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Conclusions: I-131 is very effective therapy for Graves’ disease with cure rate 100% after 4 doses. Higher first dose activity is recommended in the presence of poor prognostic factors. Second dose is not necessary increased in the non responders.
Response rate and factors affecting outcome of fixed dose of RAI131 therapy in Graves` disease: A 10 year Egyptian experience

Maha Abd El-Kareem M.D, Wajeeh Abdulrazak Derwish M.sc and Hosna Mohamed Moustafa M.D

Department of radiotherapy and nuclear medicine (NEMROCK), Nuclear medicine unit, Cairo University.

Abstract

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**Introduction:** Graves` disease (GD) is the most common cause of hyperthyroidism responsible for approximately 50-60% of the cases (1). The most common clinical presentations related to the cardiovascular system. Other disease manifestations include Graves’ ophthalmopathy and myxedema(2). Diagnostic modalities include suppressed serum TSH and an elevated serum FT4, FT3 levels, thyroid scintigraphy either with Tc-99m pertechnetate or radioactive iodine-131 (RAI-131) and ultrasonography (U.S) to detect the presence of an associated nodules (3). Three therapeutic modalities are commonly used today; anti-thyroid drugs (ATDs), RAI-131 and surgical treatment (3). The aim of RAI -131 treatment is to cure the hyperthyroidism by rendering the patient either euthyroid or hypothyroid through destruction of the over-functioning thyroid tissues (4). The use of RAI-131 in treatment of GD is increasing, particularly as a first line treatment (5) as it is easy to administer, relatively inexpensive, reliable, safe and highly effective with a cure rate approaching 100% after one or more dose (6). Different
methods have been used for determining the administered activity, varied from fixed doses to adjusted calculations based on gland size, iodine uptake and turnover (7). The dose calculation method aims to optimize the therapeutic results through administration of radioactive iodine in proportional to the size of the gland, increasing the probability of cure and providing the lowest possible radiation dose to the rest of the body (8). There is little evidence that using a calculated dose has any advantage over a fixed-dose regimen in preventing hypothyroidism or improvement in cure rate (9), but it increases significantly the cost of the therapy owing to increase the procedure complexity (10). Taking in mind that the radioactive iodine therapy is relatively inexpensive, thus the increase in its cost to determine the administered activity must be clearly justified (10). There are some predictive factors associated with RAI-131 success rate. Previous works have shown lower treatment success rates in young male patients, more severe cases of hyperthyroidism (11)(12) , larger goiters (12) (13) and in cases with low or high pretreatment thyroid uptake (12) (14). The influence of pretreatment with anti-thyroid drugs on the efficacy of radioiodine therapy is controversial. Some authors believe that the thyrostatic drugs methimazole (MMI) and propylthiouracil (PTU) have a radioresistance effect and can lead to half-life reduction and accelerate turnover (15) (16) (17), but others have shown an effect confined to PTU only (18).

**Patients and Methods:** We retrospectively evaluated 321 hyperthyroid patients due to GD referred to the nuclear medicine unit, Kasr Al ainy hospital (NEMROK), Cairo University, during the period of January 2000 till January 2010 for RAI-131 therapy as first or as a second treatment modality (following medical or surgical treatment). Our
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received 8 mCi (155 patients) (48.3%) and **Group 2:** received 12 mCi (166 patients) (51.7%), they are the commonly preferred doses in the treatment of GD in our institute. Anti-thyroid drugs, if given before therapy, were withdrawn a week before therapy and for a minimum of 1 week after to avoid any drug influence on the therapeutic effectiveness. Iodine-containing medications were also discontinued several weeks before therapy; in addition, the patients were started on a low-iodine diet for 10 days before therapy, fasted before and for 2 hours after the administration of the dose to achieve higher absorption. Patients were advised to avoid physical contact and transfer of secretions to others for several days after treatment. Regular clinical and laboratory follow up to evaluate therapeutic efficacy was done and the patients were classified according to the outcome in to: **Euthyroidism:** Absence of signs or symptoms of hyperthyroidism or hypothyroidism with normal serum TSH value without levothyroxin therapy. **Resistant to therapy:** persistence of thyrotoxic manifestation and suppressed TSH value or by requirement of repeat administration of RAI-131 therapy within 6 months of the therapy and **Hypothyroidism:** presence of symptoms or signs of hypothyroidism together with elevated TSH value on two occasions four weeks apart, that require permanent treatment with levothyroxine. RAI-131 treatment was considered to be successful if the patient was either euthyroid or hypothyroid.

**Statistical methods:** Data was analyzed using IBM SPSS advanced statistics version 20 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher’s exact test) was used to examine the relation between
qualitative variables. For quantitative data, comparison between two groups was done using Mann-Whitney test (non-parametric t-test). The receiver operator characteristic (ROC) curve was used to identify the best threshold for thyroid uptake to discriminate success and failure of RAI-131 therapy. Multivariate analysis was done using forward stepwise logistic regression method for the significant factors affecting response on univariate analysis. Odds ratio (OR) with 95% confidence interval (CI) were used for risk estimation. P-value < 0.05 was considered significant.

**Results:** Baseline, pre-therapy clinical characteristics and commonly presenting symptoms for the patients are listed in Table 1 and 2. The recorded data documented development of early complications within the 1st 3 months in 31 patients (9.6%), included transient mild increased thyrotoxic manifestations in 21 patients and transient hypothyroidism which occurred for 8 patients, 5 after a high dose and 3 after low dose. Six of the 8 patients developed transient hypothyroidism after 1st dose, while the remaining 2 patients developed it after 2nd dose. Also neck pain developed in 2 patients. There was statistically significant difference in the incidence of early complications between the patients who received 8 mCi and the second group who received 12 mCi, in favor of the latter group (p = 0.024), whereas as there was no statistically significant difference between age, gender, presence of exopthaloms, size of thyroid gland and thyroid uptake and early complications either between the two groups as shown in the table (3) or in each group separately (not included).

Exopthalmos was increased in 9 patients (9.6%) after RAI-131 therapy and remained stationary in rest. Three new cases (1.3%) developed exophthalmos from the remaining
227 patients and they were among the 170 patients who had permanent hypothyroidism (1.7%). No relation was found between the presence of exophthalmos and development of early complications as shown in tables 3.

The success rate to the first given dose was 59.8% with development of euthyroidism in 56 patients (17.4%) and hypothyroidism in 136 patients (42.4%). There was statistically significant difference in the successes rate between the patients who received 8 mCi (49%) and 12 mCi (69.9%) \( P < 0.001 \). Of the 76 patients in whom therapy was successful in group1, 25 (16.1%) developed euthyroidism and 51 (32.9%) developed hypothyroidism and at a median period of 6 months (range: 3 – 18 months) and among the 116 responding patients in the second group, euthyroidism was achieved in 37 patients (22.3%) and hypothyroidism in 79 patients (47.6%) with a median cure time 4 months (range: 2 – 18 months).

There was no statistically significant association between age, presence of ophthalmopathy and previous medical treatment & its duration and outcome, whereas there was statistically significant difference regarding gender, size of thyroid gland, Tc99m pertechnetate thyroid uptake and previous surgical treatment as demonstrated in table 4. We did not find any relationship between the previous use of methimazole & its duration and the outcome of patients either in the whole study population or G1 and G2 separately (tables 4 and 5 A&B).

Thyroid uptake was analyzed using ROC curve to discriminate the group of patients who achieved success with treatment from the group that remained hyperthyroid and we found a thyroid uptake threshold of 20.9 % with a sensitivity of 76.1 % and specificity of 65.4
% for treatment success (Fig. 1). We were unable to find an adequate cutoff value for base line TSH level.

Multiple logistic regression analysis demonstrated that age, gender and previous medical treatment were not significantly associated with the outcome, whereas Tc99m pertechnetate thyroid uptake > 20.9% (OR= 4.023), moderate and markedly enlarged thyroid gland (OR= 3.309) and the low given dose (OR= 2.601) were identified as significant prognostic risk factors for treatment failure and previous thyroidectomy for treatment success (OR= 3.071) (odds ratio; 95% confidence interval = 2.218 -7.297, 1.707 - 6.414, 1.403 - 4.822 and 1.109 - 8.502 respectively).

**Response to the second dose:** A second dose was given to the 129 non responded patients after a mean time of 6.77 months (minimum 3 months and maximum 12 months). Of these 63 patients received 8 mCi and 66 received 12 mCi. The overall response rate to the second therapy dose significantly increased compared to the first one by 27.8 % with development of euthyroidism in 56 patients (17.4%) and hypothyroidism in 136 patients (42.4%). There was no statistically significant difference in the response rate between the patients who received 8 mCi and who received 12 mCi (P value = 0.921), also there was no statistically significant difference in the response rate in relation to size of thyroid gland, Tc99m pertechnetate thyroid uptake, previous surgical treatment, age and gender (p values 0.265, 0.665, 0.242, 0.209 and 0.923 respectively) as shown in table 6.

Fifty two patients from the 79 non responded in the first group received second dose of 8 mCi while the remaining 27 patients received 12 mCi. There was no statistically
significant difference in the response rate between the patients received 8 mCi (86%) and 12 mCi (92.6 %) with $P$ value $= 0.422$. No statistically significant difference in the response rate in relation to size of thyroid gland, Tc-99m pertechnetate thyroid uptake and previous surgical treatment was found (p values $= 0.436$, 0.225 and 0.361 respectively). Eleven from the 50 non responded patients in the second group were received second dose 8 mCi while the other 39 patients received 12 mCi. There was no statistically significant difference in the response rate between the patients received 8 mCi (90.9 %) and 12 mCi (384.6 %) with $P$ value $= 0.595$ and no statistically significant difference in the response rate in relation to size of thyroid gland, Tc99m pertechnetate thyroid uptake and previous surgical treatment (p values $= 0.418$, 0.117 and 0.471 respectively). Thirteen patients from the remaining 16 non responders to the second dose responded to the 3rd RAI-131 dose with development of euthyroidism in 7 patients (43.8 %) and hypothyroidism in the remaining 6 patients (37.5%). The 4th dose controlled the remaining 3 patients with development of hypothyroidism in 2 patients and euthyroidism in the third.

The median dose for controlling GD was 12 mCi (minimum 8 mCi which controlled 23.7% of the patients and maximum 47 mCi), the doses of 12 mCi, 16 mCi, 20 mCi, 24 mCi, 28 mCi, 32 mCi, 36 mCi, 43 mCi and 47 mCi increase the overall control rate to 59.8 %, 74.1%, 85%, 96%, 96.9%, 97.8%, 99.4%, 99.7% and 100% respectively as shown in table 7. The mean dose number for controlling the hyperthyroidism was $1.46 \pm 0.62$ (range 1- 4). The first dose controlled 59.8% of the patients, this percent increased to 95% after the second dose, 99.1% following the third one and 100% after the fourth dose.
as shown in table 8.

**Discussion:** About 80% of experts from Europe preferred to start treatment with ATDs in patients over 21 years and 70% of those in the United States RAI is the initial treatment modality of choice (21). In Egypt the ATDs represent, for most endocrinologists, the initial choice of treatment. This trend was reflected in the present study, where only 22.4% of the patients underwent RAI as initial treatment modality, while 77.6% patients were previously treated with ATDs.

The influence of ATDs on the outcome of RAI treatment has received attention. Some studies have suggested that ATD treatment before or after RAI may provide a radioprotective effect for the thyroid with significantly shortened the biological half-life of RAI result in reduction of the absorbed dose and increased failure rate of single-dose RAI treatment (16-17) (22). Thionamide withdrawal was among the predictive factors for treatment success in a 10-mCi fixed-dose approach (23). More over Alexander et al. treated 261 Graves’ patients with a mean dose of 14.6 mCi of RAI demonstrated high risk of treatment failure in patients pretreated with anti-thyroid medications for greater than 4 months(12). Other studies stated that this effect confined to the use of propylthiouracil only (18). In contrast Braga et al. (24) and Andrade et al. (25) demonstrated that methimazole pretreatment has no effect on the final treatment result, including the time required for cure or the 1-year success rate of RAI therapy. Thientunyakit T et al. (26) showed that duration of anti-thyroid drug given prior to radioiodine therapy seemed not related to the treatment outcome. Moura-Neto also found that no statistically significant association between thyroid function outcome to a fixed,
15 mCi approach for treatment of Graves’ hyperthyroidism and drug used (methimazole or propylthiouracil; maintenance or withdrawal of thionamides prior to therapy (27). Our results were in agreement with the later ones, where we don’t find statistical significant difference between pre-iodine medical treatment or its duration and the outcome to RAI-131 therapy.

*Surgery* is no longer recommended as first-line therapy for GD and use in selective cases where RAI is not preferred and ATDs fail to control the disease(3). *Lal et al.* concluded that total thyroidectomy (TT) is much better than Subtotal thyroidectomy (STT) (28). *In the present study*, STT was performed in only 49 patients (15.3%) with recurrent of disease in all of them at a median period of 66 months, confirming the literature data of using it as an alternative option in selected patients.

The size of thyroid gland is an important factor influencing the outcome of therapy; *In our study*, mildly enlarged glands had more controlled rate than moderate or markedly enlarged thyroid gland with higher incidence of hypothyroidism (P = 0.042). This result is in agreement with the other multiple studies which have demonstrated that patients with larger-volume thyroid glands to fail to respond to a single dose of radioiodine (23-27-29-30-31-32).

The impact of thyroid uptake on the RAI outcome has been investigated using either 131I or Tc99m pertechnetate. Alexander et al (12) found that patients who have higher 24-hour thyroid RAI uptake values were at higher risk than others for treatment failure. Kung et al. (32) also identified 4-hour RAI uptake among the variables that could predict early treatment outcome for Graves’ disease. These results were in agreement with other
works demonstrating higher failure rates in patients with higher iodide thyroid uptake values which could reflect faster iodide turnover in thyroid cells thus making the residence time of therapeutic I-131 in the gland shorter (33). The authors suggested that a higher radioactivity of RAI be given to these patients. Using Tc99-m sodium pertechnetate Zantut-Wittmann et al. (23) have reported that in a 10 mCi fixed dose approach the pre-RIT Tc99-m sodium pertechnetate uptake under 12% among the predictive factors for treatment success. In contrast, Moura-Neto et al. stated that no statistically significant association between thyroid function outcome to a fixed 15 mCi approach for treatment of GD and Tc-99m sodium pertechnetate thyroid uptake prior to therapy(27). Tc-99 m pertechnetate uptake is routinely used in our department as a surrogate measure of thyroid uptake because it has been proved to possess a good correlation with iodide 125 uptake (34). Moreover, it is much less expensive, reliable and convenient method allows uptake within 20 minutes after intravenous injection of the radionuclide and the therapeutic dose of RAI can be administered immediately after. We found that Tc-99m pertechnetate thyroid uptake more than 20.9% was among the poor prognostic factors for the response, thus higher dose is recommended. The different RAI doses have different impact on the thyroid gland function, less than half of the patients (49%) in group 1 who received low dose of RAI achieved cure. On the other hand 69.4 % from the second group, who received higher dose of RAI, had achieved cure. This means that higher dose of RAI increase response rate by ~ 20.4 %. Franklyn et al.(35) and Sankar et al.(36) studied the therapeutic outcome of low fixed dose of RAI, the former concluded that persistent hyperthyroidism after 6 months was
present in 55.9% of the patients using small fixed dose of 5 mCi of RAI and the latter recommended increase dose of RAI to achieve response. This agree with Nordyke and Gilbert (29) who analyzed a series of 605 patients treated with RAI to find out the optimal dose to achieve cure and they concluded that cure was directly related to the dose of RAI administered and the optimal dose for curing hyperthyroidism is approximated by starting with 10 mCi and increasing it for unusually large glands or for special patient circumstances.

In the present study, 88% of patients achieved cure after administration of second dose of RAI with no statistically significant difference was found between the success rate and the given dose, only few patients require 3rd or 4th doses. This is in concordant with Sanyal et al. (37) and Franklyn et al. (35) studies that demonstrated high cure rate to the second dose of RAI ( 82.4% and 74.5% respectively) with only few require other doses.

Although it is very rare, McDermott et al.(38) reported thyroid storm in a small number of patients between 1 and 14 days after treatment with RAI. In the present study thyroid storm did not encountered in any patient. Also, Levy et al.(39) in a series of 7000 patients treated with RAI in one centre, none developed this complication. Ponto et al. (40) concluded that RAI therapy for GD is associated with definite increased risk of GO in around 20% of patients (either developing new cases or worsening of preexisting one). However In the present work there was worsening of exophtalmus in 9.6 % of the patients and three new cases were developed (1.3%) among the rest who did not have
prior exophthalmos, they were among the 177 patients who developed permanent hypothyroidism.

Conclusion: Radioiodine is clearly successful in curing hyperthyroidism in GD patients by 100 % after 4 doses; therefore it should be used as a first standard line in treatment. Treatment results using fixed RAI dose are comparable to those studies of patients treated with RAI using the prescribed absorbed dose method. The standard-dose prescription strategy is therefore an efficient, cost-effective and is also convenient to the patient. It may be possible to improve cure rates using a single fixed-dose regimen without increasing the dose in all patients. This might be achieved by the identification of subjects with poor prognostic factors who are unlikely to respond to standard doses and by administering larger doses only to these individuals. A higher fixed (12 mCi) is more effective than lower dose (8 mCi) for treatment of GD leading to better control of the disease following the first dose. Higher response rate are expected in patients who underwent previous surgery, on contrary patients with larger goiters and high thyroid uptake > 20.9% had 3.3 and 4 times less chance of remission. This different impact of different doses on the response rate is applied to the first dose, but not to the second dose where the response rate to the second dose is nearly similar in both low and high dose groups.

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**Figure Legend**

**Figure 1**: ROC curve for Tc 99m pertechnetate thyroid scan uptake according to response to 1st dose.
The reason for choose a higher dose of 12 mCi because the protocol in our institution is to give a maximum dose of 12 mCi in Graves’ disease patients.
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| Names of authors: | ► Maha Abd Elkareem Elsayed- Wajeeh Abdulrazak Derwish and Hosna Mohamed Moustafa |

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Please state briefly how each of the authors contributed to the study, to data analysis and to the writing of your paper. For a person to qualify as an author, their contribution should be sufficient for them to assume responsibility for the study.

► Dr. Wajeeh Abdulrazak, share in collecting the recorded data from thyroid clinic database. Prof Hosna Moustafa, the research was her idea, she supervise the work and review the scientific material. Dr. Maha share in collecting the recorded data, writing the review article.

### 6. STATISTICAL ANALYSIS

Kindly please let me know who performed the statistical analysis of your data.

► Manar Mohamed Moneer, MD. Professor and Head of Biostatistics and Cancer Epidemiology, National Cancer Institute, Cairo university

Other information for the Editor that may be relevant:

► None
Name of person completing this form: Maha Abd Elkareem

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**Patients and Methods:** We retrospectively evaluated 321 hyperthyroid patients due to GD referred to the nuclear medicine unit, Kasr Al ainy hospital (NEMROK), Cairo University, during the period of January 2000 till January 2010 for RAI-131 therapy as first or as a second treatment modality (following medical or surgical treatment). Our
institutional medical ethics committee approved the protocol. The diagnosis of GD was primarily based on clinical (hyperthyroid manifestations and diffusely enlarged thyroid gland) and laboratory data, including high serum free T4 level (FT4; reference Values, RV = 0.9 - 1.8 ng/dL) and low serum thyrotropin levels (TSH; RV = 0.41 - 4.5 µ IU/mL). The patients who had thyrotoxicosis due to toxic multi-nodular goiter (Plummer disease), toxic autonomous adenoma, GD associated with (cold) nodule by (scan) or palpation respectively and patients who not completed the follow up were excluded from the study. Data were retrieved from the thyroid clinic database include: age at diagnosis, gender, symptoms, dose and duration of anti-thyroid drugs, previous surgical treatment, clinical data for the presence of palpable nodules & other neck swellings and the presence or absence of eye signs, TSH level and thyroid scan using Tc-99m pertechnetate that was done 20 min after intravenous injection of 5 mCi of the tracer to evaluate the associated nonfunctioning (cold) nodule and quantitation of thyroid uptake using the methodology previously described by Maisey et al(19) and simplified for routine use. The reference values for Tc-99m pertechnetate uptake range from 0.3 to 4 % (20). Gland size were determined by combining clinical examination (palpation) and thyroid scan and was divided in to either normal size (impalpable), mild (palpably enlarged but not visible) and moderate or markedly enlargement (palpable and visible goiter). In view of our socio-economical circumstances; the simple fixed dose protocol has considerable cost saving advantages, we have adopted this protocol for the treatment of GD in our institution. The patients were divided according to the given RAI-131 dose in to 2 groups: **Group 1:**
received 8 mCi (155 patients) (48.3%) and Group 2: received 12 mCi (166 patients) (51.7%), they are the commonly preferred doses in the treatment of GD in our institute.

Anti-thyroid drugs, if given before therapy, were withdrawn a week before therapy and for a minimum of 1 week after to avoid any drug influence on the therapeutic effectiveness. Iodine-containing medications were also discontinued several weeks before therapy; in addition, the patients were started on a low-iodine diet for 10 days before therapy, fasted before and for 2 hours after the administration of the dose to achieve higher absorption. Patients were advised to avoid physical contact and transfer of secretions to others for several days after treatment. Regular clinical and laboratory follow up to evaluate therapeutic efficacy was done and the patients were classified according to the outcome in to: Euthyroidism: Absence of signs or symptoms of hyperthyroidism or hypothyroidism with normal serum TSH value without levothyroxin therapy. Resistant to therapy: persistence of thyrotoxic manifestation and suppressed TSH value or by requirement of repeat administration of RAI-131 therapy within 6 months of the therapy and Hypothyroidism: presence of symptoms or signs of hypothyroidism together with elevated TSH value on two occasions four weeks apart, that require permanent treatment with levothyroxine. RAI-131 treatment was considered to be successful if the patient was either euthyroid or hypothyroid.

Statistical methods: Data was analyzed using IBM SPSS advanced statistics version 20 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher’s exact test) was used to examine the relation between
qualitative variables. For quantitative data, comparison between two groups was done using Mann-Whitney test (non-parametric t-test). The receiver operator characteristic (ROC) curve was used to identify the best threshold for thyroid uptake to discriminate success and failure of RAI-131 therapy. Multivariate analysis was done using forward stepwise logistic regression method for the significant factors affecting response on univariate analysis. Odds ratio (OR) with 95% confidence interval (CI) were used for risk estimation. P-value < 0.05 was considered significant.

**Results:** Baseline, pre-therapy clinical characteristics and commonly presenting symptoms for the patients are listed in Table 1 and 2. The recorded data documented development of early complications within the 1st 3 months in 31 patients (9.6%), included transient mild increased thyrotoxic manifestations in 21 patients and transient hypothyroidism which occurred for 8 patients, 5 after a high dose and 3 after low dose. Six of the 8 patients developed transient hypothyroidism after 1st dose, while the remaining 2 patients developed it after 2nd dose. Also neck pain developed in 2 patients. There was statistically significant difference in the incidence of early complications between the patients who received 8 mCi and the second group who received 12 mCi, in favor of the latter group (p = 0.024), whereas as there was no statistically significant difference between age, gender, presence of exopthaloms, size of thyroid gland and thyroid uptake and early complications either between the two groups as shown in the table (3) or in each group separately (not included).

Exopthaloms was increased in 9 patients (9.6%) after RAI-131 therapy and remained stationary in rest. Three new cases (1.3%) developed exophthalmos from the remaining
227 patients and they were among the 170 patients who had permanent hypothyroidism (1.7%). No relation was found between the presence of exophthalmos and development of early complications as shown in tables 3.

The success rate to the first given dose was 59.8% with development of euthyroidism in 56 patients (17.4%) and hypothyroidism in 136 patients (42.4%). There was statistically significant difference in the successes rate between the patients who received 8 mCi (49%) and 12 mCi (69.9%) \( P < 0.001 \). Of the 76 patients in whom therapy was successful in group1, 25 (16.1%) developed euthyroidism and 51(32.9 %) developed hypothyroidism and at a median period of 6 months (range: 3 –18 months) and among the 116 responding patients in the second group, euthyroidism was achieved in 37 patients (22.3%) and hypothyroidism in 79 patients (47.6%) with a median cure time 4 months (range: 2 –18 months).

There was no statistically significant association between age, presence of ophthalmopathy and previous medical treatment & its duration and outcome, whereas there was statistically significant difference regarding gender, size of thyroid gland, Tc99m pertechnetate thyroid uptake and previous surgical treatment as demonstrated in table 4. We did not find any relationship between the previous use of methimazole & its duration and the outcome of patients either in the whole study population or G1 and G2 separately (tables 4 and 5 A&B).

Thyroid uptake was analyzed using ROC curve to discriminate the group of patients who achieved success with treatment from the group that remained hyperthyroid and we found a thyroid uptake threshold of 20.9 % with a sensitivity of 76.1 % and specificity of 65.4
% for treatment success (Fig. 1). We were unable to find an adequate cutoff value for base line TSH level.

Multiple logistic regression analysis demonstrated that age, gender and previous medical treatment were not significantly associated with the outcome, whereas Tc99m pertechnetate thyroid uptake > 20.9% (OR= 4.023), moderate and markedly enlarged thyroid gland (OR= 3.309) and the low given dose (OR= 2.601) were identified as significant prognostic risk factors for treatment failure and previous thyroidectomy for treatment success (OR= 3.071) (odds ratio; 95% confidence interval = 2.218 -7.297, 1.707 - 6.414, 1.403 - 4.822 and 1.109 - 8.502 respectively).

**Response to the second dose:** A second dose was given to the 129 non responded patients after a mean time of 6.77 months (minimum 3 months and maximum 12 months). Of these 63 patients received 8 mCi and 66 received 12 mCi. The overall response rate to the second therapy dose significantly increased compared to the first one by 27.8 % with development of euthyroidism in 56 patients (17.4%) and hypothyroidism in 136 patients (42.4%). There was no statistically significant difference in the response rate between the patients who received 8 mCi and who received 12 mCi (P value = 0.921), also there was no statistically significant difference in the response rate in relation to size of thyroid gland, Tc99m pertechnetate thyroid uptake, previous surgical treatment, age and gender (p values 0.265, 0.665, 0.242, 0.209 and 0.923 respectively) as shown in table 6.

Fifty two patients from the 79 non responded in the first group received second dose of 8 mCi while the remaining 27 patients received 12 mCi. There was no statistically
significant difference in the response rate between the patients received 8 mCi (86\%) and 12 mCi (92.6 \%) with \textit{P value} = 0.422. No statistically significant difference in the response rate in relation to size of thyroid gland, Tc-99m pertechnetate thyroid uptake and previous surgical treatment was found (p values = 0.436, 0.225 and 0.361 respectively). Eleven from the 50 non responded patients in the second group were received second dose 8 mCi while the other 39 patients received 12 mCi. There was no statistically significant difference in the response rate between the patients received 8 mCi (90.9 \%) and 12 mCi (384.6 \%) with \textit{P value} = 0.595 and no statistically significant difference in the response rate in relation to size of thyroid gland, Tc99m pertechnetate thyroid uptake and previous surgical treatment (p values = 0.418, 0.117 and 0.471 respectively). Thirteen patients from the remaining 16 non responders to the second dose responded to the 3\textsuperscript{rd} RAI-131 dose with development of euthyroidism in 7 patients (43.8 \%) and hypothyroidism in the remaining 6 patients (37.5\%). The 4\textsuperscript{th} dose controlled the remaining 3 patients with development of hypothyroidism in 2 patients and euthyroidism in the third.

The median dose for controlling GD was 12 mCi (minimum 8 mCi which controlled 23.7\% of the patients and maximum 47 mCi), the doses of 12 mCi, 16 mCi, 20 mCi, 24 mCi, 28 mCi, 32 mCi, 36 mCi, 43 mCi and 47 mCi increase the overall control rate to 59.8 \%, 74.1\%, 85\%, 96\%, 96.9\%, 97.8\%, 99.4\%, 99.7\% and 100\% respectively as shown in table 7. The mean dose number for controlling the hyperthyroidism was 1.46 \pm 0.62 (range 1- 4). The first dose controlled 59.8\% of the patients, this percent increased to 95\% after the second dose, 99.1\% following the third one and 100\% after the fourth dose.
as shown in table 8.

**Discussion:** About 80% of experts from Europe preferred to start treatment with ATDs in patients over 21 years and 70% of those in the United States RAI is the initial treatment modality of choice (21). In Egypt the ATDs represent, for most endocrinologists, the initial choice of treatment. This trend was reflected in the present study, where only 22.4% of the patients underwent RAI as initial treatment modality, while 77.6% patients were previously treated with ATDs.

The influence of ATDs on the outcome of RAI treatment has received attention. Some studies have suggested that ATD treatment before or after RAI may provide a radioprotective effect for the thyroid with significantly shortened the biological half-life of RAI result in reduction of the absorbed dose and increased failure rate of single-dose RAI treatment (16-17) (22). Thionamide withdrawal was among the predictive factors for treatment success in a 10-mCi fixed-dose approach (23). *More over Alexander et al.* treated 261 Graves’ patients with a mean dose of 14.6 mCi of RAI demonstrated high risk of treatment failure in patients pretreated with anti-thyroid medications for greater than 4 months(12). Other studies stated that this effect confined to the use of propylthiouracil only (18). In contrast Braga et al. (24) and Andrade et al. (25) demonstrated that methimazole pretreatment has no effect on the final treatment result, including the time required for cure or the 1-year success rate of RAI therapy. Thientunyakit T et al. (26) showed that duration of anti-thyroid drug given prior to radioiodine therapy seemed not related to the treatment outcome. Moura-Neto also found that no statistically significant association between thyroid function outcome to a fixed,
15 mCi approach for treatment of Graves’ hyperthyroidism and drug used (methimazole or propylthiouracil; maintenance or withdrawal of thionamides prior to therapy (27). Our results were in agreement with the later ones, where we don’t find statistical significant difference between pre-iodine medical treatment or its duration and the outcome to RAI-131 therapy.

Surgery is no longer recommended as first-line therapy for GD and use in selective cases where RAI is not preferred and ATDs fail to control the disease(3). Lal et al. concluded that total thyroidectomy (TT) is much better than Subtotal thyroidectomy (STT) (28). In the present study, STT was performed in only 49 patients (15.3%) with recurrent of disease in all of them at a median period of 66 months, confirming the literature data of using it as an alternative option in selected patients.

The size of thyroid gland is an important factor influencing the outcome of therapy; In our study, mildly enlarged glands had more controlled rate than moderate or markedly enlarged thyroid gland with higher incidence of hypothyroidism (P = 0.042). This result is in agreement with the other multiple studies which have demonstrated that patients with larger-volume thyroid glands to fail to respond to a single dose of radioiodine (23-27-29-30-31-32).

The impact of thyroid uptake on the RAI outcome has been investigated using either 131I or Tc99m pertechnetate. Alexander et al (12) found that patients who have higher 24-hour thyroid RAI uptake values were at higher risk than others for treatment failure. Kung et al. (32) also identified 4-hour RAI uptake among the variables that could predict early treatment outcome for Graves’ disease. These results were in agreement with other
works demonstrating higher failure rates in patients with higher iodide thyroid uptake values which could reflect faster iodide turnover in thyroid cells thus making the residence time of therapeutic I-131 in the gland shorter (33). The authors suggested that a higher radioactivity of RAI be given to these patients. Using Tc99-m sodium pertechnetate Zantut-Wittmann et al. (23) have reported that in a 10 mCi fixed dose approach the pre-RIT Tc99-m sodium pertechnetate uptake under 12% among the predictive factors for treatment success. In contrast, Moura-Neto et al. stated that no statistically significant association between thyroid function outcome to a fixed 15 mCi approach for treatment of GD and Tc-99m sodium pertechnetate thyroid uptake prior to therapy(27). Tc-99 m pertechnetate uptake is routinely used in our department as a surrogate measure of thyroid uptake because it has been proved to possess a good correlation with iodide 125 uptake (34). Moreover, it is much less expensive, reliable and convenient method allows uptake within 20 minutes after intravenous injection of the radionuclide and the therapeutic dose of RAI can be administered immediately after. We found that Tc-99m pertechnetate thyroid uptake more than 20.9% was among the poor prognostic factors for the response, thus higher dose is recommended.

The different RAI doses have different impact on the thyroid gland function, less than half of the patients (49%) in group 1 who received low dose of RAI achieved cure. On the other hand 69.4 % from the second group, who received higher dose of RAI, had achieved cure. This means that higher dose of RAI increase response rate by ~ 20.4 %. Franklyn et al.(35) and Sankar et al.(36) studied the therapeutic outcome of low fixed dose of RAI, the former concluded that persistent hyperthyroidism after 6 months was
present in 55.9% of the patients using small fixed dose of 5 mCi of RAI and the latter recommended increase dose of RAI to achieve response. This agree with Nordyke and Gilbert (29) who analyzed a series of 605 patients treated with RAI to find out the optimal dose to achieve cure and they concluded that cure was directly related to the dose of RAI administered and the optimal dose for curing hyperthyroidism is approximated by starting with 10 mCi and increasing it for unusually large glands or for special patient circumstances.

In the present study, 88% of patients achieved cure after administration of second dose of RAI with no statistically significant difference was found between the success rate and the given dose, only few patients require 3rd or 4th doses. This is in concordant with Sanyal et al. (37) and Franklyn et al. (35) studies that demonstrated high cure rate to the second dose of RAI (82.4% and 74.5% respectively) with only few require other doses.

Although it is very rare, McDermott et al. (38) reported thyroid storm in a small number of patients between 1 and 14 days after treatment with RAI. In the present study thyroid storm did not encountered in any patient. Also, Levy et al. (39) in a series of 7000 patients treated with RAI in one centre, none developed this complication. Ponto et al. (40) concluded that RAI therapy for GD is associated with definite increased risk of GO in around 20% of patients (either developing new cases or worsening of preexisting one). However In the present work there was worsening of exophtalmus in 9.6% of the patients and three new cases were developed (1.3%) among the rest who did not have
prior exopthalmos, they were among the 177 patients who developed permanent hypothyroidism.

Conclusion: Radioiodine is clearly successful in curing hyperthyroidism in GD patients by 100% after 4 doses; therefore it should be used as a first standard line in treatment. Treatment results using fixed RAI dose are comparable to those studies of patients treated with RAI using the prescribed absorbed dose method. The standard-dose prescription strategy is therefore an efficient, cost-effective and is also convenient to the patient. It may be possible to improve cure rates using a single fixed-dose regimen without increasing the dose in all patients. This might be achieved by the identification of subjects with poor prognostic factors who are unlikely to respond to standard doses and by administering larger doses only to these individuals. A higher fixed (12 mCi) is more effective than lower dose (8 mCi) for treatment of GD leading to better control of the disease following the first dose. Higher response rate are expected in patients who underwent previous surgery, on contrary patients with larger goiters and high thyroid uptake > 20.9% had 3.3 and 4 times less chance of remission. This different impact of different doses on the response rate is applied to the first dose, but not to the second dose where the response rate to the second dose is nearly similar in both low and high dose groups.

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**Figure Legend**

**Figure 1**: ROC curve for Tc 99m pertechnetate thyroid scan uptake according to response to 1st dose.