Chapter

RAI Therapy for Graves' Hyperthyroidism

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Abstract

Graves' Disease is the most common cause of hyperthyroidism. It has multiple manifestations and it requires appropriate diagnostic and therapeutic management. Once it has been established that the patient is hyperthyroid and the cause is GD, the patient and physician must choose between three effective and relatively safe initial treatment options: antithyroid drugs (ATDs), radioiodine (RAI) therapy, or thyroidectomy. RAI has been used to treat hyperthyroidism for more than seven decades. It is well tolerated and complications are rare, except for those related to orbitopathy. Most patients are effectively treated with one therapeutic dose of I-131. The patient usually notes symptomatic improvement within 3 weeks of therapy. However, the full therapeutic effect takes 3 to 6 months because stored hormone must first be released. Radioiodine therapy may not initially be effective in up to 10% of patients. They require repeat treatment, usually with a higher administered dose.

Keywords: RAI, hyperthyroidism, therapy, Graves' Disease, Nuclear Medicine, theranostics, guidelines

1. Introduction

Thyrotoxicosis is a very common clinical syndrome caused by an excess of thyroid hormones in the serum. It results in a generalized acceleration of metabolic processes. Occasionally, thyrotoxicosis may be due to other causes. Graves' Disease is the commonest cause of hyperthyroidism, typically presenting in patients between 40–60 years. It is characterized by the presence of thyroid stimulating hormone receptor antibodies (TRAbs) but pathogenesis is not completely understood [1]. The thyroid stimulating hormone receptor (TSHR) is a transmembrane G-protein-coupled receptor (GPCR) and when it is activated by thyroid stimulating hormone (TSH) it stimulates thyroid hormone production [2]. TRAbs mimic the action of TSH leading to hyperthyroidism. Although autoimmune mechanisms are responsible for the syndrome of GD, management has been largely directed toward controlling the hyperthyroidism. Three therapeutic methods are available: (l) antithyroid drug therapy (ATD), (2) surgery, and (3) radioiodine treatment (RAI) and have proved to be effective, safe and cost-effective. They can be the first-line treatment for hyperthyroidism not only due to Graves' Disease, but also due to toxic adenoma, and toxic multinodular goiter [3]. Nowadays research has turned its focus on the potential use of immunotherapy in GD [4, 5]. It is remarkable that the

selection of the right therapy for each patient still poses a challenge to the clinician as there is no single best therapy for all patients [6].

Radioactive iodine (I-131), has been commonly used for the treatment of both benign and malignant thyroid conditions since the 1940s. In the early days of nuclear medicine, endocrinologists were attracted to the field by the potential of radioiodine for diagnosis and therapy. Today thyroid diagnosis and therapy continue to have an important role in the practice of nuclear medicine. The story of radioiodine started in 1935 at the Massachusetts Institute of Technology in cooperation with the Thyroid Unit of the Massachussetts General Hospital. Diagnostic thyroid studies were performed for the first time in 1937 using iodine-128. In 1938, not more than one year later, I-130 and I-131 were discovered, followed by the first treatment of benign thyroid disease in. Hertz and Roberts were the first to do so on March 31, 1941; Hamilton and John Lawrence, began on October 12, 1941. In 1946 the Oak Ridge National Laboratory produced I-131 for routine use and from this time on I-131 treatment is increasingly performed not only in benign thyroid disease but also in differential thyroid cancer (DTC) [7].

Nuclear medicine involves the administration of radiopharmaceuticals to patients for diagnostic and therapeutic purposes. The theranostic approach is an established tool for specific molecular targeting, both for diagnostics and therapy. Most radiopharmaceuticals are a combination of radioactive molecule, a radionuclide, that permits external detection and a biologically active molecule or drug that acts as a carrier and determines localization and biodistribution. For a few radiotracers (e.g., radioiodine), the radioactive atoms themselves confer the desired localization properties [8]. RAI in GD includes the systemic administration of 131-I for selective irradiation of hyperfunctioning thyroid gland. The efficacy and safety of this treatment and the advantages over thyroid surgery and ATDs have been documented and are widely accepted. Several guidelines, protocols and recommendations have been released by various scientific societies including the European Association of Nuclear Medicine (EANM), and the American Society of Nuclear Medicine Molecular Imaging (SNMMI), European Thyroid Association (ETA) and American Thyroid Association (ATA) whose procedural guidelines are updated in last decade and will be discussed in this chapter.

2. Physical and radiobiological properties of (radio)iodine

Physicians responsible for treating thyroid disorders should have an understanding of the clinical pathophysiology and natural history of the disease processes. They also should be familiar with iodine uptake and metabolism. Iodine is a micronutrient of crucial importance for the health and well-being of all individuals. It is mostly obtained from food sources. Thyroid gland plays the central role in the metabolism of iodine. When iodine enters the bloodstream it is then taken up by thyroid follicular cells through an active transport system the sodium iodide symporter (NIS) which is located at the basolateral membrane of the follicular cell [9]. Then, peroxidase promotes iodine to bound to thyroglobulin (Tg) and in particular to tyrosine which is then iodinated. The latter leads to the formation of 3-monoiodotyrosine (MIT) and 3,5-diiodotyrosine (DIT) which are coupled afterwards leading to the formation of thyroid hormones. Two molecules of DIT form thyroxine (T4) hormone and when one MIT and one DIT molecule couple they form Triiodothyronine (T3) hormone. Thyroid hormones remain stored in the thyroid cells in a thick fluid that is called colloid. Colloid can store a 3 month

supply of thyroid hormones. Thyroid stimulating hormone (TSH) regulates thyroid hormone production. In particular it stimulates NIS expression which then activates follicular cells through TSH receptor (TSH-R). The uptake and metabolism of the radioactive iodine (I-123 and I-131) does not differ from nutritional iodine uptake in the normal or hyperfunctional gland.

I-131used for the treatment of thyroid disorders has a physical half life of 8.4 days and undergoes beta-minus decay emitting a principle primary gamma photon of 364 kiloelectron volts (keV) (81% abundance). The 364-keV photons are not optimal for gamma cameras. The detection sensitivity for I-131 (i.e. the amount of photons detected by the gamma camera) is poor. Approximately half of the photons penetrate a 3/8-inch crystal without being detected. Other higher energy I-131 emissions will pass though the collimators holes leading to image degradation. Beta-minus decay also results to emission of beta particles of 0.606 megaelectron volt (MeV) (89% abundance) which are responsible for the therapy outcome but cannot be used for imaging. The I-131 high-energy beta emissions and long physical half-life of gamma emissions result in a high radiation dose to the patient, particularly to the thyroid. Thyroid gland which is the target organ of RAI treatment receives ultimately a high radiation dose ~0.01Gy/μCi, and this defines the maximum applicable administered dose [10]. Radiobiological effects of radioiodine on tissues are direct (radiation deposit within DNA) or indirect. Indirect effects produce free radicals that in turn react with critical macromolecules. The cellular effect of the ionizing radiation leads to genetic damage, mutations, or cell death. The DNA damage from radiation is mediated via a combination of direct effects, through breakage of molecular bonds, or indirectly through the formation of free radicals. This leads to a decrease in thyroid function and/or reduction in thyroid size. There are neither good measures of individual radiosensitivity nor ideal methods of predicting the clinical response to RAI therapy [11].

3. Treatment choices for Graves' hyperthyroidism

Patients with overt Graves' hyperthyroidism should be treated with any of the following modalities: RAI therapy, ATDs, or thyroidectomy. Once the diagnosis has been made, the treating physician and patient should discuss each of the treatment options, including the logistics, benefits, expected speed of recovery, drawbacks, potential side effects, and costs. This sets the stage for the physician to make recommendations based on best clinical judgment and allows the final decision to incorporate the personal values and preferences of the patient. The treatment selection should also take into account the local availability and the associated costs. Whenever surgery is selected as treatment one should consider the use of expert high-volume thyroid surgeons with on average lower risk of complications; lack of that expertise should be considered against the known risk of alternative choices. Long-term continuous treatment of hyperthyroidism with ATDs may be considered in selected cases [12]. Despite the use of these three treatments for decades, selection of the optimal therapy for GD still poses a challenge for both the physician and the patient.

3.1 Thyroidectomy

Thyroidectomy, in particular subtotal thyroidectomy, is the oldest way of treating hyperthyroidism [13]. A Swiss surgeon, Theodor Kocher (1841–1917) won

the Nobel Prize for Medicine and Physiology in 1909 after performing the first successful surgeries for GD [14]. Nowadays, thyroidectomy is the least preferable therapeutic selection for GD worldwide [15]. However, in some circumstances it is regarded as the most preferable treatment option. In particular, it is indicated for women who are planning a pregnancy in less than 6 months (provided they are rendered euthyroid with ATD), in patients with large goiters (≥80 g) or with compressive symptoms, in cases of coexisting hyperparathyroidism which will lead to a surgery and when thyroid cancer is suspected. Also, surgery is preferred in patients with moderate to severe active Graves orbitopathy (GO), in cases of large thyroid nodules that are additionally cold (has lower radiopharmaceutical uptake than the surrounding thyroid tissue) on scintigraphy, when TRAb values are very high or radioiodine uptake is low. Thyroidectomy should not be considered in patients with comorbid conditions such as cardiopulmonary disease and end-stage malignancy. Lack of access to a high-volume thyroid surgeon may also, directs against the choice of surgery. During pregnancy it can be considered as an emergency treatment of hyperthyroidism, when rapid control of the latter is crucial and ATD therapy cannot be used, but it is followed by a higher rate of complications such as hypoparathyroidism and recurrent laryngeal nerve (RLN) injury [12].

Thyroidectomy can be associated with postoperative complications, such as hypocalcemia, wound infection, hematoma, recurrent laryngeal nerve (RLN) injury, and Horner's syndrome. Those complications are dependent on surgeon's experience and skills as well as on removal approaches and the type and extent of the disease, having a great impact on patient's quality of life. Studies have shown that surgeons experience and post surgery complications are inversely proportional. In rare cases, after subtotal thyroidectomy recurrence of GD may be present [16].

3.2 Antithyroid drugs

ATD represent the predominant therapy in Europe, Asia, and as a bridge therapy in the USA [17]. The thionamides, propylthiouracil (PTU), carbimazole (CBZ), and the active metabolite of the latter, methimazole (MMI) by inhibiting thyroid peroxidase enzymes they cause a decrease in thyroid hormone production. Moreover studies have shown that they have an immunosuppressive effect resulting in reduction of TSH-RAb levels, intercellular adhesion molecule-1 (ICAM-1) and soluble IL-2 receptor (sIL-2R) [18]. ATD are indicated especially in younger patients and in cases when a short term treatment is needed prior to RAI or surgery. Moreover, patients with mild disease (small size of goiter, negative or low TRAb values), of old age with comorbidities who are at high risk of postoperative complications or patients with a history of head and neck irradiation or surgery, are candidates for ATD therapy. In pregnancy ATD are the first line therapy for GD. Also ATD are indicated, in cases of people receiving care in nursing facilities and therefore radiation safety precautions cannot be preserved, in patients with moderate to severe active Graves' orbitopathy (GO) and in those who need more rapid biochemical disease control. Finally, ATD should be considered when there is lack of access to an experienced thyroid surgeon [12]. Adverse events of antithyroid medication range from milder adverse events such ascutaneous eruptions, gastrointestinal disorders and arthralgias to more serious complications as agranulocytosis, frank polyarthritis and hepatotoxicity. Adverse events of methimazole seem to be dose related (40 mg/day or more) while such thing has not been associated pylthiouracil doses [19].

3.3 RAI therapy

RAI treatment is a very effective therapy of GD. Accordintg to the NICE guidance, which is prepared for the National Health Service in England, it is used as first line treatment and in cases of hyperthyroidism recurrence post ATD therapy. The aim of this therapy is to radiate thyroid cells rendering the patient eu/hypothyroid. Although for many years it has been the most preferable treatment in USA, currently there is a tendency toward ATD therapy [20]. RAI treatment is performed after failure of ATD therapy to control hyperthyroidism or when the latter is contraindicated. Also RAI is preferred in patients with commodities who are at high risk of surgical complications, or in those with a history of prior surgery or irradiation of the head and neck. RAI treatment is the therapy of choice when there is no access to an experienced thyroid surgeon and in patients with periodic thyrotoxic hypokalemic paralysis, right heart failure pulmonary hypertension, or congestive heart failure [12]. RAI treatment is contraindicated when there is suspicion of thyroid cancer, in women who are pregnant or are breastfeeding and in those who cannot follow radiation safety rules. As RAI treatment has a risk of worsening Graves orbitopathy it is contraindicated in case of moderate to severe orbitopathy [12].

4. Patient preparation for RAI therapy

A close collaboration between, endocrinology and nuclear medicine, departments is required for the management of patients with thyroid disease who are candidates for RAI therapy. The determination of the activity, as well as the administration of radioiodine are responsibilities of the nuclear medicine physician. According to the EANM guidelines for the treatment of benign thyroid disease prior to any intervention a detailed medical history is needed including previous therapies for hyperthyroidism and especially any potential intake of iodine-containing medication (such as amiodarone and contrast media) or food [21]. The medical history should include medical conditions, surgeries, allergies and medications (especially those who may interfere with radioiodine uptake). Nuclear medicine physician should provide oral and written information about RAI therapy procedure, possible side effects, risk of recurrence and possible retreatment as well as radiation safety precautions post RAI therapy [14, 22] and rule out any possibility of pregnancy prior treatment. It is mandatory for female patients of childbearing age to undergo a pregnancy test 3 days prior to radioiodine administration and provide written signed declaration stating that they are not pregnant. Serum pregnancy test is preferable than urine test as it is more sensitive [23]. If previous hysterectomy has been reported or the patient is in postmenopausal state then the test can be omitted. Patients of both sexes should avoid conception 6 months post RAI therapy. RAI therapy is contraindicated in breastfeeding and it should be administrated 6 weeks to 3 months after lactation is disrupted [21]. To increase radioiodine uptake (RAIU), iodine restriction for 1 to 2 weeks and ATD withdrawal 3–7 days before RAI administration are also recommended.

Serum levels of TSH, FT3, FT4, TPO and TSI should be measured prior RAI therapy. Thyroid volume is assessed by ultrasonography (US) and in cases of a large goiter magnetic resonance imaging (MRI) is performed in order to estimate possible extension in the mediastinum. Computed Tomography (CT) is not preferred as the contrast media impair with the radioiodine uptake. Thyroid scintigraphy with ^{99m}Tc pertechnetate (^{99m}TcO4) and radioiodine is also mandatory to provide metabolic information of the organ. Radioactive iodine thyroid uptake (RAIU) at 4-6 h and

24 h post administration must be measured. RAIU increases gradually over 24 h but in some patients it can be increased rapidly reaching maximum values at 4 to 12 h and return to normal after 24 h. In some nuclear medicine departments a fixed dose of radioiodine is used, therefore RAIU calculation is not needed.

For nodules >1–1,5 cm, with suspicious findings in US (hypoechoic nodules solid or cystic with hypoechoic solid component, with irregular shape, calcifications and presence of invasion in adjacent structures) which appear in scintigraphy as "cold' or with a decreased uptake, fine needle aspiration (FNA) biopsy is recommended [24].

Patients with GD may present with ophthalmopathy. An experienced ophthalmologist should estimate the severity of the disease as RAI therapy has been associated with exacerbation of the ophthalmopathy. Corticosteroid therapy should be considered [12]. Studies have shown a possible correlation between Grave's ophthalmopathy (GO) progression post RAI therapy in smokers. Cessation of smoking is recommended. RAI therapy in cases of active moderate-to-severe ophthalmopathy is contraindicated [25].

As transient elevation of thyroid hormones due to actinic thyroiditis may present, ATD therapy should be discontinued approximately one week before and be resumed 3–7 days post RAI therapy [18]. B-adrenergic blockade should be administered in cases of patients who are at a higher risk of complications due to hyperthyroidism.

4.1 Patients' information for RAI therapy

Patients should be properly and adequately educated concerning the procedures they will undergo, the precautions they should take, the outcomes and possible adverse events of RAI therapy. Fulfilling these needs requires a collaborative approach among patients and health care professionals. Patients should receive both written and verbal information. More modern approaches such as mobile health (mHealth) could also be helpful [26]. Except for the pre- and posttreatment use of thyroid specific medication, risk of recurrent disease and subsequent retreatment(s), early and late side effects, health care professionals should prepare the patients regarding radiation protection initiatives to reduce radiation doses to family members and general population, according to national rules. Unlike thyroid cancer patients, those who receive RAI therapy to treat benign thyroid diseases do not need hospitalization.

RAI capsule is administered on an outpatient basis, in authorized Nuclear Medicine Departments. After RAI administration the patient is advised to avoid eating or drinking anything for 2 h, to allow time for the iodine to be absorbed. After this time patients should eat as normal and drink plenty of fluids.

For a few weeks after the treatment patient's thyroid gland will be radioactive. The amount of radioactivity is gradually decreasing. During this period, which is estimated for each patient individually, they are advised to avoid or restrict to minimum radiation exposure to their environment. Patients are guided to reduce the radiation exposure to other people by limiting the amount of time they spend with them and by keeping more than three meters away from them. They must not share a bed with anyone or sleep within 2 meters of anyone, even if there is a wall between beds. For 1–1 ½ months after RAI treatment, patients should not spend more than a few minutes each day within arm's reach of any children or pregnant women. Of course, they also need to limit close and prolonged contact with any other people, and stay away from crowded places such as cinemas, theaters, public transport as well as their work place, where they may be close to the same person for a prolonged period of time.

Although, most of the radioactivity is concentrated in thyroid gland, for a few days after RAI treatment, some of the radioiodine is excreted by urine and sweat. Around 90% of administered radioiodine activity is excreted mainly through the kidneys. Thus, patients with renal insufficiency may retain radioiodine activity over a long period, thereby leading to more intense internal exposure to radiation than that observed in normal ones [27]. Drinking plenty of fluids and emptying bladder frequently can help minimize bladder and adjacent tissues' exposure. Patients are advised to take care with personal hygiene in the first few days after treatment. They are instructed to always flush the toilet after use and always wash their hands. They are also guided to use their own towels and face cloth. Their clothes do not need to be washed separately unless they experience any incontinence [28, 29].

5. Radiation dosimetry and dose calculation

The aim of RAI therapy in GD is to cure hyperthyroidism. This is achieved by radiating and therefore destroying thyroid cells. The outcome is the patient to return to an euthyroid state or to become hypothyroid. RAI therapy is very effective, even in cases of possible retreatments, with a cure rate ~ 100%. Individualized dose of radioiodine for rendering a patient euthyroid is not feasible [30]. While several studies have been conducted, regarding the association between the optimal dose of radioiodine, thyroid's volume (based on ultrasound) and radioiodine turnover [31], there is lack of consensus for the proper dose regimen. The majority is in favor of rendering the patient hypothyroid [20] applying high radioiodine doses [32] to avoid the possibility of treatment's failure or relapse of the disease. Many nuclear departments apply fixed doses [33]. For rendering a patient euthyroid a target dose of ~150 Gy is needed. Higher doses (200–300 Gy) are applied for complete ablation.

The following equation recommended by the EANM, is used to estimate the appropriate radioiodine dose:

$$\mathrm{A}[\mathrm{MBq}] = \frac{F}{\ln 2} \times \frac{\mathrm{M}[\mathrm{g}] \times \mathrm{D}[Gy]}{\int_0^\infty RIU(t)\,dt} \tag{1}$$

A: radioiodine activity, F: conversion factor (between coulombs per kilogram and grays), M: mass of the target volume, D: the target dose.

Radioiodine uptake (RIU) is calculated as follows:

$$\mathrm{RIU} = \frac{Activity\ in\ Thyroid\ Gland}{Administered\ activity} \times 100\% \tag{2}$$

As it has been mentioned above many nuclear medicine departments apply fixed doses, in a range of 200–800 MBq with the commonest applicable doses of 400–600 MBq. Estimation of the thyroid size is needed (based on ultrasound) [21].

6. RAI therapy outcome

Initially the goal of RAI treatment was to render the patient euthyroid using low doses of I-131. Through the years it has become clear that hypothyroidism is an inevitable and unpredictable progressive outcome of RAI treatment. Nowadays,

hypothyroidism is the desired result of RAI treatment and it has been described by many authors as the elimination of hyperthyroidism [34]. RAI treatment fails when persistent hyperthyroidism occurs. In the majority of the patients thyroid hormones return to normal levels while clinical symptoms are reduced 4–8 weeks post therapy. More than 80% of the patients become hypothyroid 16 weeks post RAI therapy. Hypothyroidism, in rare cases can be transient and the patient may return to a euthyroid state or remainhyperthyroid. The latter is often associated with no decrease of thyroid size [12]. The desired outcome of RAI treatment is dependent on multivariable factors such as thyroid size, dose regimens, compensation of hyperthyroidism, iodine intake (diet or iodine containing medicine) and the timing of the withdrawal of ATDs.

When low dose regimes are preferred, then the possibilities of treatment failure increase and ATD continuance and/or RAI retreatment are needed. Unfortunately, the field of RAI dose regimen still remains vast and things become more complicated when a fixed dose is compared to an individualized one. Many authors suggest that a calculated dose of radioiodine has no advantage over a fixed dose, while others recommend individual dose showing correlation between the success of therapy and the radiation dose actually absorbed by the thyroid [35]. Other factors that influence treatment outcome have been studied as well. In their retrospective cohort study, Aung et al. found that RAI treatment failure was more frequent in patients with high levels, of thyroid hormone or TRABs and in those who received ATD after RAI treatment. There were no correlation found among RAI treatment failure and other parameters such as age, sex or smoking. Moreover approximately 7% of the patients developed GO and 13.3% of them required surgery. There seemed to be a correlation between high thyroid hormone levels and orbitopathy whereas high TRAB levels had no effect in the development of orbitopathy [36].

Despite more than 75 years' experience with RAI treatment of GD, it is not always feasible to predict the efficacy of the treatment or the factors that will eventually affect it. The "GREAT" score, a predictive model consisting of clinical and biochemical variables has been introduced as a clinical tool that predicts the success of antithyroid drug therapy for Graves' Disease. Calculation of the GREAT 6-point score is as follows: age (<40 or ≥ 40 years: 1 or 0 point, respectively), goiter (not visible to slightly visible or clearly visible: 0 or 2 points), FT4 (<3.1 or ≥ 3.1 ng/dl: 0 or 1 point), and TBII (<6; 6–19.9; >19.9 U/L: 0, 1, or 2 points) resulting in the GREAT score classes of I (0–1 point), II (2–3 points), and III (4–6 points). Higher recurrence rate at the end of follow up is observed in GREAT score class III when compared with class II or class I (16.4%) [37]. However, GREAT score has been suggested for predicting outcome before the start of ATD and to our knowledge there has not been developed yet a clinical tool that can estimate RAI results.

7. Follow-up

Regular review of thyroid function tests in patients who have undergone radioiodine treatment for thyroid disease is essential to assess the efficacy of the treatment and for timely detection of developing hypothyroidism or post treatment immunogenic hyperthyroidism. The first review of thyroid function post RAI therapy should be conducted 1–2 months later by assessing TSH, FT4 and total FT3 values and be repeated every 4–6 weeks for the first 6 months or until the patient becomes hypothyroid and is stable on LT4 treatment [13]. In patients at high risk for endocrine ophthalmopathy or who have received ATD, follow up is recommended at shorter intervals. In cases of RAI treatment for overt hyperthyroidism,

ATD should be initiated 3–5 days post RAI treatment. If RAI retreatment is deemed necessary, it can be conducted 6–12 months later. RAI retreatment is not necessary in cases of post therapy immunogenic hyperthyroidism; ATD administration for a few months is adequate. As it is mentioned above a lifelong testing of thyroid function is necessary, even in patients who have returned to an euthyroid state post RAI treatment.

8. Adverse events

Actinic thyroiditis is the result of radioiodine therapy. As radioiodine is accumulated by thyroid cells the emitted betta particles cause cellular necrosis and stored thyroid hormones are released into the circulation causing a transient exacerbation of hyperthyroidism. This effect is greater in radioiodine therapy of a toxic nodular goiter as the levels of stored thyroid hormones are bigger [38]. This transient elevation of thyroid hormones can be asymptomatic or it can lead to atrial fibrillation, heart failure and rarely to thyroid storm with a possible fatal outcome. The latter demands admission to an intensive care unit and administration of ATDs and steroids (intravenously) as well as b-blockers [16].

Hypothyroidism is another side effect of radioiodine therapy and according to the ATA guidelines, it is the main goal of the therapy [12]. This outcome is more common in GD rather than in toxic goiter or in solitary hyperfuctionong nodules [16]. It requires lifelong follow up and LT4 treatment. In cases of failure to accomplish a hypothyroid state post radioiodine treatment, an increase in cardiovascular and cerebrovascular deaths has been noted [12].

Actinic thyroiditis is accompanied by thyroid pain and swelling which is prevalent the first week post therapy. In a few patients this can lead to dyspnea while the majority is asymptomatic. In cases of a large goiter with signs of tracheal compression, corticosteroids before radioiodine therapy should be considered. Sialadenitis, xerostomia or altered taste are adverse effects seen in patients with differentiated thyroid cancer who receive radioiodine therapy, however in patients with GD no permanent damage has been reported.

Ionizing radiation has been associated with increased incidence of leukemia and many solid cancers [39]. An increase in the incidence of thyroid carcinoma in children after Chernobyl accident has been reported [40]. Many studies have evaluated the possible correlation between radioiodine therapy in GD and the risk of malignancy. In a multicenter retrospective cohort study taken place in USA and UK, known as Cooperative Thyrotoxicosis Therapy Follow-up Study Group, 35,593 hyperthyroid patients were included and evaluation of cancer mortality among those patients and especially in those who received radioiodine treatment, was made. The results showed no significant increase in cancer mortality and this was due to the fact that mean doses of radiation among organs except for the thyroid were < 200 mGy. It has to be mentioned that the study cannot provide any information for the children population as themean age of the patients was 46 years [41]. Kitahara et al. [42] extended the previous study and found that radioiodine therapy of GD was correlated with a dose dependent increase in the incidence of all solid tumors and especially of breast cancer, while Greenspan et al., [43] challenged those previous results. Ameta analysis by Hieu et al., [44] found no increase in cancer risk post radioiodine therapy in benign thyroid disorders except perhaps for the thyroid, kidney and the stomach cancer, which the authors estimate that it should be investigated with further studies. The latter has also been challenged by Salvatori et al., [45] as the main reason for increased incidence of cancer in hyperthyroid patients is not radioiodine therapy but hyperthyroidism

itself. Thyroid hormones through αvβ3, a membrane receptor which is overexpressed in tumor cells, play a crucial role in cancer cell proliferation, angiogenesis and metastasis.

9. Conclusion

Thyrotoxicosis is a very common clinical syndrome caused by an excess of thyroid hormones in the serum. Graves' Disease is the commonest cause of hyperthyroidism. Graves' Disease is the commonest cause of hyperthyroidism. It has multiple manifestations and it requires appropriate diagnostic and therapeutic management. There are three effective treatment options: RAI therapy, ATDs, or thyroidectomy. RAI treatment has been used to treat thyroid disorders, both malignant and benign, for many decades and in many cases it is preferred first- line treatment. In Graves' Disease radioiodine radiates and therefore destroys the follicle cells of the hyperfunctioning thyroid gland providing a definite therapy of hyperthyroidism as well as improving patient's quality of life. It is well tolerated with rare complications except for those related to orbitopathy.

Conflict of interest

The authors declare no conflict of interest.

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