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Editorial

Radioiodine-treatment (RIT) of functional thyroidal autonomy

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Abstract

Since 1942, therapy with radioiodine (RIT) has gained a major role in the treatment of benign thyroid disorders, notably hyperthyroidism caused by Graves' disease or toxic multinodular goitre (thyroid autonomy). In iodine deficient areas thyroid autonomy accounts for 40–50% of all cases with hyperthyroidism. RIT has become a cost-effective first-line procedure in autonomy-patients with latent or overt hyperthyroidism, especially in the absence of a large goitre, after thyroid surgery and in elderly patients with associated conditions who carry a high intra- or perioperative risk.

Decisions concerning the definitive treatment of thyroid autonomy should take into account previous episodes of hyperthyroidism, objective parameters of risk stratification in euthyroid patients as well as concomitant diseases and the probability of iodine exposure in the future. In Central Europe the majority of investigators prefer to estimate the therapeutic activity individually by a radioiodine test. TCTUs (global 99m-Tc-pertechnetate thyroid uptake under suppression) — based dose concepts have been proven to be highly effective in the elimination of autonomy and carry a low (< 10%) risk of postradioiodtherapeutic hypothyroidism.

Radioiodine therapy for autonomy has been found to be both effective and safe and without major early or late side effects. The most frequent complication is hypothyroidism requiring lifelong follow-up.

Key words: Thyroid autonomy, TCTUs, I-131, toxic multinodular goitre, radioiodine therapy

Introduction

Thyroid autonomy (Plummer's disease) can be differentiated in focal (unifocal and multifocal) or diffuse (disseminated) TSH--independent hyperfunction of the thyroid.

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From a descriptive point of view, functional autonomy is characterised by the proliferation of thyroid follicular cells with increased iodine metabolism and by a high degree of independence from the regulatory interference by the hypothalamic-hypophyseal feedback mechanism. In iodine deficiency areas nodular goitres and, as a consequence, hyperfunctioning thyroid nodules (autonomies) are highly prevalent. In these areas thyroidal autonomy is four to fivefold more frequent than in areas with a sufficient iodine supply for the population [1]. Moreover iodine supplementation leads to a significant reduction in thyroid autonomy [2]. The prevalence and functional relevance of autonomy increases with age, goitre volume and goitre nodularity [3]. In nodular goitres above 50 g a prevalence of greater than 70% can be expected [4].

Functional thyroidal autonomy is a gradual process. As the volume of autonomous tissue increases with time, suppression of TSH and the remaining thyroid will take place and subsequently spontaneous or iodine-induced thyrotoxicosis may occur. The incidence of hyperthyroidism mainly depends on the quantity of autonomous tissue and the amount and duration of iodine supply [5].

Constitutively activating thyrotropin receptor mutations and mutations of the G_Sa protein have recently been identified as the most frequent molecular factors in the pathogenesis of unilocular and multilocular toxic thyroid nodules in iodine deficient areas [6––8]. As a consequence of these changes, chronic activation of the adenylate-cyclase-cAMP-cascade takes place, followed by overexpression of the sodium iodine symporter (NIS), thyroglobulin synthesis, iodine oxidation and thyroid hormone synthesis and release. Development of autonomous nodules is a non-reversible process and therefore definitive treatment will be necessary in spontaneous and iodine-induced hyperthyroid patients and in those who carry a high risk of hyperthyroidism.

This overview summarises the diagnosis of thyroid autonomy and describes current concepts for an individual dose estimation in autonomy patients. In addition the results of different therapy--regimens and early and late side effects of I-131 treatment will be discussed.

Diagnosis of thyroid autonomy

In countries with a sufficient iodine supply thyroidal autonomy will easily be detected by suppressed TSH or a negative TRH--test, but not in iodine deficient areas. In these areas quantitative scintigraphy is indispensable in the diagnosis [3, 9–11].

In Europe 99m-Tc-pertechnetate (99m-TcO_4^-) is the most common tracer used for thyroid scintigraphy. Compared with iodine isotopes it has the advantage of daily availability in every nuclear medicine department, of a shorter physical half-life (6 h) and it offers preferable energy for scintigraphic imaging (140 keV).

Due to the comparable molecular sizes of 99m-TcO_4^-($V = 4.05 \times \times 10^{-23}$) and iodine ($V = 4.22 \times 10^{-23}$), pertechnetate is trapped by the thyroid, but the kinetics differ from iodine isotopes as 99m-TcO_4^- is not organified in the gland.

Compared with iodine isotopes 99m-TcO_4^- carries a lower radiation burden to the patient, which is due to a shorter effective half-time. Therefore higher activities can be given, resulting in superior image quality. The injected standard activity ranges from 37 to 74 MBq.

99m-TcO_4^- thyroid uptake (TCTU) increases within the first 15 minutes after intravenous application (influx > efflux), exhibits a plateau phase between 15 and 30 minutes where in- and efflux are balanced and decreases again after 30 minutes [4, 12]. The TCTU (global 99m-Tc-pertechnetate thyroid uptake) is calculated according to the following formula [12]:

$$\text{TCTU (\%)} = \frac{(\text{counts over thyroid} - \text{background counts}) \times 100}{\text{counts of injected activity}}$$

In early studies a high correlation between the TCTU and radioiodine clearance has been recognised [12]. If the TCTU is measured during the early phase (5–15 min p.i.), the correlation between thyroidal iodine clearance and TCTU is somewhat stronger than in measurements of the plateau phase, but early determination of the TCTU requires a more strict time protocol, which may be difficult to perform under clinical conditions [12, 13].

The clinical value of the TCTU in the diagnosis of thyroidal autonomy is limited because it represents iodine clearance of both normal and autonomous tissue. In addition there is a substantial overlap of the TCTU-values between endemic goitre, euthyroid and thyrotoxic autonomy and Graves' disease [10].

As a consequence scintigraphic diagnosis and quantification of autonomy can only be established if suppressible thyroid tissue has been switched off by TSH-suppression. For this purpose the TCTUs (global 99m-Tc-pertechnetate thyroid uptake under suppression) should be determined after long-standing standardised exogenous suppression with thyroid hormones [5, 10]. In our laboratory 75 μg of thyroxin are given for two weeks, followed by 150 μg for another two weeks but other regimens may equally be used with success [5].

In Germany upper normal values of the TCTUs range from < 1 to < 2% [10]. These differences are due to different regional iodine supply, different regimens of exogenous suppression and to methodological aspects. In everyday practice a lot of influences and disturbing factors have to be considered, too (Table 1). Clinical implications of TCTUs values beyond the normal will be discussed in detail in the next chapter.

Table 1. Influence and disturbing factors of the TCTU

Disturbing factors TCTU increases	TCTU decreases
Rebound after stopping	Intake of
Levothyroxin	Levothyroxin
Liothyronin	Liothyronin
Thyrostatic therapy	Perchlorate
Influences **TCTU increases**	**TCTU decreases**
Thyrotoxicosis	Subacute thyroiditis
Iodine deficiency	Chronic atrophic thyroiditis
Primary Hypothyroidism	Secondary hypothyroidism
Lymphocytic Thyroiditis	Renal insufficiency

Indication for definitive treatment

Decisions concerning the definitive treatment of thyroid autonomy should take into account previous episodes of hyperthyroidism, objective parameters of risk stratification in euthyroid patients, as well as concomitant diseases and the probability of iodine exposure in the future (Table 2).

Patients with autonomy who develop hyperthyroidism carry a high risk of recurrence, ranging from 55% up to 81% [14]. There is general agreement that if hyperthyroidism occurs or has occurred in autonomy, definitive treatment is indicated.

In euthyroid patients the spontaneous course of thyroid autonomy should be taken into account in the decision of treating definitively. In a long-term follow-up in 375 untreated patients with autonomous solitary thyroid adenoma, the mean incidence of hyperthyroidism was calculated as 4.1% per year in an iodine deficiency area, which indicates that all of these patients would have got hyperthyroid after 25 years [15]. These results show a similar mean incidence of hyperthyroidism as observed in other smaller studies carried out in iodine deficiency areas where the risk of developing hyperthyroidism ranged from 3.7 to < 6% [16, 17].

While advanced age, suppressed TSH, the scintigraphic appearance of a "decompensated" adenoma and the nodule volume have no predictive value in the individual prognosis of an euthyroid patient with thyroidal autonomy [3, 15], the TCTUs may be a more reliable predictor of hyperthyroidism [5, 18].

In patients with a TCTUs ≥ 3% the risk of spontaneous hyperthyroidism is relatively high and thyrotoxicosis was present in 20% in one study [3]. Therefore these patients should be treated definitively even if they are in a euthyroid state.

Definitive treatment should also be considered in patients with a TCTUs ranging from 2–3%, especially in the presence of con-

Table 2. Indications for definitive therapy

Radioiodine therapy or surgery indicated
Present or earlier hyperthyroidism
Borderline hyperthyroidism and clinical symptoms
TCTUs 2–3 or higher in euthyroid patients
TSH < 0.1 μU/ml in older patients
Indications for preferred surgery
Larger goitre (> 70 ml)
Suspected malignancy
Prompt control of hyperthyroidism
Iodine contamination

comitant diseases, as the risk of hyperthyroidism increases continuously in this group [3, 18]. In patients with TCTUs values smaller than 2 there is no indication for a definitive therapy, as these patients will normally not develop hyperthyroidism even if they are exposed to usual amounts (≤ 200 μg) of iodine [5, 19].

Low serum thyrotropin concentrations (< 0.1 μU/ml) have been found as an independent risk factor for atrial fibrillation in persons older than 60 years [20]. In our institution, definitive treatment (surgery or radioiodine) is performed in these patients irrespectively of their individual TCTUs values.

Radioiodine should be the therapy of choice in patients with autonomy in the absence of a large goitre, in subjects who already underwent thyroid-surgery and in elderly patients with associated conditions who carry a high intra- or perioperative risk. Pregnancy and breast-feeding are absolute contraindications for radioiodine therapy. Surgery is recommended especially in patients with large goitres and if malignancy cannot be ruled out. If prompt control of hyperthyroidism is necessary, especially in thionamide-induced agranulocytosis, other severe allergic side-effects or thionamide/perchlorate resistant thyroid storm, operative treatment should also be preferred [21] (Table 2).

Radiobiology of I-131

I-131 decays with a physical half-life of 8.1 days by β⁻-transition to Xe-131. 90% of I-131 decays to the 364 keV (γ_1), 7% to the 637 keV (γ_2) and 2% to the 723 keV (γ_3) exited level of Xe-131. All the nuclei in the 637 keV and 723 keV level decay by g-emission ($\gamma_2 + \gamma_3$) direct to the ground state whilst 7% of the nuclei in the 364 keV level decay via the 80 keV level (γ_4) and the remainder (γ_5) direct to the ground state (Fig. 1).

I-131 is taken up into the thyroid follicular cell by the sodium iodine symporter on the basolateral membrane of the thyrocyte [22]. Iodide is then transported through the intracellular space towards the apical cell surface to follicular lumen. It is suggested that pendrin, a chloride-iodine transport protein, plays a mayor role in this process [23]. The next step of iodide handling by the thyrocyte, the oxidation of iodide into iodine and organification of iodine into tyrosylresidues of the thyroglobulin molecule, takes place at the outer (luminal) surface of the apical membrane of the epithelium.

I-131 is a medium range β^--emitter with an average penetration of 0.44 mm in thyroid tissue. β^--particles of the nuclide contribute to more than 90% of the delivered dose whilst the g-emission can be used for imaging (Fig. 1).

In normal thyroid tissue an average follicular diameter of 0.05––0.5 mm can be expected. In hyperplastic glands this diameter can be considerably smaller (0.075–0.15 mm), especially in hyperfunctioning nodules with a high iodine turnover [24]. If homogeneous distribution of I-131 in the colloidal space is assumed, a homogeneous dose to all cells of the follicle can be expected (Fig. 1). A considerable dose should also be delivered to the rich network of blood vessels and the stroma between the follicles.

Thyrocytes are reverting postmitotic cells and therefore relatively radioresistant. Cellular damage of irradiated thyroid tissue, as seen in early histological specimens after large amounts of I-131 [25], may be mainly mediated by the more radiosensitive vasculature [26].

Pre-treatment

In mild hyperthyroidism normally no pre-treatment with antithyroid drugs is recommended [27], while thionamides may be used to control more severe forms of thyrotoxicosis. As some of these patients show an elevation of thyroid hormone levels early after radioiodine treatment, thionamides may be useful in preventing an aggravation of hyperthyroidism and thyroid storm. Beta-blockers may prevent clinical aggravation of symptoms equally effectively as thionamides but euthyroidism is achieved significantly more slowly [28]. As we do not

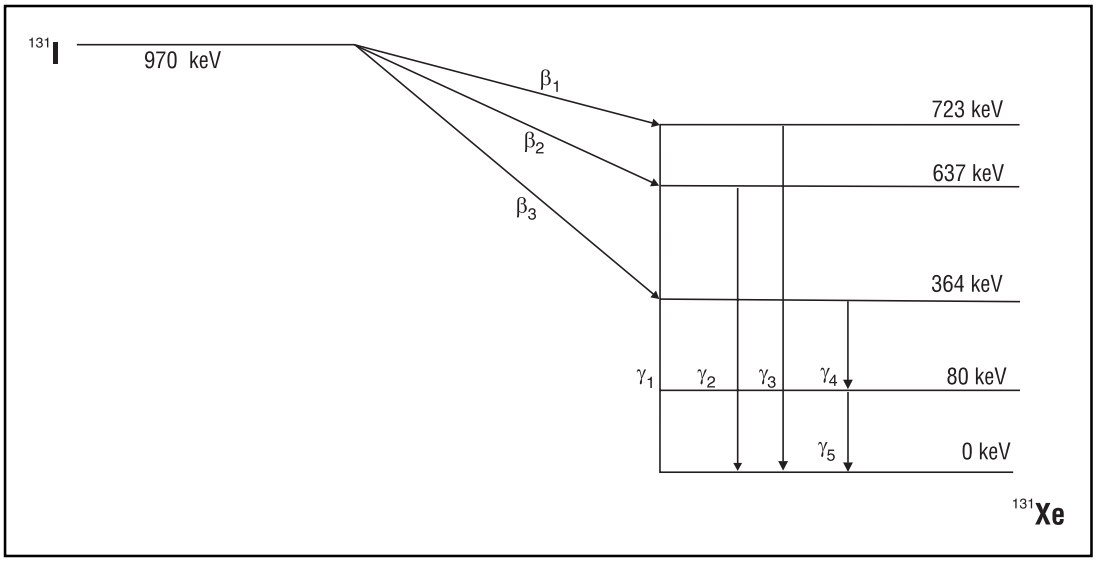

Figure 1. β^- decay of I-131

know exactly if beta-blockers are equally effective compared with thionamides in the prevention of thyroid storm we cannot recommend them as a monotherapy although they may be useful as an adjunct.

Since the early days of radioiodine therapy it has been suggested that pretreatment with thionamides may reduce the therapeutic efficacy of I-131. Some studies found a higher relapse rate and a decrease in the incidence of post-therapeutic hypothyroidism in patients pre-treated with antithyroid drugs compared with patients without premedication, especially within the first year after iodine therapy (overview of the older literature in [29]).

Thionamides, especially if given in high dosages, decrease radioiodine uptake and alter intrathyroidal iodine kinetics by shortening the intrathyroidal half-life of ^{131}I [30, 31]. In addition carbimazole, methimazole and propithiouracyl all contain sulfhydryl groupings, which may be metabolised within the thyroid gland and form disulphide bonds with thyroid cell protein, thus preventing cellular damage following radiation. The radioprotective effect of thionamides may also be due to altered H_2O_2 production of irradiated cells or to the shortening of the effective half-life of intrathyroidal ^{131}I by iodine depletion [32].

The results of these early studies remained conflicting as they may have been biased by patient selection criteria, e.g. treating only severe hyperthyroidism with thionamides. Moreover other groups could not confirm these findings even in large collectives [33]. Finally most of these studies were retrospective and did not use individual dosimetry, which is commonly used in Central Europe.

Within the last years several prospective studies have been conducted to evaluate the influence of antithyroid medication on the efficiency of radioiodine therapy in Graves' disease [34–36]. Sabri et al. found in a prospective, non-randomised study that a simultaneous thyrostasis in Graves' patients was the most important factor against successful radioiodine therapy [34]. These findings were later questioned by the results of Andrade et al. and Körber et al. [35, 36].

Andrade's prospective and randomised study in a large collective of 813 patients suffers from the fact that the authors did not correct the I-131-activities given to the individual effective intrathyroidal half-life of the isotope in their patients. Therefore their results cannot be extrapolated to a collective, treated according to the results of an individual dosimetry [35].

Körber et al. [36] prospectively investigated 141 patients with Graves' disease and 418 autonomy-patients, who were treated by I-131 according to an individual dosimetry. No influence of a comitant thyroid medication on the patients' outcome could be found in the Graves' group, while thionamides adversely influenced the results of radioiodine treatment in the autonomy group. In this study the decision criteria of whether to treat patients with thionamides or not remain unclear and therefore the results may be biased. In addition it seems that not all autonomy patients were adequately TSH-suppressed, which may have negatively influenced the results in this group. The authors themselves considered that a "steal phenomenon" of I-131 from autonomous to normal thyroid tissue could explain the unfavourable results in autonomy patients who were treated by thionamides.

Although final conclusions about thionamide treatment in autonomy patients suggested for RIT cannot be made from the available data, we recommend, if clinically feasible, discontinuing thyrostasis at least 1 day before beginning the radioiodine test. The medication should be withheld during the test and within the first 2 days following I-131 treatment and then may be continued if necessary for several weeks.

A lower incidence of post-therapeutic hypothyroidism has been recognised if the non-autonomous tissue was sufficiently suppressed during radioiodine treatment [37–40]. Therefore endogenous suppression or suppression by exogenous thyroxin (100––150 μg per day over 4–6 weeks) is recommended prior to and during radioiodine treatment in euthyroid patients and in thionamide treated with measurable TSH-levels.

Dose-estimation

The main rationale for dose estimation is to reduce the patients' radiation exposure and to prevent post-therapeutic hypothyroidism. Much disagreement exists on this topic. Some groups have successfully used standard activities without any dosis-calculation [41]. Others modify the fixed dose by giving larger activities to larger glands [42]. In some centres the activity is calculated by a fixed activity per gram multiplied with the estimated thyroid weight and normalised to the 24 hr uptake value [43, 44]. In Central Europe the majority of investigators prefer to estimate the therapeutic activity individually by a radioiodine test. For this purpose Marinelli's formula is used [45]:

$$\text{MBq } ^{131}I = \frac{\text{Gy desired} \times \text{weight of target thyroid tissue} \times 24.67}{\text{maximal uptake(\%)} \times \text{effective half-life}}$$

With this approach, determination of the maximal uptake and estimation of effective half-life of ^{131}I in the thyroid requires uptake measurements over a couple of days, as the precision of dose estimation is closely correlated with the number of measurements and the duration of the test [46]. This test should be performed under identical thyroid medication one or two weeks prior to radioiodine treatment. Early serial measurements on the first day are especially important in Graves' disease with a high radioiodine turnover, whilst in thyroidal autonomy the maximal uptake is usually seen after 24 hours or even later [21]. The reliability of this procedure has been questioned, because deviations of up to 100% between the calculated and obtained dose may theoretically occur [22]. Decrease of iodine uptake values ($<$ 30%) is usually due to severe iodine contamination, which cannot be recognised solely by the patients' history alone in up to 50% in our experience. If ever possible, determination of urinary iodine excretion should be performed prior to the test and radioiodine therapy to exclude these patients from actual radioiodine treatment.

There has been some controversy if uptake and half-life, as determined by radioiodine test, could reliably predict uptake and half-life during therapy [22, 23, 46, 47]. As a consequence, centres which found a poor correlation between these parameters rely on individual maximal uptake ratios and combine it with an empirical half-time. Others who noted a strong correlation under stable thyroid medication use individual maximal uptake ratios and individual half-time as determined under test conditions [46]. In our own experience significant differences between test and ther-

apeutic dosimetry are rare if antithyroid therapy did not change between test and radioiodine therapy and occur in < 5% (Meller et al., unpublished). In these patients additional activity is given to achieve the estimated dose.

Unifocal autonomy can usually be clearly detected by ultrasound, and therefore many investigators use ultrasonographic volumetry in the determination of the target volume. This method has some limitations. For example, cystic and other regressive changes have to be carefully subtracted to avoid overestimation of the autonomous volume [5]. In addition polyclonal nodules with sonographic homogeneous and solid appearance may contain significant amounts of non-autonomous cells.

Some groups tried to determine the autonomous volume in multifocal autonomy by ultrasonography, too [47]. This appears to be even more difficult, especially if one considers that in a multinodular goitre correlation between sonographic and scintigraphic appearance may be difficult or even impossible. In disseminated forms of autonomy ultrasound is generally considered not to be helpful in the determination of the autonomous volume.

Agreement exists that a dose of 300–400 Gy should be delivered to the autonomous tissue in unifocal autonomy (UFA) [27].

As the autonomous volume in multifocal (MFA) or disseminated autonomy (DISA) cannot be measured by ultrasonography with certainty, the sonographic approach to determine the target volume has been replaced by a so-called "dosimetric compromise" [37, 48]. For this concept the thyroid gland as a whole was taken as the target volume and the target dose was reduced to 150–200 Gy. With this approach, sufficient therapeutic success can only be achieved in patients whose TCTUs were smaller than 3.2%, thus indicating that higher doses were necessary in a certain thyroid volume if the amount of autonomous tissue exceeded a critical limit [48]. As a consequence the original concept was modified by adapting the target dose in MFA/DISA to the TCTUs-values. This modified concept uses the total thyroid volume as a target with stepwise increasing target doses between 150–300 Gy, dependent on the pre-therapeutic TCTUs [49].

A more functional approach in the determination of the target volume was carried out by authors who made an attempt to estimate the "autonomous volume" (AV) directly by a linear correlation of the sonographic volume of unifocal autonomies without any regressive changes and their corresponding TCTUs values [5, 50, 51]. In order to estimate the AV independently of its distribution in the thyroid gland this correlation was then extrapolated to multifocal and disseminated forms of thyroid autonomy. Theoretically this method should overcome both the limitations of ultrasound volumetry and of a dosimetric compromise. Preliminary data on this approach indicated success rates of 90%, if the target dose was beyond 350 Gy [52]. These results could later be confirmed by our own group [53].

Results

If elimination of hyperthyroidism is achieved, radioiodine treatment can be considered as successful. Normalisation of serum TSH and suppressible TCTU have both been proposed as criteria in the evaluation of post-therapeutic outcome.

Serum TSH > 0.5 excludes autonomous thyroid function with a probability of 88% in an iodine deficiency area [9]. Therefore normalisation of this parameter following radioiodine treatment normally indicates a preferable result.

Persistent suppressed serum TSH after I-131 on the other hand has a low predictive potential, as it may often be decreased for a longer time despite therapeutic success [52].

As quantitative scintigraphy has been shown to be more reliable in the diagnosis of functional autonomy, determination of the post-therapeutic TCTUs appears to be the most accurate predictor of whether autonomy has been treated sufficiently or not [52].

In unifocal autonomy, elimination of autonomous tissue is usually achieved if the target dose exceeds 350 Gy, regardless of whether the target volume is determined by sonography or calculated by quantitative scintigraphy [37, 39, 43, 52–54]. If the target dose is lower, adequate elimination of autonomy cannot usually be expected [37, 52].

In multifocal and disseminated autonomy, almost all Central European groups used a dosimetric compromise and took the whole thyroid volume as a target [37, 48, 49, 54–56]. An estimated dose of 160 Gy resulted in a high failure rate of 33% in one study [54]. If the target dose was beyond 200 Gy and the TCTUs did not exceed a value of 3.2 success rates > 90% were observed. TCTUs values higher than 3.2 required a higher target dose (300 Gy) to achieve the same result [55].

As a consequence of these findings Oexle et al. prospectively evaluated the efficiency of a TCTUs-adapted dosimetric compromise in patients with MFA and DISA [49]. The total thyroid was taken as the target volume and the target doses were increased from 150 Gy to 300 Gy. 150 Gy were used for a TCTUs of 1.5–2.5%, 200 Gy for a TCTUs of 2.51–3.5%, 250 Gy for a TCTUs of 3.51–4.5%, and 300 Gy for a TCTUs of > 4.5%. An average success rate of 92% could be observed. Similar results with this approach were also reported by another German group [57].

In the study of Seeger et al. TCTUs values according to Emrich's method were used in the estimation of the autonomous target volume [50, 52]. Here the target dose was calculated according to the formula: autonomous volume (AV) = TCTUs x 5. An overall success rate of 90% was reported if the target dose was beyond 350 Gy. Our group used the same method in determining the target volume in 370 patients [53]. 350–450 Gy to the autonomous tissue in our UFA-patients resulted in a high success-rate of 97%. A lower success rate of 78% was seen in the MFA/DISA group. Multivariate analysis identified independent factors that negatively influenced the therapeutic success: a high pre-therapeutic thyroid volume, a high pre-therapeutic TCTUs-value and multifocality distribution of the autonomous tissue. These data indicate that the original concept of a merely TCTUs-based RIT is effective, but has to be corrected in a minority of MFA/DISA patients with high thyroid volumes (> 100 ml) and/or high TCTUs (> 3–4%) levels. In these patients a TCTUs-adapted dosimetric compromise should be used.

Following radioiodine treatment a significant reduction of both the total and the autonomous thyroidal volume could be observed [44, 52, 53, 58, 59). RIT was followed by a gradual and dose--dependent volume reduction of the hyperfunctioning nodule ranging from 42% to 54% and by a decrease of the non-autonomous

tissue ranging from 19% to 38%. In multifocal autonomy a decrease of the total thyroid volume between 31% and 44% was observed. While this effect continued up to one year after therapy in the study of Dederichs et al., maximal reduction of the volume was seen earlier (3–6 months) by others [53, 44, 59].

Reduction of the extranodular tissue seems to be surprising and strongly suggests that small amounts of I-131 may be trapped in the non-autonomous thyroidal tissue, too. Dosimetric calculations indicate that suppressed tissue may receive as much as 8% of the total dose, which results in a dose of 3–4 Gy to the non-autonomous volume [60]. This dose is considerably lower than the known tolerance dose of 10 Gy that is expected to result in a 5% incidence of hypothyroidism, but may be high enough to produce radiation injury to the microvasculature followed by cellular damage [26].

In contrast to Graves' disease, where high rates of overt hypothyroidism have been accepted as an inevitable part of cure by many therapists, this condition should be partly avoidable in patients treated for autonomy. Post-therapeutic hypothyroidism is dependent on the patients' preparation as well as on the dose and the target volume.

Radioiodine therapy in thyroidal autonomy should only be performed if serum TSH is suppressed because the incidence of hypothyroidism increases when suppression of extranodular tissue or serum TSH is incomplete [37–40].

The rate of hypothyroidism increases with the target dose. In one study hypothyroidism increased from 12% to 40% if 400 Gy instead of 150 Gy were used in multifocal and disseminated autonomies [37].

The incidence of hypothyroidism is relatively low if the ratio between autonomous volume and perinodular tissue is low [52]. Furthermore, the volume of the autonomous nodule itself is a predictor for hypothyroidism, as dosimetric estimations indicate that the dose delivered to the perinodular tissue increases with the nodule size [60]. Actual patients with large uni- or bifocal autonomous nodules have a significantly higher incidence of hypothyroidism than patients with smaller nodules [53, 54].

Incidences from Central European centres indicate a risk of subclinical and overt hypothyroidism ranging from 0 to 56% (average risk: < 10%) in a follow-up of 0.3 to 15 years (Table 3). Direct comparisons between the studies are difficult due to heterogeneous collectives living under different conditions of iodine supply, different estimations of the target volume and delivered dose and a different length of follow-up.

The long-term risk may be even higher, as reported by Holm et al., who published retrospective data of 4473 Swedish patients treated with RIT for toxic nodular goitres [33]. 64% of these patients developed hypothyroidism within 24 years (annual incidence: 2.7%). Holm's results may indicate that fibrosis is still ongoing many years after radioiodine treatment.

Early side effects of radioiodine treatment

Early changes in hyperthyroid patients include focal necrosis, dilated vessels, oedema and the presence of large multinucleated cells. Within two weeks follicular breakdown and disruption with presence of extrafollicular colloid are seen. First evidence of fibrosis is noticed at the earliest 3–4 weeks later. Interestingly lymphocytic or granulocytic infiltration could not be observed [25].

Radiation-induced thyroiditis is a clinical entity characterised by tenderness or pain over the thyroid gland, painful swallowing and occasional swelling of the thyroid and low grate hyperthermia over the thyroid region. These clinical findings occur 1–3 days after radioiodine administration and may be due to the hyperaemia and oedema described above. Mild discomfort can be treated with routine analgesics but severe pain requires administration of glucocorticoids [9]. The incidence of radiation-induced thyroiditis in radioiodine treatment of benign thyroid diseases is not exactly known. In early reports it has been noted in 5% of patients treated with radioiodine [9]. The incidence nowadays seems to be much lower. Radiation induced thyroiditis was seen in < 2% of our patients treated for benign thyroid diseases and exclusively if relatively high activities (> 925 MBq) had been given.

Exacerbation of hyperthyroidism: Aggravation of thyrotoxicosis may be due to the release of stored thyroid hormones by acute radiation damage. Following radioiodine treatment serum concentrations of thyroid hormones have been observed elevated by some groups [61, 62], but were found to be unchanged by others [63, 64].

Kreisig et al. reported the data of early follow-up in 396 patients. They noted a significant decrease of TT-3 levels immediately after radioiodine, which was attributed to a hypothetical inhibitory effect of I-131. In only 5% of the patients was an increase of thyroid hormone serum levels observed. No differences in the serum concentrations could be noted between the patients treated with thionamides and those without treatment [64]. These results may indicate that previous studies may have suffered from bias due to rather small collectives.

Exacerbation of hyperthyroidism and thyroid storm after administration of radioiodine has been described in a number of early case reports. The determination of the incidence of radioiodine-induced severe exacerbation of thyrotoxicosis is difficult for several reasons. In earlier studies only older and multimorbid patients were included, while in more recent studies younger patients were selected for radioiodine therapy as well. Furthermore a great variability of treatment regimens prior to radioiodine existed between these studies.

In an overview by McDermott et al. the incidence of severe exacerbation was 0.88 and of thyroid storm 0.34 in 2975 patients [65]. Severe exacerbation seemed to be neither related to the activity of radioiodine nor to thyrostatic premedication, although thionamides had been discontinued in some of the patients prior to radioiodine treatment. Patients with severe reactions following radioiodine tended to be older and suffered from severe concomitant cardiovascular or cerebrovascular diseases, but the authors were not able to define a group of patients clearly at risk of development of thyroid storm.

In Kreisig's study, mentioned above, no severe exacerbation of thyrotoxicosis could be observed, which indicates that the incidence of severe reactions should be very low [64]. In our own experience, thyroid storm did not occur in 1302 patients treated for benign thyroid diseases within the last 8 years, although moderate exacerbation of thyrotoxicosis could be found in some patients.

Severe aggravation is not common but it has to be kept in mind because of its high mortality. It has been questioned if thyro-

Table 3. Results of radioiodine treatment in thyroidal autonomy

Reference	Patients	Autonomy	Target volume	Target dose (Gy)	Elimination of autonomy	Hypothyroidism	Follow-Up
Berding and Schicha	152	UFA/BFA	AV (Sono)	300–400	78–100%	24%	1 yr.
		MFA/DISA	TV	167	67–89%	9%	
Debrand-Passard et al.	126	UFA	AV (Sono)	300	95%	36%	0.5–7
		MFA	AV (Sono)	120-200	80%	21%	
		DISA	TV (Sono)	120-200	98%	56%	
Emrich and Reinhardt	38	UFA/MFA/ DISA	TV (Sono)	200			
		TCTU ≤ 3.2			90%	3%	0.6 yr.
		TCTU > 3.2			67%	0%	
Guhlmann et al.	230	UFA	TV (Sono)	300	93%	5%	1 yr.
		MFA	TV (Sono)				
Heinze et al.	185	UFA		300–400	98%	11%	0.3–8 yr.
Heinze and Bohn	301	UFA	AV (Sono)	400	97%	10%	< 7 yr.
Hoeschel et al.	130	UFA	TV (scintigraphic)	60–150	74%	3.8%	0.6 yr.
		MFA					
Moser et al.	448	UFA	AV (Sono)	400	95%	23%	5.7 yr.
		MFA	TV (Sono)	150	88%	12%	0.2–5.4 yr.
				400	95%	40%	0.2–5.4 yr.
Müller Gärtner et al.	56	UFA	AV (Sono)	200	93%	1.7%	2–15 yr.
Reinhard et al.	89	MFA/ DISA	TV (Sono)				
		TCTU ≤ 3.2		150	95%	–	
		TCTU > 3.2		150	45%		
				200	50%	1.7%	0.5 yr.
				300	90%		
Ross et al.		UFA	AV (Sono)	160	91%	4.5%	0.5–14 yr.
Seeger et al.	131	UFA	AV (TCTUs x 5)	< 350	57%	< 1%	0.9 yr.
		MFA /DISA		> 350	90%		(median)
Oexle et al.	75	MFA /DISA	TV (Sono)	150–330	92%	1.5%	0.7 yr.
Meller et al.	370	UFA	AV (TCTUs x 5)	350–450	97%	3%	1.5 yr.
		MFA /DISA			78%		
Dunkelmann et al.	641	UFA	TV (Sono)	150–330	91%	3.4%	1.5 yr.
		MFA /DISA					

UFA — unifocal autonomy, MFA — multifocal autonomy, DISA — disseminated autonomy, AV (Sono) — autonomous volume estimated by sonography, TV — total thyroidal volume estimated by sonography, AV (TCTUs x 5) — autonomous volume by quantitative scintigraphy

static medication is useful in this respect as it cannot prevent release of hormones from damaged thyrocytes. Although we lack data on this topic, thyrostatic pre-treatment and adequate treatment of concomitant diseases should be routinely performed prior to radioiodine therapy in all patients [27].

Local compression: Theoretically acute swelling and compression of the trachea and oesophagus may occur after administration of radioiodine in patients with large goitres, especially following high activities. Many authors therefore claim that in these patients radioiodine should be used with care. Fractional therapy or single dose therapy with steroid administration is recommended in patients at risk [66].

We lack data if these side effects have ever been observed in patients treated with I-131 for benign thyroid diseases. Up to now only one case report tried to relate an intrathyroidal haemorrhage with acute tracheo-oesephageal compression to I-131 treatment 2 months earlier [67]. It remains doubtful if this complication was really due to radioiodine treatment or to spontaneous clinical course. In a recent publication in 30 patients suffering from non-toxic and toxic multinodular goitre, the ultrasonographically determined volume did not increase in the first days after radioiodine administration [68]. Further prospective studies concerning early changes of thyroid volume following I-131 seem to be necessary.

Late side effects of radioiodine treatment

Histopathological specimens of glands late (4 mth. to 12 yr.) after radioiodine show evidence of marked fibrosis, follicular disruption and small irregularly shaped follicles. The vascular lesions most frequently seen were eosinophilic cuffing and telangiectasia [25]. Post-radiation fibrosis is progressive over several years. Regeneration is just focal and irregular. The balance between fibrosis and regenerative potential may determine if post-therapeutic hypothyroidism occurs and cannot be individually predicted .

Patients receiving radioiodine treatment for thyrotoxicosis have no excess of radiogenic thyroid neoplasms. This is usually ascribed to the predominance of substantial cell killing at high dose rates that are achieved during I-131 therapy [65]. Dobyns et al. [69] found no excess of thyroid carcinoma in 16000 patients in a ten-year follow-up and similar results were reported by Holm et al. [70] and Shore [71]. Unfortunately mean follow-up of these studies was less than 20 years, but regarding the data from external irradiated collectives some excess tumours should already have been observed within this time.

The cooperative thyrotoxicosis follow-up study group reported no increase in leukaemia in an 8-year follow-up in 19,200 patients, which was also noted in 1000 patients treated in the Mayo Clinic [72]. Increased risk of breast cancer, as discussed in thyroid cancer patients treated with high activities of I-131, was not observed in 1005 patients treated for thyrotoxicosis (mean follow--up: 15 years).

The data concerning survivors of the atomic bombings of Hiroshima and Nagasaki indicate that irradiation at moderated doses did not significantly increase the genetic risk of these subjects and the following generation [66]. In patients treated with radioiodine for hyperthyroidism such studies have not been undertaken, but it seems unlikely that genetic risk would be observed at gonadal doses of the same magnitude as seen in radiological procedures like intravenous pyelograms and abdominal CT.

Conclusion

Radioiodine therapy for autonomy has been found to be both effective and safe in thyroid autonomy and without major early or late side effects. If modern dosimetric and therapeutic approaches are used, an overall success rate of 90% or higher can be achieved. Radioiodine has become the procedure of choice in autonomy patients with latent or overt hyperthyroidism especially in the absence of a large goitre, after thyroid surgery and in elderly patients with associated conditions who carry a high intra- or perioperative risk.

References

1. Reinwein D, Benker G, König MP, Pinchera A, Schatz H, Schleusener. Klinische Aspekte der Hyperthyreose in Gebieten unterschiedlicher Jodversorgung. Schweiz Med Wochenschr 1987; 117: 1245–1255.
2. Lamberg BA. Endemic goiter in Finland and changes during 30 years of iodine prophylaxis. Endocrinol Exp 1986; 20: 35–47.
3. Hillenhinrichs H, Emrich D. Jodmangelstruma mit und ohne funktionelle Autonomie in der euthyreoten Phase: Ein Vergleich. Nuklearmedizin 1998; 37: 95–100.
4. Bähre M, Hilgers R, Lindemann C, Emrich D. Thyroid autonomy: sensitive detection and estimation of its functional relevance using quantified high-resolution scintigraphy. Acta Endocrinol (Copenh.) 1988; 117: 145–153.
5. Joseph K. Estimation of Volume of autonomously functioning thyroid tissue. Exp Clin Endocrinol 1994; 102 (Suppl. 3): 12–19.
6. Parma J, Duprez L, Van Sande J, Cochaux P, Gervy C, Mockel J, Dumont J, Vassart G. Somatic mutations in the thyrotropin receptor gene cause hyperfunctioning thyroid adenomas. Nature 1993; 365: 649–651.
7. Krohn H, Führer D, Holzapfel HP, Paschke R. Clonal origin of toxic thyroid nodules with constitutively activating thyrotropin receptor mutations. J Clin Endocrinol Metab 1998; 83: 130–134.
8. Krohn K, Wohlgemuth S, Gerber H, Paschke R 2000 Hot microscopic areas of iodine-deficient euthyroid goitres contain constitutively activating TSH receptor mutations. J Pathol 192: 37–42.
9. Becker W, Börner W, Rendl J. Ist ein TSH-Sceening zur Diagnose oder zum Ausschluß der funktionellen Autonomie der Schilddrüse sinnvoll? Nuklearmedizin 1992; 31: 132–136.
10. Becker W, Wolf F. Thyroid scintigraphy: Tc-99m-pertechnetate and I-123. Exp Clin Endocrinol 1994; 102 (Suppl. 3): 1–11.
11. Joseph K, Mahlstedt J, Pries HH, Schmidt U, Welke U. Früherkennung und Abschätzung des Hyperthyreoserisikos autonomen Schilddrüsengewebes. NucCompact 1977; 8: 134–137.
12. Mahlstedt J, Schmidt H, Joseph K. Untersuchungen zur Verlässlichkeit des ^{99m}Tc- Speichertestes als Schätzer der thyroidalen Stimulation. Fortschr Röntgenstr 1979; 131: 536–544.
13. Joseph K. Statische, dynamische und quantifizierte Schilddrüsenszintigraphie. Nuklearmediziner 1979; 2: 83–101.
14. Voth E, Dickmann N, Schicha H, Emrich D. Rezidivrisiko nach thyreostatischer Therapie immunogener und nicht immunogener Hyperthyreosen. Nuklearmedizin 1990; 29: 1–6.
15. Sandrock D, Olbricht T, Emrich D, Benker G, Reinwein D. Long-term follow-up in patients with autonomous thyroid adenoma. Acta Endocrinol (Copenh.) 1993; 128: 51–55.
16. Belfiore A, Sava L, Runello F, Tomaselli L, Vigneri R. Solitary autonomously functioning thyroid nodules and iodine deficiency. J Clin Endocrinol 1983; 56: 283–287.
17. Zieseniss K, Zeidler U, Creutzig H, Hundeshagen H. Ist das autonome Adenom der Schilddrüse therapiebedürftig? Med Klin 1981; 76: 193––196
18. Emrich D, Erlenmaier U, Pohl M, Luig H. Determination of the autonomously functioning volume of the thyroid. Eur J Nucl Med 1993; 20: 410–414.
19. Schneider D, Joseph K, Höffken H, Kümmel H, Nebe R, Skamel HJ, Stapp J, Welke U. Werden Patienten mit funktioneller thyreoidaler Autonomie durch Optimierung der täglichen Jodzufuhr gefährdet? In: Röher HD, Weinheimer B. (eds.). Schilddrüse 1991. Berlin: de Gruyter, 1992; 400–407.
20. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, Wilson PWF, Benjamin EJ, D'Agostino RB. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 1994; 331: 1245–1252.
21. Schicha H, Scheidhauer K. Therapie mit offenen radioaktivenStoffen In: Büll U, Schicha H, Biersack HJ, et al. (eds.). Nuklearmedizin. Stuttgart, New York: Georg Thieme 1994; 460–475.
22. Dai G, Levy O, Carrasco N. Cloning and characterization of the thyroid iodine transporter. Nature 1996; 379: 458–460.
23. Royaux IE, Wall SM, Karniski LP, Everett LA, Suzuki K, Knepper MA, Green ED. Pendrin, encoded by the Pendred syndrome gene, resides in the apical region of renal intercalated cells and mediates bicarbonate secretion. Proc Natl Acad Sci USA 2001; 98: 4221–4226.

24. Capen CC. Anatomy, comparative anatomy, and histology of the thyroid. In: Bravermann LE, Utiger RD. (eds.). Werner and Ingbar's The Thyroid. Lippincott, Philadelphia 1991; 22–43.
25. Kennedy JS, Thomson JA. The changes in the thyroid gland after irradiation with ^{131}I or partial thyroidectomy for thyrotoxicosis. J Path 1974; 112; 65–81.
26. Mettler Jr FA, Upton, AC. Medical effects of ionizing radiation. W.B. Sunders Philadelphia, London, Toronto 1995.
27. Reiners C. Radiojodtherapie. Dt Ärtzebl 1993; 90: 2996–3003.
28. Aro A, Huttunen J K, Lamberg B A, Pelkonen R, Ikkala E, Kuusisto A, Rissanen V, Salmi J, Tervonen S. Comparison of propranolol and carbimazole as adjuncts of iodine-131 therapy of hyperthyroidism. Acta Endocrinol (Copenh.) 1981; 96: 321–327.
29. Rendl J, Börner W. Einfluß vorrausgegangener diagnostischer und therapeutischer Maßnahmen auf die Radiojodtherapie gutartiger Schilddrüsenerkrankungen. Nuklearmediziner 1991; 14: 29–36.
30. Müller B, Bares R, Büll U. Untersuchungen zur effektiven Halbwertszeit des ^{131} J bei der Radiojodbehandlung der Schilddrüsenautonomie. Nuklearmedizin 1991; 30: 71–76.
31. Urbannek V, Voth E, Moka D, Schicha, H. Radioiodine therapy of Graves' disease — a dosimetric comparison of different strategies concerning antithyroid drugs. Nuklearmedizin 2000; 40: 111–115.
32. Connell JMC, Hilditch TE, McCruden DC, Robertson J, Alexander WD. Effect of pretreatment with carbimazole on early outcome following radio-iodine (^{131}I) therapy. Eur J Nucl Med 1984; 9: 464–466.
33. Holm LE, Lundell G, Israelsson A, Dahlqvist I. Incidence of hypothyroidism occurring long after iodine-131 therapy for hyperthyroidism. J Nucl Med 1982; 23: 103–107.
34. Sabri O, Zimny M, Schulz G, Schreckenberger M, Reinartz P, Willems K, Büll U. Success rate of radioiodine therapy in Graves' disease: The influence of thyrostatic medication. J Clin Endocrinol Metab 1999; 84: 1229–1233.
35. Andrade VA, Gross JL, Maia AL. The effect of methimazole pretreatment on the efficacy of radioactive iodine treatment in Graves' hyperthyroidism. One-year follow-up of a prospective randomized study. J Clin Endocrinol Metab 2001; 86: 3488–3493.
36. Körber C, Schneider P, Körber-Hafner N, Hänscheid H, Reiners C. Antithyroid drugs as a factor influencing the outcome of radioiodine therapy in Graves' disease and toxic nodular goitre? Eur J Nucl Med 2001; 28:1360–1364.
37. Moser E, Pickardt CR, Mann K, Engelhardt D, Kirsch CM, Knesewitsch P, Tatsch K, Kreisig T, Kurz C, Saller B. Ergebnisse der Radiojod-Behandlung von Patienten mit immunogener und nicht immunogener Hyperthyreose bei Anwendung unterschiedlicher Herddosen. Nuklearmedizin 1988; 27: 98–104.
38. Heinze HG, Pickardt CR, Swoboda G, Horn K, Erhardt F, Scriba PC. Schilddrüsenfunktion nach Radiojod-Resektion des autonomen Adenoms der Schildddrüse. Nuklearmedizin 1977; 16: 224–231.
39. Heinze, HG, Bohn U. ^{131} Jod-Therapie des autonomen Adenoms der Schilddrüse. DMW 1987; 112: 1073–1079.
40. Goldstein R, Hart IR. Follow-up of solitary autonomous thyroid nodules treated with 131I. N Engl J Med 1983; 309: 1473–1476.
41. Ratcliffe GE, Cooke S, Fogelman I, Maisey MN. Radioiodine treatment of solitary functioning thyroid nodules. Br J Radiol 1986; 59: 385–387.
42. Irvine WJ, Toft AD. The diagnosis and treatment of thyrotoxicosis. Clin Endocrinol 1976; 5: 687–695.
43. Ross DS, Ridgway EC, Daniels GH. Successful treatment of solitary toxic thyroid nodules with relatively low-dose iodine-131, with low prevalence of hypothyroidism. Ann Int Med 1984; 101: 488–490.
44. Hegedüs L, Veiergang D, Karstrup S, Hansen JM. Compensated ^{131}I therapy of solitary autonomous thyroid nodules: effect on thyroid size and early hypothyroidism. Acta Endocrinol (Copenh.) 1986; 113: 226–232.
45. Marinelli LD, Quinby EH, Hine GJ. Dosage determination with radioactive isotopes. Practical considerations in therapy and protection. Am J Röntgenol 1948; 59: 260–281.
46. Bockisch A, Jamitzky T, Derwanz R, Biersack HJ. Optimized dose planning of radioiodine therapy of benign thyroid diseases. J Nucl Med 1993; 34: 1632–1638.
47. Debrand-Passard A, Barzen G, Richter W, Wenzel K. W, Felix R. Therapieergebnisse der Radiojodtherapie hyperthyreoter Schilddrüsenerkrankungen. Med Klein 1994; 89: 319–323
48. Emrich D, Reinhardt M. Ergebnisse der definitiven Behandlung der Autonomie bei Jodmangelstruma. Nuklearmedizin 1989; 28: 11–16.
49. Oexle C, Reinhardt M, Moser E. Erste Ergebnisse der Radioiodtherapie bei multifokaler und disseminierter Autonomie der Schilddrüse unter Verwendung eines TcTUs-adaptierten Dosiskonzepts. Nuklearmedizin 1998; 37: 192–196.
50. Emrich D. Estimation of the autonomous volume. Exp Clin Endocrinol 1994; 102 (Suppl. 3): 20–22.
51. Kreisig T, Pickardt CRF, Vaitl C, Kirsch CM, Knesewitsch P. Regionaler 99mTc-Uptake der Schildddrüse(TcTU) in Kombination mit der Sonographie bei fokaler Autonomie. In: Börner W, Weinheimer B. (eds.). Schilddrüse 1989. Berlin: de Gruyter 1991; 208–211.
52. Seeger T, Emrich D, Sandrock D. Radiojodtherapie der funktionellen Autonomie unter Verwendung des funktionelle autonomen Volumens. Nuklearmedizin 1995; 34: 135–140.
53. Meller J, Wisheu S, Munzel U, Behe M, Becker W. 99m-TcO_4^- thyroid uptake-based radioiodine therapy (RIT) of Plummer's disease. Eur J Nucl Med 2000, 27: 1286–1291.
54. Berding G, Schicha H. Ergebnisse der Radiojodtherapie der manifesten Hyperthyreose und der autonomen Struma mit Euthyreose. Nuklearmedizin 1990; 29: 158–165.
55. Reinhardt M, Emrich D, Krause T, Bräutigam P, Nitzsche E, Blattmann H, Schümichen C, Moser E. Improved dose concept for radioiodine therapy of multifocal and disseminated functional thyroid autonomy. Eur J Endocrinol 1995; 132: 550–556.
56. Guhlmann CA, Rendel J, Börner W. Radioijodtherapie der funktionellen Autonomie und des M. Basedow. Nuklearmedizin 1995; 34: 20–23.
57. Dunkelmann S, Endlicher D, Prillwitz A, Rudolph F, Groth P, Schümichen C. Ergebnisse der TcTUs-optimierten Radioiodtherapie bei multifokaler und dissemineirter Autonomie. Nuklearmedizin 1999; 38: 131–139.
58. Dederichs B, Otte R, Klink JE, Schicha H. Volumenreduktion der Schilddrüse nach Radiojodtherapie bei Patienten mit Schilddrüsenautonomie und Morbus Basedow. Nuklearmedizin 1996; 35: 164–169.
59. Luster M, Jacob M, Thelen MH, Michalowski U, Deutsch U, Reiners C Reduktion des Schilddrüsenvolumens nach Radiojodtherapie wegen funktioneller Autonomie. Nuklearmedizin 1995; 34: 57–60.
60. Gorman CA, Robertson JS. Radiation dose in the selection of ^{131}I or surgical treatment for toxic thyroid adenoma. Ann Int Med 1987; 89: 85–90.
61. Riggs DS. Elevation of serum protein bound iodine after large doses of radioactive iodine. Fed Proc 1948; 7: 251–254.
62. Glennon JA, Gordon ES, Savin CT. Hypothyroidism after low dose 131-I treatment of hyperthyroidism. Ann Intern Med 1972; 76: 721––723.
63. Tamagna EI, Levine GA, Hershman JM. Thyroid-hormone concentrations after radioiodine therapy for hyperthyroidism. J Nucl Med 1979; 20: 387–391.
64. Kreisig T, Abenhardt W, Mann K, Kirsch CM, Moser E. Frühveränderungen der Schilddrüsenhormone nach Radiojodtherapie der Hyperthyreose unter Berücksichtigung von Ätiologie und begleitender Medikation. Klin Wochenschr 1989; 67: 386–392.
65. McDermott MT, Kidd GS, Dodson Jr LE, Hofeldt FD. Radioiodine-induced thyroid storm. Am J Med 1983; 75: 353–359.

66. Becker W. Grundzüge der Radiojodtherapie In: Köbberling J, Pickardt CR. (eds.). Struma. Berlin, Heidelberg, New York: Springer 1990; 168–180.
67. Wilson M, Davis TME, Bade PG, Castelden WM. Tracheo-oesophageal compression due to rapid thyroid enlargement after radioiodine therapy. Med J Aus 1995; 162: 485–486.
68. Nygaard B, Faber J, Hegedüs L. Acute changes in thyroid volume and function following ^{131}I therapy of multinodular goiter. Clinical Endocrin (Oxf.) 1994; 41: 715–718.
69. Dobyns BM, Sheline G E, Workman JG, Tompkins EA, McConahey WM, Becker DV. Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the Cooperative Thyrotoxicosis Study. J Clin Endocrinol Metab 1974; 38: 976–998.
70. Holm LE. Malignant disease following iodine-131 therapy in Sweden. In: Boice Jr. JD, Fraumeni Jr. JF. eds: Radiation carcinogenesis: Epidemiology and biologic significance. Raven Press, New York 1984; 263–281.
71. Shore RE. Issues and epidemiological evidence regarding radiation-induced thyroid cancer. Radiat Res 1992; 131: 98–111.
72. Saenger EL, Thoma GE, Tomkins EA. Incidence of leukaemia following treatment of hyperthyroidism. J Am Med Ass 1965; 205: 855––873.