# Radioiodine Therapy of Benign Thyroid Diseases

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**Abstract:** Radioiodine-131 (I-131) is used in treatment of benign thyroid diseases with hyperthyroidism; toxic diffuse goiter, toxic nodular goiter and toxic multinodular goiter for long years. Treatment success depends on various factors. The most important factor affecting the success of treatment is the susceptibility to target tissue I-131. This review aims to give information about the physical and biological characteristics of I-131, advantages and disadvantages, indications and contraindications for I-131 therapy, patient preperation and administiration of I-131, dose selection, precautions on possible side effects, evaluation of treatment response and make an overview on the clinical studies about I-131 therapy.

**Keywords:** Iodine, Thyroid diseases, Hyperthyroidism, Radioiodine-131, Graves disease.

## INTRODUCTION

Radioiodine-131 (I-131) is used in treatment of benign thyroid diseases with hyperthyroidism; toxic diffuse goiter (Graves disease), toxic nodular goiter (toxic adenoma) and toxic multinodular goiter for several years as well as non toxic diffuse goiter, non toxic adenoma and non toxic multinodular goiter. Advantages of this treatment are good tolerability, easy application, safety and efficacy. The critical organ is thyroid gland. I-131 is taken up by follicular cells. Retention of I-131 in the cells depends on the metabolic activity of the cells. Radioiodine-131 emits beta minus *($\beta^-$)* used for therapy. Due to the penetration of beta particles in tissue, damaging effect of $\beta^-$ radiation is limited to thyroid cells. The physical and biological characteristics of I-131, advantages and disadvantages, indications and contraindications for I-131 therapy, patient preperation and administiration of I-131, dose selection, precautions on possible side effects, evaluation of treatment response and an overview on the clinical studies about I-131 therapy in benign thyroid diseases are presented under this title.

## RADIOPHARMACEUTICAL

### Physical Characteristics

Iodine-131 Sodium iodide (NaI) is a radiopharmaceutical obtained by Uranium (235U) fission or by means of neutron bombardment. High gamma energy (364 keV) is used for diagnostic purposes, high beta energy (610 keV) for ablation and therapy. Beta radiation destroy the cells within 0.5-2 mm distance from the center. Radioiodine has capsule and liquid forms for oral administration. The capsule is prepared by evaporating a no carrier added (NCA) I-131 NaI alcohol solution to the inner surface of the gelatin capsule. I-131 in the isotonic saline solution is clear and colorless. The pH value is between 7.5 and 9. The physical half-life is 8.1 days. Shelf life is 4 weeks after calibration [1].

### Pharmacokinetics and Pharmacodynamics

Radioiodine is absorbed from the intestines after oral intake and reaches a maximum blood level within 3 hours. Approximately 90% of the administered dose is excreted from the kidneys, while 10% is excreted in faeces and sweat. The urinary excretion is about 50% after 24 hours of application [2]. High-energy β-particle radiation causes damage to thyroid tissue. The penetration of $\beta^-$ radiation is about 0.8 mm on average. By the radiation exposure of thyroid follicle cells, cell necrosis and DNA damage occurs in surviving cells. This results in inflammation and subsequent fibrosis. Thus, synthesis capacity of the thyroid gland decreases [3-8].

### Advantages And Disadvantages

The first radioactive iodine treatment in benign thyroid diseases was performed in the USA in 1941 [9]. It is used in Europe since 1950s [10].

As with any treatment modality, radioiodine treatment has advantages and disadvantages. Advantages are; It is cheap and effective (because it is selective and destructive in the target cell), easy to apply, reliable, and avoids possible complications of surgery. Disadvantages are; Hypothyroidism, the need for lifelong medication, slow hyperthyroidism therapy, the possibility of recurrence after initial treatment, the need for repeat treatment and development and/or worsening of ophthalmoplegia [7, 11].

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## Indications

Indications include thyroid diseases with hyperthyroidism are classified as; Toxic diffuse goiter (Graves disease), toxic nodular goiter (toxic adenoma) and toxic multinodular goiter, non toxic diffuse goiter, non toxic adenoma and non toxic multinodular goiter [12, 13]. Small and medium-sized thyroid gland, patients with recurrence after medication and surgical treatment, cases where medication and surgery are contraindicated, patients over 40 years of age and cases with high risk of surgery are preferred.

## Toxic Diffuse Goiter (Graves' Disease)

Graves' disease is the most common cause of hyperthyroidism, and 70-80% of patients presenting with thyrotoxicosis have Graves' disease etiology. The disease shows a peak in the fourth and fifth decades with the occurrence in all age groups. It is five times more common in females than in males. Thyroid-stimulating immunoglobulins similar to TSH bind to the follicular cells causing hyperplasia and autonomous thyroid hyperfunction [14].

The diagnosis of Graves' disease is often simple. Thyrotoxicosis, diffuse goitre without nodule and characteristic ophthalmopathia and presence of pretibial dermopathy are of clinical value. However, in some patients the diagnosis is doubtful and not certain [14].

If surgery or medical treatment is contraindicated in patients with Graves' disease, radioactive iodine treatment in elderly patients with the consent of the patient is the first treatment option.

For patients who do not take regular medications (drug interactions, leukopenia, liver function deterioration) and in patients where long-term antithyroid drug treatment is not appropriate (due to the need for fewer visits to the doctor and antithyroid medication is not successful) or where side effects are observed and if hyperthyroidism persists despite 12-18 months of treatment, radioiodine is indicated.

Graves' disease heals with this treatment except for very few cases. The duration of the effect depends on the applied doses. Cure occurs in most patients. In patients who are not cured, the severity of symptoms decreases. Treatment is repeated if the disease continued despite treatment (6 months to 1 year later, recurrent or 25% overdose). Approximately 10% of patients necessitate a second dose. Cure is achieved in 10-40% of Graves' patients who received a second dose [15].

## Graves Ophthalmopathy and Radioactive Iodine Treatment in Smoking

There is a high risk of developing graves ophthalmopathy in smokers after radioactive iodine treatment, especially in male sex. Patients with inactive ophthalmopathy can also receive radioactive iodine without steroids. Patients who smoke, who have positive thyroid receptor antibodies (TRAb) and clinical activity score (CAS) >1 should be reevaluated for radioiodine therapy. In patients who smoke and don't have graves ophthalmopathy, ophthalmopathy may occur after radioiodine therapy. Prophylactic steroid administration is not routinely recommended if smoking patients don't have graves ophthalmopathy. If smoking patients with graves ophthalmopathy are treated with radioiodine therapy, ophthalmopathy may worsen [16, 17].

## Toxic Solitary Nodular Goiter (Toxic Adenoma, Autonomous Toxic Nodule)

Hyper functioning thyroid nodules are the second most common cause of hyperthyroidism. It is usually seen after fifth decade and is often associated with cardiovascular symptoms. They do not show immunologic, ophthalmologic and dermatological changes while they present with thyrotoxic symptoms and signs similar to Graves' disease [18]. Despite surgery is an option in treatment, radioiodine therapy is often preferred [14, 19, 20]. Thyroid cancer should be ruled out for radioiodine therapy.

## Toxic Multinodular Goiter (Plummer's Disease)

Toxic multinodular goiter is often seen in older age group. This disease is associated with tachyarrhythmia, weight loss, depression, anxiety and insomnia. Radioiodine therapy may be preferred, especially in patients with no pressure symptoms [21]. Thyroid cancer should be ruled out before radioiodine therapy.

## Non Toxic Diffuse/Nodular/Multinodular Goiter

In the presence of large and symptomatic goiters without thyrotoxicosis, especially if there is a high risk of surgery, intentional radiotherapy may be considered to reduce the size of the thyroid gland. Prior to non-toxic goiter therapy, rhs TSH can be stimulated to increase iodine uptake and improve the efficacy of treatment [13]. Improved I-131 uptake by rhTSH stimulation and administration of a radioiodine dose of

30 mCi in non-toxic multinodular goiter resulted in better results, such as a 34% reduction in basal volume [22]. There are no significant side effects detected after rhTSH administered 24 hours before treatment compared to treatment without rhTSH stimulation [16].

### Absolute Contraindications

Pregnancy is an absolute contraindication. The radioiodine pass freely through the placenta. The fetal thyroid concentrates iodine after 10-12 weeks. Thus, severe hypothyroidism occurs with damage to the thyroid gland. Maternal bladder activity also causes fetal irradiation. The presence of accompanying thyroid cancer is another contraindication. It is recommended that women who receive treatment are not conceived for at least 6 months (usually 1 year). Male patients who are treated with radioiodine are advised not to be fathers for at least 4 months (usually 6 months) [11, 15, 21].

### Relative Contraindications

Uncontrolled urinary incontinence (patient should be catheterized), renal insufficiency, active advanced ophthalmopathy (especially in patients with cigarette smoking) are relative contraindicaitons. In mild and moderate ophthalmopathy, radioiodine can be given with steroids, but it is often not recommended in severe ophthalmopathy as it may lead to worsening of ophthalmopathy. Under 15 years of age it is increasingly used although it is still a matter of debate [11, 21, 23, 24].

Even in patients with known iodine susceptibility, radioiodine therapy is not contraindicated. Since the elemental iodine content of I-131 preparations is as low as 0.05-0.18 µg, the hypersensitivity reaction is unlikely to occur in these patients [21].

### Patient Preperation

Low iodine diet is administered for 2 weeks before treatment (Table **1**). For better absorption of radioiodine, fasting is important for 4-6 hours before oral administration. In order to prevent nausea and vomiting, it is advised not to take solid food for 2 hours and liquids for 1 hour after treatment. Drugs and/or substances affecting iodine involvement in the functional of the thyroid gland should be discontinued at given times (Table **2**). Written and verbal information about radiation protection should be given before treatment. Women should be tested for pregnancy during the fertility period.

Patients with heart failure and uncontrolled atrial fibrillation should be treated with appropriate diuretics and antiarrhythmics (excluding amiodarone) as well as medical antithyroid treatments. Beta blockers (propranol 20-40 mg) may be used in symptomatic patients (tachycardia, tremor). Beta blockers should be started before radioiodine therapy and should continue until clinical findings disappear after treatment [25, 26].

**Table 1: Avoided Food**

| |
|---|
| Iodized salt |
| Milk and derivatives (cheese, yoghurt, ice-cream etc. |
| Seafood |
| Processed meat products (salami, sausage etc.) |
| Packed food (chips, cookies, biscuits etc) |
| Canned vegetables and fruits |
| Greean vegetables (spinach, lettuce etc) |
| Red pepper |
| Red food dye |

**Table 2: Drugs Decreasing Radioidine uptake in Thyroid Cells and Recommended Withdrawal Time**

| Drug or Molecule | Recommended Withdrawal Time |
|---|---|
| Propylthiouracil, perchlorate, sulfonamides, tapazole, thiocyanate, penicillin, nitrates, antihistamines, anticoagulants | 1 week |
| Iodine containing solutions (Lugolsolution, betadin), antitussives and vitamin preparates Triiodothyronin (T3) | 2 weeks |
| Tetraiodothyronin (T4) | 4-6 weeks |
| Amiodarone | 4-12 weeks |
| i.v. contrast agents | 1-3 weeks |
| Oral cholecystographic agents | 2-3 weeks |

### Administration

Radioactive iodine is administered peroral (capsule or solution) or intravenously. During the first 24-48 hours the patient is recommended to chew gums or drink lemon juice to increase salivation. If the patient is still thyrotoxic at 3-6 months (often 6 months) after treatment, second treatment may be applied. Increased dosed by at least 25%of the first dose is recommended, rarely repeated doses are needed [11, 21].

## Dose Selection

The effectiveness of radioiodine therapy is related to the size of the thyroid gland, radioactive iodine uptake (RAIU) value, and I-131 metabolism [7, 29]. The target tissue mass and the dose administered are the two most important factors in the efficacy of the treatment [29, 30]. Some researchers have reported that the most important factors determining treatment efficacy are gland size and serum free triiodothyronine (FT3) concentration before treatment [31]. Studies on this subject have shown that therapeutic doses of radioactive iodine are determined by thyroid ultrasonography (USG), thyroid scintigraphy and RAIU results [32, 33]. However, there is no consensus on the optimal radioactive iodine dose regimen for benign thyroid diseases [15]. There are three approaches for dose determination.

### *1. Dosimetric Approach: Absorbed dose Method*

The activity required for radiation dose (MBq) that thyroid gland absorbs as gray (Gy) is most often calculated by the Marinelli formula [34-40]. The desired radiation dose to be absorbed per gram of thyroid gland was calculated as 100-200 Gy for toxic multinomial goiter, 120-400 Gy for toxic adenoma, 80 Gy for upper gastrointestinal tract and 70 Gy for goiter below 70 g [35, 41]. However, Graves' disease can range up to doses of 150-300 Gy/gr [41]. The formulation is based on the size of the thyroid gland. The chance of cure increases by this method as I-131 is applied in proportion to the size of the gland [29, 32, 33]. To find the volume of the thyroid gland, the volume of both lobes are calculated separately and than summed up. Isthmus and pyramidal lobe are not considered in the calculation, so there is an average ± 15% error magrin [38, 42].

In patients with toxic nodule, the volume of the functional nodule is determined by USG. However, the presence of cystic and / or necrotic component of the nodule makes it difficult to calculate the volume of the functioning tissue in the nodule. The fact that the thyroid gland is generally heterogeneous makes it difficult to determine the correct dose. Technetium thyroid uptake (TcTUs) study can be used to calculate the size of autonomic thyroid tissue under TSH suppression to exclude it [37-39, 41, 42]. Among these, Emrich is the most preferred formula [39, 43].

### *2. Dose Given Per Gram Thyroid (µCi/g) Method*

It is the method by which the treatment dose is determined by using estimated tissue weight and RAIU values calculated by USG and scintigraphy. Calculation is done with this formula:

Dose (mCi): Estimated weight of autonomic function (gr) x 80-200 (µCi/gr)

24. hour RAIU(%) x 10

### *3. Fixed dose Application (Most Common)*

It is the treatment approach based on the administration of a similar dose of radioiodine in certain clinical categories. It is an easier and more effective application than dose calculation techniques [39-41, 43, 44]. Starting from 3-5 mCi, up to 10-15 mC in Graves, higher doses of 10 mCi to 30 mCi in toxic nodular and multinodular goiter can be administered [45].

Whichever technique is used, outcome is the same: As the dose increases, the patient becomes hypothyroid sooner, as the dose decreases, the patient stays in the hyperthyroid state for a longer time and the recurrence rate increases [45].

## Side Effects

After radioactive iodine treatment for benign thyroid diseases, early side effects such as sensitivity on thyroid gland, swelling in salivary glands, and nausea can be seen. Sensitivity and swelling in the thyroid gland respond to nonsteroidal antiinflammatory agents. After treatment, hyperthyroidism can be exacerbated, called thyroid storm. It is rarely seen but can be fatal. Tracheal compression is a severe but rare complication which is more frequently seen in patients with large thyroid gland. Another rare side effect is vocal cord paralysis [7, 46]. In the literature a rare case of Graves' disease induced by the destruction of follicular cells by I-131 therapy of toxic nodular disease is reported [47].

Hypothyroidism can be seen at various frequencies after radioactive iodine therapy. The development of hypothyroidism following radioiodine therapy is due to the effect of radiation on the ability of the follicular cell to regenerate hormone production and to decrease the follicular cell population. In Graves' disease, hypo-thyroidism is a natural consequence of autoimmune pathophysiological process. The incidence of early

hypothyroidism showes a linear relationship with radiation doses. However, the development of late hypothyroidism is at a constant rate, not dose independent and is associated with the natural course of the disease [15]. It can develop in 26% to 43% of cases in the first year after treatment. This rate increases regularly every year after then. It is not possible to predict which patient will develop hypothyroidism before treatment. The incidence of long-term hypothyroidism is dose-independent [15, 45]. When studies conducted by various researchers are evaluated together, the efficacy of radioactive iodine treatment in solitary toxic nodular goitre was determined to be 85-100% and it has been reported that hypothyroidism develops by 10-20% after treatment. considering the incidence of late recurrence, the success of radioactive iodine therapy has been reported to be higher in by surgery [41, 47-53]. The success rate in toxic multinodular and toxic diffuse goiter patients using different dosing protocols were reported as 92% [37, 38, 54].

Whether the dose of radioactive iodine administered for the treatment of hyperthyroidism increases the risk of developing secondary malignancy or not is still being discussed. In the literature, there is no reported case of a malignancy with secondary and single doses given for the treatment of hyperthyroidism. However, the leukemia development was reported at high cumulative doses administered at multiple sessions [55-57].

### Evaluation of Treatment Response

After treatment, normalization of thyroid function and clinical signs occurs within the first 4-8 weeks, often improved within 2-6 months. Early hypothyroidism can be observed in rare cases, followed by recurrent hyperthyroidism. If hyperthyroidism persists after 6 months, it should be evaluated again for treatment. Second dose should be administered on time if clinically evidenthyperthyroidism persists. Patient should be directed to surgery if hyperthyroidism persists despite several treatments [13, 14, 29, 41, 45].

### Radiation Safety

The radioactive iodine doses used in benign thyroid diseases do not require hospitalization. To reduce the radiation dose the patients will be exposed to, hydration and frequent urination should be recommended. Patients should be informed that radiation will exist in sweat, urine and saliva secretions for a long time after treatment, they will spread radiation to the environment in their surrounding and that they should be avoided from pregnant and young children in accordance with the period specified in the radiation safety guide [11].

### Use of Radioiodine in Childhood Hyperthyroidism

Graves is the most common cause of hyperthyroidism in children as well as in adults. Radioiodine therapy is less preferred than other methods because of radiation exposure and associated secondary cancer. However, since there is no proven effect, it can be used in the presence of Graves in children over five years of age. The risk of developing thyroid cancer in children under five years of age receiving radioiodine treatment is two times higher than that of children receiving five-nine years of age, five times higher than children treated at ten to fourteen years was reported. Thus, it is wise to avoid radioiodine therapy in children under age 5. It can be considered for children between the ages of five and fifteen [13].

In cases of nodular hyperthyroidism, radioiodine therapy may not be appropriate for the treatment of toxic nodules in children due to the possibility of cancer risk associated with low radiation exposure to the normal thyroid gland adjacent to the nodule [58].

## DISCUSSION

Radioiodine-131 is used in treatment of benign thyroid diseases with hyperthyroidism; Graves disease, toxic nodular/multinodular goiter for a long time as well as benign euthyroid thyroid diseases; non toxic diffuse goiter, non toxic adenoma and non toxic multinodular goiter. Cost-effectivity, good tolerability, easy application, safety and efficacy are advantages of this treatment. The effectiveness of radioiodine therapy is related to various factors; the size of the thyroid gland, RAIU value, dose and metabolism of I-131. Fixed dose application is the most commonly prefered method among all treatment approaches due to its easier and more effective application than dose calculation techniques. It is based on the administration of a similar dose of radioiodine in certain clinical categories. For Graves' disease it starts from 3-5 mCi, up to 10-15 mCi, for toxic nodular/multinodular goiter higher doses are required as from 10 mCi to 30 mCi can be administered. Possible complications are tolerable. Multidisciplinary approach is very important in the treatment of benign thyroid disease and improves treatment effectiveness.

## CONCLUSION

Radioiodine therapy is widely used in treatment of hyperfunctioning thyroid diseases and should be considered as a safe and costeffective alternative to surgery and medical therapies.

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