Am J Nucl Med Mol Imaging 2020;10(5):235-242
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0112546

Original Article

Effectiveness of radioactive iodine (^{131}I) in the treatment of Graves' disease: single center experience in Assiut University hospital

Nsreen RA Mohamadien, Mohamed HM Sayed

Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Assiut University, Egypt

Received April 14, 2020; Accepted September 14, 2020; Epub October 15, 2020; Published October 30, 2020

Abstract: To evaluate the effectiveness of radioactive iodine (^{131}I) therapy in patients with Graves' disease (GD) in Assiut University Hospital. We retrospectively evaluated two hundred and seven patients with GD, after their therapy with ^{131}I. Before therapy all the included patients underwent neck ultrasound, hormonal assay and ^{99m}Technetium-pertechntate (^{99m}Tc) thyroid scintigraphy to evaluate percentage uptake of the thyroid gland, after therapy all patients followed up clinically and laboratory every 3 months for at least one year to detect outcome; where euthyroid or hypothyroid status denotes successful therapy. Successful outcome obtained in 165/207 patients representing 79.7% of the study population while in the remaining 42 (20.3%) patients a second dose was required. In Univariate analysis only dose of ^{131}I and previous thyroid surgery are the important factors (*P* value = 0.003 and 0.001 respectively). We concluded that ^{131}I therapy is highly effective and cost-effective method for treatment of GD, higher doses are associated with higher success rate.

Keywords: Graves' disease, radioactive iodine (^{131}I) therapy

Introduction

Graves' disease (GD) is an autoimmune thyroid disease with hyperthyroidism is the main clinical feature [1, 2]. It is due to the excess production of thyroid hormones by follicular cells, as a result of stimulation by autoantibodies against the thyroid stimulating hormone (TSH) receptor [3].

Both antithyroid drugs (ATDs) and radioactive iodine (^{131}I) therapy are useful options for treatment of hyperthyroidism while surgery is preferred in selected patients with nodular goiter or recurrent GD, in those with a suspicion of malignancy, and when there is a severe compression of surrounding structures or in those with severe adverse effects to ATDs [4].

GD is usually managed initially with the ATDs, however remission occurs in only 20-25% of patients [5]. Relapse usually occurs within the first 3 to 6 months after stoppage of medications, also potential adverse effects may occurs with ATDs such as agranulocytosis and hepatotoxicity [6].

As postulated in American Thyroid Association (ATA) guidelines 2016, the goal of ^{131}I therapy in GD is to control hyperthyroidism by rendering the patient hypothyroid; this treatment is very effective, provided that a sufficient radiation dose is delivered to the thyroid. This outcome can be achieved equally by either administering a fixed activity or by calculating the activity based on the size of the thyroid gland and its ability to trap ^{131}I [7].

The aim of this retrospective study is to evaluate effectiveness of using a fixed dose range of ^{131}I in the therapy of patients with GD.

Patients and methods

Patients

Two hundred-seven patients with documented GD were enrolled in this retrospective study (78 male 37.7% and 129 female 62.3%); age range

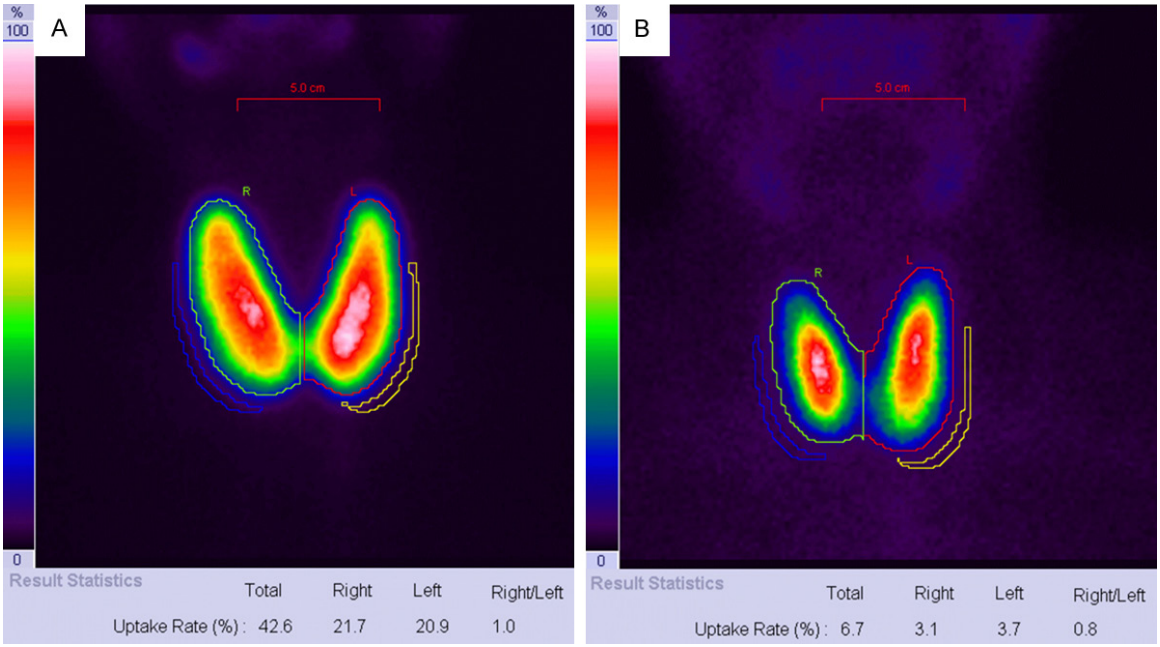

Figure 1. Thyroid uptake, Patient's first thyroid scan (A) showed diffuse goiter and a 42.6% ^{99m}Tc-pertechnetate uptake. This was followed by administration of a 555 MBq (15 mCi) of ^{131}I. Subsequent follow up showed persistent suppression of TSH and elevation of FT3 and FT4, and ATDs was reintroduced. 6 months after ^{131}I therapy, Patient's second thyroid scan (B) showed a 6.7% ^{99m}Tc-pertechnetate uptake. Consequently, a second dose of 370 MBq (10 mCi) ^{131}I was administrated. Three months later, laboratory workup showed overt hypothyroidism (TSH: 75 uIU/mL, FT3: 1.04 pg/mL, and FT4: 0.35 ng/dL), and levothyroxine replacement therapy was initiated.

(12-70 years) patients were referred to Nuclear Medicine Unit, Assiut University hospital to receive therapeutic dose of ^{131}I. The study protocol was approved by the Medical Ethics Committee of faculty of medicine-Assiut University. Patients with multinodular goiter and large goiter with retrosternal extension were excluded.

Patients preparation

The procedure and precautions were explained to all patients; including keeping on a low-iodine diet and avoidance of iodide-containing medications for 7-14 days before therapy. Exclusion of performing water soluble iodinated contrast investigations within the previous 2 months had been confirmed. Pregnancy and breast feeding were excluded, and contraception was confirmed for all female patients in the child bearing period. ATDs should be discontinued at least 2-3 days prior to ^{131}I therapy.

Laboratory investigations including TSH, Free triiodothyronine (FT3), free thyroxin (FT4) levels with normal reference ranges as follow: TSH: 0.5-4.5 uIU/mL, FT3: 2.3-4.2 pg/mL, FT4: 0.89-1.76 ng/dL. Neck ultrasound was done to evaluate glandular size and to detect the presence of nodules. Thyroid scan with ^{99m}Technetium-pertechnetate (^{99m}Tc) was done for all patients to calculate the percentage thyroid uptake and exclude the presence of cold nodules (**Figure 1**).

All the patients signed an informed consent prior to ^{131}I administration in which the probable side effects and radiation protection measures that should be adopted are described in details.

To avoid transient exacerbation of hyperthyroidism after ^{131}I therapy; B-adrenergic blockade and ATDs were prescribed (3-7 days after ^{131}I administration) especially in patients who were at increased risk for complications due to worsening of hyperthyroidism (i.e., elderly patients and patients with comorbidities).

Patients with Graves' ophthalmopathy (GO) receive their ^{131}I dose under cover of prophylactic prednisolone (0.5 mg/kg) therapy for about 6 weeks.

Table 1. Characteristics of 207 hyperthyroid patients treated with ^{131}I

Patients characteristics	Number of cases	Percentage/Mean ± SD
Gender		
Male	78	(37.7%)
Female	129	(62.3%)
Age: (years)	207	38.79 ± 11.99
Family History		
Present	30	(14.5%)
Absent	177	(85.5%)
Medical treatment		
Yes	198	(95.7%)
No	9	(4.3%)
GO*		
Present	15	(7.2%)
Absent	192	(92.8%)
Previous surgery		
Present	40	(19.3%)
Absent	167	(80.7%)
Baseline Thyroid uptake (%)	207	18.6 ± 11.2%
Dose of ^{131}I (mean ± SD)	207	488.4 ± 129.5 MBq (13.2 ± 3.5 mCi)

*GO: Graves' ophthalmopathy.

^{131}I administration

Fixed dose of ^{131}I (as Sodium iodide ^{131}I in capsule or liquid form) [ranges from 296-555 MBq (8-15 mCi) for primary cases and 740 MBq (20 mCi) for recurrent cases after surgery] were given to all patients, with 12 months follow up guided by FT3, FT4, and TSH levels every 3 months post-therapy. Successful treatment was considered when the patient became euthyroid or hypothyroid. Euthyroid state was defined as within the normal range serum level of TSH (0.5-4.5 uIU/mL). Hypothyroidism was defined as increased serum level of TSH more than 4.5 uIU/mL.

Statistical analysis

Data was analyzed using SPSS software package v.21.0 software (IBM Corp., Armonk, NY). Qualitative data were expressed as frequencies and percentages; whereas quantitative data were summarized and expressed as mean ± SD and median (range). The 95% confidence interval was reported whenever possible. In all analyses a two-tailed *p*-value <0.05 were considered significant. Univariate and multivariate analysis conducted to predicts significant influencing factors.

Results

207 patients with GD were enrolled in this study (78 male 37.7% and 129 female 62.3%) (**Table 1**). Age ranges from 12-70 (mean 38.79 ± 11.99) years. Family history of thyroid disease were present in 30/207 (14.5%) patients. As regard medical treatment, 198/207 (95.7%) patients received medical treatment with a mean duration of 13.5 ± 12.1 months, while the remaining 9/207 (4.3%) patients did not receive any medical treatment.

GO was present in 15/207 (7.2%) patients. History of thyroid surgery was present in 40/207 (19.3%).

Mean baseline TSH, FT3 and FT4 were; 0.02 ± 0.04 uIU/mL, 11.1 ± 11 pg/mL and 8.4 ± 6.1 ng/dL respectively. Mean baseline thyroid uptake values were 18.6 ± 11.2%. Dose range of ^{131}I was 296-740 MBq (8-20 mCi) with mean 488.4 ± 129.5 MBq (13.2 ± 3.5 mCi).

Overall successful outcome obtained in 165/207 (79.7%) patients while failure of treatment was observed in 42/207 (20.3%) who required a second dose.

During the first follow up after 3 months 117/207 (56.5%) patients became hypothyroid and started replacement therapy with levothyroxine, 24/207 (11.5%) patients became euthyroid and 66/207 (31.9%) patient were still toxic.

By six months; 45/207 (21.7%) patients still toxic, 117 (56.5%) hypothyroid and 45 (21.7%) patient became euthyroid.

By 9 months 42 (20.3%) patient still toxic and required a second dose of ^{131}I, 48 (23.2%) were euthyroid and (56.5%) 117 on replacement therapy (**Figures 2**, **3**).

All patients who received a second dose of ^{131}I, achieved successful outcome three months after ^{131}I administration.

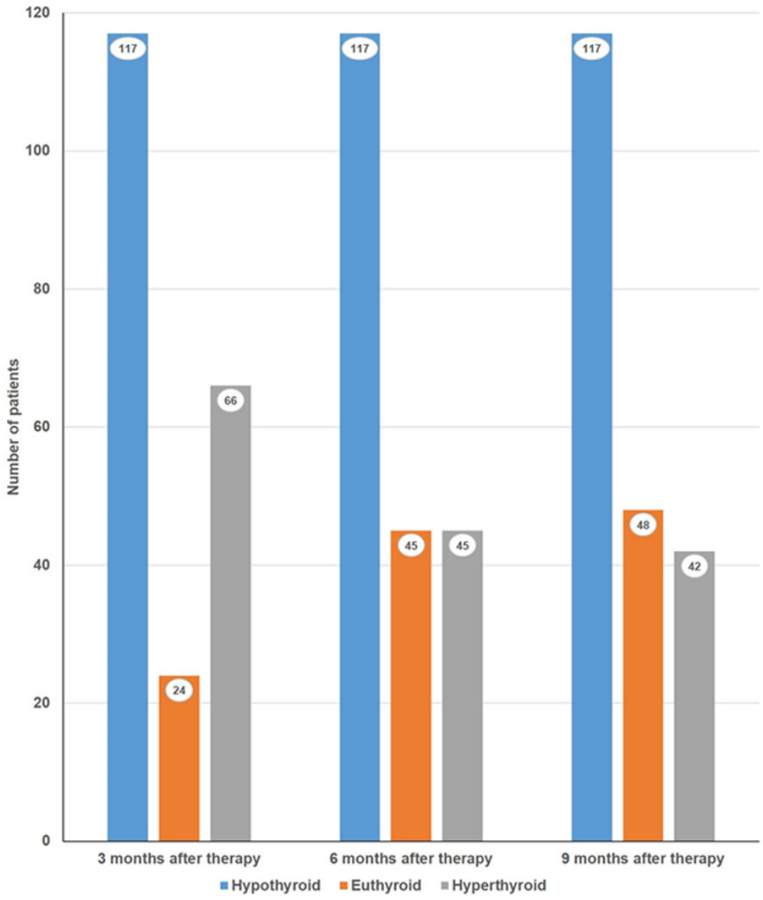

Figure 2. Outcome of ^{131}I treatment in 207 hyperthryoid patients.

Univariate analysis

To analyze the factors associated with successful outcome, we conducted univariate analysis of all baseline variables and only history of surgery and the dose of ^{131}I were statistically significant (*P* value =0.001 and 0.02 respectively) as illustrated in **Table 2**.

Multivariate analysis

We constructed a multivariate logistic regression model to screen the significant variables from all the related factors. Backward Stepwise (Conditional) method (P=0.05) was used to screen the independent variables. The resulting model was calculated as follows:

$z = 1.012 + 2.534 \times \text{surgery} - 0.039 \times FT3 + 0.07 \times T4$.

$P = 1/1 + e^{-z}$ Where p is the probability of success.

Factors affecting successful outcome included surgical history [odds ratio (OR) = 12.599, 95% Confidence Interval (CI): (1.669, 95.089)] and baseline FT3 [OR = 1.040, 95% CI (0.926, 0.999)], **Table 3**.

Discussion

GD is an autoimmune thyroid disease with hyperthyroidism is the main clinical feature. The prevalence of GD is 0.5% of the population and is the underlying etiology for 50-80% of cases of hyperthyroidism [1, 8]. The management guidelines of ATA and American Association of Clinical Endocrinologists for GD recommend any of the following modalities: ^{131}I therapy, ATDs, or thyroidectomy [7].

According to the 2016 ATA guidelines, medical treatment are preferred in patients with mild disease, small goiters, negative or low TSH-receptors antibody titer, contraindication to surgery or ^{131}I, patients with moderate to severe active GO, and patients who need more rapid biochemical disease control [7].

In the early 1900s, ^{131}I was first introduced as a treatment option for hyperthyroid patients other than surgery and evolved quickly as a favored treatment due to higher complication and cost of surgery at that time [6].

The efficacy of ^{131}I has been reported in various studies with a cure rate ranging between 50%-90% after a single therapeutic dose [9].

The success of radioactive iodine therapy for GD depends on several factors including thyroid volume, antibody levels, age and preceding treatments, as well as nutritional iodine intake [10]. Earlier dosimetry-based ^{131}I treatment regimens achieved a high rate of euthyroidism utilizing a targeted thyroid absorbed dose of 60-100 gray (Gy) in areas with moderate iodine deficiency. Whereas, in areas with high nutritional iodine intake, lower doses were utilized

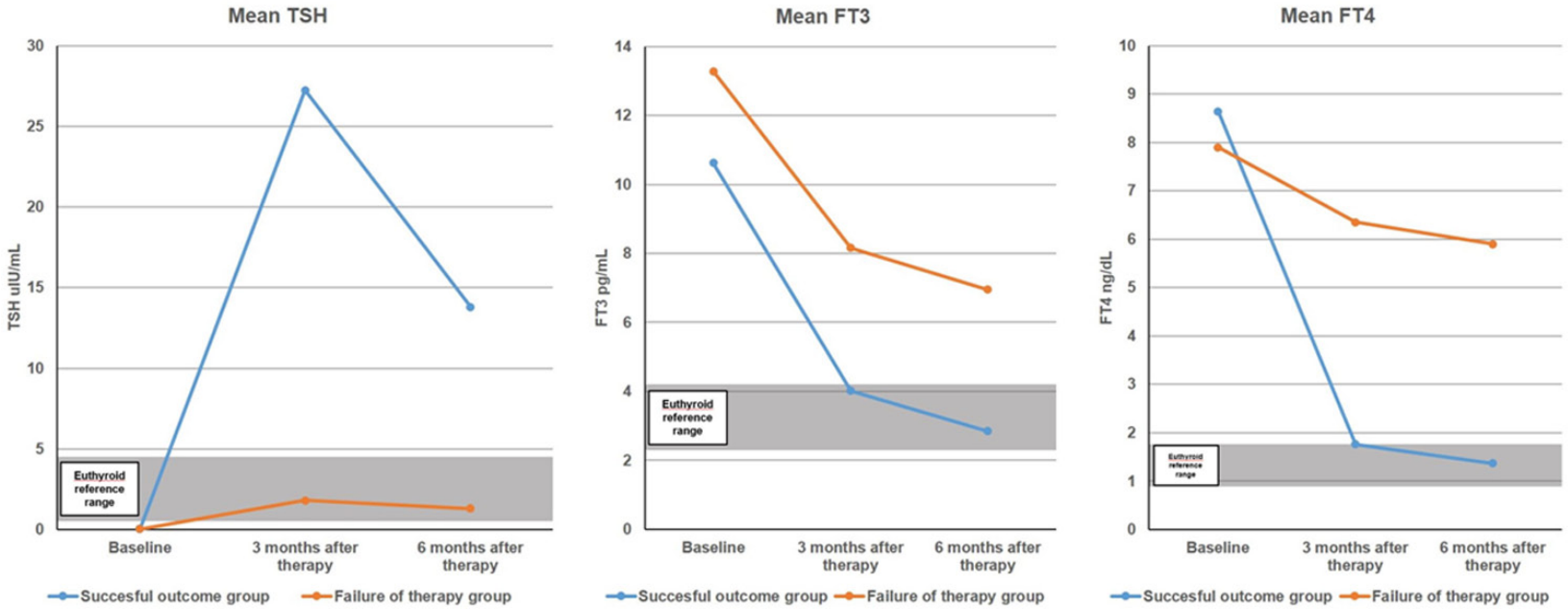

Figure 3. The pattern of changes in serum concentrations of thyroid function studies following ^{131}I therapy. Comparison of the mean serum levels of TSH (left), FT3 (middle), and FT4 (right) at baseline, 3 months and 6 months after ^{131}I therapy between those who successfully treated with a single dose of ^{131}I and those who experienced ^{131}I treatment failure.

Table 2. Analysis of factors associated with successful outcome using univariate logistic regression analysis (n = 207)

Factors	Failure of ^{131}I Treatment N = 42 (%)	Successful ^{131}I Treatment N = 165 (%)	*p*-value
Gender			
Male	21 (50%)	57 (34.54%)	0.076
Female	21 (50%)	108 (65.45%)	
Family history of thyrotoxicosis			
Negative	37 (88.1%)	140 (84.85%)	0.806
Positive	5 (11.9%)	25 (15.15%)	
History of medical treatment			
Negative	0 (0.0%)	9 (5.45%)	0.209
Positive	42 (100%)	156 (94.54%)	
History of surgery			
Negative	41 (97.62%)	126 (76.36%)	0.001
Positive	1 (2.38%)	39 (23.64%)	
GO*			
Absent	39 (92.86%)	153 (92.73%)	0.977
Present	3 (7.14%)	12 (7.27%)	
Patient age (mean ± SD)	38.36 ± 13.37	38.90 ± 11.66	0.795
Baseline TSH (mean ± SD)	0.036 ± 0.061	0.027 ± 0.038	0.241
Baseline FT3 (mean ± SD)	13.28 ± 12.84	10.63 ± 10.58	0.167
Baseline FT4 (mean ± SD)	7.90 ± 5.94	8.64 ± 6.19	0.490
Baseline thyroid uptake (mean ± SD)	21.33 ± 12.57	17.72 ± 11.16	0.070
^{131}I dose in (mean ± SD)	434.4 ± 99.9 MBq (11.74 ± 2.7 mCi)	502.8 ± 136.9 MBq (13.59 ± 3.7 mCi)	0.003

*GO: Graves' ophthalmopathy.

Table 3. Parameter estimation and hypothesis testing of the Logistic model

	B	S.E.	Wald	Df	Sig.	Exp (B)	95% C.I. for EXP (B)	
							Lower	Upper
Surgery	2.534	1.031	6.036	1	0.014	12.599	1.669	95.089
Baseline FT3	0.039	0.019	4.077	1	0.043	1.040	0.926	0.999
Baseline FT4	0.070	0.040	3.060	1	0.080	1.072	0.992	1.160
Constant	1.012	0.300	11.358	1	0.001	2.752		

to achieve comparable results. This difference could be attributed to the higher rate of thyroid autonomy in iodine-deficiency areas [11].

Various ^{131}I treatment strategies have been utilized, such as administering doses as low as 80 MBq, fixed but varied doses, and "formulae based doses" calculated according to the thyroid size and percentage ^{131}I uptake [12].

A recent study utilized the dosimetry-based ^{131}I treatment approach in GD to achieve euthyroidism utilizing a targeted thyroid absorbed dose of 60 Gy. This approach delayed the long-term onset of hypothyroidism in 26% of patients, and resulted in control of the disease in 62% of patients with significantly lower ^{131}I activities than the fixed dose approach [13].

The reported recurrence rates after ^{131}I therapy range from 10-40% of patients, with more severe cases of hyperthyroidism associated with higher failure's rates [14].

The higher rate of relapse and risk for deterioration of thyroid eye disease with such approaches, resulted in the development of "Ablative concepts" where the aim of ^{131}I treatment was to achieve early destruction of antigen and a higher rate of disease control, and accepting

that a significant proportion of patients will require life-long levothyroxine with this approach. In order to achieve this target the ATA recommends administering a dose of 370-555 MBq (10-15 mCi) or 5.5MBq (150 μCi) ^{131}I per gram of thyroid tissue [7]; and the Royal College of Physicians (UK) recommends a fixed activity of 400-600 MBq [16].

On the other hand, the European Association of Nuclear Medicine still recommends only achievement of euthyroidism by administration of a calculated activity of ^{131}I to give an absorbed dose of 150 Gy to the thyroid [4], which is also higher than the recommended doses in earlier studies.

Cheah et al. evaluated 166 patient with GD treated by ^{131}I fixed dose method and concluded that this method is convenient and achieves comparable outcomes to a calculated dose approach [15].

Failure rate in our study was 20.3% which is less than that reported by Schneider, et al., and de Jong et al., (23% and 26% respectively) [14, 16].

The cure rate in our study is higher than that reported by Yang et al., and de Jong et al. (79.7% versus 76% and 74% respectively) [10, 16].

The minor discrepancy between our results and other studies can be attributed to the variability in treatment strategies used, different populations and different risk factors.

In our study, the higher ^{131}I dose and previous history of surgery predicted a favorable response to therapy. Similarly, other studies proved that higher ^{131}I dose not only associated with higher cure rate but also reduced the time needed to achieve cure [9, 17].

The majority of our patients 117 (56.5%) achieved successful outcome 3 months after ^{131}I therapy. Additionally, the forty two patients who treated with a second dose of ^{131}I were cured. Our findings are adherent to the current guidelines that recommend monitoring thyroid functions 4-6 weeks after ^{131}I therapy and advice repeating ^{131}I therapy after 6 months for those with treatment failure [7].

Bartalena et al. demonstrated that steroid coverage reduces the adverse effects of ^{131}I on GO [18]. Fifteen patients of our study population with established GO were treated with prophylactic prednisolone before ^{131}I and none of them developed worsening of GO.

Conclusion

We concluded that ^{131}I is highly effective and cost-effective method for therapy of GD, and higher doses of ^{131}I are associated with higher success rate.

Disclosure of conflict of interest

None.

Address correspondence to: Nsreen RA Mohamadien, Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Assiut University, Egypt. Tel: 00201015089066; E-mail: mkeshk2010@gmail.com

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