Efficacy of a single fixed 131I dose of radioactive iodine for the treatment of Hyperthyroidism

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Abstract:

A total of 135 patients were treated for hyperthyroidism with 131I 15 mCi radioiodine ablation. The therapeutic target was achieving hypothyroidism.

Between January 2014 and December 2018, clinical records were reviewed and data was collected and reviewed for 135 patients with hyperthyroidism that were referred to the Nuclear Medicine Department at Salmaniya Medical Center, for radioactive iodine (RAI) thyroid gland ablation procedure for definitive treatment of hyperthyroidism.

About 39.7% of our patients achieved response between 4-6 months out of which 35.7% of the patients showed response in the first 3 months. 21.4% of the patients took between 7-12 months to show response and only 3.2% responded after 12 months. The most significant response was hypothyroidism comprising of 94.4%. It is also worth mentioning that 4.0% of patients achieved euthyroidism and did not require any follow-up medication.

Using fixed dose of RAI of 15mCi for treating various type of Hyperthyroidism, successful treatment with a single dose of RAI can be achieved in 92.7% of the patients, with first therapy failure rate in 7.3%, with few patients requiring additional doses of RAI.

Keywords: radioactive iodine treatment; hyperthyroidism; 131I; fixed dose

Introduction

Overt Hyperthyroidism affects 0.1- 0.5% of the population worldwide, with female preponderance (F5–10:M1) peaking between 40 and 60 years (1). Radioactive iodine ^{131}I (RAI) has been used as a treatment of hyperthyroidism, used as a first line or second line treatment for the past six decades, ^{131}I being selectively concentrated by functioning thyroid tissue and subsequently destroyed by beta-radiation (1-3). ^{131}I as a treatment is safe and well-tolerated for hyperthyroidism, which is caused by Graves' disease, multinodular goiter and autonomously hyper functioning nodule. (4)

There is a lot of publication on various treatment protocols for using the RAI therapy which are used by different institutions to achieve the goal of treatment.

It remains a matter of debate when opting for the treatment protocol, whether to opt for a calculated dose versus a fixed dose, or a high dose versus a low dose of ^{131}I (2).Also, whether the target should be immediate hypothyroidism versus long term medical management of hyperthyroidism continues to be a subject of interest (5).

Furthermore, another debate is the treatment methodology, some use proposed fixed doses of administered ^{131}I, usually between (5–15 mCi), whilst others have adopted dose metric approaches, based on calculations that take into account RAIU measurements and thyroid volume (1).

In our institute the fixed dose protocol administration been used over the last 6 years. The Objective of this study is to evaluate the success rate of therapeutic administration of a single fixed ^{131}I (15mCi) activity for eliminating different causes of hyperthyroidism.

Methods and materials:

Patients

This was a retrospective cross-sectional study. We reviewed clinical records and collected data of 135 hyperthyroid patients for radioactive ablation therapy in our center, Salmaniya Medical Complex, between January 2014 and December 2018.

Thyrotoxicosis is a condition that occurs due to excessive thyroid hormonein the body. Thyrotoxicosis was diagnosed on the basis of elevated free T4 (FT4) and/or total T3 (TT3) values and suppressed TSH to < 0.25 mIU/L. Subclinical hyperthyroidism was diagnosed as normal FT4 and TT3 values with TSH suppressed < 0.25 mIU/L on more than one occasion over several months of observation. The etiology of hyperthyroidism in all patients was based on their biochemical profile (TSH, T4, T3 and TSH receptor antibody), thyroid sonography or imaging of the thyroid with Radioiodine uptake scan.

Patients on antithyroid medication were asked to withhold it for at least 5-7 days prior to thyroid imaging and also to avoid food containing iodized salts and to avoid eating or drinking eight hours prior to the procedure.

The Radioactive iodine ($I-^{131}$) is swallowed in capsule form; once it is ingested it is quickly absorbed into the bloodstream in the gastrointestinal(GI) tract and concentrated from the blood by the thyroid gland, where it begins destroying the gland's cells. Although the radioactivity from this treatment remains in the thyroid for some time, it is greatly reduced within a few days. We used a fixed dose of 15 mCi ^{131}I in all the patients. The outcome of this treatment on the thyroid gland usually takes about one to three months to develop, with maximum benefit occurring three to six months after treatment. Generally, a solitary dose is required in successfully treating hyperthyroidism. However, less commonly, a second or third treatment may be needed to achieve the wanted result.

Patients were followed up at 6 -12 weeks post ablation, and advised about the symptoms of hypothyroidism and to test for TSH and T4 earlier if any symptoms developed. After 3 months the patients were again followed up at 6 months and at 12 months. Once hypothyroidism was established based on symptoms and laboratory data of a low T3 and T4 and prior to the development of high TSH, thyroxine hormone replacement therapy was initiated. Persistent evidence of hyperthyroidism was defined as treatment failure.

Statistical analysis

SPSS 23 was used for data entry and analysis. Frequencies and percentages were computed for the categorical variables. Mean and standard deviation were computed for the quantitative variables. Simple bar charts and pie charts were used to represent the categorical variables. Clustered bar charts were used to represent the relationship between two categorical variables. Line charts were used to represent the relationship between the response to RAI and each of TSH level and T4 level. Cross-tabulation was done between the demographical variables and Type of Hyperthyroidism. Fisher's exact test was used to test whether there is a significant relationship between the response to RAI and each of number of times of RAI and Medication. P-value less than 0.05 was statistically considered significant.

Results:

Over a four year interval, 135 patients with hyperthyroidism were treated with RAI.

92.7% of the patients received RAI therapy once only and 7.3% of the patients required it more than once (Table 1, Figure 1).

		n	%
Number of times of RAI	One time	126	92.7%
	More than one time	10	7.3%
	Total	136	100.0%
Number of times of Thyroid Scan	One time	108	79.4%
	More than one time	28	20.6%
	Total	136	100.0%
Type of Hyperthyroidism	Toxic diffuse goiter	118	86.7%
	Toxic multinodular goiter	11	8.1%
	Toxic single nodule	7	5.2%
	Total	136	100.0%
	Response	126	92.7%

Response to RAI	Fail	10	7.3%
	Total	136	100.0%
Type of Response	Hypothyroidism	119	94.4%
	Subclinical Hypothyroidism	1	0.8%
	Subclinical Hyperthyroidism	1	0.8%
	Euthyroid	5	4.0%
	Total	126	100.0%
Response Duration to RAI	1 – 3 months	45	35.7%
	4 – 6 months	50	39.7%
	7 – 12 months	27	21.4%
	>12 months	4	3.2%
	Total	126	100.0%

Table 1 summarizes the number of patients who took one dose and more than one of RAI, also shows patients with different types of hyperthyroidism among the study, response duration to RAI and total successful and failure rates of response to RAI.

This response is very significant because it also represents our criteria – getting RAI only for one time- to signify a patient as a successful responding patient to RAI therapy. Fortunately, more than 90% who received RAI therapy for the first time has shown a response to RAI (Table 1, Figure 2) which was measured by a rise in the levels of TSH and a fall in the level of T4.

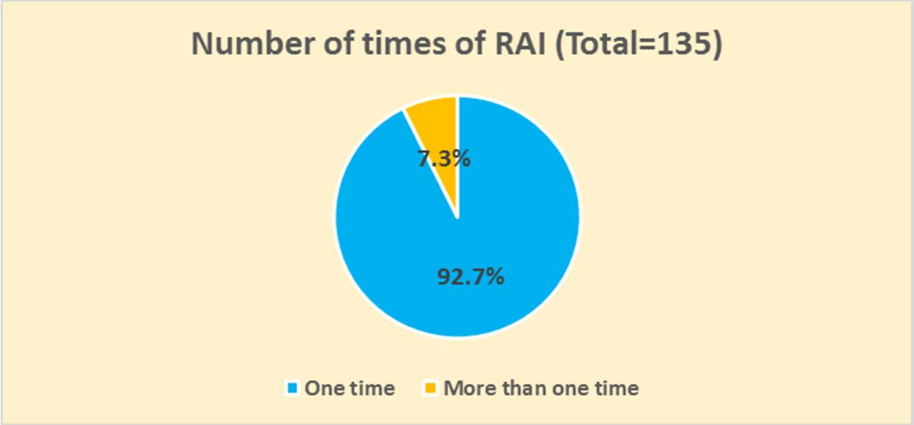

Figure 1: Pie chart summarizing the percentage of patients who received RAI therapy only for one time and others who took it more than once.

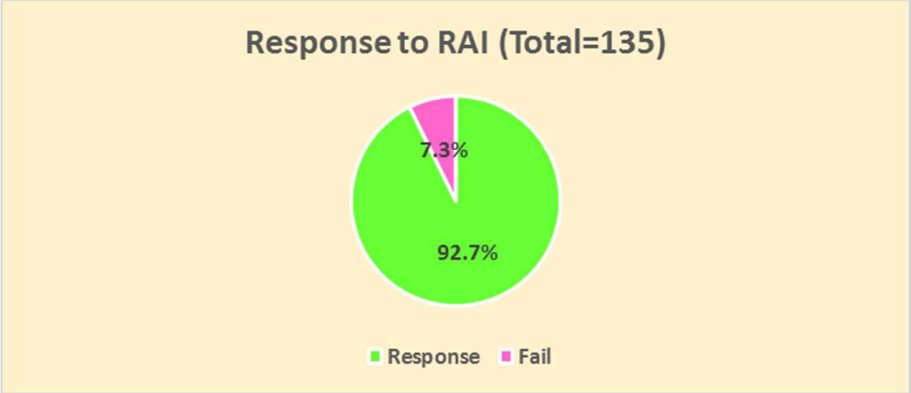

Figure 2: Pie chart summarizing the percentage of patients who responded to RAI therapy and who failed to respond.

Among all causes of hyperthyroidism among our patients, toxic diffuse goiter was the most common type of hyperthyroidism with a percentage of 86.7%. Toxic multinodular goiter and toxic single nodule comprised a percentage of 8.1% and 5.2% respectively (Table 1, Figure 3).

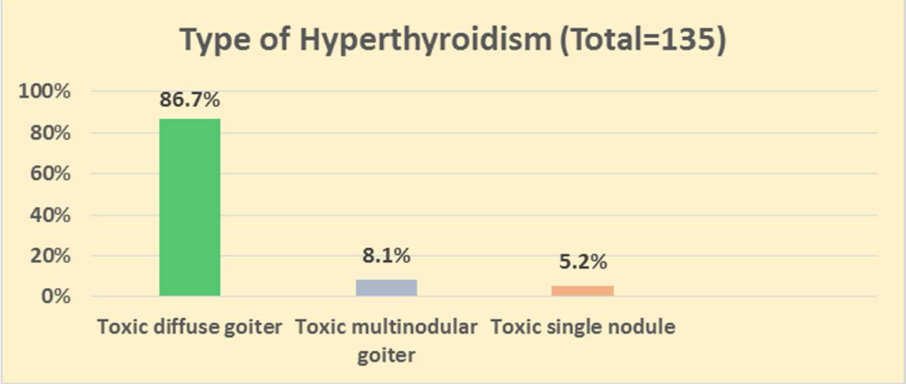

Figure 3: A bar graph illustrating the commonest types of hyperthyroidism among our patients.

It is worth noting that other clinical diagnosis such a thyroiditis and thyroid cancer were excluded.

Hypothyroidism was the most dominant response comprising a percentage of 94.4% (Table 1, Figure 4).

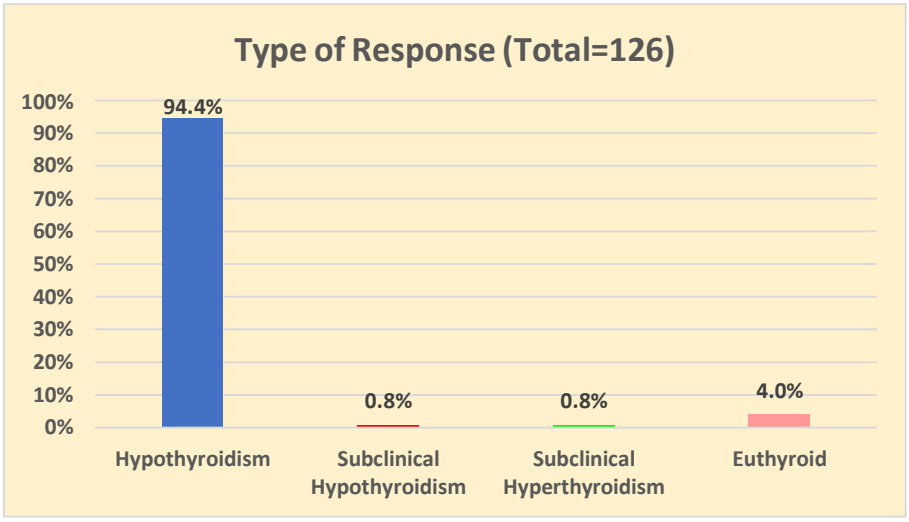

Figure 4: A bar graph illustrating the type of response that patient showed after receiving the RAI therapy

It is also worth mentioning that 4.0% of patients became euthyroid and require no follow-up medication. 79.4% % of patients had a thyroid scan only once while 20.6% required it again (Table 1, Figure 5).

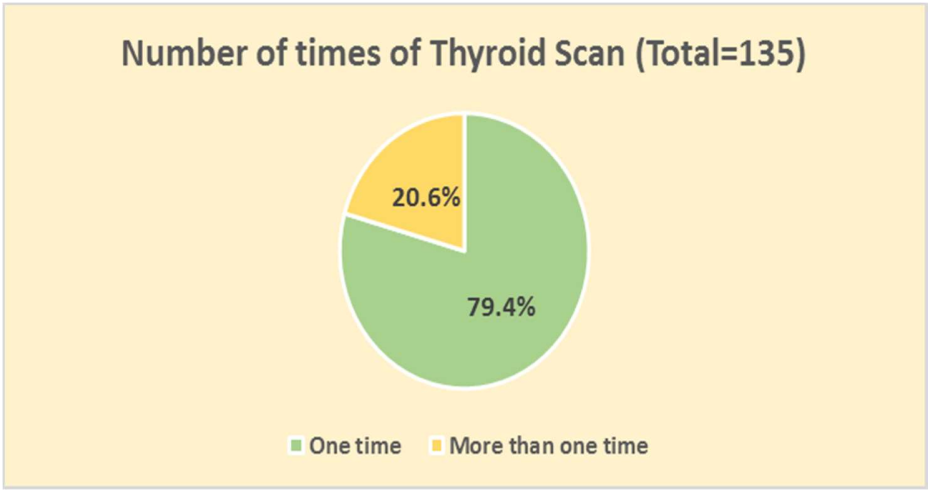

Figure 5: A pie chart representing the percentage of patients who received thyroid scan only one time and more than one.

About 39.7% of our patients responded between 4-6 months. 35.7% of the patients responded between 1-3 months. 21.4%patients took between 7-12 months to show a response and only 3.2% showed a response after 12 months (Table 1, Figure 6).

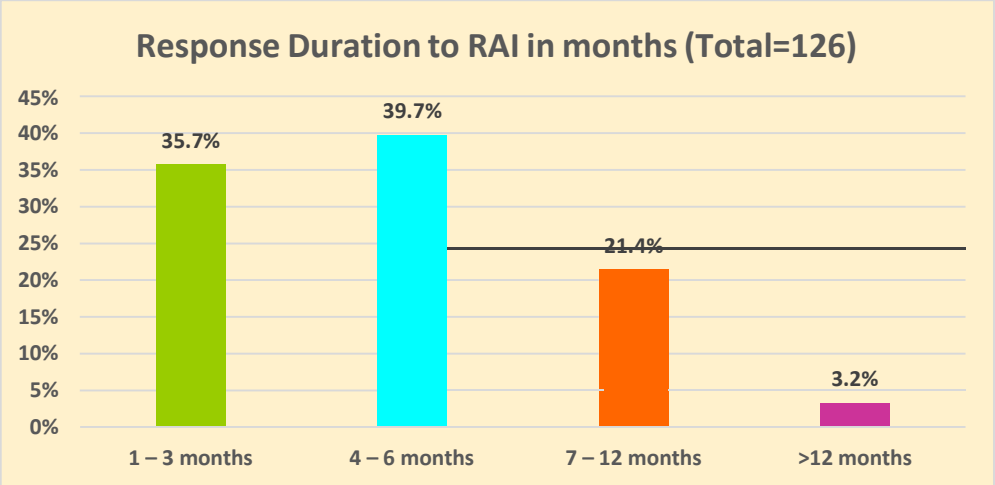

Figure 6: A bar graph depicting the duration needed by patients to respond to RAI therapy.

From our study we can roughly conclude that a trend is generated, starting with toxic diffuse goiter to be the most common type in all ages. However, there is a gradual decrease in its prevalence from younger ages reaching older ages (exclusively 100% in <20 years and 77.8% in >60 years) (Table 2, Figure 7).

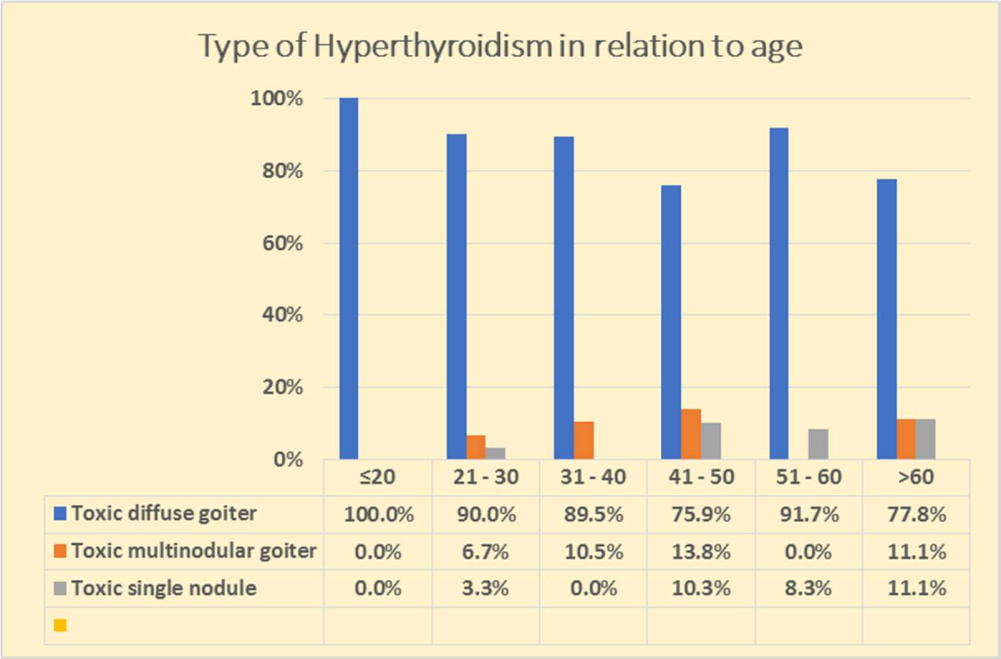

Figure 7: A bar graph illustrating the type of hyperthyroidism in relation to age of patients.

The prevalence of other types of hyperthyroidism such as toxic multinodular goiter and toxic single nodule showed a gradual increase from younger ages till older ages. Toxic multinodular goiter was 0% prevalent in <20 years but reached to be 11.1% in >60 years. Exactly the same trend and percentages is applied to toxic single nodule (Table 2, Figure 7).

		Toxic diffuse goiter		Toxic multinodular goiter		Toxic single nodule	
		n	%	n	%	n	%
		5	100.0%	0	0.0%	0	0.0%
	21 - 30	27	90.0%	2	6.7%	1	3.3%
	31 - 40	35	89.5%	4	10.5%	0	0.0%
	41 - 50	22	75.9%	4	13.8%	3	10.3%
	51 - 60	22	91.7%	0	0.0%	2	8.3%
	>60	7	77.8%	1	11.1%	1	11.1%
Gender	Male	36	90.0%	1	2.5%	3	7.5%
	Female	82	85.3%	10	10.5%	4	4.2%
Nationality	Bahraini	96	87.2%	8	7.3%	6	5.5%
	Non-Bahraini	22	84.6%	3	11.5%	1	3.8%

Table 2: summarizes the type of hyperthyroidism among patients in relation to their age, gender and nationality.

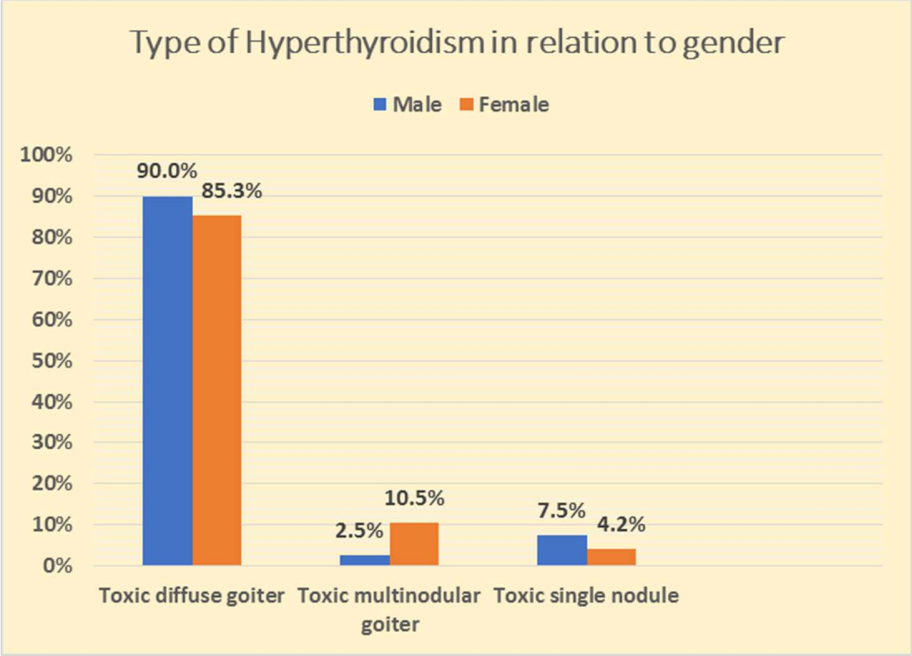

Figure 8: A bar graph illustrating the type of hyperthyroidism in relation to gender.

Toxic diffuse goiter is the most common type among both genders comprising a percentage of 90% among males and 5% less among females (Table 2, Figure 8).

However, they differ in other types in that toxic single nodule was the 2nd most common type among males (7.5%) while toxic multinodular goiter was the 2nd most common type among females (10.5%) (Table 2, Figure 8).

We also studied if there was any difference on the different causes of hyperthyroidism in relation to the nationality of the patients. Toxic diffuse goiter was the commonest type among both Bahraini and non-Bahraini. However, toxic multinodular goiter was more among non-Bahrainis than Bahraini's (11.5% and 7.3% respectively). In addition, toxic single nodule was slightly more in Bahraini's than non-Bahraini's (5.5% and 3.8% respectively) (Table 2, Figure 9).

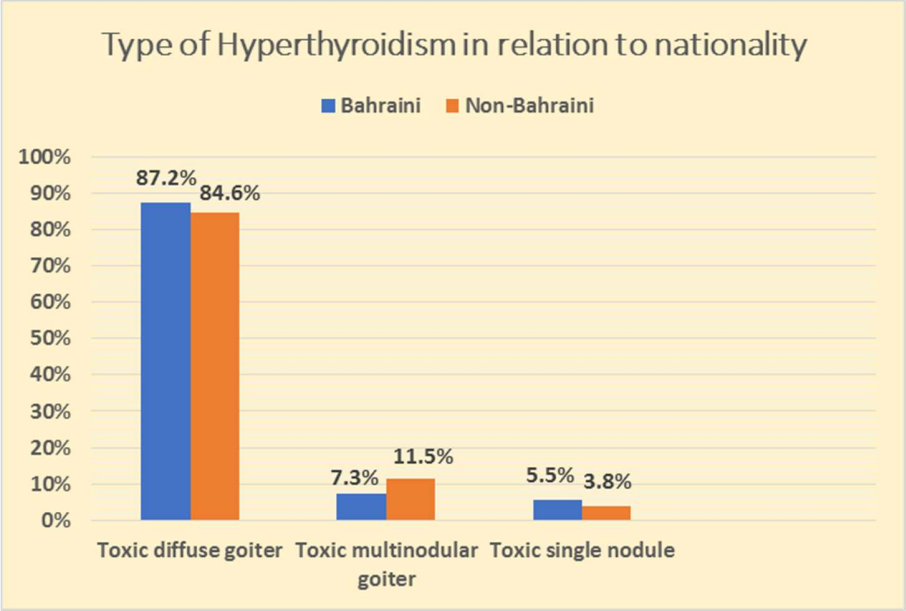

Figure 9: A bar graph illustrating the type of hyperthyroidism in relation to nationality whether the patient is Bahraini or not.

The percentage of response and failure of patients after receiving RAI therapy once in comparison to response and failure of patients receiving RAI more than once was approximately the same (Table 3, Figure 10).

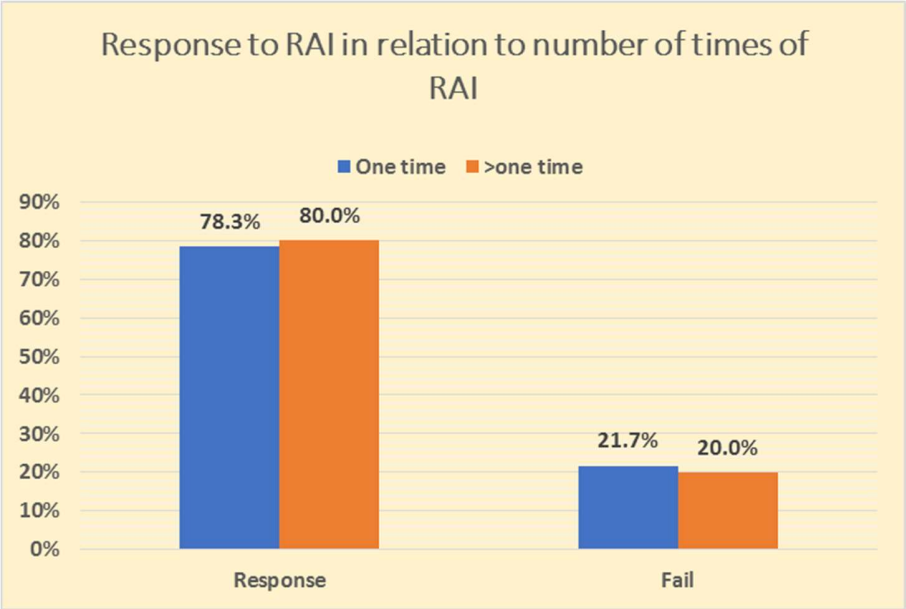

Figure 10: A bar graph showing the percentage of response and failure of patients after receiving RAI therapy once in comparison to response and failure of patients receiving RAI more than once.

However, patients who received RAI more than once showed a slight higher response (80% response for more than once and 78% for a single RAI therapy). These results were mirrored on failure rates as patients who received only a single RAI therapy were slightly higher than who received more than once RAI (21.7% and 20.0% respectively) (Table 3, Figure 10).

Table 3: Number of times of RAI and Medication in relation to Response to RAI						
		Response to RAI				Fisher's Exact Test P-value
		Response		Fail		
		n	%	n	%	
Number of times of RAI	One time	126	100%	0	0.00%	1.000
	>one time	0	0.00%	10	100%	
Medication	Yes	63	81.8%	14	18.2%	0.298
	No	43	74.1%	15	25.9%	

Table 3: summarizes the number of patients who responded to RAI therapy after the 1st time administration and those who failed to respond after 1st time administration of it. It also includes the ones who took medications among the responded patients in comparison to failure of showing response patients.

The study also looked at the response of patients to single RAI therapy and failure of patients to show response if they received more than once RAI therapy- in relation to either pre or post RAI therapy medication (Table 3).

Apparently the patients who took medications showed a higher rate of response than the patients who did not (81.8% and 74.1% respectively). These results were also reflected on failing to respond patients as those who did not receive medications had a higher failure rate than those who received it (25.9% and 18.2% respectively) (Table 3, Figure 11).

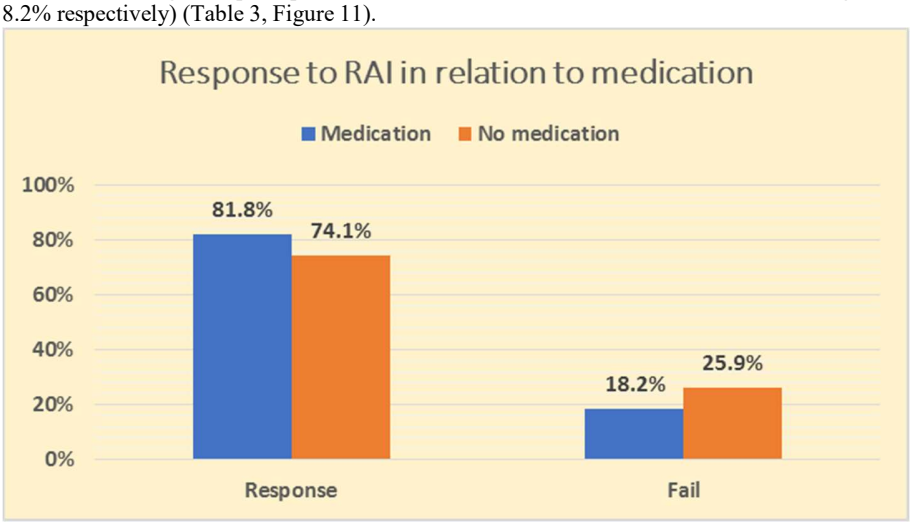

Figure 11: A bar graph representing the response of patients to single RAI therapy and failure of patients to show response.

For assessing the response of RAI therapy, an average of 2 TSH readings was taken before RAI and 3 readings after RAI therapy (Table 4).

Table 4: TSH and T4 in relation to Response to RAI				
	Response to RAI			
	Response		Fail	
	Mean	SD	Mean	SD
TSH level reading 1 before RAI	0.88	4.38	0.01	0.00
TSH level reading 2 before RAI	0.03	0.11	------	------
TSH level reading 1 after RAI	11.84	25.49	8.60	23.27
TSH level reading 2 after RAI	29.95	42.28	7.07	15.39
TSH level reading 3 after RAI	20.00	32.06	8.71	13.97
T4 level reading 1 before RAI	44.0	27.0	96.8	26.1
T4 level reading 2 before RAI	44.4	28.7	------	------
T4 level reading 1 after RAI	24.3	41.8	16.8	8.5
T4 level reading 2 after RAI	12.3	9.0	16.5	3.6
T4 level reading 3 after RAI	13.0	5.8	15.2	4.6

Table 4: summarizes the mean and standard deviation of an average of 2 readings of TSH and T4 levels before RAI therapy and 3 readings after RAI therapy.

After RAI was given, a gradual increase in TSH is observed, reaching from 0 to until a maximum of 30mU/L until it returns to decline at the 3rd reading (Table 4, Figure 12).

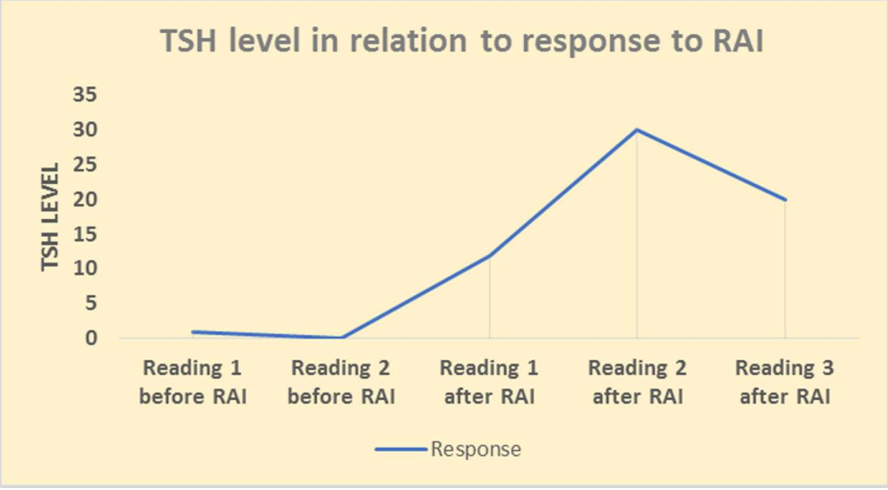

Figure 12: A line graph depicting the changes in TSH levels before RAI therapy in comparison to TSH levels after RAI.

There was a dramatic decline in the levels of t4 by about three quarters falling from a maximum of 45 ug/dl to about 10 ug/dl after the 3rd reading after RAI therapy (Table 4, Figure 13).

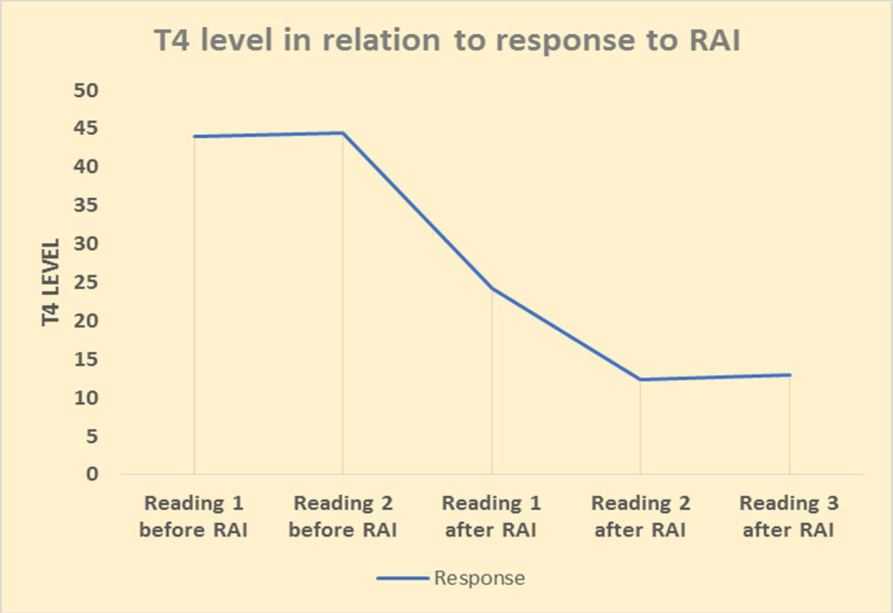

Figure 13: A line graph representing the changes of t4 levels before and after RAI therapy. The graph shows a dramatic decline in the levels of t4 by about three quarters falling from a maximum of 45 ug/dl to about 10 ug/dl after the 3rd reading after RAI therapy.

Discussion:

American Thyroid Association (ATA) guidelines advocate the target of achieving a state of hypothyroidism as a treatment for hyperthyroidism, which can be accomplished with basic fixed versus dosimetric approaches, in spite of the fact that there is a suggestion for calculated doses > 150 microCi per gram of thyroid tissue (1).

An ablative dose of radioactive iodine to treat hyperthyroidism is advocated by numerous endocrinologists. However, the dose of radioactive iodine to be prescribed remains a matter of debate as to whether to opt for a fixed dose or an individualized calculated dosimetry.

To reduce to the complications of hyperthyroidism and to get a rapid response, a dose of ^{131}I in the scope of 0.15–0.2 mci per gram of thyroid is preferred (9).

Although lower doses may be related to failure of achievement of the goal of therapy and re-exposure to the RAI treatment, higher doses of ^{131}I may have its own potential risks of excessive radiation exposure to the patients and the surrounding community.

Our target was to achieve hypothyroidism with RAI treatment using a fixed dose in patients with hyperthyroidism as it is easier to manage patients with hypothyroidism with levothyroxine resulting in fewer complications, in contrast to treating hyperthyroidism with oral medications in the long term which may consequently result in undesirable effects of therapy in terms of cost and side effects (10).

Treating hyperthyroidism with oral medications has the unpredictability of calculating the optimal dose required to achieve euthyroidism, with a higher chance of recurring hyperthyroidism despite being on optimal dose once the euthyroidism is achieved. Treatment may also incline towards a state of hypothyroidism even after achieving euthyroidism on a fixed dose (11, 12).

In this study we used 15 mCi of ^{131}I as a fixed dose for all patients, with the results showing persistent hyperthyroidism in 7.3% of the patients with the response rate being good in patients who had taken prior anti-thyroid medication.

The study also assessed different variables including age, gender, and patient's nationality to see if it had an overall impact of the type of response.

Response was achieved within 4-6 months in about half the patients with the majority responding within 12 months of treatment and only 4% showing a response beyond 12 months. We did not have data on the RAI uptake to comment on whether it had an impact on the response rate.

Different studies have looked into the efficacy of treatment of hyperthyroidism with RAI therapy using fixed or calculate doses versus treatment with anti-thyroid drugs (ADT).

Chen and co-workers studied patients treated with calculated doses of RAI treatment over a period of nine year in a prospective study with the conclusion of a short cure time using ^{131}I. The patients were treated with a dose of 8 mCi to 12 mCi. The patients did not get any prior treatment and the study concluded that the remission rate was higher in the ^{131}I group in comparison to ATD group. Also noted was the lower recurrence of hyperthyroidism, persistent hyperthyroidism or long term hypothyroidism in the ^{131}I treatment group.
At 100 months, their study showed that 100% of the patients achieved permanent hypothyroidism, with 24.4% and 62.2% patients converting to hypothyroid state at 6 months and 2 years respectively. In conclusion the authors demonstrated better cure rates with RAI therapy using a low dose of RAI than ATD, with lower relapse rate although with a higher rate of conversion to hypothyroid state (10). In comparison to our study, around half of our patients responded in the first 6 months and only 4% showed a response after 12 months.

In one randomized control trial by Abraham and Acharya, a higher success rate of eliminating hyperthyroidism of 71% was reported with a fixed dose in comparison to a 58% success rate with a calculated dose.
Nonetheless, the favorable outcome was conversely related to thyroid size in the fixed dose regimen and the success rate decreased to only 25% with increase in the thyroid gland volume. In larger thyroid volumes of more than 75 ml, a calculated dose had a better response of 45% positive result. The study advocated a fixed dose of 550 MBq (15 mCi) as a fixed dose unless for patients with large goiters where a dose of 800 MBq (21.6 mCi)

was recommended (2).
The recommended dose is comparable with our recommendation of 15 mCi as a fixed dose, however we cannot comment on the reason of failure in our study as the thyroid volume was not available in the patients data.

Traino and group studied three different calculated doses based on the thyroid gland volume and concluded that this approach avoided excess dose exposure, at the same time however effectively achieving the treatment goal. They found an absorbed dose of 400 Gray (Gy) to achieve the highest favorable outcome (13), thus also advocating the use of a fixed dose.

The variable response rate to treatment can be due to various factors. However, in a study by Vijayakumar V. and group, evaluating the different possible factors influencing the manifestation of hypothyroidism at 4-5 months following RAI therapy, concluded that no particular factor was responsible, and the occurrence of early hypothyroid was unpredictable (14).
Another study by Kristoffersen U. et al, included 72 patients to evaluate if there was any effect on the outcome of RAI treatment by the 24 h radioiodine uptake. The study concluded that when the RAI dose was calculated on the basis of 24 h RIU, outcome is poorer for patients with high 24 h RIU when compared with low 24 h RIU measured prior to treatment (15). Our study however could not assess whether the thyroid scan uptake had any inference on the treatment response.

However, different studies advocate different opinions. A meta-analysis with the objective to prove effectiveness of fixed dose versus calculated dose of RAI demonstrated equality of favorable outcome in estimated and calculated doses of radioiodine with inconclusive result for superiority (16).

While assessing the efficacy of calculated doses, a study by Schiavo and colleagues, demonstrated the outcome of 119 patients with Grave's disease treated with calculated doses of RAI. The patients were followed up for 12 months post treatment, and the authors concluded that high level of individual dose optimization was required as only 53% of the patients were initially successfully cured for hyperthyroidism and the remainder required a higher dose titration. The desired outcome was then achieved in 89% of the patients (17).This shows a lower initial response rate and the need for further follow up for the patients requiring additional doses to reach the desired result.

Howarth and group tried to determine the minimal optimal therapeutic dose of radioactive iodine ablation for successful treatment of Grave's disease. The conducted a randomized control prospective trial enrolling 58 patients with one group receiving a dose of 60 Gy and the other group receiving 90 Gy thyroid tissue absorbed dose. The latter group achieved hypothyroidism in higher rate (P=0.246) at 6 months. Those who did not respond in the low dose group had a larger thyroid gland mass (respective means: 35.9 ml versus 21.9 ml). No significant superiority was demonstrated by using a dose of 90 Gy (18).

When four different protocols of treatment based on calculated doses depending on thyroid gland weight were compared for efficacy by Calegaro JU and group, it was demonstrated in patients previously not subjected to anti thyroid medication, a low dose RAI (1 mCi/10 gm of estimated thyroid gland weight) protocol was effective in reducing Grave's hyperthyroidism (19).
There remains controversy on the effect of RAI therapy and the use of antithyroid medications. This study also assessed the effect of prior ATD treatment on the response and demonstrated treatment failure with persistent hyperthyroidism in this group despite being on higher calculated dose protocol (19).
Adjunctive anti-thyroid drugs demonstrated failure of radioactive iodine treatment if given in the week prior to treatment with RAI, regardless of the drug prescribed. Such patients are at risk of treatment failure and have reduced risk of hypothyroidism (9).
Different fixed doses of ^{131}I have been compared for efficacy with variable response rates.

In a study by Esfahani AF et al, there was no noted correlation of age, gender and the size of the gland with the outcome of the treatment in different groups of patients, although the dose given in each of the groups had a significant impact on the resulting outcome (P<0.003). The group given a smaller dose of 185 MBq (5mCi) had more non-responders, increased office visits, and persistence of hyperthyroidism. The group given a higher dose of 370 MBq (10mCi) of ^{131}I had a better response to treatment and thus this study advocates the use of a dose of 370 (10mCi) MBq (20).

In another study by Alexander E. et al, over a seven year duration including 261 patients, the efficacy of a dose of 8 mCi was studied. 86% of the patients achieved the target of euthyroidism or hypothyroidism after 1 year of treatment, while 14% required a second treatment due to persistent hyperthyroidism. This study advocated the use of a higher dose of ^{131}I in patients at risk of treatment failure including young patients, those with large glands, higher T4 levels and prior treatment with anti-thyroid medications (21).

Schneider D. and group conducted a retrospective review of multivariate analysis, in which higher T4 and methimazole treatment were associated with unsuccessful treatment with RAI ablation suggesting the use of higher doses of RAI in order to avoid repeated treatments or surgery for patients with persistent hyperthyroidism (22).

As literature shows variable experiences by using different approaches for treating hyperthyroidism, RAI ablation is the recommended treatment. Different doses have been compared with suggestion of high dose, calculated dose and fixed doses. Our study has shown the efficacy of a fixed high dose of 15 mCi ^{131}I with good results and this is a practical approach for treating patients with hyperthyroidism.

Study limitations:

One of the limitation of our study is its inability to comment on the reason of treatment failure due to unavailability of data related to thyroid volume and RAI uptake.
The data on the gland size was not assessed, thus whether the treatment failure was due to a higher gland volume could not be assessed.

The 24 h uptake rate of thyroid scan was not available as a variable, and thus could not be assessed to see its effect on the response of therapy. Which type of hyperthyroidism had a better response or failure could was not assessed as well.

The study lost follow of the patients after 12 months so they could not be reassessed for complications or response beyond 12 months of therapy.
We could not also comment on the side effects of the RAI ablation as this was not documented consistently in the medical record.

When assessed for response to treatment, the patients were assessed on their follow up appointments which may have under estimated the actual time of achieving the target of hypothyroidism. However those patients who developed the symptoms of hypothyroidism were pre counseled to check TSH levels on developing any symptoms, so this difference may be minimal.

However, the result of this study is applicable to our daily practice although however more data to look into the causes of treatment failure would be of added advantage.

Conclusion:

Effective treatment for different types of Hyperthyroidism with a solitary dose of RAI of 15mCi ^{131}I can be accomplished in majority of the patients, as is demonstrated in our study, with 94.4% the patients achieving a successful cure, and 7.3% unsuccessful rate for the initial treatment thus resulting in the requirement of additional doses of RAI in some patients

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