroid enlargement is a symptom of different thyroid diseases with varying underlying pathogenetic principles (Table 6.1). From the epidemiological point of view, endemic and sporadic goiters have to be distinguished. Goiter endemia is assumed by definition in regions with a prevalence of more than 10% among the population under investigation [1].

In most endemic areas, iodine deficiency is the main cause of goiter development. Another cause of goiter endemia is the intake of goitrogens via the drinking water as in Columbia and the Himalayas (Chapter 3(c)). In other regions iodine deficiency and dietary goitrogens from vegetable foodstuffs are together responsible for this kind of endemic disease [2], which is best documented for Zaire. Vegetables with goitrogenic effect contain thioglycosides or cyanogenic glycosides. In this context cigarette smoking is thought to be a cofactor for goitrogenesis, since it increases serum thiocyanate concentration. Regions with iodine deficiency and endemic goiter are found all over the world, particularly in mountainous areas and continental regions, where iodine prophylaxis is not used [1,3]. The known data concerning the severity and degree of iodine deficiency and goiter prevalence in Europe are shown in Figures 6.1, 6.2. USA, Canada and Japan and the coastal areas of all continents are free of iodine deficiency diseases. In iodine deficient regions, iodine insufficiency is the most probable cause of goiter. But neither morphological nor functional criteria can discriminate specifically between endemic and sporadic goiter in an affected individual.

Sporadic goiter can be divided into cases with a genetic background, including individuals with congenital goiters in non-endemic areas, and other cases induced by goitrogenic drugs. Spontaneous cases may also arise from thyroiditis or growth stimulating globulins, especially when thyroid enlargement occurs suddenly. The different genetic defects of thyroid hormone synthesis

Table 6.1 Causes of multinodular goiter

Endemic	*Sporadic*
Iodine deficiency	Genetic defects of thyroid hormone synthesis
Dietary goitrogens	Genetic defects of thyroid hormone action
Environmental goitrogens	Goitrogenic drugs
	Thyroiditis syndromes
	Acromegaly
	TSH producing pituitary adenoma

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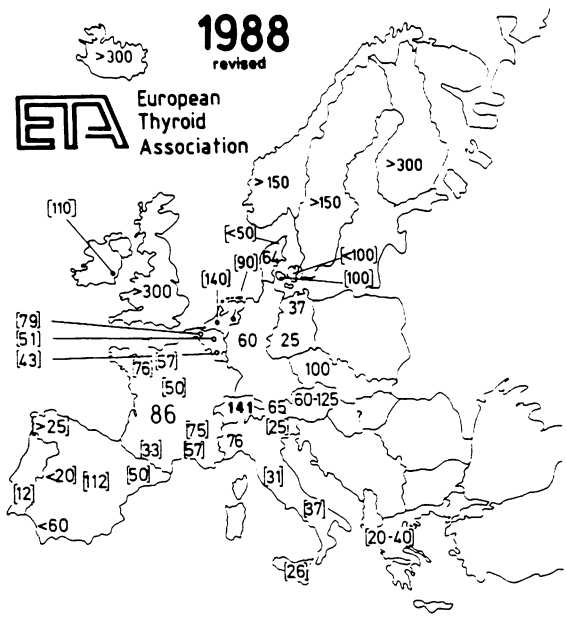

Figure 6.1 Urinary iodine excretion (μg/g creatinine); updated map of the original publication [4]. (Regional values are denoted in brackets.)

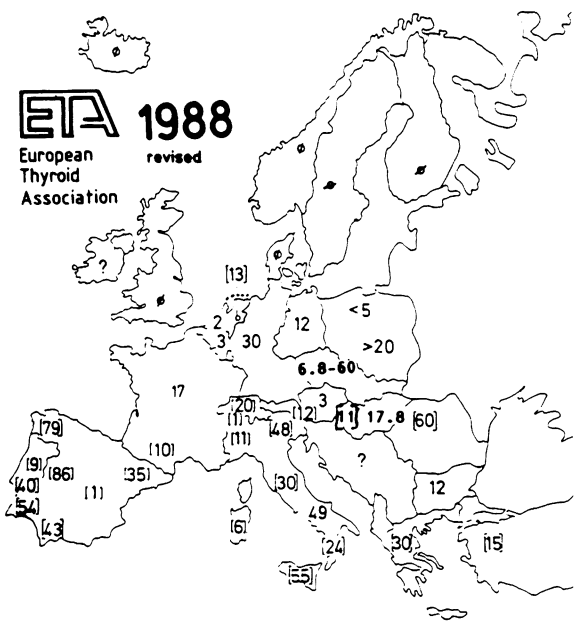

Figure 6.2 Goiter prevalence (%); updated map of the original publication [4]. (Regional values are denoted in brackets.)

or thyroid hormone action (T_4 receptor defect) are rare causes of goiter formation, which can however result in multinodular goiter in affected families. In the minor forms of these defects there may be compensation of thyroid function so that the individual remains euthyroid, whereas the major forms will be detected by evidence of hypothyroidism and goiter or even cretinism early in the childhood.

Sporadic goiter induced by drugs interfering with thyroid hormone synthesis or release is now a rare event. This is due to the fact that indications for antithyroid drug treatment are established, dosage for hyperthyroidism is easy to control, and side effects of substances such as lithium, carbutamide, fluoride and aminoglutethimide are well recognized in medical practice.

Iodine induced goiters are observed mainly in limited areas in Japan, where excessive intake of seaweed is thought to be responsible for a defect of the escape from the Wolff–Chaikoff effect. This population may develop hypothyroidism.

An acute development of multinodular goiter gives rise to the suspicion of inflammatory thyroid disease, which is painful in the case of acute thyroiditis and the subacute thyroiditis of De Quervain, or painless in the case of granulomatous diseases such as sarcoidosis or tuberculosis.

In general, nodular transformation of the enlarged thyroid is the consequence of earlier diffuse thyroid enlargement under the continuing influence of the goitrogenic principle [5,6]. Therefore, patients with multinodular goiter usually are older than those with diffuse thyroid enlargement [5,7]. It has been shown for sporadic goiter that there is a linear relationship between age and thyroid volume and nodularity, respectively, with an average yearly increase of 4.5% of goiter volume, as calculated by Berghout, *et al.* [5,8]. During nodular transformation hypo-, normal, and hyperfunctioning nodules may develop within the same

gland. Also, multiple autonomously functioning nodules can be observed in multinodular goiters with associated euthyroidism. This so-called multifocal functional autonomy is a disease with a relatively high frequency in regions with endemic goiter, but little attention has been paid to this final consequence of chronic iodine deficiency. As long as iodine deficiency persists, these patients often remain frequently euthyroid or develop borderline hyperthyroidism. Only when the amount of autonomously functioning tissue is high does spontaneous hyperthyroidism occur. However, this group of patients bears an unknown risk of iodine induced hyperthyroidism when there is a brisk and/or prolonged increase of iodine intake (Chapter 5(d)). In our hospital, this disease is twice as often the cause of hyperthyroidism as immunogenic thyroid disease.

6.1 CLINICAL PICTURE

In endemic goitrous areas, the medical history of multinodular goiter reveals a long-standing thyroid enlargement in most cases [9,10]. As long as the patient has no signs or symptoms of thyroid dysfunction and no local complications, the disease is often unnoticed and may be detected just by chance. In other cases, increasing growth of the whole organ, or of one or more nodules, is responsible for local symptoms (Table 6.2) and brings the patient to medical attention. This history is typical of endemic goiter in iodine deficient regions as well as for endemic goiter in areas with a significant intake of goitrogens. Depending on the degree of iodine deficiency or dietary intake of goitrogens, patients may be euthyroid or have more or less pronounced signs of hypothyroidism. In European countries with mild iodine deficiency, the goitrous population is euthyroid with few exceptions [3,11]. Other causes of multinodular goiter, such as defective thyroid hormone synthesis or hormone action, induce gradual and differing degrees of hypothyroidism. In the more complete forms of these genetically determined diseases the affected individuals are overtly hypothyroid. Patients with sporadic goiter due to drugs are also usually euthyroid. In lithium treated individuals, however, hypothyroidism has been observed. The rare condition of TSH-producing pituitary tumor has already been discussed. Patients with acromegaly and goiter are euthyroid.

Table 6.2 Clinical symptoms of multinodular goiter

Feeling of tightness
Feeling of a foreign body
Dysphagia
Urge to cough
Hoarseness
Dyspnea, stridor
Upper venous obstruction

Symptoms from nodular goiter are summarized in Table 6.2. A feeling of tightness or of a foreign body may be nonspecific and independent of the actual thyroid volume or nodules; these complaints may draw the attention of the patient and his medical attendant to the thus incidentally detected disease. Dysphagia and an urge to cough may result also from retrotracheal thyroid tissue which may be detected only by the surgeon. Hoarseness can be a sign of functional impairment of the recurrent laryngeal nerve; this functional impairment can also be induced spontaneously in rare cases by benign thyroid nodules. Dyspnea and stridor may be due to tracheal compression or dislocation by episternal or intrathoracic goiters. Both true and false endothoracic goiter can cause compression of the upper venous system, accompanied by a more or less pronounced venous bypass of the ventral thoracic wall (Figure 6.3). So-called downhill varicosis of the esophagus usually remains symptomless (Figure 6.4).

Patients with acute and subacute thyroiditis present with a painful enlarged goiter; pain usually disseminates over the neck to

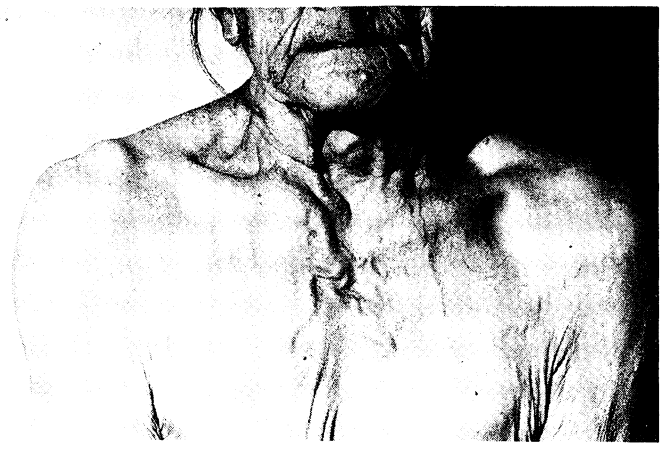

Figure 6.3 Venous bypass of the ventral thoracic wall in a female patient with endothoracic parts of a nodular goiter.

the ears or teeth. Palpation of the nodules intensifies the pain. In chronic inflammatory diseases, such as sarcoidosis, the nodules are painless and local symptoms do not differ from those of endemic goiter. With respect to the usually short history of these nodular goiters, thyroid malignancy also has to be considered.

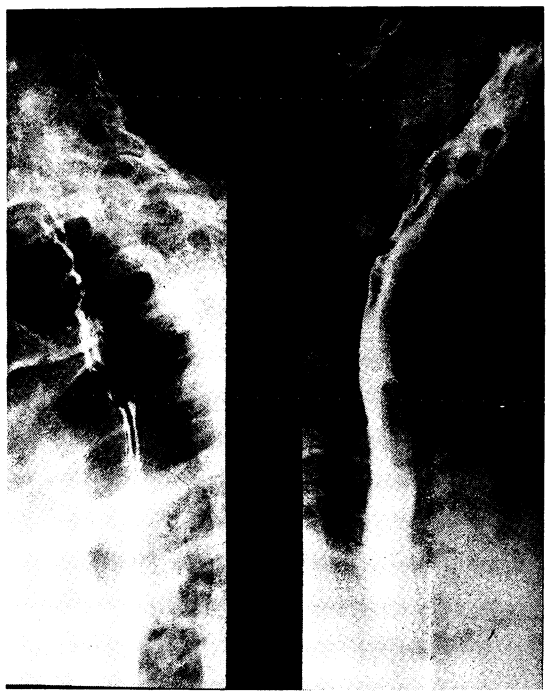

Figure 6.4 So-called downhill varicosis of the esophagus in a patient with recurrent goiter.

6.2 DIAGNOSTIC PROCEDURES

6.2.1 PALPATION AND INVESTIGATION BY ULTRASOUND

Diagnostic procedures are summarized in Table 6.3. Conventionally, the multinodular thyroid is detected by simple palpation [7–9,12]. We perform palpation standing behind the sitting patient. In this way, thyroid tissue can be defined by the movement induced by swallowing a gulp of water. Nodularity can be detected and described separately for each lobe and for the thyroid isthmus, while also noticing the consistency. It is of importance to state whether the lower pole can be defined clearly in the episternal part of the neck, thus generally excluding endothoracic parts of the thyroid.

Historically, goiter size is estimated according to the WHO classification (Table 6.4) which was originally proposed for epidemiological purposes. Today, individual goiter size can be estimated with greater

Table 6.3 Diagnostic procedure

Palpation
High resolution ultrasonography
Adequate evaluation of thyroid function (basal TSH, FT_4, FT_3)
Radioisotopic scintiscan (with quantitative evaluation of Tc uptake; in special situations, radioiodine scan)
Cytologic evaluation of fine needle biopsy
Appropriate evaluation of local complications

Table 6.4 Estimation of thyroid size, WHO classification

Stage	*Clinical findings*
0–A	No goiter
0–B	Goiter detectable only by palpation and not visible even when the neck is fully extended
I	Goiter palpable, but visible only when the neck is fully extended; this stage also includes nodular glands, even if not goitrous
II	Goiter visible with the neck in normal position; palpation is not needed for diagnosis
III	Very large goiter which can be recognized at a considerable distance

accuracy and reproducibility by ultrasound investigation [6,11–15]. Thickness, width and length of both thyroid lobes have to be measured. The thyroid volume can then be calculated by the formula for an ellipsoid using an empirical correction factor of 0.479 or II/6, respectively [6]. The formula is:

$$\text{volume} = a \cdot b \cdot c \cdot II/6$$

where a is the maximal length, b the maximal width and c the maximal thickness.

If the investigator has some expertise, the reproducibility is sufficient for clinical purposes. The deviation of the results is ±10%. This method has limitations in large nodular goiters, where coupling of the transducer to the neck surface may not be feasible, and in patients with endothoracic thyroid tissue. Evaluation of nodularity in a thyroid with normal or enlarged volume [5,9,11,14,16,17] can be performed with a much higher sensitivity by high resolution ultrasonography when compared with palpation. By this method, in patients with uninodular thyroids on palpation, multinodularity was documented with a four times higher sensitivity as shown by Hay and co-workers [14]. Moreover, by this method, sonomorphological criteria can be used to differentiate between solid, cystic and mixed solid and cystic nodules. Among the solid nodules, those of high or normal echogeneity can be distinguished from those with reduced echogeneity by comparison with the normal thyroid and the neighboring muscular tissue. This may be helpful in determining the nodule(s) to be investigated further by fine needle aspiration to exclude or confirm malignancy [18], but it has to be emphasized that the sonomorphological appearance of a nodule *per se* never definitely excludes malignancy.

In patients with thyroiditis, all thyroid nodules appear hypo-echogenic. When inflammatory thyroid disease is assumed, white blood cell count and determination of the ESR can be helpful. In patients with acute thyroiditis due to bacterial infection, or

in those with suspicion of a granulomatous inflammation, general investigations have to be performed because disseminated manifestations have to be excluded.

6.2.2 EVALUATION OF THYROID FUNCTION

The diagnosis comprises appropriate evaluation of thyroid function. For practical purposes, a normal basal TSH level, when determined by a sensitive assay system, provides the information that the patient is euthyroid. An elevated basal TSH has to be expected in a patient with decreased thyroid hormone effect or with impaired thyroid hormone synthesis, whereas completely or partially suppressed TSH will indicate elevated thyroid hormone synthesis and action.

When the TSH levels are completely suppressed (below the limit of detection) preclinical or overt hyperthyroidism has to be excluded by determination of free thyroid hormone levels (FT_4 and/or FT_3). Preclinical and overt hyperthyroidism has a relatively high incidence in patients with multinodular goiter in iodine deficient areas.

6.2.3 RADIOISOTOPIC IMAGING

Visualization of intrathyroidal functional heterogeneities and calculation of regional differences of functional activities in the thyroid can only be achieved by radioisotope scintiscan [13] and calculation of the uptake [19,20]. In nodular goiters, the technetium-99m pertechnetate scintiscan can detect hypo- and non-functioning nodules as well as hyperfunctioning hot nodules. Under exogenous or spontaneous TSH-suppressive conditions, quantitative determination/calculation of the regional technetium uptake represents a measure of the autonomous functional activity of hot nodules [19,20]. In contrast, the documentation of hypofunctioning so-called 'cold' nodules is independent of the TSH secretion.

There is considerable variation in the diagnostic use of radioisotopic imaging of the thyroid world-wide. In euthyroid patients with a sonographically solitary nodule, radioisotopic investigation may be omitted when malignancy can be excluded cytologically. Also, in solitary pure thyroid cysts the confirmation of the lack of isotope uptake is not needed. In all other conditions of uni- or multinodular goiter, the impact of isotopic imaging is high with respect to further diagnostic and therapeutic decisions and should therefore be recommended.

In endemic goitrous regions, the multinodularity may be caused by cold and hot nodules within the same gland. Patients with this thyroid disease are at risk of hyperthyroidism in the future. Moreover, there is no reasonable form of medical treatment for this situation. In patients with sporadic goiter without defects of thyroid hormone synthesis or action, if multinodularity is present, scintiscan has to be recommended for the same reasons. Especially in non-endemic areas, metastases of non-thyroidal malignancy (bronchial, renal and breast carcinomas), parasitic infections and granulomatous diseases have to be considered as the causes of these nodules.

6.2.4 CYTOLOGICAL INVESTIGATION BY FINE NEEDLE ASPIRATION

Cytological investigation of smears of fine needle aspiration (FNA) material has its main significance in patients with solitary nodules [9,10]. In multinodular goiters, this investigation should be used when one of the nodules shows recent growth or has a hypo-echogenic structure in comparison with the normal thyroid tissue. It can also be used simply to exclude malignancy in all nodules, when surgical treatment is refused. In inflammatory thyroid diseases, FNA provides the material for the microbiological identification of any bacterial infection.

The validity of cytological investigation depends on the experience of the person

performing FNA as well as on the cytologist. It may reach approximately 90% sensitivity in the documentation of malignancy in solitary cold nodules. The result should include a clear description of thyroid cell morphology, and of any visible infiltration by lympho- or granulocytes or cells of foreign origin. Classification according to Papanicolaou criteria is not helpful because it does not refer to the thyroid morphology and the possible different morphological types of thyroid cancer.

The result of cytological investigation can show clearly benign or unequivocally malignant cells, but there can also be a suspicious zone. Moreover, the investigation can indicate a follicular adenoma of high cellularity. The consequences of the latter two findings are discussed controversially in the Anglo–American literature [10,21]. In the case of a suspicious result, biopsy can be repeated but for follicular adenoma, cytological measures are unsuitable to exclude a low grade follicular carcinoma. Therefore, we prefer surgical removal of the nodular lobe with histological classification of the tumor.

6.2.5 APPROPRIATE EVALUATION OF LOCAL COMPLICATIONS

In most patients with multinodular goiter clinical investigation gives sufficient information to exclude major local complications, but, if surgical treatment is considered, more intensive exploration of tracheal and vocal cord function has to be performed [9,13]. Dislocation and compression of the trachea can be excluded by standard X-ray investigation of the thorax. Varicosis of the esophagus (Figure 6.4) may be diagnosed by contrast studies. This complication can be expected mainly in patients with large recurrences. Tracheal compression with functional impairment should be investigated by measuring the inspiratory and expiratory airway resistance, which can exclude bronchial obstruction immediately in dyspnoeic patients. Hoarseness or vocal fatigue requires a laryngeal inspection. During preoperative preparation of every patient this latter investigation is recommended for medico-legal reasons.

In patients with a nodular goiter and an intrathoracic mass, identification of the mass as thyroid tissue requires radioiodine imaging and is part of the preoperative investigation. Computerized tomography is also required; this allows the exact visualization of the anatomical relationship between the intrathoracic thyroid tissue and the surrounding structures and the distinction between a false or true endothoracic goiter. The use of iodine containing contrast media must be avoided, otherwise an unexpected malignant thyroid tumor cannot be subsequently treated by radioiodine. If available, MRI may be used in cases with difficult anatomical interrelationships between the endothoracic goiter and thoracic structures (Figure 6.5). However, in uncomplicated situations, the use of the latter two methods seems to be inappropriate.

6.3 TREATMENT

6.3.1 MEDICAL TREATMENT

The treatment of nodular thyroid disease by TSH suppressing doses of T_4 is controversial [10,12,13,21–24]. It is, however, thought to be appropriate in order to select patients who respond to this treatment sufficiently from those who do not respond, assuming that the latter group clearly should be operated upon for their resistant nodular goiter [10]. Reported results of T_4 medication range from a response rate of 55.7% [22] to approximately zero [21] in solitary nodular disease. In our own investigation of patients with diffuse endemic goiters [23] reduction of the total thyroid volume reached 30%. These data were confirmed by others [12], but there is no study in which normalization of the thyroid volume and the disappearance of

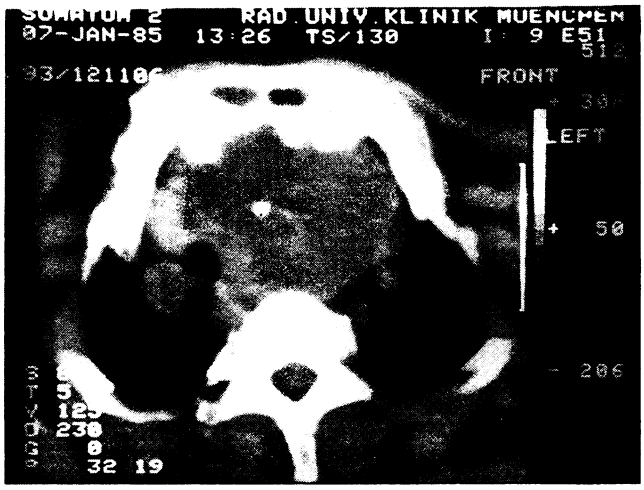

Figure 6.5 (*a*) Computerized tomography, axial slice orientation, without contrast agent. The figure demonstrates a huge mass in the upper mediastinum. The trachea is laterally displaced and can be identified as a hypodense structure. Note the calcification in the central portions of the tumor.

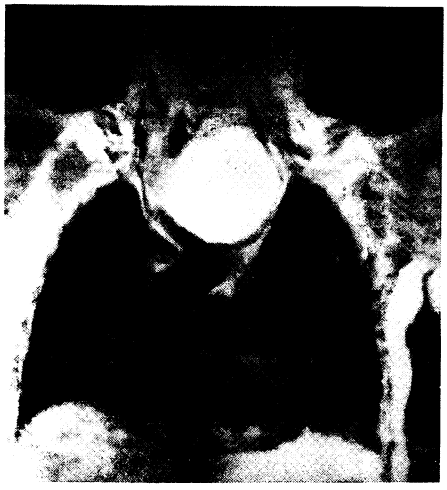

Figure 6.5 (*b*) MRI, T2 weighted sequence, coronal slice orientation: demonstrates a huge mass with high signal intensity, and some irregularities. The mass displaces the trachea to the right side and additionally leads to an enormous compression of the brachiocephalic trunk. No infiltration is shown and histology proved this to be a multinodular goiter without any malignant invasion. (We thank our colleagues of the Klinik and Poliklinik für Radiologie of the University of Munich for these two figures: 6.5(*a*)(*b*).)

nodules is documented convincingly. Thus, hormonal suppressive treatment cannot be accepted as a reasonable long term treatment for euthyroid nodular disease. In patients with nodular disease due to dyshormogenesis or reduced thyroid hormone action, thyroid hormone supplementation is indicated in order to optimize the metabolic status. In this group thyroid hormone treatment may induce a limited reduction in thyroid volume, and may be used to avoid surgery. In all other situations, thyroid surgery is indicated and necessary if mechanical complications are to be prevented or have to be treated, and if the possibility of malignant neoplasia has to be excluded.

More recently, treatment with stable iodine has had a renaissance, at least in Germany, a country with endemic goiter [12,15,25]. This method of treatment is successfully used after exclusion of autonomy in hypothyroid neonates [25] in peripubertal children [15] and in younger adults [12] with diffuse goiters due to iodine deficiency. However, in these groups of patients, with the exception of the neonates, normalization

of thyroid volume was rarely reached. Thus, iodine supplementation in iodine deficiency induced goiters is not a promising concept with respect to nodular shrinking. It may however be a reasonable way to prevent further growth of pre-existent goiters after exclusion of functional and morphological complications.

6.3.2 RADIOIODINE TREATMENT

In patients with recurrent goiter or elderly patients, radioiodine treatment is a useful alternative to reduce goiter volume significantly [26]. The precondition is that the mechanically effective parts of the enlarged gland consist of functionally active thyroid tissue with sufficient radioiodine uptake. This treatment is safe and the reduction of the thyroid volume is sufficient to improve respiratory obstructive symptoms and dysphagia. Hypothyroidism may result during long term follow-up.

6.3.3 SURGICAL TREATMENT

Mechanical complications are the reason for surgical treatment of multinodular goiter in more than 60% of patients in Germany; among these, tracheal compression is the main complication. In some cases, parts of thyroid tissue may be inserted between esophagus and trachea, thus impressing the pars membranacea of the trachea from behind, resulting in dry cough and dyspnea. The situation is difficult to diagnose before surgical intervention. Patients with dysphagia and Horner's syndrome should be operated on for both diagnostic and treatment purposes.

In general, intrathoracic goiters, with or without mechanical complications, should be removed surgically because of the risk of significant, perhaps even life threatening, pressure effects developing in the future and because malignancy cannot be excluded with certainty.

The unequivocal indication for thyroid surgery is the suspicion of malignancy. In patients with one or more so-called 'cold' nodules, especially those with recent growth, malignancy has to be considered even before the classical signs of a malignant tumor can be recognized clinically. The discussion concerning the minimal volume of a nodular lesion which gives rise to the suspicion of a malignant tumor seems nowadays to be senseless with regard to our knowledge of papillary thyroid cancers (Chapter 11). Suspicion of malignancy in small nodules arises from the cytological findings only. The reported prevalence of malignant tumors of the thyroid depends mainly on the preselection of patients undergoing the evaluation. For patients below 20 years or above 60 years of age, and for males, the risk of malignancy in thyroid nodules is believed to be increased when cold nodules can be diagnosed. Other authors [10] do not see an increased probability of malignancy with age, but differentiated carcinomas are more often observed below the age of 40 years, whereas the prevalence of undifferentiated carcinomas increases thereafter.

The possibility of malignancy is increased in hypofunctioning solitary thyroid nodules, especially in those with reduced echogeneity when compared with the surrounding thyroid tissue [18], but it has to be pointed out that most of these data refer to solitary nodules. Since comparable investigations for multinodular goiters are lacking, we propose that during the initial investigation of these conditions ultrasound investigation, technetium scintiscan, and, in cases of cold nodules, FNA with cytological investigation, should be combined to exclude or confirm a malignant tumor with the greatest possible accuracy. If cytological investigation leads to the suspicion of a follicular adenoma, surgical treatment and histological exclusion of a highly differentiated follicular carcinoma is mandatory. When malignancy has thereby become unlikely, the decision for surgical

treatment depends on the local symptoms and sometimes also on cosmetic reasons.

In multinodular goiters, bilateral resection usually has to be performed because of bilateral nodular degeneration. In order to avoid recurrence, it is recommended that all nodules be resected completely [27]. In large goiters with pronounced multinodularity, it may be difficult to define normal thyroid tissue intraoperatively, so that a near total thyroidectomy has to be performed.

The functional result depends on the volume of residual functionally intact thyroid tissue. If the remnant has a volume of a normal sized thyroid gland, euthyroidism is a possible result, whereas for smaller remnants hypothyroidism has to be expected.

The classical permanent complications of surgical treatment of all thyroid diseases are palsy of the recurrent laryngeal nerve and hypoparathyroidism. The frequency of these complications depends strongly on the experience of the surgeon. These complications are seen less often after surgery for multinodular goiter compared with Graves' disease [28] and increase significantly in operations for recurrent goiter [29].

6.3.4 LONG TERM FOLLOW-UP AFTER SURGERY AND RADIOIODINE

After surgical and radioiodine treatment of multinodular goiter, thyroid hormone treatment is necessary for those who have overt or borderline hypothyroidism. The appropriate substitution dose of T_4 should be chosen to normalize basal TSH levels. If postoperative basal TSH remains normal, iodine supplementation of 100 to 200 μg per day should be given in regions with nutritional iodine deficiency [30].

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