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Role and Outcome of RA^{131} I Therapy in Patients with Autonomous Toxic Adenoma

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ABSTRACT

Radioactive iodine (RAI) therapy is preferred in the treatment of toxic autonomous adenomas because of its effectiveness, noninvasiveness, and low costs[(1)]**.** Among patients with toxic adenomas, radioiodine therapy not only ameliorates hyperthyroidism but also reduces the size of the adenomas[(2)]**.Objective**: The aim of this retrospective study is to detect the long term effects of this therapy on the thyroid function of patients with toxic adenoma treated in our department. **Patients and methods:** The study population included 60 cases with autonomous toxic adenoma seen at Nuclear Medicine Unit, Cairo University during the period of January 2004 till December 2010 for RAI-131 therapy. All patients were followed for 4 to 6 years (mean 5, 61± 0.53, median 5) following RAI-131 therapy till December 2014. Clinical examination was done for all patients together with laboratory investigations including TSH level, FT3, FT4 measured by a radioimmunoassay (RIA).Thyroid imaging using 99m-Tc pertechnetate was done and thyroid uptake was estimated for all cases with normal reference range (0.5-4%). Neck U/S for detection of nodule size was also done. RAI dose were given us infixed dose according to nodule size (20-29 mCi).Follow up was done through clinical and laboratory evaluation guided by FT3, FT4, and TSH levels 3, 6 months after treatment then every year to exclude any possible complications. **Results:** ^{131}I therapeutic dose was given to all patients. The studied population was divided into two groups: **Group (1):** 12 patients (20%) with moderate sized nodule received 20 mCi of I-131. **Group (2):** 48 patients (80%) with large sized nodule received 25-29 (mCi). No differences were observed between patients who became hypothyroid and those who became euthyroid after ^{131}I treatment of toxic adenoma, as regards age at the time of treatment, pre ^{131}I medical treatment, 99m-Tc pertechnetate thyroid uptake, size of the adenoma (smaller or larger than 3 cm) or pre ^{131}I TSH levels.. Normal level of TSH is seen in 52 patients (86.7%) in their 1st follow up

visit 6 months after treatment with euthyroid state, while 8 patients (13.3%) had hypothyroidism with TSH level (>5 mIu/L) within 7.82 ±0.58 months. Among the 40 patients (66.6%) had nodules with complete suppression to the rest of thyroid tissue, no patients turned hypothyroid, whereas in the 20 patients (33.6%) who had partial suppression to the rest of thyroid tissue, 8 patients turned hypothyroid, 5 of them received 20 mCi, while the other 3 patients received 25-29 (mCi).Persistence or recurrence thyrotoxicosis was not observed in the studied population. **Conclusion**, Treatment of toxic adenoma with ^{131}I in the dose of 20-29 mCi is a well-tolerated therapy, leading to rapid relief of hyperthyroid symptoms. Hypothyroidism is a late side effect of RAI that needs life-long treatment and regular follow-up once or twice a year; it developed within the first year after ^{131}I administration in 13.3% of the patients, specially those patients with partial suppression.

Keywords; Toxic adenoma, 131I treatment, hypothyroidism

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INTRODUCTION:

Solitary hyper functioning thyroid adenomas are lesions tumors characterized by their capacity to grow and produce thyroxin (T4) and triiodothyronine (T3) autonomously, i.e. in the absence of TSH stimulation[(3)]**.** Toxic adenoma cause autonomous, unregulated synthesis of thyroid hormone. In some cases, the cause is a mutation in the thyrotropin receptor gene, which results in constitutive activation. In rare cases, toxic adenoma may have spontaneous infarction of a toxic adenoma[(4)]**.**The rate of development of toxic symptoms in patients with hyper functioning adenomas who are euthyroid is seen in 4% per year and depends on the size of the adenoma, iodine intake and age of the patient[(3)]**.**Toxic autonomous nodules are rarely malignant and they require radionuclide scan for assessment[(5)]**.**Serum TSH measurement has the highest sensitivity and specificity in the evaluation of suspected toxicity. However, diagnostic accuracy improves when both a serum TSH and free thyroxin (FT4) are assessed at the time of the initial evaluation which have an inverse log-linear relationship (suppressed TSH with elevated FT4 level) therefore, small changes in free T4 result in large changes in serum TSH concentrations[(6)]**.**Thyroid scintigraphy (with ^{123}I or ^{99m}Tc) depicts a region of increased radionuclide uptake as compared to the normal extra nodular thyroid tissue. The diagnosis of toxic adenoma is established in the

presence of a "hot" thyroid nodule along with complete or partial suppression of the remaining thyroid tissue on scintigraphy, in combination with biochemical evidence of hyperthyroidism[7]. Thyroid ultrasound (US) is the most sensitive method to detect thyroid nodules which may be malignant and influence choice of the treatment[8]. It does not generally contribute to the differential diagnosis of hyperthyroidism, however when RAI is contraindicated, such as during pregnancy or breast feeding, (US) showing increased color Doppler flow which may be helpful in confirming a diagnosis of thyroid hyperactivity[9]. Radioactive iodine (RAI) therapy is preferred in the treatment of toxic autonomous adenomas because of its effectiveness, noninvasiveness, and low cost[1]. Among patients with toxic adenomas, radioiodine therapy not only ameliorates hyperthyroidism but also reduces the size of the adenomas [2].A variety of methods have been used to select the amount of administered activity. These include the calculated dose aiming to deliver a specific dose to the thyroid based on gland size which was determined by calculation of thyroid volume using radionuclide scanning or ultrasound, maximal uptake and effective half-life of iodine of the thyroid [10].Empiric fixed doses of 131RAI are frequently determined by the quantity that would not require hospitalization of the patient on the basis of local and national regulations. The doses range from 370 MBq to 1.1 GBq (10–30 mCi)[10]. (RAI) treatment avoids surgery but requires radiation safety education and planning ***(5).***Follow-up examination at 6 months intervals is advised for patients after the completion of radioactive iodine therapy. These check-ups should be continued until patients return to their euthyroid state and their condition stabilizes[11].Hypothyroidism is rare complication following treatment of autonomous adenoma with radionuclide in view of intake of radionuclide by nodule, while suppressed thyroid tissue will recover with return of gland to euthyroid state[12].The main argument against the use of ^{131}I versus the surgical approach in the treatment of toxic adenoma is rare possible coexistence of thyroid cancer[13].

PATIENTS AND METHODS:

Case selection: Autonomous toxic adenoma was defined as one which demonstrated uptake with partial or complete suppression in the surrounding thyroid tissue in a thyroid scan in individual with clinical hyperthyroidism [14].

This retrospective study included 60 cases with autonomous toxic adenoma seen at Nuclear Medicine Unit, Cairo University during the period of January 2004 till December 2010 for RAI-131 therapy. All patients were followed for 4 to 6 years after RAI-131 therapy.

Inclusion criteria: This study population included 60 patients with autonomous toxic adenoma more than 18 years old with different sex.

Exclusion criteria: All patients with other causes of hyperthyroidism, patients with non-toxic autonomous adenoma, children less than 18 years, any pregnant or lactating patients

All patients were subjected to full history taking include in gage, sex, symptoms, duration of illness, history of anti-thyroid medications, and history of any thyroid surgery. Medical treatment was given in 43/60 patients using Carbemazol with median dose of 30 mg/day for a median period of 12 months. All of them stopped medical treatment several months before RAI dose except for 10 patients where medical treatment stopped 4 days before radio iodine therapy**.** No patients had previous surgery.

Clinical examination for gland size, consistency, nodularity and exclude other neck swellings.

Laboratory investigations including TSH level, FT3, FT4.with normal reference ranges as follows: TSH: 0.5- 5 mIU/L, T3: 60- 181 ng/mL, T4: 5.5- 12.3 ng/ml. They were measured by a radioimmunoassay (RIA)**.**

Thyroid imaging using 99m-Tc pertechnetate: 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 was done using computer system based on images of the gland and syringe counts before and after tracer injection. Thyroid uptake with Tc 99m was estimated for all patients with normal reference range = (0.5-4%). Qualitative evaluation for size of the gland, presence of nodules and radioactivity distribution in nodules and presence or absence of retrosternal extension was done.

Neck U/S for detection of gland size, presence of nodules, detection of the nodules size, nature of nodule either hyper echoic or mixed echo pattern.

Treatment: RAI doses were given using fixed dose according to nodule size:

Group 1 (12 patients): Moderate sized nodule (less than 3 cm) receiving 20 mCi of I-131.

Group 2 (48 patients): Large sized nodule (> 3 cm and less than 5 cm) receiving 25-29 mCi of I-131.

Follow up and Evaluation of Therapeutic Efficacy was done through clinical and laboratory evaluation ranged from 4 to 6 years (mean 5, 61± 0.53, median 5) guided by FT3, FT4, and TSH levels every 6 months for one year after treatment then every year. Successful treatment was considered when the patient turned euthyroid or hypothyroid after RAI therapy. The patients were classified according to the outcome in to patients with: a).

Euthyroidism*:* 52 patients (86.7%) Absence of signs or symptoms of hyperthyroidism with normal TSH value.)

Hypothyroidism*:* 8 patients (13.3%) was defined as presence of symptoms or signs of hypothyroidism together with elevated TSH value (> 5mIU/L).

No evidence of recurrent hyperthyroid following ^{131}Itreatment was recorded.

Statistical methods: 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 retrospective study included 60 patients, 50 (83.3%) females and 10males (16.7%) referred for RAI therapy for Autonomous toxic adenoma in Nuclear Medicine Unit, Cairo University during the period of January 2004 to December 2010.Twenty eight patients (46.7%) their age ranged from 18-50, years while the remaining 32 patients (53.3%) were > 50 years their mean age was 52.7 years. As regards symptoms, neck swelling was the commonest symptom recorded in 48 patients in the studied group (80%), followed by palpitation in 42 patients (70%), weight loss in 16 patients (26.7%).

Thyroid scan showed 56 patients (93.3%) with homogenous tracer uptake in the autonomous adenoma while, 4 patients (6.7%) had heterogeneous uptake with central Photopenia denoting central degeneration. In 40 patients (66.6%) the nodule caused complete suppression to the rest of thyroid tissue, while 20 patients (33.6%) had partial suppression.

Thyroid uptake calculated from ^{99}m-Tc pertechnetate thyroid scan with normal range of thyroid uptake (0.5% - 4%). In the studied group thyroid uptake ranged from 3 to 15.6% and the patients were divided into 2 groups:

Group (1): 38 patients (63.3%) with autonomous toxic adenoma had normal thyroid uptake,

Group (2): 22 patients (36.7%) with autonomous toxic adenoma had high thyroid uptake.

Maximum TSH suppression of 0.01mIU/L was seen in 34 patients (56.6%), 10 patients had TSH level of 0.02mIU/L and 16 patients had TSH ranging (0.03-0.05 mIU/L). Thyroid ultrasound was done for all patients and it divided patients according to maximum diameter of thyroid nodules into 48 patients (80%) with nodules ≥3cm diameter and less than 5 cm, (large sized nodules), and 12 patients (20%) with nodules <3cm and more than 1.5 cm diameter (moderate sized nodules).

According to RA^{131}I therapeutic dose given to the patients, the studied population was divided into two groups:

Group (1):12 patients (20%) with moderate sized nodules received 20 mCi.

Group (2): 48 patients (80%) with large sized nodules received 25-29 mCi. (Table 1).

Table (1): Patients Characteristic of 60 patients with autonomous nodule.

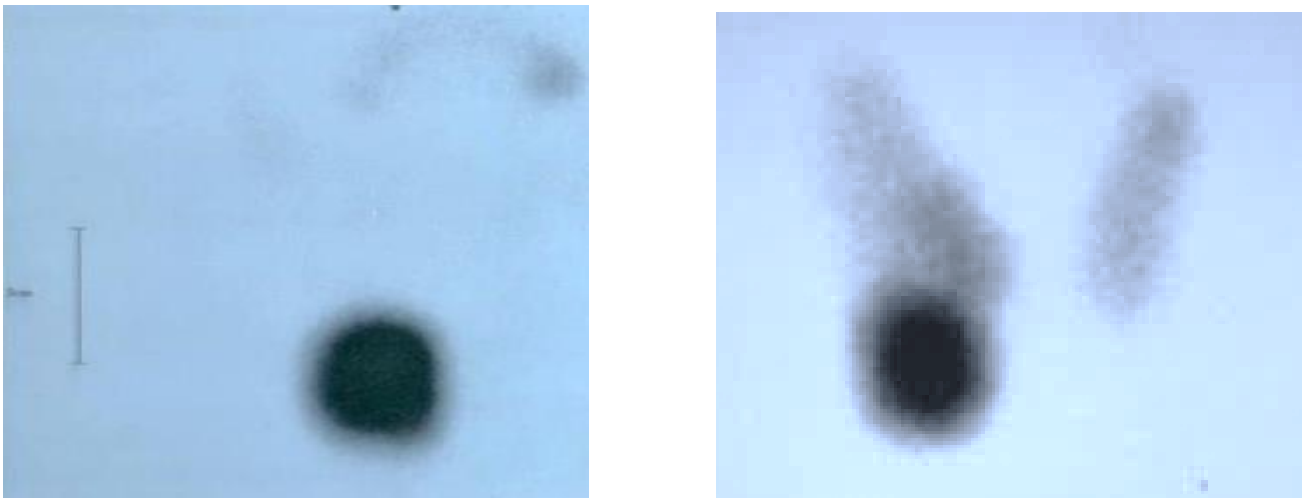
Variables		**Number**	**%**
sex	Male	10	16.7%
	Female	50	83.3%
Age	18-50	28	46.7%
	>50	32	53.3%
U/S (size of nodule)	**Moderate** (Received 20 mCi	12	20%
	Large (Received 25-29 mCi 131I)	48	80%
Thyroid Scan:			
Distribution of activity	Homogenous	56	93.3%
	Heterogeneous	4	6.7%
Suppression of rest of gland	Complete	40	66.6%
	Partial	20	33.3%

Follow up was done for the studied group of patients with autonomous toxic adenoma who had taken ablative dose of radioactive iodine therapy for 4 to 8 years (mean 5, 61± 0.53, median 5) guided by FT3, FT4, and TSH levels 6 months after treatment in the first year then every year till patient becomes euthyroid or hypothyroid. Normal level of TSH is seen in 52 patients (86.7%) in their 1st follow up after 6 months, while 8 patients (13.3%) had hypothyroidism with TSH level (>5 mIu/L) within 7.82 ±0.58 months(Table2).

Table (2): Outcome of 60 Patients with Autonomous Toxic Adenoma Treated with RA ^{131}I.

variables	number	Percent %
Euthyroid outcome	52	86.7%
Hypothyroid outcome	8	13.3 %
total	60	100 %

No differences were observed between patients who became hypothyroid and those who became euthyroid after 1-31I treatment of toxic adenoma, as regards age at the time of treatment, pre 131I medical treatment, 99m-Tc pertechnetate thyroid uptake, size of the adenoma (smaller or larger than 3 cm). Among the 40 patients (66.6%) in which the nodule caused complete suppression to the rest of thyroid tissue, no one turned hypothyroid, while in the 20 patients (33.6%) who had partial suppression to the rest of thyroid tissue ***(figure.1 a,b).*** 8 patients turned hypothyroid (5 of them received 20 mCi, while the rest 3 patients received 25-29 mCi) . All the 8 patients became hypothyroid within 7.82 ±0.58 months. Persistence or recurrence of hyperthyroidism was not observed in the studied population. None of our patients developed any malignancy during the follow up period.



(a) **(b)**

Figure (1 a): Autonomous toxic adenoma of the RT lobe of thyroid gland with complete suppression of the thyroid gland **(b):** Autonomous toxic adenoma of the RT lobe of thyroid gland with partial suppression of the gland.

DISCUSSION:

The current study included 60 patients with autonomous toxic adenoma, 50 patients (83.3%) were females and 10 patients (13.7%) were males similar date was reported by. **Ioanna,et al** [7]**.** They treated 126 patients with hyperthyroidism due to toxic adenoma, (110 females, 16 males) [7].

The mean age of our patients was 52.7 years, **Harach et al** [15] showed similar date of nearly the same mean age.

Our study showed that all patients with autonomous toxic adenoma had suppressed base line TSH, whereas **Chami,et al**[16] in a study on 368 patients with toxic adenoma stated that serum TSH is an effective tool in the diagnosis of toxic adenoma as some patients may have euthyroid state[16]**.**

In the present study, complete treatment rate of hyperthyroidism was achieved in all 60 patients with autonomous toxic adenoma treated with single ablative dose of 131I (20-29 mCi) with different nodule size with no recurrence of thyrotoxicosis was observed during follow-up period.

Whereas **O'Brien et al**.[11] using 10-19.7mCi 1-31I, reported a 8.7 % recurrence rate of hyperthyroidism in 23 patients with typical toxic adenoma after 1-31I, they also showed higher level of hypothyroidism developed in approximately 35% of the patients within 3 months to 16.3 years post-treatment(17). In another study of 29 patients, using 10-40 mCi, the recurrence rate recurrence rate of hyperthyroidism was 52% and hypothyroidism developed in 17% of the subjects in 10 years and 44% in 20 years of follow-up (18).Also, in the study by Goldstein & Hart (19), hypothyroidism occurred in 36% of the 23 patients followed for 8.5 years and treated with a dose of 23±10 mCi. The lower treatment rate and higher incidence of post treatment hypothyroidism in the above studies as compared to our results might be attributed to the lower dose of 1-31I used and larger period of follow up.

In the current study among the 40 patients (66.6%) in which the nodule caused complete suppression to the rest of thyroid tissue, no one turned hypothyroid, while in the 20 patients (33.6%) who had partial suppression to the rest of thyroid tissue, 8 patients turned hypothyroid. This finding can be explained by the protective effect of the functional suppression of the extra nodular thyroid tissue by the hyper-functioning toxic adenoma leading to a lower iodine uptake of the normal thyroid cells at the time of the 1-31I administration, while in case of partial suppression, some 131I uptake by the partially suppressed thyroid tissue occurred as evidence in accordance with other studies [20].

Post treatment hypothyroidism in our patients did not correlate with the adenoma size, patient's age or 131-I dose. None of our

patients developed any malignancy during the follow-up period, in agreement with reports of no increased risk for thyroid malignancy(21), other cancers[22], and leukemia[23] post 131I treatment with very low risk (»1.5 %), although rates as high as 2.5-5.4% have been reported in some studies[23,24].

In the contrary, surgery in the form of lobectomy can be another modality for treatment of toxic adenoma, offers only partial protection due to the well documented multi-focality, especially in papillary carcinoma where microscopic foci of cancer are detected in the opposite lobe in 30-82% of patients[25]. However, no reported patients performed surgery in the present study.

In conclusion, our findings suggest that treatment of toxic adenoma with ^{131}I in the dose of 20-29mCi is a well-tolerated therapy, leading to rapid relief of hyperthyroid symptoms. Hypothyroidism is a late side effect of RAI is uncommon. However it's more likely present in patients with partial suppression of the rest of thyroid gland. So regular follow-up once or twice a year is needed as the replacement therapy with thyroxin is easy, safe and cost-free. In addition, the observation that hypothyroidism in all our patients developed within one year post treatment is of major importance. Since our follow-up is 4-8 years, we suggest that if hypothyroidism does not develop within the first year, the likelihood of developing it later is very small, so that follow- up visits should be less frequent after the first year.

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