Chapter 1

Radioiodine Treatment for Benign Thyroid Diseases

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Additional information is available at the end of the chapter

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Abstract

Radioiodine (RAI) is becoming the preferred treating option for benign thyroid diseases. Hyperthyroidism is defined as hypermetabolic state caused by high levels of circulating thyroid hormones of the thyroid gland. The most common hyperthyroidism causes are Graves' disease, toxic multinodular goitre, and solitary hyperfunctioning nodule, for which RAI can be preferred as a definitive treatment option. It is rapidly incorporated into the thyroid and with its beta emissions with a path length of 1–3 mm cause extensive local tissue damage and necrosis. The thyroid gland is effectively ablated over a period of 8–18 weeks and can no more produce normal amount of thyroid hormones. It is an individualized therapy that can either be a first-line therapy, or an alternative therapy to neck surgery or to use of antithyroidal drugs after 1 year. For the optimal efficiency, before the RAI treatment, the patients should be extensively assessed and they also should be given clear information about the treatment, as well as written instructions for precautions to avoid irradiation exposure to other people. Moreover, after RAI treatment patients should have their regular follow-up. This chapter summarizes all the points for a RAI treatment.

Keywords: radioiodine treatment, hyperthyroidism, Graves' disease, toxic multinodular goitre, benign thyroid diseases

1. Introduction

Radioiodine (RAI) has been used for over 70 years as a treatment for benign thyroid diseases [1]. Regarding massive amount of past data, RAI treatment is broadly accepted as a safe and effective treatment for benign thyroid diseases with low incidence of acute or chronic adverse effects.

Thyrotoxicosis is thyroid-induced hypermetabolism, either secondary to thyroid hormone release from an overactive or inflamed thyroid gland or introduced from an extra-thyroidal

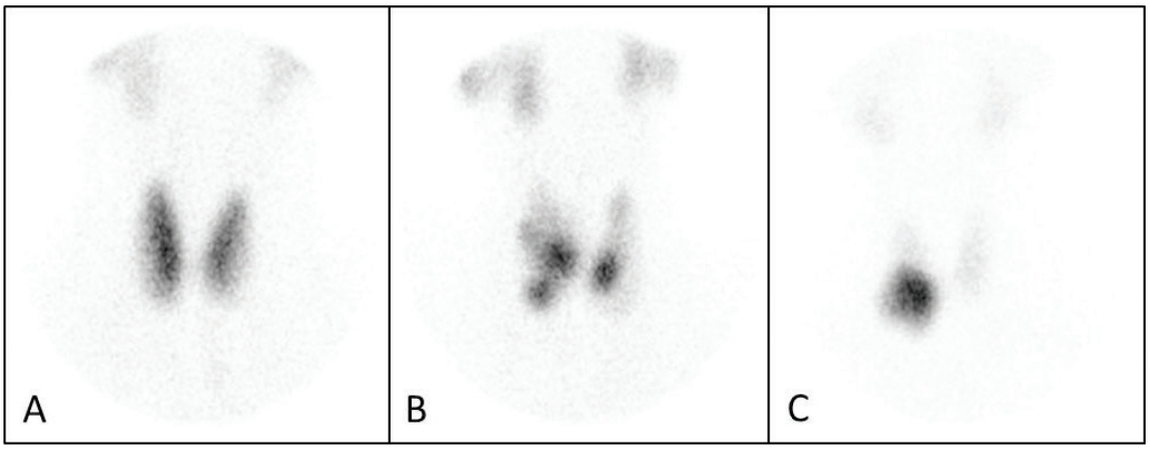

Figure 1. The thyroid scans examples of the main causes of hyperthyroidism. (A) Graves' disease, (B) toxic multinodular disease, and (C) solitary hyperfunctioning nodule.

source. A suppressed serum thyroid stimulating hormone (TSH) level, below 0.4 mU/L, confirms the diagnosis of hyperthyroidism, meaning the pathology is within the thyroid gland [2]. To differentiate the cause of hyperthyroidism, RAI uptake test can be performed and a thyroid scan can give additional information. **Figure 1** shows the thyroid scans of the main causes of hyperthyroidism: Graves' disease and toxic multinodular disease and solitary hyperfunctioning nodules.

The symptoms of hyperthyroidism are nonspecific such as tachycardia, tremor, nervousness, anxiety, heat intolerance, sweating, and weight loss.

Hyperthyroidism can be treated with antithyroid drugs (ATDs), RAI therapy, and surgery. The actual therapy selected varies on the characteristics of the patient and the underlying cause of hyperthyroidism.

The aim of RAI therapy in patients with hyperthyroidism is to achieve a nonhyperthyroidal status that is not responding to ATDs and also to reduce the size of the nodules and to decrease the symptoms related to hyperthyroidism and gland enlargement in patients with toxic nodular goiter.

This chapter includes RAI treatment for benign thyroid diseases, I131 information, administration, effect mechanism, indications and contraindications, patient preparation, I131 dose selection and withdrawal of antithyroid drugs, lithium and recombinant human TSH usage under a seperate topic, named special conditions, precautions, advers effects and patient follow-up.

2. Iodine131

I131, known as sodium iodine, is the most commonly used radionuclide therapy and also the first radiopharmaceutical to be used for the treatment of the thyroid gland in benign thyroid diseases since the 1940s [1].

The principle mechanism of RAI treatment depends on the destructive effect of the radioactivity that is directed to the target tissue thorough "cross fire effect" in a continuous manner. RAI is a beta-emitting radionuclide with a physical half-life of 8.02 days, a principal gamma ray of 364 keV, and a principal beta particle with a maximum energy of 0.61 MeV, average energy of 0.192 MeV, and average range in the tissue of 0.4 mm. The principal gamma ray of 364 keV enables imaging with a gamma camera.

Oral capsule or in liquid form is the most common way to administer to patients; however, it can also be administered intravenously. When it is swallowed, it is absorbed in the gastrointestinal tract from blood circulation and then it accumulates in the thyroid gland.

2.1. The effect mechanism

The sodium iodide symporter (NIS) is an intrinsic plasma membrane glycoprotein that mediates the active transport of iodide in the thyroid gland and also in some extrathyroidal tissues, like lactating breast, gastric mucosa, and salivary and lacrimal glands [3]. RAI uptake occurs across the basolateral membrane of thyroid follicular cells via an active transport process mediated by the NIS, like inorganic iodine.

NIS protein expression is revealed to be heterogeneous at the basolateral membrane of a minority of follicular cells in normal thyroid gland tissue [4]; it is increased in thyroid tissue in acute Graves' disease, consistent with the clinical observation of diffusely increased radioiodine uptake [5]. In toxic multinodular goiters (TMNG), heterogeneous NIS protein expression appears to be stronger than the normal thyroid gland and less than the Graves' thyroid tissue [6].

RAI is rapidly concentrated by the follicular cells and accumulated in colloid cells after iodide organification. Beta particles emitted by RAI destroy the functioning thyroid tissue. Hence, cell function is inhibited and proliferation capacity is affected by destructing follicular thyroid cell. The severity of this effect is directly proportional to the given dose.

The main effect of RAI treatment causes an intense radiation thyroiditis that leads to apoptosis and necrosis of hyperactive/active follicular thyroid cells, glandular atrophy, and loss of the thyroid capacity to synthesize and decrease thyroid hormones [7].

3. Indications and contraindications

Mainly, RAI therapy indications in benign thyroid diseases include Graves' disease, toxic multinodular goitre, solitary hyperfunctioning nodule, nontoxic multinodular goitre, goitre recurrence after surgery, and also amiodarone-induced hyperthyroidism with special precautions and ablation of residual thyroid tissue in case of malignant ophthalmopathy after surgery, but during an inactive state of the orbitopathy.

RAI therapy's absolute contraindications are pregnancy and breastfeeding, and relative contraindications are incapable patients to comply with radiation safety precautions, uncontrolled hyperthyroidism, and active thyroid orbitopathy.

3.1. Graves' disease

Graves' disease patients in iodine-sufficient areas are approximately 80% of patients with thyrotoxicosis or hyperthyroidism [8]. Graves' disease, also known as toxic diffuse goiter, is an autoimmune disease characterized by elevated levels of TSH receptor antibodies with increased production of thyroid hormones. TSH receptor antibodies bind to the TSH receptor and stimulate it chronically, which results in thyroid gland function becoming autonomous and independent of TSH feedback.

In general, Graves' disease therapeutic options are ATDs, RAI, and surgery. Thus, a therapeutic strategy should be individualized in patient considering several situations such as patient's clinical characteristics, age, and life style of the patient. ATDs are the most common treatment especially in children, teenagers, and pregnant women and also ATDs should be used as a first-line therapy to have the patient in euthyroidal status before the choice of treatment.

Commonly, methimazole is the first option drug, although propylthiouracil may be administrated in rare cases. ATDs' key adverse effects are rash, artralgy, agranulocytosis, and hepatitis. The usual ATDs administration should be for 6–18 months and time to initial improvements are 2–4 weeks. However, in about half of the patients relapse of hyperthyroidism may be experienced when the ATDs are withdrawn after a standard 1–2 years of therapy [9].

Surgery is usually preferred in cases of large goiters with compressive symptoms or during second trimester of pregnancy. However, hospitalization and surgery complications including hypoparathyroidism and recurrent laryngeal nerve injury and also anesthesia complications can be practiced.

RAI treatment is increasingly preferred in Graves' disease as first treatment and also after ATDs treatment or thyroid surgery in uncontrolled hyperthyroidism patients. Most patients are effectively treated with a single therapeutic dose of RAI. The symptoms of hyperthyroidism are expected to improve within 3 weeks of therapy; yet, the therapeutic effect takes 3–6 months because of the stored thyroid hormone to be released [10]. However, RAI therapy may not be effective in approximately 10% of patients [10]. In these patients, the repeat RAI treatment can be administered and usually the administered repeat dose should be of similar or higher than the first dose of RAI.

3.2. Toxic nodular goiter

Toxic nodular goiter (TNG) is the second most common cause of hyperthyroidism, after Graves' disease [11], which may be presented with toxic multinodular goiter (TMNG) also known as Plummer's disease or solitary hyperfunctioning nodule, also known as toxic adenoma. Hyperthyroidism may occur in both presentations. TNG autonomously produces excess thyroid hormones, resulting in hyperthyroidism. TSH receptor mutations in TNG have been reported to be as high as 80%. Somatic activating mutations of the TSH receptor activate the cAMP pathway and cause clonal autonomous growth and hyperfunctioning of the thyroid follicular cells, which results in TNG.

Toxic nodules are more resistant to RAI therapy than Graves' disease [10]. Considering this fact, the administered therapeutic RAI dose is often increased by 50% compared to what would be given in Graves' disease.

3.3. I131 induced hyperthyroidism

Excessive I131 exposure, usually following the use of I131 containing drugs such as amiodarone, expectorants, and contrast agents, is the main cause of I131-induced hyperthyroidism and can cause destructive thyroiditis. The symptoms are similar to autoimmune thyroiditis, but because of the long biologic half-life of amiodarone and its metabolites the symptoms, it lasts longer. High I131 may induce increased synthesis of thyroid hormone, known as Jod-Basedow, usually occurring in nodular thyroid glands and is more common in endemic goiter areas. It can be treated with ATDs and also combination of potassium perchlorate may help to decrease thyroidal iodine content. Persistent cases may be treated with RAI definitively if the thyroid uptake is adequate, provided that the agent has been discontinued for sufficient time of up to 2 years (mean period of 6 months) for the excess iodine load to be eliminated [12].

4. Patient preparation

Radioiodine therapy for patients with thyroid disease requires close cooperation between the nuclear medicine physician and the endocrinologist. The assurance of adequate therapy conditions is the overall responsibility of the nuclear medicine physician.

Evaluation of the patient before RAI therapy should include previous treatment of the patient (e.g., use of ATDs, amiodarone, contrast media, other iodine-containing medication, and iodine-containing food) and laboratory testing, including free T4, free T3, and TSH [13]. Thyroid scan preferably with I123, otherwise with Tc-99m, may be acquired.

Before RAI therapy, RAI uptake test should be performed for the differential diagnosis of hyperthyroidism to determine the I131 usage by the thyroid gland, and the calculation of the treatment dose. Increased RAI uptake values in patients with hyperthyroidism shows that elevated thyroid hormones belong to hyperfunctioning thyroid gland [14].

The 24-hour thyroid uptake in Graves' disease is generally high; on the other hand, it is often normal or mildly elevated in TNG. RAI uptake test level obtained at 24-hour should be greater than 20%. If this level is lower than 20%, other treatment methods should be considered [13].

Thyroid gland volume and intrathoracic thyroid extension assessment should be acquired by ultrasonography. In patients with large goiters, intrathoracic extension can be evaluated with thyroid scan with sternal notch marked, magnetic resonance imaging, or computed tomography. If the evaluation is held with radiocontrast computed tomography, it should be kept in mind that radiocontrast agents will reduce the radioiodine uptake for weeks to months and as such disabling radioiodine therapy during that time.

The nodules larger than 1–1.5 cm with a suspicious ultrasonographic look with nonfunctioning cold scan appearance in the thyroid scan should be assessed by fine needle aspiration biopsy to rule out malignancy.

The status of eye disease should be examined in patients with Graves' ophthalmopathy by an experienced ophthalmologist.

In patients with severe thyrotoxicosis with high risk of thyroid storm and elderly patients should be maintained in euthyroidism status with ATDs, preferably with methimazole.

And treatment of other comorbid diseases should be regulated.

Patients receiving more than 444 MBq of RAI for benign thyroid diseases have dose rates of 0.02 mSv per hour at 1 meter and so precautions are imposed. They do not require isolation, but they have to be cautioned to avoid contact with children and pregnant women, to sleep alone, to flush the toilet two to three times after use, and use separate utensils for 2–4 days and the effects of time and distance on dose should be indicated.

All patients receiving RAI should be given clear information about the treatment as well as written instructions for relevant precautions to avoid exposing others to unnecessary irradiation after treatment. Female patients in child bearing age and during pregnancy must be excluded and these patients should be counseled to avoid pregnancy for 3–6 months and to use contraception for 4 months after therapy.

5. I131 dose selection

Generally, the dose of RAI depends on the gland size, RAI uptake test, and biologic half-life of RAI in the thyroid gland [15], which may widely differ; however, several methods have been experienced for selecting adequate dose of RAI therapy in patients with hyperfunctioning thyroid gland [10].

A standard dose of 185–555 MBq is often prescribed. Yet, large glands need a relatively higher therapeutic dose and patients with a high RAI uptake test results need a lower dose.

Another method is using a standard formula with gland size, the RAI uptake test, and the proposed administered I131 dose per gram of thyroid tissue. Thus, an individual therapy dose for each patient is calculated by using the following formula [10]:

$$\text{I131 administered dose} = \frac{\text{Gram size of thyroid gland} \times 100 - 180\ \mu\text{Ci/g}}{\text{24 hour \% RAI uptake}} \quad (1)$$

Another approach is to calculate the MBq per gram dose. The patients with nodular goiters and patients with very large toxic diffuse goiters are often referred for repeated therapies. In this method, the referring physician often prefers the higher dose (4.44–6.66 MBq/g tissue) for a higher likelihood of success with a single therapeutic dose.

Moreover, a higher RAI dose requirement is needed in patients, with a 4-hour I131 uptake result exceeding the 24-hour I131 uptake result, suggesting the rapid iodine turnover [15, 16].

6. Special conditions

6.1. Withdrawal of antithyroid drugs

ATDs are the initial treatment option for patients with hyperthyroidism. ATDs pretreatment diminishes thyroid hormone stores and therefore decreases the risk of thyrotoxicrisis and the aggravation of symptoms after RAI treatment, constituting a safe patient preparation for RAI treatment [17]. However, ATDs pretreatment may lead to undesirable effects, such as an increased risk of radioiodine failure and worsening of thyrotoxicosis after discontinuation for pretreatment of RAI [17, 18].

Even though some studies support that pretreatment of ATDs may reduce the effect of RAI treatment [19, 20], some studies claim that they have no obvious effect [21, 22]. This side effect of ATDs is the possible radioprotective effect that seems to depend on a sulphhydryl group contained in ATDs. On the other hand, ATDs such as methimazole and carbimazole, which do not possess sulphhydryl groups and may be, do not possess radioprotective effect either [23]. Thus, pretreatment with thiouracils has been shown to reduce the therapeutic effectiveness of RAI, but the usage of carbimazole or methimazole has not been observed with similar effect [24]. This negative impact on RAI treatment can be compensated by discontinuation of the medication before RAI administration if the patient can tolerate it. Pretreatment with propylthiouracil (PTU) is stopped for at least 2–3 weeks (if possible 8 weeks) before RAI treatment is given due to radioprotective effect of PTU [13]. Owing to methimazole and carbimazole having no side effect on cure rate, these drugs are stopped a few days before planned RAI administration [25, 26]. Beta-adrenergic antagonists (usually propranolol) can be used as an alternative to control hyperthyroidism symptoms during ATDs withdrawal. After RAI administration, ATDs should be restarted from the same recommended dose before RAI treatment. ATDs do not have to be restarted in young patients or in patients with mild hyperthyroidism.

6.2. Lithium usage

Lithium can block RAI release from the thyroid but does not interfere with RAI uptake. In general, lithium pretreatment is not routinely recommended but its administration can be considered for 7 days if 24-hour RAI uptake test is less than 20% [27]. However, a randomized controlled trial has found no evidence of an effect of lithium on RAI therapy when it is given for a few days after RAI treatment. The authors commented as it may increase the efficiency of RAI, but this effect is unclear [28]. Another research showed that lithium treatment prevents the rise in serum thyroid hormones after withdrawal of ATDs for RAI therapy [29].

6.3. Recombinant human TSH (rhTSH)

Recombinant human TSH (rhTSH; Thyrogen, Genzyme Transgenics Corp.) is developed to provide TSH stimulation without withdrawal of thyroid hormones. The therapeutic effect of I131 in patients with nodular goiter depends to some extent on the RAI uptake. The main cause of a low RAI uptake in patients with TNG is normal or below normal serum TSH levels. In patients with nontoxic or TNG with low I131 uptake, the administration of rhTSH increases

RAI uptake significantly and retention in the thyroid gland and minimizes the radiation dose to the remainder of the body without increase in serum thyroid hormones levels [15, 30]. Besides, by stimulating I131 uptake in relatively cold areas, more than in relatively hot areas, a more homogeneous distribution of I131 within the thyroid gland is observed in patients with nodular goiter, after single low dose rhTSH administration [31].

For the optimization of rhTSH dose, different rhTSH doses have been utilized. A study showed that a dose of 0.01 mg rhTSH administered 24 hours before RAI increases 24-hour RAIU from 29 to 51%, while 0.03 mg rhTSH increased 24-hour RAIU from 33 to 63% [32]. Another study presented that RAI treatment after the administration of a single, low dose of rhTSH in patients with nodular goiter resulted in thyroid volume reduction 1 year after treatment by 35% in the group pretreated with 0.01 mg rhTSH and by 41% in the group pretreated with 0.03 mg rhTSH [33].

The leading side effects in nodular goiter are sensation of thyroidal swelling, transient thyroiditis, and transient goiter volume enlargement, which may lead to a significant cervical compression within the first month of treatment after the administration of 0.3 mg of rhTSH [34].

In the adjunct therapies with very small doses of rhTSH (0.03–0.1 mg) in patients with multinodular goiter, either they were euthyroid or hyperthyroid, few safety concerns have been observed [35, 36]. Currently, the adjunct therapy with rhTSH is not indicated in patients with TMNG because of the risk of exacerbating patient's hyperthyroidism [37].

7. Precautions for RAI therapy

The RAI preparations have negligible content of 0.05–0.18 μg large stable I131, which is much lower than the average daily iodine intake [13]. Therefore, even patients with known I131 sensitivity can be treated with RAI safely.

On the other hand, approximately 7 days following RAI administration, temporary increase in serum thyroid hormone levels may be expected. Hence, RAI is contraindicated in patients who has uncontrolled symptoms of hyperthyroidism or high levels of free T3. The elevation of thyroid hormones may trigger atrial fibrillation or heart failure, leading to thyroid storm. These patients should continue using ATDs and beta-blockers for symptomatic control. Likewise, beta-blockers need not be stopped before RAI treatment. But, if ATDs are contraindicated (e.g., due to agranulocytosis or posttherapy liver failure) and surgery cannot be performed due to symptoms of hyperthyroidism, RAI may be given under steroid treatment (usually hydrocortisone 50–100 mg i.v.) and beta-blockers [13].

Similarly, patients with large nodular goiters should be treated under steroid treatment to prevent RAI-induced swelling thyroid, which rarely aggravates airway obstruction.

7.1. Graves' ophthalmopathy

Graves' disease exophthalmos cannot be controlled by ATDs and RAI therapy [38]. Furthermore, RAI may cause progression of Graves' ophthalmopathy. After RAI therapy, 15% of

the patients with Graves' disease may acquire newly evolving Graves' ophthalmopathy [39] and up to 39% of patients may experience worsening of the former ophthalmopathy within 6 months [40].

The risk factors for progression of Graves' ophthalmopathy are preexisting ophthalmopathy, smoking [41], high levels of pretreatment serumT3 and TSH receptor antibody and thyrotropin receptor antibody levels (>7.5 IU/L) [42], severity of hyperthyroidism, and post-RAI hypothyroidism [38, 43, 44].

Thus, all patients who will receive RAI treatment should first be maintained in euthyroid state with ATDs and should be advised to quit smoking because of the increased risk of evolving of ophthalmopathy in smokers after RAI therapy [45]. The use of ATDs does not seem to be associated with the developing or worsening of preexisting ophthalmopathy in patients with Graves' disease [46]. In patients with active ophthalmopathy, the risk can be reduced by a short cycle (3 months) of oral prednisone (0.3–0.5 mg/kg/d) started 1–3 days following RAI therapy and continued for 1 month, with tapering over the subsequent 2 months and by avoiding post-RAI hypothyroidism with synthetic thyroid hormone placement [38, 43]. Despite the widespread usage of steroid prophylaxis, its optimal schedule is undefined. The European Group on Graves' Orbitopathy (EUGOGO) Consensus Statement on management of Graves' ophthalmopathy suggested that a shorter term (about 2 months) of oral steroids treatment might be equally protective [38]. A recent retrospective cohort study suggested that starting from a few days after RAI therapy, 0.2 mg/kg/day of oral prednisolone for 6 weeks may be effective in preventing RAI-associated progression of Graves' ophthalmopathy [47].

Patients with inactive Graves' ophthalmopathy, if they do not have the risk factors for Graves' ophthalmopathy, can have RAI therapy without steroid coverage as long as hypothyroidism is avoided [38].

8. Adverse effect of I131 therapy

The common acute side effects in the gastrointestinal tract are heartburn, nausea, diarrhea, and vomiting.

The acute adverse effects of RAI therapy include radiation-induced thyroiditis that is associated with neck pain thyroid swelling and transient thyrotoxicosis. Thyroid swelling may appear after a few days following the therapy. The symptoms can be managed by nonsteroidal antiinflammatory drug. Early after RAI therapy, even though the goiter volume and the impact on the respiratory function remain unchanged [48], the critical thyroid swelling and respiratory distress can be experienced, fortunately it is a rare complication [49]. If the presence of tracheal compression is previously known, especially in large goiter patients, 25 mg prednisolone may be given daily for 14 days to prevent thyroid swelling from RAI therapy [48].

Transient thyrotoxicosis, a transient elevation of the thyroid hormone levels, can be practiced due to the secretion of stored hormones from the thyroid gland. Thyroid storm or thyrotoxicrisis is a rare but severe and potentially life-threatening hypermetabolic condition induced

by excessive release of thyroid hormones. The treatment must include i.v. infusion of ATDs, steroids, and beta-blockers to avoid a fatal outcome.

Other side effects of RAI therapy include sialoadenitis leading to temporary or permanent salivary gland dysfunction and lacrimal canal obstruction, which can be demonstrated as RAI-induced acute histopathological changes as well. Hydration should be encouraged to minimize these problems. Sour candy can be suggested for salivary gland dysfunction. However, there are also studies demonstrating that permanent xerostomia is significantly more common in patients having sour candy in the first 24 hours of RAI therapy than in patients having the candy after the first day [50]. Consequently, several antioxidant agents are under evaluation to reduce these changes in many researches [51–53].

The main and long-term adverse effect of RAI therapy is the hypothyroidism. Usually in the first 2 years after RAI therapy, hypothyroidism occurs in up to 50% of patients and the risk increases in patients with small goiter size, positive TPO antibodies, and a family history of autoimmune thyroid disease [54]. Pretreatment of ATDs does not affect the frequency of hypothyroidism. Generally, it is very difficult to predict if the development of hypothyroidism is either transient or permanent. In a few months after RAI therapy, if the level of serum TSH is still above 45 mU/L, transient hypothyroidism is ruled out [55]. A transient hypothyroidism develops a few months after RAI therapy and continues about 1–4 months and does not require thyroid hormones replacement. The patients should be offered annual follow-up testing of thyroid hormones.

Another adverse effect is the post-RAI autoimmune thyroiditis and immunogenic hyperthyroidism/Graves' disease. About 1% of patients following RAI therapy of nodular goiter may develop Graves' disease. This risk increases approximately 10-fold when TPO antibody levels are elevated before RAI. The release of thyroid antigens and other immunogenic effects of RAI on thyroid-autoreactive lymphocytes are the presumed mechanisms. In addition, there is an estimated 1.3% risk of a temporary increase of TSH receptor antibodies after RAI for autonomous thyroid disease without the development of clinically apparent hyperthyroidism [56].

Finally, even though, the chromosomal damage in peripheral lymphocytes is induced after RAI therapy for benign thyroid diseases [57], the role of I131 in radiation-induced cancers remains unclear. There is no evidence of the risk of malignancy as a consequence of thyroid and whole-body irradiation. Though there is low risk of preexisting or coexisting thyroid cancer in patients with toxic nodular goiter and Graves' disease unrelated to RAI therapy [58].

9. Results

The success of RAI therapy is defined as the elimination of hyperthyroidism, in which the patient may be either in euthyroid state or in hypothyroid state that is compensated by synthetic thyroid hormone. The successful therapy rate depends on thyroid volume, compensation of hyperthyroidism, I131 intake in the diet, the timing of the withdrawal of ATDs, and the dosage in the different thyroid diseases.

The low fixed activity (185 MBq) of I131 seems to be effective in 73% of Indian patients with Graves' disease, 1 year after RAI therapy [59]. Another study compared doses of 370 and 555 MBq of RAI and the success rates at 12 months of both doses brought about a similar remission of the hyperthyroidism in patients with Graves' disease [27, 60].

A study based on tissue-absorbed dose calculations demonstrated that the frequency of persistent hyperthyroidism decreased to 27% after 150 Gy, to 23% after 200 Gy, and to 8% after 300 Gy [61]. However, the possibility of occurrence of hypothyroidism increases over years and patients need to be in regular follow-up.

RAI therapy is more successful in patients with nodules smaller than 2 cm [62]. However, there is currently no consensus about the appropriate RAI dose in TNG, both the fixed dose or calculated dose can be given. Effect of fixed and calculated doses on hyperthyroidism was compared in a meta-analysis that reported both methods to be equally successful [63].

Zakavi et al. compared fixed low and fixed high RAI doses for treating a single toxic thyroid nodule in patients with no age, sex ratio, thyroid uptake, and thyroid weight differences. Ten months after RAI therapy, the success of hyperthyroidism treatment was higher in patients calculated with high dose therapy than other groups [64].

Glucocorticoids did not influence the final outcome following RAI [65]. At least 2 days of methimazole withdrawal was long enough to restore the success of RAI therapy [26].

10. Follow-up

After the RAI administration ATDs should be restarted after 3–5 days and withdrawn as soon as thyroid function normalizes and synthetic thyroid hormone replacement should be started as soon as hypothyroidism occurs [8].

Patients who have been given RAI therapy should be essentially followed up in regular review of thyroid function tests to evaluate the effectiveness of the treatment and for timely detection of developing hypothyroidism or posttreatment immunogenic hyperthyroidism. Follow-up should be basically performed with TSH and serum T4 tests, 4–6 weeks after RAI treatment. The patients receiving ATDs or having increased risk of developing or worsening of Graves' ophthalmopathy due to hypothyroidism, shorter intervals of the tests should be performed 2–3 weeks after RAI treatment is recommended [13]. All the patients should have annual laboratory tests, at least TSH levels should be checked regularly. In patients with relapse or persistent hyperthyroidism, RAI treatment can be repeated after 6–12 months.

11. Conclusion

With over 7 decades of experience, RAI therapy is an individualized, safe, and effective treatment modality, which is doubtlessly going to be still available in the future with possible up coming features in genetics.

In several types of hyperthyroidism TSH receptor gene mutations may be expressed, for instance, familial gestational hyperthyroidism, autonomous toxic adenomas, hereditary or sporadic toxic thyroid hyperplasia, familial nonautoimmune hyperthyroidism, and Graves' disease. Genetic studies focusing on the mutations of TSH receptor gene and their alterations with the related genes would probably open a new door in the understanding of the process and may support the prospective treatments.

In addition to safeguard the other tissues especially nonthyroidal NIS-expressing tissues, e.g., lactating breast, gastric mucosa, lacrimal glands, and salivary glands, for example, temporarily opening tissue-specific NIS expression or downregulating the functional expression of NIS in different cellular models may certainly provide an optimal use by directly affecting the RAI dose received by the specific target tissue [66].

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