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GUIDELINES

EANM procedure guidelines for therapy of benign thyroid disease

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Abstract The purpose of the present guidelines on the ^{131}I therapy of benign thyroid disorders formulated by the European Association of Nuclear Medicine (EANM) Therapy Committee is to provide advice to nuclear medicine clinicians on how to treat benign thyroid conditions employing optimal ^{131}I activities. The recommendations were formulated based on recent literature and expert opinion regarding rationale, indications and contraindications for the use of ^{131}I procedures, as well as the adequate ^{131}I activities in different thyroid disorders, and the administration and patient preparation techniques to be used. Recommendations are also provided on history and examinations before ^{131}I therapy, patient counselling and precautions associated with ^{131}I therapy. Furthermore, potential side effects and alternative treatment modalities are reviewed. Special attention is paid to these aspects in the treatment of children undergoing this procedure.

Disclaimer These guidelines summarize the views of the Radionuclide Therapy Committee of the EANM and reflect recommendations for which the EANM cannot be held responsible. The recommendations should be taken in the context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions.
The EANM has approved guidelines to promote the cost-effective use of high-quality nuclear medicine procedures. These generic recommendations cannot be rigidly applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. Advances in medicine occur at a rapid rate. The data of guidelines should always be considered in determining their current applicability.
The Dosimetry Committee was involved in the writing of these guidelines, and they have been reviewed by the Oncology Committee, the Paediatrics Committee and the Physics Committee. The guidelines have been brought to the attention of the National Societies of Nuclear Medicine.

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I. Purpose

The purpose of these guidelines is to assist nuclear medicine practitioners to:

1. Evaluate patients who might be candidates for ^{131}I treatment of benign thyroid disease
2. Perform the treatment
3. Understand and evaluate the consequences of the treatment

II. Background information and definitions

A. Definitions

1. ^{131}I is a beta-emitting radionuclide with a physical half-life of 8.02 days, a principal gamma ray of 364 keV and a principal beta particle with a maximum energy of 0.61 MeV, average energy of 0.192 MeV and an average range in tissue of 0.4 mm.
2. Therapy in this context means the oral or intravenous administration of ^{131}I as sodium iodide.
3. Benign condition in this context means Graves' disease (diffuse toxic goitre), toxic or nontoxic goitre and solitary hyperfunctioning thyroid nodule.
4. Malignant conditions are not included in these guidelines (see respective document available at www.eanm.org).

B. Background

Oral administration of ^{131}I has been used to treat benign conditions of the thyroid gland since the 1940s. Physicians responsible for treating thyroid disorders should have an understanding of the clinical pathophysiology and natural history of the disease processes. They also should be familiar with other forms of therapy and should be able to collaborate closely with other physicians involved in managing these patients. For practical purposes it is helpful to define two subpopulations:

1. Patients with *hyperthyroidism*, which is a consequence of excessive thyroid hormone action. The causes of hyperthyroidism include the following: (1) autoimmune hyperthyroidism called previously toxic diffuse goitre (Graves' disease); (2) solitary hyperfunctioning thyroid nodule; (3) toxic multinodular goitre (Plummer's disease); (4) silent thyroiditis; and (5) painful subacute thyroiditis. The first three entities constitute a clear indication for radioiodine treatment, while silent thyroiditis and subacute thyroiditis are never treated with radioiodine. There is an emerging role for ^{131}I in the treatment of so-called subclinical hyperthyroidism caused by any one of first three entities [1].
2. Patients with a large *nontoxic goitre* (NTG). This group includes patients who are euthyroid but who may benefit from a reduction in thyroid volume.

C. Treatment options for hyperthyroidism and nontoxic goitre

Antithyroid drugs (ATDs) and radioiodine therapy are both useful options for treatment of hyperthyroidism. Surgery is preferably performed in selected patients with nodular goitre or recurrent Graves' disease, in those with a suspicion of malignancy, and when there is a severe compression of neighbouring structures or a necessity for immediate effectiveness, e.g. in those with severe adverse effects of ATDs. Although ATDs – propylthiouracil and methimazole or its derivative carbimazole – can all normalize serum free T4, free T3 and TSH concentrations, thyrotoxicosis recurrence after cessation of therapy is greater than 90% for multinodular goitre [2] and about 40–50% in patients with Graves' disease [3]. This difference is obvious, as in nonimmune hyperthyroidism there is no chance for permanent inhibition of thyroid hormone production which is activated by somatic mutations. Apart from that, ATD treatment is not without the risk of adverse reactions, including minor rashes and, in rare instances, agranulocytosis and hepatitis; success of this therapy depends to a high degree on patient compliance with physician recommendations.

Radioiodine is in most cases the first-line treatment for solitary hyperfunctioning thyroid nodules, or it can be administered if hyperthyroidism is not controlled or recurs after initial antithyroid drug treatment, such as in Graves' disease. The main indications for radioiodine treatment of NTG are to reduce the size of a goitre that is causing cosmetic difficulties for the patient and to relieve compressive signs or symptoms. The available treatment options in NTG patients in whom the risk of malignancy is considered low are a "wait and see" policy, surgery, laevothyroxine (LT4) at a dose to keep the TSH levels at the lower end of the normal range, and radioiodine administration. In patients with postoperative goitre recurrence radioiodine therapy is often considered the first-line therapy, and the physician should not wait until the patient becomes symptomatic. With LT4 medication some patients may achieve clinically relevant (more than 50%) nodule or goitre shrinkage; however, this occurs only in 10–20% of patients [4]. The only available controlled long-term investigation [5] showed no significant nodule size reduc-

tion after 5 years of continuous LT4 therapy. Additionally, a comparative study showed the superiority of ^{131}I treatment over LT4 therapy [6]. Radioiodine treatment is indicated in patients with medical contraindications to thyroid surgery, patients with slight or moderate compressive symptoms, patients with a large goitre, and patients who whish to avoid surgery. The interdisciplinary approach to patients followed by well-balanced decision making and informed consent allow individualized selection between the alternative treatment options. Special consideration should be given to the patient's profession as ^{131}I is without risk of paralysis of the recurrent laryngeal nerve.

D. Physical and radiobiological properties of radioiodine

Iodine is an indispensable component of thyroid hormones: LT4 (tetraiodothyronine, T4) and L-triiodothyronine (T3). Thyroid cells extract and concentrate iodide from plasma. Shortly after administration, radioiodine is taken up from the blood via the sodium iodine symporter and accumulates within thyroid follicular cells. About 20% of the circulating iodide is removed at each passage through the gland. Ingested iodine is absorbed through the small intestine and transported in the plasma to the thyroid, where it is concentrated, oxidized, and then incorporated into thyroglobulin (Tg) and later T4 and T3. After storage in thyroid follicles, Tg is subjected to proteolysis and the released hormones are secreted into the circulation. In subjects with normal thyroid function up to 20–30% of orally administered iodine is taken up by the thyroid. In hyperthyroid patients this fraction is increased – in extreme cases even up to more than 90%.

^{131}I used for the treatment of thyroid disorders decays to stable ^{131}Xe by beta emission. The physical characteristics of ^{131}I are as follows: $T_{1/2\ phys}$=8.02 days; β^-_{max}= 0.807 MeV, β^-_{avg}=0.192 MeV; gamma ray range 80 to 723 keV, most abundant γ (82%) 364 keV. The average range of the beta particles in soft tissue is approximately 0.4 mm; the maximum range is about 3 mm. Radiobiological effects of radioiodine on tissues are direct (radiation deposit within DNA) or indirect. Indirect effects produce free radicals that in turn react with critical macromolecules.

III. Aims of treatment

In patients with hyperthyroidism, the aim of treatment with ^{131}I is to achieve a nonhyperthyroid status, which can be euthyroid or hypothyroid, recompensated by LT4 medication.

In patients with NTG, the aim of treatment with ^{131}I is to diminish the size of the goitre and, consequently, to reduce the symptoms related to gland enlargement and nodule formation.

IV. Indications and contraindications

Indications

- Graves' disease
- Toxic multinodular goitre
- Solitary hyperfunctioning nodule
- Nontoxic multinodular goitre
- Goitre recurrence
- Ablation of residual thyroid tissue in case of malignant ophthalmopathy after surgery, but during an inactive state of the orbitopathy.

Contraindications

Absolute

- Pregnancy
- Breastfeeding

Relative

- Uncontrolled hyperthyroidism
- Active thyroid orbitopathy (especially in smokers)

V. Procedure

A. Facility and personnel

The facility requirements will depend on national legislation on the therapeutic use of radioactive agents. If inpatient therapy is required by national legislation, this should take place in an approved environment with appropriately shielded rooms. The facility in which treatment is performed must have appropriate personnel, radiation safety equipment, and procedures for waste handling and disposal, handling of incidental contamination, and monitoring of personnel for accidental contamination and controlling/limiting its spread.

The administration of ^{131}I should be undertaken by appropriately trained medical staff with supporting nursing staff and an available medical physics expert. Physicians responsible for treating patients should have a general knowledge of the pathophysiology and natural history of the respective diseases, should be familiar with alternative forms of therapy, and should be able to liaise closely with other physicians involved in managing the patients. Clinicians involved in unsealed source therapy must also be knowledgeable about and compliant with all applicable national and local legislation and regulations.

B. Patient preparation

Radioiodine treatment of patients with thyroid disease necessitates close cooperation between the endocrinologist and nuclear medicine physician. The assurance of adequate

therapy conditions is the overall responsibility of nuclear medicine physician.

Patient evaluation before radioiodine therapy should include:

1. Patient history with special emphasis on previous treatments (e.g. use of ATDs, contrast media, amiodarone, other iodine-containing medication and iodine-containing food).
2. Laboratory testing, including free T4, free T3, TSH, TPO and TSI titres.
3. Thyroid ^{99m}Tc scintigraphy and radioiodine 24-h uptake: T24 should be >20%, if lower other treatment modalities should be considered. Uptake measurements are not absolutely required when fixed activities are used. Measurement of uptake at 4–6 h after administration is also recommended to identify patients with early discharge.
4. Assessment of thyroid target volume (ultrasonography) [7] and intrathoracic extension in those with a large goitre (magnetic resonance imaging/computed tomography) [8]. It has to be realized, however, that assessment of the target volume by computed tomography using contrast agents will impair the radioiodine uptake for weeks to months, making therapy with ^{131}I impossible during that time.
5. Fine needle aspiration biopsy (FNAB) of nodules larger than 1–1.5 cm with a suspicious sonographic appearance and scintigraphically hypofunctioning or "indifferent". In autonomous nodules, as the risk of malignancy is very low, FNAB should only be considered in those with suspicious sonographic features [9]. On the other hand, ^{123}I scintigraphy with late imaging 24 h after injection is a strategy to confirm autonomously functioning nodules and to exclude ^{99m}Tc-pertechnetate "trapping only" nodules.
6. In female patients of child-bearing potential routine testing for pregnancy within 72 h before the administration of ^{131}I. When the patient history clearly indicates that pregnancy is excluded, a pregnancy test may be omitted at the discretion of the treating physician. Contraception for 4 months after ^{131}I therapy is also necessary. As the result is evaluated 6 months after therapy, this interval is recommended in clinical practice to avoid interference with retreatment in the event of recurrent disease.
7. In patients with Graves' ophthalmopathy, establishment of the status of thyroid eye disease activity by an experienced ophthalmologist.

C. Special considerations

1. *Antithyroid drugs* are often used in the initial treatment of patients with hyperthyroidism. As pretreatment with ATDs depletes thyroid hormone stores, it constitutes a safe patient preparation for radioiodine treatment, especially beneficial in patients with overt hyperthyroidism or distinctly elevated free T3. However, since thyrostatic drugs may lower the uptake of radioiodine as well the effective half-life they can decrease the effectiveness of radioiodine treatment. Another side effect of ATDs is the possible radioprotective effect which seems to depend on chemical compounds contained in the thyrostatic medication (methimazole and carbimazole, which do not possess sulphydryl groups and probably do not have radioprotective effects) [10]. The potentially negative impact of thyrostatic drugs can be compensated for by discontinuing medication shortly before treatment; carbimazole and methimazole should be withdrawn, respectively, for at least 2 days before planned radioiodine administration [11–13] if tolerated by the patient. Propylthiouracil which has a more distinct radioprotective action that may further reduce the effectiveness of radioiodine should be stopped at least 2 to 3 weeks (if possible 8 weeks) before radioiodine treatment [14]. Beta adrenergic antagonists (usually propranolol at a dose adjusted to clinical symptoms) may be helpful for the interim relief of hyperthyroidism symptoms during ATD withdrawal, provided that there are no contraindications. Finally, ATDs should be restarted after ^{131}I has been administered; the same dose can be recommended as used prior to ^{131}I therapy. ATDs do not have to be restarted in selected patients (mild hyperthyroidism/young people).
2. In patients with Graves' ophthalmopathy, if not already on steroid therapy, prednisolone should be administered. [15, 16]. In this respect, however, it has to be realized that evidence-based dose concepts do not exist.
3. In patients with thyrotoxicosis induced by *amiodarone* or in those receiving compounds that contain iodine (e.g. radiographic contrast agents), radioiodine can be administered as definitive therapy, providing the drug has been stopped sufficiently long for the excess iodine load to be eliminated. This can take up to 2 years (average 6 months) in amiodarone-induced thyrotoxicosis [17]. In this respect, the assay of urinary iodine excretion can be used as an indicator of normalization of iodine upload.
4. *Lithium* can block radioiodine release from the thyroid but does not interfere with radioiodine uptake. It may enhance the effectiveness of radioiodine when given for a few days immediately after treatment, but the clinical significance of the effect is unclear and side effects may be experienced by 10% of patients. Although lithium it is not routinely recommended, one can consider its

administration for 7 days if 24-h thyroid uptake is less than 20% (usually 2×250 mg) [18–20].

5. In patients presenting with unmanageable urinary incontinence, inpatient treatment (if not regular standard of care) may be considered according to the national legislations. Consequently, information on this is important and should be part of the patients' evaluation before therapy.
6. In patients with nontoxic multinodular goitre, recombinant human TSH (rhTSH) may be used to maximize ^{131}I uptake in the thyroid gland and to minimize the radiation dose to the remainder of the body [21–24]. However, rhTSH is not yet approved for this indication and administration in a patient with NTG represents an off-label use.

D. Precautions

1. Since ^{131}I administration may cause a transient elevation in free T4 and free T3 levels approximately 7 days following administration, uncontrolled symptoms of hyperthyroidism or high levels of free T3 constitute relative contraindications for therapy (further elevation of thyroid hormone may trigger atrial fibrillation or heart failure or, rarely, lead to thyroid storm). In such patients pretreatment with ATDs combined, if necessary, with β-blockers should be administered first. In the symptomatically well controlled patient radioiodine therapy will have little effect on clinical symptoms. In highly selected cases where ATDs are contraindicated (e.g. due to agranulocytosis or posttherapy liver failure) and surgery cannot be performed due to symptoms of hyperthyroidism, ^{131}I may be administered under steroid coverage (usually hydrocortisone hemisuccinate 50–100 mg intravenously) and β-blockers.
2. Patients with a large goitre and tracheal narrowing to <1 cm should be treated under the cover of steroids. If the tracheal diameter is <5–6 mm, due to the risk of severe dyspnoea, surgery rather than radioiodine therapy should be performed. Patients with a high risk of severe posttreatment complications (elderly with a risk of heart failure, or patients with a small tracheal diameter, large thyroid goitre or uncompensated hyperthyroidism) should always be treated in an inpatient facility to provide continuous medical surveillance [5, 6, 25].
3. Radioiodine administration is very unlikely to precipitate a hypersensitivity reaction because ^{131}I free of large stable iodine contamination is administered, so even in patients with known iodine sensitivity, the ^{131}I therapy can be performed safely. The stable iodine content of radioiodine preparations is 0.05–0.18 μg. This is very significantly lower than average daily iodine intake.

E. Patient information and instruction

Patients should receive both written and verbal information about the procedure before receiving therapy. Written informed consent from the patient is recommended. The following items should be discussed:

1. The purpose of the treatment and the strategy (fixed vs calculated activity) that is used to achieve this.
2. Pre- and posttreatment use of thyroid-blocking agents and hormone supplementation. Concurrent use of other medication should be checked, especially medication whose serum levels may alter after stopping these agents and T4 substitutes.
3. Risk of recurrent disease and subsequent retreatment.
4. Early and late side effects, including the risk of hypothyroidism.
5. Radiation protection initiatives to reduce radiation doses to children, family members, and other people in the general population, according to national rules.

VI. Radiopharmaceutical and administration

Radiopharmaceutical: ^{131}I.

Radioiodine is preferentially administered orally, but in patients with severe swallowing difficulties, it can be administered in liquid form or intravenously in patients in whom vomiting is a problem. The liquid form has the advantages over capsules that it is less expensive and it can be stored and easily dispensed as needed, but the risk of spoiling and contamination is higher. The facilities required to perform radioiodine therapy will depend on the national legislation for the emission of pure beta- or beta/gamma-emitting therapy agents. In many countries the therapy is performed in an outpatient setting. Care should be taken in patients who are incontinent of urine; an indwelling catheter is recommended before radioiodine administration to allow safe disposal of urine containing radioiodine.

The requirement to admit patients due to administered ^{131}I activity varies considerably across Europe. Patients with a risk of severe complications should be treated in an inpatient facility even if the applied radioiodine activity allows outpatient treatment. Patients should be encouraged to drink a large volume of fluid for a 24-h period following radioiodine therapy to lower the radiation dose to the bladder. The restrictions on work and contact with small children depend on national dose limits. Generally in Europe, the exposure should not exceed 1 mSv for other individuals in the general population, which is a cumulative value per year. Usually the patient is advised to keep as much distance as possible between themselves and others, including children, and to keep contact times as short as

possible for a limited amount of time depending on dosimetry and other contacts [26–29].

VII. Radiation dosimetry and ^{131}I activity in adults

In Europe, the aim of radioiodine treatment in hyperthyroidism is often to restore euthyroidism [30, 31] with the exception of "definitive" treatment of Graves' disease. In this respect, there have been many studies attempting to identify an optimal regimen for radioiodine treatment that minimizes the risks of developing hypothyroidism while maximizing the cure rate of hyperthyroidism. However, this is a very challenging issue: first because a maximum cure rate inevitably results in the highest rate of hypothyroidism, and second because any single method to determine the optimal activity cannot practically encompass all of the variables affecting outcome. Nevertheless, there is an ongoing discussion on the establishment of the optimal method to determine the activity that can be recommended for clinical practice: estimation (the so-called "fixed dose") versus calculation (based on radioiodine uptake measurements). It is beyond the scope of these guidelines to discuss this issue in detail. However, the individual calculation approach seems advisable in patients <45 years of age, and especially in children in whom radioiodine therapy is under consideration.

In either toxic or nontoxic multinodular goitre, radioiodine doses have been empirically established. Currently, an absorbed radiation dose of 100–150 Gy is recommended, requiring about 3.7–5.5 MBq per gram of thyroid tissue corrected for the 24-h ^{131}I uptake [32]. To increase radioiodine uptake and retention in NTG, rhTSH has been used in some studies [12, 13]. rhTSH can increase the absorbed radiation dose and permits a more equal distribution in the gland [21, 23, 24, 33]. In this respect, a low dose of 0.03 mg rhTSH has already been shown to be highly effective in nontoxic large multinodular goitres. Its future role, however, still has to be established. In patients with autonomous nodules, the recommended dose is 300–400 Gy. In patients with Graves' disease, the dose with the aim of restoring a euthyroid status is approximately 150 Gy, whereas the dose to achieve complete ablation is in the range 200–300 Gy.

The recommended formula to calculate the activity required to achieve the dose in the thyroid is as follows:

$$A[MBq] = \frac{F}{\ln 2} \cdot \frac{M[g] \cdot D[Gy]}{\int_0^\infty RIU(t)dt}$$

where A is the activity, F is a conversion factor, M is the mass of the target volume, and D is the target dose. The F factor is the conversion factor between coulombs per kilogram and grays, so it converts between the amount of ionization in air and the absorbed dose in tissue. In this context, the radioiodine uptake (RIU) is calculated as follows:

$$RIU = \frac{\text{activity in thyroid gland}}{\text{administered activity}} \times 100\%$$

The fixed dose approaches are usually based on an estimation of the size of the gland by palpation or by measurement with ultrasonography or scintigraphy. The range of activities currently prescribed, irrespective of the method used, vary in the range 200–800 MBq, with the majority of patients receiving 400–600 MBq. It is beyond the scope of these guidelines to give a detailed description of the dose assessment in benign thyroid disorders. To get more insight into the procedure guidelines for pretherapeutic "radioiodine testing", some papers are recommended in which comprehensive updates are provided for clinical practice [34–43].

VIII. Radioiodine treatment in children

Hyperthyroidism is in children mostly caused by Graves' disease and the risk of relapse in this age group is much higher than in adults. Children with Graves' disease are usually treated with prolonged antithyroid therapy, often followed by thyroid surgery, because prepubertal children have a poorer remission rate after ATD therapy, but also have a greater risk of developing drug-induced side effects [44, 45]. An important concern related to ATD use in children is the occurrence of adverse events. Up to 25% of the children may have minor side effects, including pruritus, hives, myalgias and leucopenia. Furthermore, it is important to realize that the thyroid gland is unique in its developmental sensitivity to malignancy after radiation exposure. Linearity best describes the dose response in children exposed to radiation before the age of 15 years. In different studies, the risk of thyroid carcinoma after irradiation in children has been extensively investigated. The Cooperative Thyrotoxicosis Therapy Follow-up Study showed that thyroid neoplasms develop in children treated with lower, rather than higher doses of ^{131}I [46–51]. The reports of the effects of the Chernobyl reactor explosion confirm the role of ^{131}I in the development of thyroid cancer in children. However, it is also important to note that iodine deficiency and exposure to nuclides other than ^{131}I may have contributed to this increased risk. In a recent mini-review by Reiners [52], it was shown that the highest incidence of thyroid cancer following the Chernobyl disaster occurred in the age group of 0–4 years. These findings are in agreement with the data presented in 1998

by Ron et al. [53]. They show that the risk of developing thyroid carcinoma after irradiation below the age of 5 years is twofold higher than in children treated between 5 and 9 years of age and even fivefold higher than in children treated between 10 and 14 years of age [53]. It may therefore be prudent to avoid radioiodine therapy in children younger than 5 years. For children between 5 and 15 years of age, radioiodine therapy may be considered. The side effects should be clearly discussed by all involved in the treatment of a young patient with Graves' disease [53].

As in adults, ^{131}I activity is typically calculated to deliver the desired amount of radiation dose based on gland size and radioactive iodine uptake. Gland size also influences treatment outcome, as higher activities of ^{131}I are needed to achieve a nonhyperthyroid status for a large gland (up to 60 g). When the thyroid gland exceeds 80 g, remission rates after ^{131}I therapy are poor, and consequently surgery is preferred when the gland is large (>60–80 g) [30, 54–57].

IX. Side effects of ^{131}I therapy

Acute Patients with a large goitre may notice transient swelling of the goitre and dyspnoea. Thyroid swelling lasts for approximately 1 week following therapy and some discomfort or dyspnoea may be associated with it. Slight discomfort of the salivary glands may be present, but in contrast to thyroid cancer, permanent injury is uncommon. There may be a transient rise in free T4 and free T3 levels 7–10 days following radioiodine treatment, and patients who have been poorly controlled before radioiodine therapy may experience an exacerbation of heart arrhythmias and heart failure. In some patients a thyroid storm may develop. This rare condition must be treated with intravenous infusion of ATDs, corticosteroids and β-blockers.

Hypothyroidism The main side effect of radioiodine treatment is hypothyroidism [41, 49]. Its rate varies and its incidence continues to increase over time, so that life-long follow-up is essential. Pretreatment prediction is not possible using current variables; however, the incidence is higher in Graves' disease than in toxic goitre and is rare in solitary hyperfunctioning nodules. Late permanent hypothyroidism subsequently occurs at an earlier time in the group of patients with transient hypothyroidism than in those without. LT4 medication is needed in all patients with elevated TSH after ^{131}I therapy, and also in patients with subclinical hypothyroidism.

Ophthalmopathy Prospective randomized controlled trials have shown that radioiodine treatment is associated with a greater risk of the appearance or worsening of ophthalmopathy in patients with Graves' disease than in those receiving antithyroid treatment [58, 59]. The risk is especially increased in smokers in keeping with the importance of smoking as a susceptibility factor in the development of ophthalmopathy; consequently, patients should be strongly advised to quit smoking. Administration of prednisone helps prevent exacerbation of ophthalmopathy, and this is now the standard approach in patients who have clinically active ophthalmopathy at the time of treatment [15]. In addition, elevated TSH levels may worsen the ophthalmopathy after ^{131}I therapy, so thyroxin substitution must be started in these patients as soon as this is measured.

Autoimmune thyroiditis This phenomenon is observed in 1% of the patients following radioiodine therapy of goitre/autonomous nodules. The risk is increased up to 10% in patients with preexisting thyroid peroxidase or Tg antibodies.

Radiation-induced cancers A small excess of mortality from malignancy (standardized mortality ratio 1.09; confidence interval 1.03–1.16) has been reported [60], but the study was biased by the increased surveillance, changes in reporting and a higher proportion of smokers in the hyperthyroid patients. A small increase in relative risk of diagnosis of or death from thyroid cancer after radioiodine treatment has been reported in large epidemiological studies carried out in different countries. The reported absolute risk, however, was still very small in these studies and, in addition, it seems to be more associated with the underlying disease than treatment with radioiodine [46–48, 61, 62].

X. Results

The success rate of radioiodine therapy depends on thyroid volume, compensation of hyperthyroidism, the timing of the withdrawal of ATDs, alimentary iodine intake, and the dose concepts in the different thyroid diseases. The superiority of dosimetric approaches over the use of fixed activities or of volume-adapted activities remains controversial, although the dosimetric approach is mandatory in some European countries.

A. Graves' disease

Most authors have defined success of radioiodine therapy as the elimination of hyperthyroidism (the patients showed euthyroid or hypothyroid function) compensated by LT4. A low fixed activity of 185 MBq ^{131}I was effective in 73% of the Indian patients with Graves' disease 1 year after radioiodine therapy [63]. In a study from Brazil, the

activities of 370 MBq ^{131}I and 555 MBq ^{131}I were compared and the success rates at 12 months were 88% and 79%, respectively [64]. A retrospective audit in Scotland showed the efficacy of 370 MBq ^{131}I and of 555 MBq ^{131}I in about 90% of patients without significant differences in the success rate between the lower and higher activities [65]. In a volume-adapted design the success rate 1 year after radioiodine therapy was 60% only, glucocorticoids did not influence the effect of radioiodine therapy [66]. In some comparative studies 2 or 3 days of carbimazole withdrawal was long enough to restore the success of radioiodine therapy [67–69]. A significant dose dependency in therapeutic outcome was found in a study which included predominantly patients with moderate or larger goitres. The frequency of persistent hyperthyroidism decreased from 27% after 150 Gy to 23% after 200 Gy and to 8% after 300 Gy [70]. Dose concepts aiming at euthyroidism ("function oriented") have result in success rates of less than 70% [71]. The probability of hypothyroidism increases over many years and makes regular follow-up necessary.

These unsatisfactory long-term results of function-oriented radioiodine therapy are the main argument for the ablative dose concept which is preferred today. In an observational study, after optimizing the complete management as compensation for hyperthyroidism, withdrawal of ATDs some days before pretherapeutic dosimetry assessments and therapy, calculation of the posttherapeutically achieved absorbed dose by serial uptake measurements and – if necessary – administration of a second ^{131}I capsule, a high success rate of 96% was reached even in large goitres of more than 40 g [42].

B. Toxic multinodular goitre

Two studies with an intended absorbed dose of 150 Gy to the thyroid and higher doses in selected patients with a high ^{99m}Tc pertechnetate uptake under suppression showed a success rate of more than 90% [72, 73]. In a comparative study from Switzerland 3 days of carbimazole withdrawal was sufficient for a high success rate of radioiodine therapy [69].

C. Solitary hyperfunctioning nodule

Studies in which the radiation absorbed dose to the hyperfunctioning nodule was measured posttherapeutically or, at least, a target absorbed dose was determined pretherapeutically have shown a success rate of 85–100% and an incidence of hypothyroidism of 10–20% [74]. In a comparative study, successful elimination of functional thyroid autonomy occurred at 12 months after radioiodine therapy in 90% of patients receiving 300 Gy to the nodule volume and in 94% of patients receiving 400 Gy to the nodule volume [75].

D. Nontoxic multinodular goitre

The volume reduction in large goitres increases with higher ^{131}I activities per gram thyroid tissue, higher achieved thyroid doses, and a homogeneous distribution of ^{131}I within the goitre. In most previous studies the administered amount of radioiodine has been in the range 3.7–5.5 MBq per gram of thyroid tissue corrected for the 24-h ^{131}I uptake, leading to an absorbed dose of 100–150 Gy in the thyroid. The decrease in thyroid volume has been in the range 30–60% [76]. Most of the shrinkage occurred within the first year and goitre volumes continued to decrease for several years. Symptomatic swelling of the goitre is uncommon and severe stenosis of the trachea can be excluded by adequate imaging procedures. In a patient group with goitres of at least 80 ml residing in an area of longstanding iodine deficiency calculations based on pretherapeutic uptake measurements over 5 days and an intended thyroid dose of 150 Gy (resulting in mean activities of 1721±440 MBq ^{131}I, equivalent to 14 ±4.19 MBq ^{131}I per gram of thyroid tissue) led to a mean volume reduction of 42% after 3 months and 66% after 1 year [25]. Individualized approaches aiming at higher doses may prove appropriate in most patients in the future. Finally, better results of 34% reduction from baseline volume have been achieved with high ^{131}I uptake, increased by pretreatment stimulation with rhTSH administering up to a 30 mCi dose [77].

XI. Follow-up after radioiodine treatment

Regular review of thyroid function tests in patients who have undergone radioiodine treatment for thyroid disease is essential to assess the efficacy of the treatment and for timely detection of developing hypothyroidism or post-treatment immunogenic hyperthyroidism. First, TSH and free T4 examination should be performed not longer than 4–6 weeks after radioiodine therapy. Shorter intervals of about 2–3 weeks are recommended for patients who have received ATDs or who have an increased risk of endocrine ophthalmopathy because of hypothyroidism. If the treatment was performed for (overt) hyperthyroidism, about 3–5 days after the radioiodine administration ATDs should be restarted. In those with persistent hyperthyroidism radioiodine treatment can be repeated after 6–12 months. In those with posttherapy immunogenic hyperthyroidism, ATDs for some months appears to be adequate and a second radioiodine treatment is not necessary in most patients. Annual laboratory tests (at least including TSH)

are necessary for life, even in patients with euthyroidism after ^{131}I therapy.

XII. Issues requiring clarification

1. The value of dosimetrically determined versus fixed empirically activities for ^{131}I therapy.
2. The role of rhTSH in the treatment of patients and the long-term outcome.
3. The recommended times of drug withdrawal.
4. Stunning. This phenomenon refers to a reduced uptake of ^{131}I in the thyroid tissue (or tumour) during radioiodine ^{131}I therapy compared with the uptake measured after the previous administration of ^{131}I for diagnostic purposes.
5. Inhomogeneous uptake of ^{131}I.
6. Use of glucocorticoids in patients with Graves' disease but without preexisting ophthalmopathy.
7. Duration and dosage of glucocorticoids in patients with Graves' disease and ophthalmopathy.

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