Original Paper, Therapy

Role of Radioactive Iodine-131 in Management of Hyperthyroid Patients Seen at NEMROCK: a Local Experience Study

Younis, J[1]. and El-Haddad, Sh.[2]

Nuclear Medicine Unit[1] and Oncology Unit[2],(NEMROCK Center),Cairo University, Cairo, Egypt

ABSTRACT:

The study aimed to assess the response of Graves Disease (GD) and Toxic Multi-Nodular Goiter (TMNG) to RAI-131 therapy within a follow up duration of 6 months - 3 years. **Methods:** 200 patients with thyrotoxicosis were evaluated at Nuclear Medicine Unit ,Cairo University during the period of January 2007 till March 2012.All patients (120 females and 80 males) were subjected to full history taking, clinical examination ,lab tests (FT3, FT4,TSH and thyroid antibodies), neck ultrasound, thyroid scan with Tc-99m pertechnetate. Thyroid gland uptake was estimated for all cases. Different doses RAI-131 therapy (12 – 29 mCi) were given to all patients with 3 years follow up guided by T3,T4 and TSH **Results.** The current study population included 100 patients of GD (group1) and 100 patients of TMNG (group2), Mean age in group1 was 33±9.8 while mean age in group 2 was 42±11.78 , with significant difference between age and prevalence of each type of thyrotoxicosis (***P*<** 0.001). In group 1, 40 patients received 12 mCi of RAI-131, while 35 patients received 15 mCi. Both of them showed clinico-laboratory evidence of euothyroid state, where as the rest of this group (25 patients) received 20 mCi after which most of them developed hypothyroidism. On the other hand, group 2, it was divided into 35 patients received 20 mCi, 45 patients received 25 mCi & the remaining 20 patients received 29 mCi. The former two sub groups showed predominance of euothyroid state on follow up, while those received 29 mCi, 8 of them developed hypothyroidism. As regard number of doses, only 16 out of the 200 patients received repeated doses of RAI-131, while the rest received single dose of RAI-131. There was significant high incidence of hypothyroidism among patients received large doses of I-131 ranging 25 - 29 mCi compared to those received small doses ranging from 12 to 15 mCi, with ***P***-value (0.05). **Conclusion**: RAI-131 has a very important role in treating both GD and TMNG. Different doses of RAI-131 has different impact on the thyroid gland function. Hypothyroidism is a common outcome after high dose of RAI-131 treatment.

Key words: Thyrotoxicosis. RAI-131.Thyroid hormonal profile. Thyroid scan and uptake.

Corresponding Author: Younis, J. **Email:** jehan.nuc@hotmail.com

INTRODUCTION:

Thyrotoxicosis is the hyper metabolic condition associated with elevated levels of thyroxin (FT4) & free tri-iodothyronine (FT3). The most common cause of thyrotoxicosis is Graves' disease (50-60%)[1]. Women have a higher reported incidence of Graves' disease than men, with a female to male incidence ratio of approximately 7:1 to 10:1[2]. *Graves' disease* is an autoimmune disease caused by an activating autoantibody that targets the TSH receptor[3]. *Toxic Multi-nodular Goiter* (TMNG)**,** also known as *Plummer's disease*, is a condition in which the thyroid gland contains multiple nodules that are hyper-functioning causing an over-production of thyroid hormones[4]. TMNG usually presents in individuals older than 50 years of age who have had a long previous history of multi-nodular goiter[5].

Serum Hormonal Level is diagnostic findings show that 95% of patients with hyperthyroidism have a combination of suppressed serum TSH levels of <0.05 mIU/L and an elevated serum free T_4 level[6].The measurement of Thyroid-stimulating hormone receptor antibodies (TRAb) may occasionally be helpful in the diagnosis and management of Graves' disease[7].Thyroid scintigraphy usually performed with technetium-99m pertechnetate or radioiodine[8,9,10].The thyroid radioactive iodine uptake test with scanning is a key diagnostic tool in the evaluation of hyperthyroidism [11,12]. Thyroid sonography may be useful in identifying thyroid nodules that may not be readily apparent on examination[13]. Treatment of thyrotoxicosis includes Beta-blocker therapy, Anti-thyroid drugs & RAI-131[14].

Radioactive iodine is the treatment of choice for most patients with Graves' disease and toxic nodular goiter. It is inexpensive, highly effective, easy to administer, and safe[15]**.**

There are 2 common approaches for determining the administered dose **.**One is to prescribe a fixed dose for all patients. The other is to calculate a dose based on the size of the thyroid and its percentage uptake at 24 h [16].

When a patient is not rendered euothyroid or hypothyroid, a second treatment is advised. Some authors advise a second treatment after 3 months, some prefer a delay of 6 months or more because a proportion of patients respond later[17].

The aim of the study is assessment the response of Graves disease (GD) and toxic multi-nodular goiter (TNG) to RAI-131 therapy within a follow up duration of 3 years.

PATIENTS & METHODS:

The study population included 200 cases with thyrotoxicosis seen at Nuclear Medicine Unit (NEMROCK), Cairo University during the period of January 2007 till March 2012 for RAI-131 therapy after failure of either medical or surgical treatment. All patients were followed for 6 months -3 years after RAI-131 therapy till March 2012.The study included 120 females and 80 males patients with Primary and secondary types of thyrotoxicosis with different age groups above 18 years. They were subjected to history taking Including age, sex, symptoms, duration of illness, type

and response to previous treatment. Pre RAI-131 medical treatment was given to 162/200 patients at a median dose of 30 mg/day for a median period of 12 months. Patients who received medical treatment were (90%) in primary type and (72%) in secondary type .Concerning surgery, 76% of secondary type had previous surgery compared to only 4% of patients with primary type. The surgery was either hemi-thyroidectomy or subtotal thyroidectomy. Clinical examination for gland size, consistency, nodularity, & other neck swellings, eye signs examination. laboratory investigations including T3, T4, TSH levels and antibodies (measured by radioimmunoassay), with normal reference ranges as follow : TSH: 0.5- 5 mIU/L, T3: 60- 181 ng/mL,T4: 5.5- 12.3 ng/ml. Neck ultrasound to detect size, nodularity & other neck swellings. Thyroid scan with technetium-99m pertechnetate (Tc 99m): The patients were imaged in a supine position with neck extension on anterior view using gamma camera fitted with low energy high resolution parallel-hole collimator, with the window at+_15% centered on 140 Kev in a 128x128 matrix for 500,000 count per view, to evaluate gland size, and nodules . Quantitative evaluation of thyroid uptake based on images of the gland and syringe counts before and after tracer injection. Thyroid uptake with Tc 99m was estimated for all cases with normal reference range = (0.5-4) %. Different doses of RAI-131 therapy (12-29mCi) were given to all patients with 3 years follow up guided by FT3, FT4, and TSH levels 3, 6 months after treatment then every year till patient becomes euothyroid. Successful treatment was considered when the patient turned euothyroid or hypothyroid. **Statistical Evaluation:** Data analysis of 200 cases with primary and secondary types of thyrotoxicosis including: Age group and type of thyrotoxicosis, sex of patient and type of thyrotoxicosis, most predominant symptoms in each type of thyrotoxicosis, thyroid hormone levels and the type of thyrotoxicosis, type of previous treatment of each type of thyrotoxicosis, response to different dose values of radioactive iodine, relationship between dose value of radioactive iodine and onset of hypothyroidism. Statistical analysis was done using the Statistical Package of Social Sciences (SPSS) advanced statistics version 17(SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation .Qualitative data were expressed as frequency and percentage. Chi-square test was used to examine the relation between qualitative variables. A P-value<0.05 was considered significant.

RESULTS:

This study included 200 patients, that were clinically & radio-laboratory categorized into two groups; Group 1: includes 100 patient diagnosed as GD, while Group 2 includes the other 100 patients that were diagnosed as TMNG. Both groups show statistically significant difference as regard the age with P-value 0.001, where mean age was 33+/- 9.79 years in group 1, while it was 42+/- 11.78 years in group 2. The same significant difference was illustrated on the basis of prevalence in both sexes, where GD was more common among females (66%), while TMNG was more common among males (65%).

Concerning symptoms of toxicity, we noticed that palpitation, tachycardia, loss of weight tremors nervousness, heat intolerance, exophthalmus, & neck swelling were common among both groups, however loss of weight & neck swelling were the most common among GD patients, while palpitation & dyspnea were the most common among TMNG.

With respect to severity of thyrotoxicosis, and by using normal reference range for serum TSH from 0.5 to 5 mIU/L, 68% of GD patients were localized in first stage (0.01-0.05) "Severely suppressed TSH", while 49% of TMNG patients were localized in second stage (0.06-0.1) "Moderately suppressed TSH" (Table 1).

In an attempt to explore the relationship between different values of RAI-131 doses (that were administered only once in 92% of patients) and outcome response (on basis of 3 years follow up), we found out that in group 1; when administered doses about 12 or 15 mCi, euothyroid state is more likely as shown in 41/75 patients, while with administering a dose equals to 20mCi the hypothyroid state is the most predicted outcome as shown in 22/25 patients with statistical significance of P<0.001 (Table 2).

On the other hand in patients with TMNG (group 2), administering a dose about 25 or 29 mCi is commonly associated with euothyroid outcome as shown in 32/65 patients with statistical significance of P-value 0.04 & 0.03 respectively (Table 3).

As expected there was a strong relationship between the amount of administered RAI-131 & the onset of hypothyroidism, as shown in our study 32 % of our population (64 patients) turned hypothyroid on follow up and after administration of RAI-131. 7/40 of patients who received 12 mCi & 6/35 of those who received 15 mCi. All of these patients were diagnosed as GD. Meanwhile hypothyroidism was also noticed in 9/45 patients that received 25 mCi & 8/20 of patients that received 29 mCi. Both of which were TMNG (Table 4).

Table (1): Relation between TSH level and type of thyrotoxicosis

TSH Level	Grave' disease			Toxic multi-nodular type			P Value
	Number of Patients (100)	Percent	Mean &SD	Number of patients (100)	Percent	Mean& SD	
0.01– 0.05	68	68%	0.025±0.003	30	30%	0.035±0.012	<0.05
0.06 - 0.1	24	24%	0.073±0.013	49	49%	0.091±0.001	<0.05
0.11- 0.15	8	8%	0.123±0.031	21	21%	0.142±0.058	0.06

Table (2) Relationship between responses of GD to different dose values of RAI-131 during 3 years follows up

Dose of radioactive iodine-131	Toxic		Hypothyroid		Euothyroid		P-value
	Percent	Number	Percent	Number	Percent	Number	
12mCi	37%	15/40	18%	7/40	45%	18/40	0.04
15mCi	17.1%	6/35	17.1%	6/35	65.7%	23/35	0.03
20mCi			88%	22/25	12%	3/25	<0.001

GD= Grave's disease

Table (3) Response of TMNG to different dose values of RAI-131 during 3 years follows up

Dose of Radioactive iodine-131	Toxic		Hypothyroid		Euothyroid		P-value
	Percent	Number	Percent	Number	Percent	Number	
20 mCi	38%	13/35	34%	12/35	28%	10/35	0.06
25 mCi	31%	14/45	20%	9/45	49%	22/45	0.04
29 mCi	10%	2/20	40%	8/20	50%	10/20	0.03

TMNG: Toxic Multinodular Goiter

Table (4) Relationship between the dose value of radio-active iodine and the onset of hypothyroidism.

Dose of RAI-131	6 months		12 months		More than 12 months	
	Percent	Number	Percent	Number	Percent	Number
12 mCi (40 patients)	14%	1/7	29%	2/7	57%	4/7
15 mCi (35 patients)	17%	1/6	33%	2/6	50%	3/6
20 mCi (60 patients)	38%	13/34	24%	8/34	38%	13/34
25 mCi (45 patients)	44.4%	4/9	22.3%	2/9	33.3%	3/9
29mCi (20 patients)	50%	4/8	38%	3/8	12%	1/8

DISCUSSION:

Thyrotoxicosis is a common endocrine disease. The essential goal in its management is to reduce the hyper-secreation of thyroid hormones. RAI-131 is considered to be the treatment of choice for most patients[18]. The current study included 200 patients, 100 of GD (group 1) and 100 of TMNG (group 2). Group 1 mean age was 33 +/- 9.79 years , while secondary type mean age was 42+/- 11.78 years. There was high significant difference between age and prevalence of each type of thyrotoxicosis) (P-value <0.001) Also, **Zimmerman**, demonstrated that the peak age-specific incidence of Graves' disease was between 20 and 49 years. [19]**.** Women were affected two to eight times more than men across the age range. Recent further analysis suggested that the incidence of thyrotoxicosis was increasing in women but not in men between 1997 and 2001[20]. Our study population was 120 female and 80 male patients; GD is more between females (66%) while TMNG is more common among males (65%). On the contrary to our results**, Basaria and Salvatori**, reported that**,** toxic nodular goiter occurs more commonly in women than men[21]. Similar to our results, women have a higher reported incidence of Graves' disease than men, with a female to male incidence ratio of approximately 7:1 to 10:1 as confirmed by **Nayak and hodak**[2].

In our study, Pre RAI-131 medical treatment was given to 162/200 patients at a median dose of 30mg/day for a median period of 12 months. Patients who received medical treatment were (90%) in primary type and (72%) in secondary type. We found that medical treatment has no effect on the final result of iodine therapy, as all patients who were on anti-thyroid medications stopped treatment 5 days before Iodine therapy. **koornstra, et al,** reported that anti-thyroid medication has a significant role in rendering patients euothyroid before treatment with I^{131} or thyroidectomy [22]**.** On the other hand and similar to our results, **Braga, et al,** demonstrated that methimazole pretreatment has no effect on the final result of I^{131} therapy [23]**.**

Alexander, et al,.treated 261 patients with Graves' disease with I^{131} [mean dose, 14.6 mCi]. Patients pretreated with anti-thyroid medication for greater than 4 months had higher risk for treatment failure [24]

Concerning surgery, 76% of TMNG and 4% of GD patients of our study were underwent thyroidectomy either as a first or a second line of treatment. Some surgeons promote thyroidectomy as the treatment of choice for Graves' disease[25]. **Lal, et al**, reported thyroidectomy in 103 patients during the period of 1991-2002 for whom the indications were patient preference (26%), cold nodule (24%), eye symptoms (20%), large goiter size (18%), allergy to anti-thyroid medications (15%), and young age (14%)[25]**.**

Different dose values of radioactive iodine has different impact on the thyroid gland function. In our study, patients with GD received different doses based on gland size and serum thyroid hormonal profile, doses ranged from 12 mCi to 20 mCi .We reported that there were significant difference between the response to radioactive iodine dose equal to 12, 15mCi toward the euothyroid variant, while the statistical significant difference of the

response to iodine dose equal to 20mCi was towards the hypothyroid variant.

Mazzaferri, et al, in their study on 813 GD patients, divided them into two groups. The first group received (5 mCi), and the second group received (10 mCi). At the end of their study period, the first group had an incidence of hypothyroidism of 41.3%, and the second group had an incidence of 60.8 %.[26]

In our study, 35 patients of TMNG received RAI dose equal 20mCi, 45 patients received 25mCi, 20 patients received 29mCi. Higher doses in the multi-nodular goiter showed significant difference only in the 25 & 29 mCi range towards the euothyroid response.

Similar to our result, **Giovanella, et al**, reported that (20 mCi) of iodine-131 administered to 146 patients of toxic nodular goiter; 92% became euothyroid within 3 months, and 97% became euothyroid at 1 year. 3% became clinically or biochemically hypothyroid[27].

Out of 200 patients of the study population, 184 patients (92%) received one dose of radio-active iodine treatment, while only 16 patients (8%) received repeated doses after which they turned either euothyroid or hypothyroid.

Hypothyroidism is inevitable consequence of the treatment of hyperthyroidism with RAI even in low doses .Its occurrence in the first year is related to the dose, while the subsequent occurrence is due to a combination of radiation-mediated injury and underlying autoimmunity[28].

In our study, we observed that the higher the dose of RAI-131 the earlier the onset of hypothyroidism. Forty patients (20%) of all cases treated with RAI became hypothyroid after one year, 64 patients (32%) turned hypothyroid after 3 years of treatment on further follow up investigations. Similar results was reported by **Howarth, et al,** who compared low radiation doses to the thyroid trying to minimize the number of patients requiring thyroid hormone replacement after I^{131} therapy**.** Euo-thyroidism was achieved in 46% of the patients and 47% were rendered hypothyroid at the final follow-up 3 years[29]

Also, Ahmed, et al, reported that the cumulative incidence of hypothyroidism following RAI treatment was 38.2% after 6 months. The incidence increased to 55.8% after 1 year and to 86.1% at 10 years [30].

CONCULUSION:

Radio-active iodine is safe, effective in both types of thyrotoxicosis, its effect appears shortly after the first dose and very small percent need a second dose. Single high dose of radioactive iodine is better to avoid the risk of re-exposure to repeated doses. Different doses of RAI-131 has different impact on the thyroid gland function. Hypothyroidism is a common outcome after radio-active iodine treatment that should be considered. Hypothyroidism should be diagnosed clinically and biochemically and thyroxin replacement therapy should be started once the diagnosis is confirmed.

REFERENCES:

1- Bahn Chair RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid. Jun*. (2011**)**; *21(6):456-520.*

2-Nayak B and Hodak SP. Hyperthyroidism. *Endocrinol Metab Clin North Am.* (2007); 36:617-656.

3- C. Kamath, M. A. Adlan and L. D. Premawardhana. The role of thyrotrophin receptor antibody assays in Graves' disease. *Journal of Thyroid Research*. 27 January (2012); 8 pages.

4-Werner SC, Ingbar SH, Braverman LE, et al. The Thyroid*: A Fundamental and Clinical Text*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins. (2000); 564-572.

5-Larsen PR, Davies TF, et al. Thyrotoxicosis. In: Larsen PR, Kronenberg HM,Melmed S,et al. editors. Williams' *textbook of endocrinology*. (2002); 10th ed. Philadelphia: WB Saunders Co;. p. 374–421.

6-Ladenson P. Diagnosis of thyrotoxicosis. In: Braverman LE, Utiger RD, editors.Werner's and Ingbar's the thyroid. 9th ed. Philadelphia: Lipincott, Williams & Wilkins. (2005); p. 660–4.

7-Costagliola S, Morgenthaler NG, Hoermann R, et al. Second generation assay for thyrotropin receptor antibodies has superior diagnostic sensitivity for Graves' disease. *J Clin Endocrinol Metab*. (1999); 84 (1): 90,

8-Meller J and Becker W. The continuing importance of thyroid scintigraphy in the era of high-resolution ultrasound. *Eur J Nucl Med Mol Imaging*. (2002); 29:425-38.

9- Summaria V, Salvatori M, Rufini V, et al. Diagnostic imaging in thyrotoxicosis. *Rays.* (1999); 24:273-300.

10-Smith JR and Oates E. Radionuclide imaging of the thyroid gland: patterns, pearls, and pitfalls. *Clin Nucl Med*. (2004); 29:181-93.

11-Intenzo CM and dePapp AE. Scintigraphic manifestations of thyrotoxicosis. *Radiographics*. (2003); 23: 857-869.

12-Meier DA and Kaplan MM. Radioactive iodine uptake and thyroid scintiscanning. *Endocrinol Metab Clin North Am.* (2001)*;* 30:291-313.

13- Chung J. Ultrasonographic features of papillary thyroid carcinoma in patients with Graves' disease. *Korean J Intern Med*. (2010); 1(25):71-6.

14-Abraham P. Antithyroid drug regimen for treating Graves' hyperthyroidism. *Cochrane database of systematic reviews*. (2010); (1): p. CD003420.

15- Zheng W. Analysis of 131I therapy and correlation factors of Graves' disease patients: a 4- year retrospective study. *Nuclear medicine communications*. (2012); 33 (1): p. 97-101.

16- Schiavo, M., et al. A study of the efficacy of radioiodine therapy with individualized dosimetry in Graves' disease: need to retarget the radiation committed dose to the thyroid. *Journal of endocrinological investigation*.(2011); 34 (3): p. 201-5.

17-Kinuya S, Michigishi T, Nakajima K, et al. Failure of radioiodine treatment in

Graves' disease intentionally caused by a patient: suspected Munchausen syndrome. *Ann Nucl Med.* (2004); 18:631-632.

18-Iagaru, A. and I.R. McDougall, Treatment of thyrotoxicosis. *Journal of nuclear medicine*: official publication, Society of Nuclear Medicine. (2007); 48 (3): p. 379-89.

19-Zimmerman MB. Iodine deficiency. *Endocr Rev*. (2009); 30:376-408.

20-Leese GP, Flynn RV, Jung RT, et al. Increasing prevalence and incidence of thyroid disease in Tayside, Scotland: The Thyroid Epidemiology, Audit and Research Study (TEARS). *Clin Endocrinol (Oxf*). (2008); 68:311-16.

21-Basaria S and Salvatori R. Images in clinical medicine. Pembertons sign N *Engl JMed*. (2004); (13):1338.

22-Koornstra JJ, Kerstens MN, Hoving J, et al. Clinical and biochemical changes following 131I therapy for hyperthyroidism in patients not pretreated with antithyroid drugs. *Neth J Med*. (1999); 55:215–221.

23-Braga, M., Walpert, N., Burch, H.B., et al. The effect of methiamazole on cure rate after radioiodine treatment for graves' hyerthyroidisdm. *Thyroid*. (2002); 12 (2): 135-139.

24-Alexander E and Larsen PR. High dose of (131) I therapy for the treatment of hyperthyroidism caused by Graves' disease. *J ClinEndocrino Metab*. (2002); 87: 1073–1077.

25- Lal G, Ituarte P, Kebebew E, et al. Should total thyroidectomy become the preferred procedure for surgical management of Graves' disease? *Thyroid.* (2005);15:569–574.

26-Mazzeferri, E.L. and Lorraine, AYear book of Endocrinology. *North America, Mosby*. (2001).

27- Giovanella L, De Palma D, Ceriani L, et al. Radioiodine treatment of hyperthyroidism using a simplified dosimetric approach: clinical results [in Italian]. *Radiol Med (Torino*). (2000); 100: 480–483.

28-Boelaert et al. Prediction and cure of risk of hypothyroidism in patients receiving 131I for hyperthyroidism. *Clin Endocrinol (Oxf*. (2009); 70:129-38.

29-Howarth D, Epstein M, Lan L et al. Determination of the optimal minimum radioiodine dose in patients with Graves' disease: a clinical outcome study. *Eur J Nucl Med*. (2001); 28:1489–1495.

30-Ahmed, A.F., Ahmad, M., and Young, E.T. Objective estimates of the probability of developing hypothyroidism following radioactive iodine treatment of thyrotoxicosis. *Eur. J. Endocrinol.* (2002); 146 767–775.