Chapter

Radioiodine for Graves' Disease Therapy

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Abstract

Radioiodine-131 (RAI) is an isotope of the chemical element iodine and is commonly used for hyperthyroidism, including Graves' Disease. It is given orally, and its concentration in the thyroid gland. The RAI transport involves a natrium iodide symporter (NIS) role that brings two cations sodium (Na+) and one anion of iodide (I-) across the membrane. The process is facilitated by the enzyme Na+/K+ ATPase. RAI is a beta (β) and gamma (γ) particles emitter. β particle is used for therapy and γ particle for imaging (theranostic). β particle inhibits cell growth by inducing cell death through apoptosis or necrosis of some of the sufficient thyroid cells. The aim of RAI therapy in Graves' Disease is to control hyperthyroidism and render the patient hypothyroidism. It is easier to manage patients with hypothyroidism with levothyroxine and fewer complications. This review will focus on RAI's therapeutic approach in Graves' Disease, including patient preparation, selecting activity dose, adverse events, contraindication, controversies issues such as malignancy and fertility, the follow-up to ensuring the patient remains euthyroid or need a replacement therapy if they become hypothyroidism. RAI therapy is safe as definitive therapy and cost-effective for Graves' Disease therapy.

Keywords: hyperthyroidism, hypothyroidism, malignancy, pregnancy, replacement therapy

1. Introduction

Graves' Disease is an autoimmune disorder that affects the thyroid gland, and it causes 50–80% of hyperthyroid cases and is associated with a firm diffuse goiter [1–3]. Its etiology is not entirely understood. The disease occurs in patients with having a genetic history and combination with environmental factors and lifestyles. Graves' Disease (GD) is characterized by elevated thyroid-stimulating receptor antibodies with increased thyroid hormone production [4–6]. GD can also affect other organs, including the eyes and skin. The annual incidence rate has been estimated at 14–50 cases per 100,000 persons. The peak incidence is between 30–50 years. Even though the disease may affect every age, the incidence is higher in women than men, with a 6:1 ratio [2, 5].

Graves' Disease treatments depend on the presentation. The treatment consists of symptomatic therapy and reduction of thyroid hormone synthesis. The symptomatic therapy, such as a beta-adrenergic blocker, is given for patients with tachycardia, a history of cardiovascular disease, and elderly patients [2, 6]. Therapies for reducing thyroid hormone synthesis are antithyroid drugs (ATDs), radioactive iodine (RAI), and thyroidectomy [2, 3, 6–8]. All three options have advantages and

disadvantages. There is no consensus on which one is the best choice, and it is one of the more debatable issues. The treatment choice is likely to be influenced by local availability, treatment cost, patient's preferences, and socio-economy that caused vary from country to country.

Antithyroid drugs are widely used in Europe and most of Asia as first-line therapy. However, RAI is used by most physicians in the United States of America. [3, 6–8]. Hertz and Roberts were used radioiodine I-130 for the first time on March 31, 1941, for hyperthyroidism treatment [9, 10]. Its radiation was delivered rapidly to the thyroid cells over a day or two. Since the Atomic Energy Commission was allowed to supply the fission products for peaceful medical use in August 1946, I-130 was replaced by I-131 because I-131 was much cheaper [9]. RAI is used for therapy and imaging (theranostic). It is a beta (β) and gamma (γ) emitter with a half-life of 8.05 days. A β particle has a peak energy of 0.606 MeV, with a maximum range of ~3 mm in the tissue used for therapy. The peak of γ particle is 0.364 MeV is used for imaging [4, 11, 12]. The longer physical half-life of RAI ensures long-term irradiation of the target tissues, becoming a potential advantage.

RAI therapy aims to treat hyperthyroidism by destroying sufficient thyroid cells to reach either euthyroid or hypothyroid conditions. Radioactive iodine is safe as definitive therapy, cure rates ~80–90%, and cost-effective, rarely or minor side-effects. [4, 6, 7, 11–14]. The choice of therapy depends on the patient's preference. The choice of therapy should take into account local availability and cost-effectiveness. In practical terms, RAI is administrated as an outpatient visit, and it is an advantage. RAI is recommended for optimal treatment of Graves' Disease by the American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE) guidelines for the management of thyrotoxicosis 2011 and ATA 2016 [3, 6, 15]. The recent guidelines of the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) recommend that radioiodine should now be the first-line treatment for Graves' Disease in the UK [7].

2. Transport radioiodine

RAI is administrated in a capsule or liquid. Once it is ingested, it is quickly absorbed into the bloodstream in the gastrointestinal (GI) tract. It is taken up by

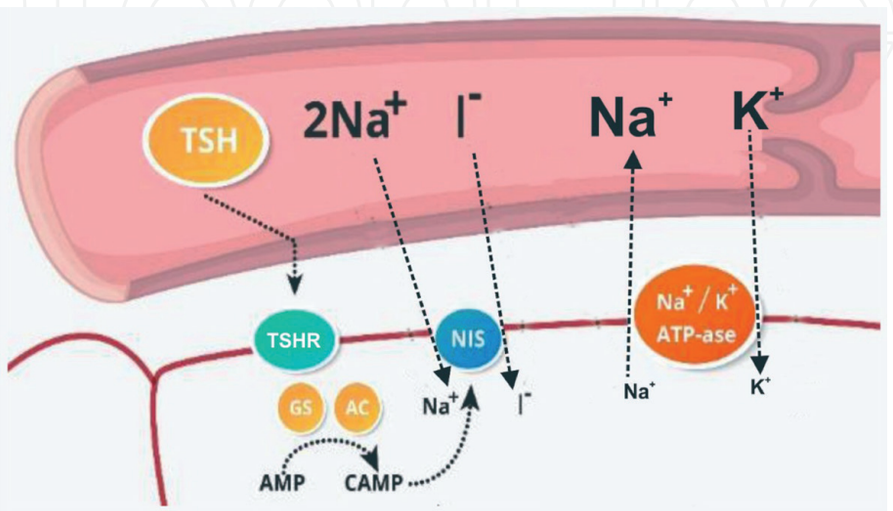

Figure 1.
Natrium iodide symporter brings two cations of sodium (Na^+) and one anion of iodide (I^-) cross the epithelial thyroid cells' at the basolateral membrane. The process is facilitated by the enzyme Na+/K+ ATPase.

thyroid cells through active transport, which is the same natural iodine process. The transport involves a natrium iodide symporter (NIS) role that brings two cations sodium (Na^+) and one anion of iodide (I^-). The process is facilitated by an enzyme Na+/K+ ATPase, as shown in **Figure 1**. NIS is a transmembrane glycoprotein that contains 13 membrane-spanning segments and three N-linked carbohydrates. It resides in the basolateral membrane of epithelial thyroid cells [16–20]. Besides the thyroid cell, NIS is expressed by extra-thyroid tissues [20]. NIS expression increased RAI uptake for diagnostic and therapy in thyroid extra-thyroid organ.

3. The mechanism action of RAI

β particle of RAI inhibits cell growth by inducing cell death through apoptosis or necrosis. Cell responses to radiation are influenced by various factors that lead to different responses between cells. The amount of RAI radiation received by cells is affected by the capture and accumulation of RAI and its biological half-life, which correlates with the effects. Cell responses to radiation are influenced by the cell's sensitivity and the complexity of the cells' micro-environments [21, 22]. Due to the small therapeutic range of β particles within the tissues, naturally, no β particles escape from the thyroid. So, the remaining non-target tissue (i.e., parathyroid glands) still safe even though high activity RAI dose is given to the patients. [4, 11, 23].

A β particle of RAI has a low Linear Energy Transfer (LET) value (0.2 KeV/μm). It causes cell death, direct and indirect. The decay of radioisotopes in the cell (self-dose) cause DNA damage through direct breakage of molecular bonds. The formation of free radicals or the decay of radioisotopes in adjacent cells (cross-fire) indirectly causes cell death, as shown in **Figure 2**. The condition leads to a reduction of thyroid function and diminished thyroid size [24, 25].

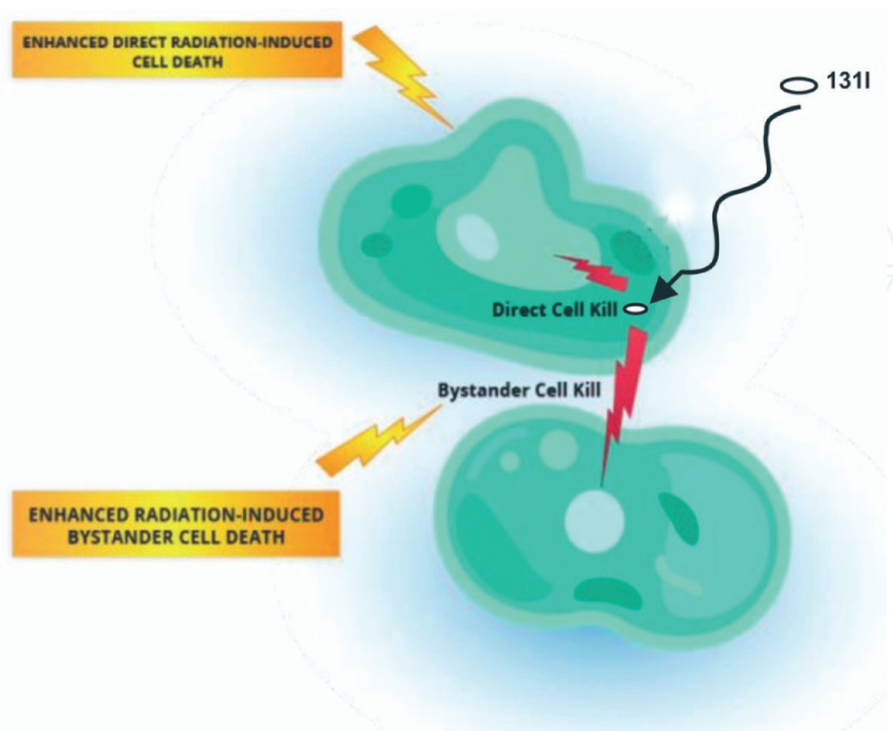

Figure 2.
RAI radiation damages a DNA directly (lethal and sub-lethal) or indirectly from adjacent cell radiation (cross-fire/bystander).

4. Treatment protocol

Many studies reported various approaches to RAI therapy published by different institutions. It remains a matter of debate when choosing the treatment protocols, whether a calculated dose that considers radioiodine uptake (RAIU) and thyroid volume measurements versus a fixed-dose, or a high dose versus a low dose, or whether short term versus long term medical management. RAI administrates as low as reasonably achievable (ALARA) dose that is an essential principle for radiation treatment [23, 25].

5. Radioiodine dose

RAI therapy is well established for the definitive treatment of GD. However, Its approach remains controversial due to differing treatment control goals. It is between hyperthyroidism versus avoidance of hypothyroidism. Various methods of RAI doses have been used to deliver adequate radiation to the thyroid gland. Radiation dose to the thyroid depends on the RAI uptake, thyroid volume, and biologic half-life of the RAI. Actually, RAI activity dose measured based an amount of the radiation delivered to the thyroid gland rather than administered activity, but few publications confirm this unequivocally [23]. Three approaches for determining the administered RAI activity doses. 1. Based on the calculation of thyroid volume and the RAI uptake 24 hours. 2. Based on thyroid volume, RAI uptake, effective half-life. 3. Fixed activity dose [4, 11].

In calculation approaches, the thyroid volume, RAI uptake, and effective half-life are factors determine the activity dose. It is recommended a delivered activity of RAI about 3–8 MBq (80–220 μCi) per gram of thyroid mass, with absorbed radiation dose 100–150 Gy to restore a euthyroid status, whereas the total ablation dose is in the range 200–300 Gy [12, 14, 23]. Naturally, the normal thyroid mass is about 20 grams. Ultrasound, x-ray/MRI studies, and scintigraphy thyroid can be used to evaluate thyroid volume. However, ultrasonography is superior to all of these techniques because of its relatively low cost, wide availability, ease of technically.

The RAI uptake should be appropriately prepared to ensure its real thyroid uptake. The patient should be advised to avoid meals for at least 2 hours before and 2 hours after the oral administration of RAI for the test. The thyroid uptake can also be measure by intravenous administration of Tc-99 m pertechnetate. The pertechnetate is trapped but not be organification by the thyroid. The measurement usually after 20 minutes of the injection [6, 11, 23]. GD uptakes usually high unless the patient has a history of iodine intake recently. However, the calculated dose versus fixed-dose effectiveness is an equally successful outcome [6, 26]. Radioactive iodine uptake (RAIU) can be calculated using formula (1) [12].

$$\text{RIAU}(\%) = \frac{\text{thyroid counts}(cpm)}{\text{Administrated counts}(cpm)} x\,100. \quad (1)$$

An effective half-life is needed for an accurate absorbed dose calculation to the thyroid [6, 11]. Effective half-life is the combination of the physical half-life (constant for a particular nucleus) and the biological half-life (varies from patient to patient). A radionuclide in a living tissue decays in two ways, physical decay and biological elimination from the body is called biological half-life. The effective half-life of RAI in the thyroid can be determined by measuring its uptake at several

different periods following RAI administration. It may vary from 1.2 to 7.5 days in hyperthyroidism (i.e., the variation factor is 6.25). The effective half-life calculation is cumbersome. It has a lot of calculations and assumptions that may have a human error. Effective half-life calculation will increase the accuracy of RAI activity dose [11]. However, the outcome has not been shown to be better, so the method is rarely used [6].

Fixed-dose of RAI activities is a simple protocol and convenient to use. It can be administered as a single dose and be repeated as necessary, with a range of 185–740 MBq (5- 20 mCi). The administration dose is given based on validated clinical parameters and an estimated thyroid size by palpation or measurement by ultrasonography or scintigraphy [26, 23, 25].

The majority of patients cure with a single RAI dose [11, 13]. Many physicians prefer a single high RAI dose, which leads to hypothyroidism. Cure rate high dose reach 85% - 94.4%, and 66–74% for low dose [4, 11, 14]. A single high dose or ablative dose concept is preferred by a physician today. It can avoid patients' frequent visits and laboratory testing for hypothyroid onset detection. It decreases the risk of persistent or recurrent hyperthyroidism [23]. A low dose is administered to achieve a euthyroid state to avoid hypothyroidism. 50%–90% of patients become hypothyroidism within 3–12 months [13]. Around 14% of hyperthyroid patients required second therapy. Persistence hyperthyroidism showed 7.3% after received 555 MBq (15 mCi) RAI [12, 13].

On the other hand, the low activity dose is generally not recommended because many patients need RAI retreatment. Furthermore, most patients will become hypothyroid after RAI [4, 23, 25]. Finally, therapy aims to control hyperthyroidism and render the patient to be hypothyroidism. The therapy outcome can be accomplished equally by administering a fixed RAI activity dose or calculating the activity based on the thyroid RAIU and size.

6. Patient preparation

Certain evaluations for adequate treatment include the treatment history such as ATDs, food or medication containing iodine that blocked radioiodine uptake that needs to discontinue before the treatment, and the duration of their period as shown in **Table 1**.

Pharmaceutical	**Withdrawal duration**
ATDs (propylthiouracil, methimazole carbimazole)	7–14 days before therapy 7 days after therapy
Thyroid hormones • Triiodothyronine • Thyroxine	 10–14 days 3–4 weeks
Lugol solution	2–3 weeks
Vitamins containing iodine	7–10 days
Amiodarone	3–6 months
Intravenous radiographic contrast agents • Water soluble • Lipophilic	 6–8 weeks 1–6 months

Table 1.
Pharmaceuticals containing iodine block of RAI uptake [4, 6, 11, 23, 25].

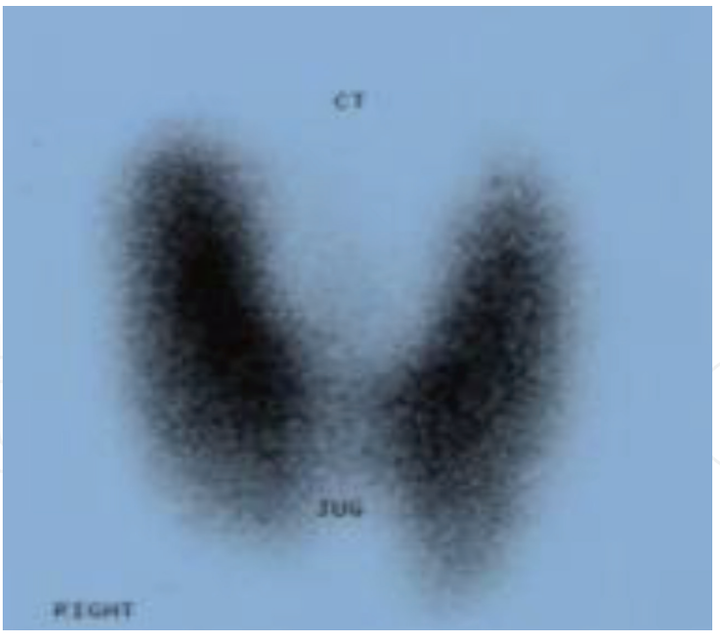

Figure 3.
Scintigraphy thyroid showed enlargement of both thyroid lobes, with high diffuse uptake of a Tc-99 m pertechnetate.

The patient should also be advised to avoid meals for at least 2 hours before and 2 hours after the oral administration of RAI. Large meals can slow the absorption of RAI. Laboratory results, including free T4, free T3, Thyroid-stimulating hormone (TSH). Thyroid scintigraphy is used to assess the potential variability distribution of RAI in the thyroid gland. Graves' Disease scintigraphy pattern is a diffuse high uptake at the thyroid gland. It can differentiate between Graves' Disease with toxic adenoma and toxic multinodular goiter, as shown in **Figure 3**. Ultrasonography assessment may be useful if patients have a contraindication for the scintigraphy, such as during breastfeeding and pregnancy [6]. The choice of testing depends on cost, local availability, and expertise. RAIU measurements are not required when fixed activities are used. Thyroid ultrasonography can be used to determine thyroid volume. Pregnancy test for child-bearing females within 72 hours before the RAI administration, and when pregnancy is excluded, the test can be omitted.

For patients with ophthalmopathy, RAI can exacerbate existing Graves' ophthalmopathy (GO) [11, 12, 23]. Smokers, high serum triiodothyronine pre-treatment, posttherapy hypothyroidism, and thyroid-stimulating receptor antibody are also associated with an increased risk of developing or worsening ophthalmopathy [23]. Steroids prevent the risk of RAI-induced ophthalmopathy without influence the outcome of therapy. Mild and active ophthalmopathy pre-exists patients with high-risk factors associated with development or worsening of ophthalmopathy should receive steroid prophylaxis [25, 27, 28].

RAI therapy may need to be repeated. Patients also need a long-term follow- up because of the likelihood of eventual hypothyroidism and very uncommon side effects. Written information must be provided, and the patient should obtain written informed consent before therapy.

7. Contraindication

Absolute contraindications of RAI are in pregnancy and during breastfeeding and in patients who cannot comply with radiation safety regulations. Relative contraindications are uncontrolled hyperthyroidism and active thyroid orbitopathy

(especially in smokers) [4, 6, 12, 25]. RAI is not contraindicated in large goiters, even if partially retrosternal or intrathoracic [25]. A higher cure rate reaches up to 96%, even for thyroid size of more than 40 gram [12].

8. Adverse effects

Some patients, especially those who have large thyroid mass, may notice a transient swelling of goiter for approximately one week after therapy, salivary gland discomfort, or dyspnoea. Nausea that could develop into vomiting depends on the amount of administered activity for RAI. Antiemetic treatment can reduce the symptom. The effects are infrequent when the patients received <1.1 103 MBq (<30 mCi). Those effects are usually observed on a high dose >3.7 103 MBq (> 100 mCi) of RAI [29].

RAI treatment can cause a transient exacerbation of hyperthyroidism. The β- adrenergic blocker should be considered in symptomatic and asymptomatic patients who have hyperthyroidism risk (i.e., elderly patients and patients with comorbidities) [6]. Even though it is rare, the radiation can induce thyroiditis and thyroid hormone release into the circulation leading to thyroid storm precipitation [4, 6, 12]. The condition is more likely occurring in patients with a large thyroid mass and who received higher RAI activities. Elderly patients and patients with significant pre-existing heart disease, severe systemic illness, or debility may benefit from pre-treatment with ATDs. However, ATDs should be withdrawn for one week before RAI therapy and resumed a week afterward [4, 6, 23, 25].

The aim of RAI therapy in GD is to control hyperthyroidism and render hypothyroidism. It is easier to manage hypothyroidism with levothyroxine and fewer complications compared to treat hyperthyroidism with ATDs in the long term, leading to undesirable therapy effects [30]. The number of mortality reduced in hyperthyroid patients who become hypothyroidism after RAI therapy. The condition is implying the survival advantages of hyperthyroidism control. The risk of mortality of patients with hyperthyroidism, whether caused by cardiovascular or cancer, appears to be driven by thyroid hormone excess [4, 31].

9. Malignancy

The challenge of RAI's late effect is concern developing the risk of malignancy after RAI treatment. Based on multi-center trials, there was no association of any clinical malignancy of RAI for the therapy. [7, 9, 11, 13, 23, 29, 31]. The malignancy is associate with a small risk of pre-existing or coexisting thyroid cancer in patients with toxic nodular goiter. Graves' Disease was not related to cancer development after RAI therapy [23].

10. Pregnancy

Conception should be delayed after six months of the therapy. The same period applies for males to allow irradiated spermatozoa and complete ovarian recovery for patients without undergone gonadal function and thyroid hormone under control [12]. Child-bearing women have no evidence of decreased fertility after received RAI treatment and no adverse outcome on subsequent pregnancies [32]. The incidence of intrauterine growth restriction, neonatal gender, and premature birth did not significantly differ between patients who received RAI therapy and

antithyroid drugs (ATDs). However, a higher abortion rate was found in Graves' Disease patients who received RAI and ATDs [33].

Furthermore, patients with intractable Graves' Disease and too high thyroid-stimulating receptor antibody who want to pregnant soon should not receive radioiodine therapy to avoid developing fetal or neonatal hyperthyroidism [34]. RAI exposures in the first ten weeks of pregnancy do not affect fetal growth, but after ten weeks, the exposures can affect the growth [35]. Studies reported have no evidence of genetic damage and congenital anomaly, miscarriage, and preterm birth in patients who received RAI with the general population [7, 11, 13, 25, 36–38].

11. Follow-ups

Long-term follow-up after RAI therapy is needed. The likelihood of eventual hypothyroidism can occur within 2–3 months after therapy or even decades later, with a small, ongoing annual incidence. Lifelong thyroid hormone supplementation would then become necessary and should be started when thyroid-stimulating hormone elevation is detected and should have as its goal a euthyroid, symptom-free state [23]. Transient hypothyroidism is reported in 3–20% of cases. It does not invariably lead to permanent hypothyroidism, but thyroid hormone supplementation is generally recommended.

12. Conclusions

RAI therapy is safe as definitive therapy and cost-effective for Graves' Disease definitive treatment. The treatment has to be individualized. Patients should fully understand the treatment procedures to reach the desired outcome and handle the risks and adverse effects. Three approaches for determining the administered RAI activity doses. 1. Based on the calculation of thyroid volume and the RAI uptake 24 hours. 2. Based on thyroid volume, RAI uptake, effective half-life. 3. Fixed activity dose. However, the effectiveness is an equally successful outcome between them. RAI treatment aims in GD is to control hyperthyroid rather than avoidance of hypothyroidism. Hypothyroidism can occur within the first three months after RAI therapy or even decades later. Lifelong follow-up is needed to ensure recurrence of disease, and hypothyroidism is detected. Thyroid hormone supplementation would then become necessary and should be started when thyroid-stimulating hormone elevation is detected. Long-term studies show that radiation does not induce genetic damage or malignancy. However, conception should be delayed at least for six months after the therapy. So, the physician needs to provide written information for the patients to avoid miss interpretation.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Chen YK, Lin CL, Chang YJ, Cheng FTF, Peng CL, et al. Cancer Risk in Patients with Graves' Disease: A Nationwide Cohort Study. Thyroid.2013;32(7):879-884

[2] Pokhrel B, Bhusal K. Graves Disease. [Updated 2020 Jul 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448195/

[3] Karyampudi A, Hamide A, Halanaik D, Sahoo JP, Kamalanathan S. Radioiodine therapy in patients with Graves' disease and the effects of prior carbimazole therapy. Indian J Endocrinol Metab. 2014;18(5):688-693

[4] Mumtaz M, Lin LS, Hui KC, Mohd Khir AS. Radioiodine I-131 for the therapy of graves' disease. Malays J Med Sci. 2009;16(1):25-33.

[5] Campi, Irene & Salvi, Mario. Graves' Disease. 2018;doi: 10.1016/B978-0-12-801238-3.98495-2.

[6] Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, Walter MA. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26(10):1343-1421. doi: 10.1089/thy.2016.0229.

[7] Okosieme OE, Taylor PN, Dayan CM. Should radioiodine now be first line treatment for Graves' disease?. Thyroid Res. 2020;13:3. doi:10.1186/s13044-020-00077-8

[8] Kornelius E, Yang YS, Huang CN, Wang YH, Lo SC, Lai YR, Chiou JY. The trends of hyperthyroidism treatment in Taiwan: A nationwide population-based study. Endocr Pract. 2018;24(6):573-579. doi: 10.4158/EP-2017-0266.

[9] Bonnema SJ, Hegedüs L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. Endocr Rev. 2012;33(6):920-980. doi: 10.1210/er.2012-1030.

[10] Slonimsky E, Tulchinsky M. Radiotheragnostics Paradigm for Radioactive Iodine (Iodide) Management of Differentiated Thyroid Cancer. Current Pharmaceutical Design. 2020;26:3812.doi: 10.2174/1381612826666200605121054

[11] Wazir M. Radioactive iodine therapy for hyperthyroidism: Physics, treatment protocols and radiation protection in Handbook of Hyperthyroidsm.2009

[12] Stokkel, M. & Handkiewicz-Junak, Daria & Lassmann, Michael & Dietlein, Markus & Luster, Markus. EANM procedure guidelines for therapy of benign thyroid disease. European journal of nuclear medicine and molecular imaging. 2010;37. 2218-28. doi :10.1007/s00259-010-1536-8.

[13] Al-Kaabi JM, Hussein SS, Bukheit CS, Woodhouse NJ, Elshafie OT, Bererhi H. Radioactive iodine in the treatment of Graves' disease. Saudi Med J. 2002;23(9):1049-1053.

[14] Radhi HT, Jamal HF, Sarwani AA, Jamal AJ, Al Alawi MF. Efficacy of a single fixed 131I dose of Radioactive iodine for the treatment of hyperthyroidism. Clin. Invest. 2019; 9(4): 111-120

[15] Bahn RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, et al. Hyperthyroidism and other causes of thyrotoxicosis: Management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Endocr Pract. 2011;17:456-520.

[16] Ravera S, Reyna-Neyra A, Ferrandino G, Amzel LM, Carrasco N. The Sodium/Iodide Symporter (NIS): Molecular Physiology and Preclinical and Clinical Applications. Annu Rev Physiol. 2017;79:261-289. doi: 10.1146/annurev-physiol-022516-034125.

[17] Elliyanti A, Rusnita D, Afriani N, Susanto YD, Susilo VY, Setiyowati S, et al. Analysis natrium iodide symporter expression in breast cancer subtypes for radioiodine therapy response. Nucl Med Mol Imaging. 2020;54(1):35-42.

[18] Darrouzet E, Lindenthal S, Marcellin D, Pellequer JL, Pourcher T. The sodium/iodide symporter: state of art of its molecular characterization. Biochim Biophys Acta. 1838;2013:244-253.

[19] Elliyanti A, Susilo VY, Setiyowati S, Rao PV. An Iodine Treatments Effect on Cell Proliferation Rates of Breast Cancer Cell Lines; In Vitro Study. Open Access Maced J Med Sci. 2020;8(B):1064-1070.

[20] Micali S, Bulotta S, Puppin C, Territo A, Navarra M, et al. Sodium iodide symporter (NIS) in extrathyroidal malignancies: focus on breast and urological cancer. BMC Cancer. 2014;14:303.

[21] Kogai T, Brent GA. The Sodium Iodide Symporter (NIS): Regulation and Approaches to Targeting for cancer Therapeutics. Pharmacology&Therapeutics.2012;135:355-370

[22] Kim HW, Kim JE, Hwang MH, Jeon YH, Lee SW, Lee J, Zeon SK, Ahn BC. Enhancement of natural killer cell cytotoxicity by sodium/iodide symporter gene-mediated radioiodine pretreatment in breast cancer cells. PLoS One. 2013;8(8):e70194. doi: 10.1371/journal.pone.0070194.

[23] Silberstein EB, Alavi A, Balon HR, Clarke SE, Divgi C, Gelfand MJ, Goldsmith SJ, Jadvar H, Marcus CS, Martin WH, Parker JA, Royal HD, Sarkar SD, Stabin M, Waxman AD. The SNMMI practice guideline for therapy of thyroid disease with 131I 3.0. J Nucl Med. 2012 ;53(10):1633-1651. doi: 10.2967/jnumed.112.105148.

[24] Hingorani M, Spitzweg C, Vassaux G, Newbold K, Melcher A, Pandha H, Vile R, Harrington K. The biology of the sodium iodide symporter and its potential for targeted gene delivery. Curr Cancer Drug Targets. 2010;10(2):242-67. doi: 10.2174/156800910791054194.

[25] Kahaly G, J, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce S, H: 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J 2018;7:167-186. doi: 10.1159/000490384

[26] de Rooij A, Vandenbroucke JP, Smit JW, et al. Clinical outcomes after estimated versus calculated activity of radioiodine for the treatment of hyperthyroidism: systematic review and meta-analysis. 2009. In: Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]. York (UK): Centre for Reviews and Dissemination (UK); 1995-.https://www.ncbi.nlm.nih.gov/books/NBK78254/

[27] Vannucchi G, Covelli D, Campi I, Currò N, Dazzi D, Rodari M, Pepe G, Chiti A, Guastella C, Lazzaroni E, Salvi M. Prevention of Orbitopathy by Oral or Intravenous Steroid Prophylaxis in Short Duration Graves' Disease Patients Undergoing Radioiodine Ablation: A Prospective Randomized Control Trial Study. Thyroid. 2019 ;29(12):1828-1833. doi: 10.1089/thy.2019.0150.

[28] Shiber S, Stiebel-Kalish H, Shimon I, Grossman A, Robenshtok E. Glucocorticoid regimens for prevention of Graves' ophthalmopathy progression following radioiodine treatment:

systematic review and meta-analysis. Thyroid. 2014 ;24(10):1515-1523. doi: 10.1089/thy.2014.0218.

[29] Tulchinsky M, Brill AB. Spotlight on the Association of Radioactive Iodine Treatment With Cancer Mortality in Patients With Hyperthyroidism is Keeping the Highest Risk From Antithyroid Drugs in the Blind Spot. Clin Nucl Med. 2019;44(10):789-791. doi: 10.1097/RLU.0000000000002792.

[30] Chen DY, Jing J, Schneider PF, et al. Comparison of the long- term efficacy of low dose 131I versus antithyroid drugs in the treatment of hyperthyroidism. Nucl Med Commun.2009; 30: 160-168

[31] Ron E, Doody MM, Becker DV, et al. Cancer mortality following treatment for adult hyperthyroidism. Cooperative Thyrotoxicosis Therapy Follow-up Study Group. JAMA. 1998;280(4):347-355. doi: 10.1001/jama.280.4.347.

[32] Vini L, Hyer S, Al-Saadi A, Pratt B, Harmer C. Prognosis for fertility and ovarian function after treatment with radioiodine for thyroid cancer. Postgrad Med J. 2002;78(916):92-93. doi:10.1136/pmj.78.916.92

[33] Zhang LH, Li JY, Tian Q, et al. Follow-up and evaluation of the pregnancy outcome in women of reproductive age with Graves' disease after 131Iodine treatment. J Radiat Res. 2016;57(6):702-708. doi:10.1093/jrr/rrw049

[34] Hamada N, Momotani N, Ishikawa N, Yoshimura Noh J, Okamoto Y, Konishi T, Ito K, Ito K. Persistent high TRAb values during pregnancy predict increased risk of neonatal hyperthyroidism following radioiodine therapy for refractory hyperthyroidism. Endocr J. 2011;58(1):55-58. doi: 10.1507/endocrj.k10e-123.

[35] Tran P, Desimone S, Barrett M, Bachrach B. I-131 treatment of graves' disease in an unsuspected first trimester pregnancy; the potential for adverse effects on the fetus and a review of the current guidelines for pregnancy screening. Int J Pediatr Endocrinol. 2010;2010:858359. doi: 10.1155/2010/858359.

[36] Brandão Carmen Dolores G., Miranda Angélica E., Corrêa Nilson Duarte, Sieiro Netto Lino, Corbo Rossana, Vaisman Mario. Radioiodine therapy and subsequent pregnancy. Arq Bras Endocrinol Metab. 2007; 51(4): 534-540.

[37] Dottorini ME, Lomuscio G, Mazzucchelli L, Vignati A, Colombo L. Assessment of female fertility and carcinogenesis after iodine-131 therapy for differentiated thyroid carcinoma. J Nucl Med. 1995;36(1):21-27.

[38] Balenovic A, Vlasic M, Sonicki Z, Bodor, Kusic Z. Pregnancy Outcome after Treatment with Radioiodine for Differentiated Thyroid Carcinoma, Coll. Antropol. 2006; 30 : 743-748