^{131}I Therapy in Primary Hyperthyroidism and Non-toxic (Multi)Nodular Goitre

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1. Introduction

Uptake and organification of iodine for the production of thyroid hormone takes place in the thyroid. The protein responsible for iodide transport, the so-called sodium/iodide symporter or NIS, is located at the basolateral plasma membrane of thyrocytes. Iodine is incorporated into thyroid hormones which are bound to thyroglobulin. In this form it is stored in thyroid follicles. Certain other (glandular) tissues can also incorporate iodine, but organification is not possible in these tissues. There is no prolonged retention of iodine outside the thyroid. This distinction is used in therapeutic applications of ^{131}I sodium iodide.

2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications

Treatment of primary hyperthyroidism due to:

- Graves' disease
- Solitary autonomous nodule (toxic adenoma)
- Toxic multinodular goitre

Size reduction of a non-toxic multinodular goitre.

3.1 Contraindications

Pregnancy

This is an absolute contraindication, and must be excluded before ^{131}I therapy is given. Therefore, female patients with reproductive capacity, must have a pregnancy test on the day of therapy. This test can only be omitted in sterilized patients or patient older than 50 years.

Lactation

The ^{131}I excretion in breast milk is substantial and would form an unacceptable ^{131}I intake for the infant. Breastfeeding should be omitted for at least 14 days. Breast milk can be pumped and discarded during these 14 days.

Active Graves' ophthalmopathy

The relative contra-indication for ^{131}I treatment in a patient with active ophthalmopathy is controverse. In patients with double vision, conjunctival suffusion, chemosis or any (other) suspicious symptoms, an ophthalmologist should be consulted prior to therapy. Ophthalmological consent is required if ^{131}I therapy is contemplated in a patient with

active ophthamopathy, for instance, because of intolerability to anti-thyroid drugs. In patients with clinically very active ophthalmopathy, ^{131}I treatment must be postponed. In less severe cases ^{131}I can be administered under prednisolone prophylaxis. Patients must always be advised to quit smoking because this has a negative impact on eye symptoms.
Children < 5 years

3.2 Relative contraindications
Coexisting (or suspicion of) thyroid cancer
Reduced self care
Childhood (age between 5-10 years)
Some clinicians who manage childhood Graves' disease are wary of using ^{131}I therapy. There is, however, data from a study with nearly 40 years of follow-up that showed no increased risk of thyroid cancer or leukaemia in children and adolescents treated with radioiodine.
Low iodine uptake
When the 24-h RAIU is significantly lower than expected (<35%, especially in patients with Graves' disease), the following possibilities should be considered: medication has not been discontinued, the patient is not hyperthyroid at present or the thyrotoxicosis is not primary hyperthyroidism. In these cases, treatment with ^{131}I may not be indicated.

4. Relation to other therapies

- *Graves' hyperthyroidism* can be adequately treated with antithyroid drugs in combination with levothyroxine. After a treatment period of 1-1,5 years, a number of patients (30-50%) will achieve lasting euthyroidism. Prolonged use of antithyroid drugs carries the risk of serious side effects (agranulocytosis, aplastic anaemia) which may be fatal in 1:100.000 cases.
  Near total or total thyroidectomy can be considered in Graves' disease in case of contraindication(s) for ^{131}I treatment. Total thyroidectomy has a nearly 0% risk of recurrence whereas subtotal thyroidectomy may have an 8% chance of persistence or recurrence of hyperthyroidism at 5 years. Thyroidectomy can be the treatment of choice in children who are too young for radioactive iodine.
- *Toxic multinodular goitre:* ^{131}I treatment is preferable, even with large goitres. Surgery is not preferred because of the associated morbidity. The risk of recurrence of goitre following surgery is estimated to be 15-40%. Drug therapy has a limited effect and only lasts as long as the medication is taken adequately.
- *Toxic adenoma:* ^{131}I is the treatment of choice as no permanent remission can be achieved with drugs. Surgical removal is a second choice treatment unless the adenoma is very large.
- *Non-toxic multinodular goitre:* Surgery is usually the first choice, but because of comorbidity or other (relative) contraindications, ^{131}I is an attractive alternative, especially in the elderly. ^{131}I treatment can achieve a volume reduction of about 50%. Radioiodine also has a favourable effect on tracheal compression and inspiratory lung function. If desired, ^{131}I treatment can be repeated after 1 year, but one has to keep in mind that the iodine uptake may be significantly decreased. A single treatment is therefore preferred to treatment in multiple tempi. Drug therapy with levothyroxine is not effective.

5. Medical information necessary for planning

Treatment of primary hyperthyroidism:

- Hyperthyroidism symptoms and duration
- Biochemical confirmation of diagnosis and cause
- Findings on palpation
- Active ophthalmopathy symptoms
- Serum concentrations of TSH, FT4 (and FT3 if necessary), values at presentation and current values
- Smoking

Reduction of a non-toxic (multi) nodular goitre:

- Symptoms (aesthetic and / or mechanical)
- Findings on palpation
- Growth pattern of the goitre over the course of time
- FNA findings
- Serum concentrations of TSH, FT4 (and FT3 if necessary)
- Previous (medical) treatments
- Current medication

Radiopharmaceutical

Preparation:	Sodium ^{131}I
Nuclide:	Iodine-131
Activity:	3,7-11,1 MBq/ml or fixed activities 370-740 MBq
Administration:	Oral or intravenous

Activity

In general, an absorbed radiation dose of 150-200 Gy to the thyroid gland is sufficient to cure thyrotoxicosis. To achieve euthyroidism, the ^{131}I dose should be calculated per individual patient, taking into account thyroid volume, thyroid radioactive iodine uptake (24-h RAIU) and the iodine turnover in the thyroid (in Graves' hyperthyroidism and multinodular goitres).

When a quick or definitive therapy-result is desired e.g. in anti-thyroid drug allergy, cardiac problems, pregnancy wish, etc., the calculated activity should be increased. In such cases the dose is often doubled. The underlying cause of hyperthyroidism must be taken into account when determining the ^{131}I dose.

Dose formula

The indicated dose (D) is calculated using the formula: $D = k \cdot V / U$ (MBq). D equals the therapy dose (MBq), V thyroid volume (ml) and U equals the thyroid 24-h radioactive iodine uptake (%). The conversion factor k has the unit MBq%ml^{-1}.

Graves' hyperthyroidism

For thyroid volumes < 50 ml, an activity of 3,7 MBq/ml is usually sufficient (k = 370). For thyroid volumes > 50 ml, activities from 3,7 to as high as 11 MBq/ml are recommended. The dose should also depend on the iodine kinetics (24-h RAIU and turnover rate). These are, apart from thyroid volume, the most important independent prognostic factors for the

treatment outcome in a given dose of ^{131}I. In patients with high iodine turnover (5 / 24 h ratio >0,8) or high 24-h RAIU (>80%), activities of > 3,7 MBq/ml are recommended. As an alternative, fixed activities of 370 or 555 MBq can be used. These doses result in hypothyroidism in 69% to 90% of patients. With this regimen, a high incidence of ("early") hypothyroidism is taken for granted.

Non-toxic goitre-reduction

Activities of 3,7 MBq/ml of functioning thyroid tissue are indicated. The dosage may be determined in consultation with the patient and depends mainly on the acceptance of the risk of persistent hypothyroidism.

The actual dose given may, in practice, be less than the calculated dose: The dose is often limited in such a way that the 24-h retention does not exceed 400 MBq. This keeps the number of days in hospital to a reasonable limit. However, it means more patients will require multiple therapies.

Toxic adenoma

A fixed activity of 740 MBq is advised. With this dosage, there is a relatively low risk of hypothyroidism, provided the uptake in the perinodular normal thyroid tissue is (almost) completely suppressed.

A second validated strategy for toxic adenoma is a dose of 7,4 MBq / ml of adenoma tissue. In both schemes, the recommended dosage is to be halved when the suppression of the normal thyroid tissue is incomplete. As an alternative, ^{131}I treatment can be delayed until complete suppression has occurred. In the meantime, the patient is treated with anti-thyroid drugs.

Toxic multinodular goitre

The recommended activity is 3,7- 7,4 MBq/ml (k=370 or 740). The dosage may be determined in consultation with the patient and depends mainly on the acceptance of the risk of persistent hypothyroidism or recurrent hyperthyroidism.

Measurements prior to therapy

Thyroid volume

Using scintigraphy, the thyroid volume can only be approximated. The average error is about 30%. Thyroid palpation is, in experienced hands, an almost equivalent instrument. Ultrasound is the investigation of choice. In dose calculation, however, several other factors play a role, such as iodine kinetics. As long as the associated uncertainties remain, scintigraphy is a permissible method for volume measurement (acquisition and processing parameters are described in the thyroid gland scintigraphy chapter:

Thyroid radioactive iodine uptake.

The incorporation of iodine is measured by means of an oral tracer dose of ^{131}I or ^{123}I, followed by planar scintigraphy or thyroid probe measurement. The implementation of this measurement is discussed under "acquisition and processing".

The measurement at t=24 h after administration is used in dose calculation. There are circumstances, however, in which an earlier measured iodine uptake is higher in

comparison to the 24-h uptake. This indicates rapid iodine kinetics and thus a lower radiation dose to the thyroid. At a very high iodine uptake (> 80%), the kinetics are also often accelerated. Therefore, in some institutions, the iodine uptake is also measured at an earlier time (t=4-6 h).
Please note that the iodine uptake in an individual undergoes large fluctuations within a relatively short period of time. Therefore, the measurement of iodine uptake for the calculation of a therapeutic dose of ^{131}I should take place as shortly as possible prior to treatment. An interval of up to 1-2 weeks between measurement and therapy is considered permissible in Graves' hyperthyroidism.
In (non) toxic goitres the interval may be longer. However, the iodine uptake in (non) toxic goitres strongly depends on the current TSH-level. So a longer interval, requires re-assessment of the uptake if the TSH-level changes.

Toxicity / adverse effects
When using relatively low therapeutic doses, clinically relevant radiation thyroiditis and / or temporary worsening of thyrotoxicosis (mostly between 3 and 10 days) as a result of thyroid hormone emissions, are seen only incidentally. Thyroiditis (usually within a few weeks) can occur after ^{131}I treatment of a large goitre, which can lead to swelling and trachea compression, sore throat and stomatitis. The symptoms usually disappear within one week, the use of antiphlogistics may reduce symptoms. If compression symptoms exist prior to ^{131}I therapy, prophylactic treatment with prednisolone is recommended for the prevention of critical obstructive complications. In higher doses, sialoadenitis (within 1 week) may form a possible complication which can usually be prevented by adequate stimulation of the salivary glands (e.g. use of sour sweets) during the first 2 days after ^{131}I therapy. Gastritis may also occur (1-2 days after therapy), this can be treated with medication. Very rarely, transient laryngeal nerve dysfunction occurs.
In patients with (non)toxic multinodular goitre, Graves' disease is occasionally induced by radioiodine treatment. This is a relatively rare complication of ^{131}I therapy, which is probably caused by the emission of degraded thyroid cells, which start to function as antigen.

Hypothyroidism.
There is a high occurance rate of hypothyroidism within 6-12 weeks of ^{131}I therapy (for the occurrence of transient hypothyroidism, see Patient). In toxic adenoma the probability of developing hypothyroidism is however, less than 5%.
The one-year risk of hypothyroidism after treatment of large *non-toxic goitres* is estimated to be 14-22%. Regular follow-up is recommended in all patients.
In *Graves' hyperthyroidism* , hypothyroidism seems almost inevitable on the long run. Within 25 years 80% of patients will become hypothyroid. After ^{131}I therapy, the incidence is around 3% per year.

Ophthalmopathy
After radioiodine therapy, both an increase in the number of patients with ophthalmopathy and an increase in the severity of ophthalmopathy has been described. Patients with active ophthalmopathy can therefore be treated prophylactically with prednisolone. Some therapists advise that patients who have had active eye symptoms in the past, also be

treated with prednisolone. There are different regimens in use. We recommend the prednisolone treatment scheme as published by the Nederlandse Internisten Vereniging (NIV revised guidelines 2012):
30 mg of prednisone daily for 4 weeks directly following ^{131}I therapy, after that 20 mg / day for 4 weeks and then reduce by 5 mg per week. Prednisolone has no adverse effect on the efficacy of ^{131}I therapy.
Risk factors for progression of eye disease after ^{131}I therapy include pre-existing thyroid ophthalmopathy, cigarette smoking, severe hyperthyroidism, late correction of post-radioiodine hypothyroidism and high TSH-receptor antibody titres. Early administration of thyroxine to prevent hypothyroidism can reduce the risk of Graves' ophthalmopathy after radioiodine. Also, patients who have been adequately pre-treated with anti-thyroid medication show a reduced risk of developing ophthalmopathy symptoms after therapy.

6. Radiation exposure (pregnancy / lactation)
As stated above, pregnancy and/or lactation are absolute contraindications for ^{131}I therapy.

Tabel 1: Radiation Dosimetry for Adults

Radiopharmaceutical	Administered Activity MBq	Organ which receives the largest radiation dose mGy/MBq	Effective Dose Equivalent mSv/MBq
Na^{123}I iodide	3,7-11,1 p.o.	3,2 Thyroid	0,11
^{99m}Tc-pertechnetate	74-370 i.v.	0,062 upper large intestine	0,013
Na^{131}I iodide*	0,15-0,37 p.o.	360 Thyroid	11* 25**

*assuming 25% uptake
**assuming 35% uptake

Radiation Dosimetry for Children (5 years old)

Radiofarmaceutical	Administered Activity (MBq/Kg)	Organ Receiving The Largest Radiation Dose mGy/MBq	Effective Dose Equivalent mSv/MBq
$Na^{123}I$ iodide*	0.1 – 0.3 p.o.	16T Thyroid	0.54
^{99m}Tc pertechnetate	1.8 – 9.2 i.v.	0.21 upper large intestine	0.04

* assuming 25% uptake

[SNM procedure guideline thyroid uptake measurement, 2006]

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2. ICRP Publication 53. Radiation Dose to Patients from Radiopharmaceutcals, 1994 edition
3. Loevinger R, Budinger T, Watson E. MIRD Primer for Absorbed Dose Calculations, Society of Nuclear Medicine, 1991

7. Patient preparation/essentials for procedure

^{131}I therapy may only be given if there is specific authorization. Depending on the license granted, up to 400 MBq can, in principle, be given on an outpatient basis, under certain well-defined conditions.

Patient preparation

- Patients with primary hyperthyroidism or with a non-toxic multinodular goitre who are referred to a nuclear medicine physician, have in almost all cases been under the care of an internist / endocrinologist for some time. A structured consultation with the referring specialist is essential to achieve optimal treatment result. All specialists involved in the treatment of thyroid diseases should have regular meetings in which individual patients and treatment protocols are discussed in a multidisciplinary setting.
- A patient with Graves' hyperthyroidism should, as a rule, first be treated with anti-thyroid drugs and levothyroxine for 1-1,5 years, after which 30-50% of them will require no further therapy.
- Determining the cause of thyrotoxicosis has implications for treatment. It is important to verify that the diagnosis "primary hyperthyroidism" is adequately made.
- Patients with symptoms of thyrotoxicosis must receive thyrostatic drugs in order to achieve euthyroidism. This is to avoid a so called thyrotoxic crisis, which can be life threatening, especially in elderly patients with cardiac co-morbidity.
- Patients suffering from congestive heart failure should be treated with diuretics; patients with atrial fibrillation should be treated with anti-arrhythmic drugs (but no

amiodarone!).
- Patients with symptoms of Graves'ophthalmopathy must be referred to an ophthalmologist.
- Numerous drugs, foods and cosmetics may affect the iodine uptake. In some cases, these must be discontinued for a certain period of time. If the patient has had a recent CT-scan with iodine-containing contrast, ^{131}I must be postponed for at least 4 weeks.
- Anti-thyroid drug therapy with thiamazol in patients with hyperthyroidism (whether or not in combination with thyroxine) must be discontinued 3-5 days prior to ^{131}I treatment, and may be resumed 3 days after the ^{131}I therapy. Anti-thyroid therapy with Propylthiouracil (PTU) must be discontinued for at least 15 days because of its negative effect on ^{131}I treatment.
- If necessary, beta-blockers can be prescribed in symptomatic hyperthyroid patients. This medication does not have to be interrupted during ^{131}I therapy. Thiamazol and thyroxine must also be discontinued for 3-5 days and PTU for at least 15 days prior to iodine uptake measurement(s) (and for scintigraphy).
- The use of thyroxine in non-toxic multinodular goitre must be interrupted (levothyroxine for 4 weeks, triiodothyronine for 2 weeks).
- A low iodine diet is not necessary in patients with hyperthyroidism. In patients with (non)-toxic multinodular goitre, this may be a useful measure to increase the uptake of ^{131}I in the thyroid.
- In toxic multinodular goitres or toxic adenomas, the normal thyroid must be suppressed to save thyroid function. If thyroid suppression has not occurred, consider postponement of the ^{131}I therapy.
- When the aim is volume reduction of non-toxic goitres, a balance must be achieved between surgery and ^{131}I therapy.

» The treatment and /or ^{131}I activity is partly determined by the expectations people have regarding ^{131}I therapy. Is a fast result desired or is a rapidly developing hypothyroidism due to the treatment an objection?
» How relevant is the radiation exposure to persons in the vicinity? Does the patient have the daily care for children? In this case, appropriate measures must be taken.
» The patient must be informed verbally as well as in writing about the pros and cons of outpatient treatment (and the conditions under which this can occur), inpatient treatment, the necessary radiation protection measures, the risk of hypothyroidism or recurrent hyperthyroidism, follow-up and the treatment after ^{131}I therapy.
» Treatment with ^{131}I should take place as quickly as possible (within 7 days) after the iodine uptake measurement(s), so the thyrostatic therapy may remain suspended. Also, variations in the iodine kinetics may occur quickly.

Execution
- On the day of ^{131}I therapy, pregnancy must be excluded by means of a pregnancy test, in all female patients with reproductive capacity. To this end, the patients' morning urine is tested.
- Patients must fast for four hours prior to the uptake measurement(s) and administration of the ^{131}I. In practice, this means patients may eat a light breakfast

early in the morning.
- The administered ^{131}I must be in the same form (formulation) as was given for the uptake measurement(s). Preferably, a capsule.
- At discharge, the exposition dose rate is measured. This may not exceed 20 μSvh^{-1} at 1 m distance from the patient.

Aftercare staff and patient
Staff
- With respect to the staff, risks arise from the possibility of external and internal radiation. Specific training and adequate education of nurses in relation to the properties of ionizing radiation and the principles of radiation protection is required. Written instructions should be available (a) to shorten the time spent in the immediate vicinity of the patient as much as possible, (b) to prevent contamination by wearing protective clothing, footwear, gloves, etc. and (c) to minimize the consequences of an identified contamination.
- Nursing staff are not identified as a radiological workers, unless the therapy department is part of the department of nuclear medicine. Nevertheless, it is recommended that a direct reading dosimeter is worn.

Patient
- During the first 24 h, the patient is advised to drink extra, thus minimizing the radiation dose to the bladder. With an average effective half-life of 5,5 days in hyperthyroid patients, each additional day in isolation will accomplish only a marginal dose reduction for third parties. The current standard for discharge is an exposition rate of 20 μSvh^{-1} at 1 m from the patient. Provided the proper permit, the patient may be sent home immediately after administration of activities up to 400 MBq (outpatient administration).
- Up to 3 weeks after discharge, sufficient distance to small children or pregnant women must be kept. For further detail we refer to the publication "Recommendations on working with therapeutic doses of radionuclides" by the ministry of VROM, the ministry of SWZ and NVNG.
- Women should be advised not to try to become pregnant in the first 4 months after treatment. Men also should be discouraged from procreating for 4 months.
- The therapeutic effect of the ^{131}I treatment (with respect to the reduction of thyroid function) usually occurs within 3-6 months. Thyroid function should be monitored within that period so thyrostatic treatment can be adjusted in a timely fashion. If the first treatment has insufficient effect, subsequent ^{131}I treatment is recommended.
- Attention should be paid to distinguish "transient" hypothyroidism from permanent hypothyroidism. Transient hypothyroidism is a temporary decrease in thyroid function, below the indicated standard, which occurs around 2-3 months after ^{131}I therapy in 10-15% of all patients. Normalization spontaneously occurs within a few months. If hypothyroidism persists after 3 months, thyroid function should be re-evaluated after approximately 6 months, thus preventing unnecessary lifelong thyroid hormone supplementation.
- The effect with respect to goitre reduction also takes place for the most part within the first 6 months. However, a slight further reduction may be observed up to 12-18 months post treatment.

- The patient should be monitored for the possible occurrence of (early) hypothyroidism or recurrent thyrotoxicosis. The patient and the general practitioner should be aware of this. More than 80% of patients with Graves' disease become hypothyroid within 25 years (the incidence after ^{131}I therapy is up to 3% per year).
- There is no need for special instructions in case a patient unexpectedly dies shortly after ^{131}I therapy. The relevant ministries have no preference for burial or cremation shortly after therapy or diagnosis with radioactive substances. Autopsy may also be done, but only after consultation with a radiation expert.

8. Acquisition and processing

See chapter thyroid gland scintigraphy.

Uptake measurement

The measurement of thyroid uptake, as stated above, is usually performed 24 h after administration of 0,4 MBq ^{131}I sodium iodide. In some institutions radioactive iodine uptake is also measured between 2 and 6 h after radioiodine ingestion. The uptake is usually measured with 25-30 cm between the face of the crystal and the anterior aspect of the neck or phantom. Neck counts, body background counts (lower thigh), counts of a calibrated standard in a neck phantom and room background counts should be obtained at each counting session.

Alternatively, the radioiodine dose can be counted in the neck phantom before oral administration, and the counts obtained can be corrected for decay at each patient counting session.

Radioiodine uptake (RAIU) is calculated using the following equation:

$$\text{RAIU} = \frac{\text{Neck Counts (cpm)} - \text{Thigh Counts (cpm)}}{\text{Admin. Counts (cpm)} - \text{Background Counts (cpm)}} \times 100\%$$

9. Interpretation

See chapter thyroid gland scintigraphy.

10. Report

After outpatient treatment or after discharge from the hospital, both the referring specialist and the general practitioner are informed in writing about the treatment carried out, the occurrence of any complications, the recommended precepts and the agreements regarding medication and follow-up.

11. Literature

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