Radioiodine treatment of hyperthyroidism

Success rate and influence of thyrostatic medication

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ABSTRACT

Objective: The aim of this study is to evaluate the response rate of hyperthyroidism to radioactive iodine (RAI) treatment, optimum effective dose, effect of pretreatment with thyrostatic medications, etiology, ophthalmopathy, mortality and cancer incidence post RAI treatment.

Methods: Retrospective study analysis of 360 patients records who received RAI treatment (dose 5-15 mCi) for hyperthyroidism in Hamad Medical Corporation, Qatar between 1984-1999, treated and analyzed. Follow-up data was available in 215 patients, with a follow-up range of 2-10 years, of these 84 were males and 131 were females, with an age range of 12-74 years. Eighty percent were toxic diffuse goiter, 13.5% were toxic multinodular goiter and 6.5% were toxic single nodule. Eighty-seven percent had been pre-treated with anti-thyroid medications. Free thyroxine$_4$, and thyroid stimulating hormone were recorded at diagnosis; 6 months, one year and yearly post RAI treatment.

Results: The incidence of hypothyroidism was 55.8% at 6 months and 67.9% at one year. There was no significant difference in the response rate to different doses of RAI treatment groups (50-59%, p=0.46). The response rate was significantly higher in the group without pre-treatment with anti-thyroid medications (95% versus 80.9%, p<0.0001) and 27.4% of our patients had ophthalmopathy. There was no significant worsening or new development of ophthalmopathy post RAI treatment. Three of our patients developed cancer: one with colonic, one with breast and one with acute leukemia. The mortality rate according to the age group was linear in the positive direction of age and the highest was 74-year-old (10.5 per 10,0000 population).

Conclusion: Radioactive iodine treatment is an effective modality for definitive treatment of hyperthyroidism with long-term cure approaching 80%. Response rate was not related to gender, etiology or RAI dosage. Pre-treatment with anti-thyroid medication reduces the response rate. Radioactive iodine treatment has no significant influence on ophthalmopathy, mortality or thyroid cancer.

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There are different modalities of treatment for hyperthyroidism, none is ideal. The goal of radioactive iodine (RAI) treatment is to cure the hyperthyroidism and achieve the long-term control.[1] Radioiodine has been frequently administered to patients with hyperthyroidism since early 1940's.[2] At present, it has become the cornerstone in the treatment of hyperthyroidism. Despite several reports that suggest pretreatment with thyrostatic medications reduces the efficacy of radioiodine treatment (^{131}I) therapy in patients with Grave's disease, the issue remains controversial.[3,4] Moreover, the optimum dose of ^{131}I

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therapy has been controversial. Some are trying to avoid the post therapeutic hypothyroidism when calculating the estimated dose of RAI, while others assume that hypothyroidism is inevitable and therefore their treatment goal was to deliver a sufficiently large dose to assure thyroidal ablation, and a certain cure of hyperthyroidism.[5] Previous studies have shown that high dosage cures hyperthyroidism in 90% of patients, but eventually it causes hypothyroidism in >70%, whereas low dose RAI therapy is more likely to result in treatment failure.[6] In this form of treatment, several issues are still controversial including the most appropriate dose to be used, the risk of malignancy, increased mortality and worsening of ophthalmopathy. Therefore, we retrospectively studied all the cases of hyperthyroidism in Qatar treated with radioiodine during the period 1984-1999. The objectives of this study are to evaluate the response rate of hyperthyroidism to radioiodine treatment, the optimum effective dosage, effect of pre-treatment with thyrostatic medications, the etiology, ophthalmopathy, mortality and cancer incidence post RAI treatment.

Methods. Three hundred and sixty consecutive patients were treated with RAI for hyperthyroidism in Hamad Medical Corporation, Qatar between 1984 and 1999, records were analyzed retrospectively. One hundred forty-five patients were excluded due to incomplete follow-up data and 215 patients' records were reviewed, the follow-up range was 2-10 years. Other characteristics of patients are listed in **Table 1**. The radioiodine dosage was recorded and grouped into 5 groups (**Figure 1**). Free thyroxine$_4$ (FT_4) and thyroid stimulating hormone (TSH) were recorded at diagnosis, then post-radioiodine treatment at 6 month, one year and yearly intervals up to 12 years. (The TSH was measured with Beckman Access. The access hypersensitive thyroid stimulating hormone is a 2 sided immunoenzymatic "sandwich" immunoassay). The FT_4 assay is a 2 step enzyme immunoassay (Beckman Access).

Radioiodine treatment, properties and technique. Thyroid gland scintigraph and uptake were obtained, (gamma camera with pin hole collimator), 20 minutes after the injection of technetium^{99m} pertechnitate (tech^{99m} pert) the patients with mild to moderate hyperthyroidism were treated with radioiodine without pre-treatment with anti-thyroid medications, whereas those with severe hyperthyroidism, associated with cardiovascular diseases or within an old age group, were initially pre-treated with anti-thyroid medications (carbimazole or propylthiouracil [PTU]). Anti-thyroid medications were usually discontinued from 48-72 hours prior to RAI treatment. Anti-thyroid medications were restarted within 5-7 days post RAI in the high-risk group, while adrenergic blocking drugs were maintained prior, during and post RAI treatment.

Dose strategies. The practice was to use delivered millicurie/gram giving 60 µCi/gm thyroid tissue. Radioactive iodine uptake was estimated by neck sodium iodide probe, after 24 hours of oral dose of ^{131}I, thyroid uptake was used mainly to differentiate low uptake hyperthyroidism (thyroiditis) from high uptake hyperthyroidism (diffuse or nodular goiter). From 1995 we used a fixed millicurie (mCi) dose regimen: 10 mCi is usually given for small and medium size glands, and 15 mCi for large glands, multinodular goiter and autonomous nodules. The thyroid uptake function was estimated by using tech^{99m} pert based on gamma camera technique.

Results. The incidence of hypothyroidism (TSH > 6.1 mIU/L) was recorded at 6 months (55.8%). Then the cumulative incidence at one year (67.9%). Thereafter, the yearly rate was 2% up to 5 years, and 0.5% between 5-10 years (**Figure 2**). Following analysis of the data at 6 months post RAI treatment, we looked at the incidence of hypothyroid (TSH > 6.1 mIU/L) and euthyroid (TSH 0.21-6 mIU/L) in the different RAI dosage groups. We found no significant difference in the rate of response to the different doses of RAI used, Chi-square test was used, $p = 0.46$ **(Table 2**). The response rate (hypothyroid and euthyroid) at 6 months post RAI treatment was significantly higher in the group without pre-treatment with anti-thyroid medications (95.2% versus 80.9%). Chi-square test was used, $p < 0.0001$ (**Table 3**). Further comparative analysis between the subgroups of patients who received anti-thyroid medications prior to RAI treatment (carbimazole 73% versus PTU 14.3%) showed no significant difference in the rate of hypothyroidism at 6 months (PTU 50% versus carbimazole 59%), and the non-parametric (Kruskal-wallis) tests were used, $p = 0.76$. The analysis also showed that there is no significant difference in response between the different etiological groups of hyperthyroidism who received RAI treatment ($p = 0.313$) (**Table 4**). The incidence of ophthalmopathy in the studied group was 27.4% (N = 59). We reviewed those cases to see if ophthalmopathy had worsened post RAI treatment and we found no significant worsening of ophthalmopathy post RAI treatment. However, detailed analysis showed that 13.3% of the patients who failed to respond to RAI treatment and continued to be hyperthyroid have worsened ophthalmopathy. Chi-Square test was used, $p < 0.048$ (**Table 5**). A further subgroup analysis showed that the group who responded to treatment and became either euthyroid (N = 14) or hypothyroid (N = 30) did not show significant worsening of ophthalmopathy (**Table 5**). None of the patients who did not have ophthalmopathy prior to RAI treatment developed it afterwards. Data analysis comparing the outcome of the RAI treatment between males (38.7%) to females (61.3%) showed no significant difference in the response. The incidence of hypothyroidism was 52.3% in males and 58.1 in females ($p = 0.43$). On the post RAI treatment period, 3 cases of malignancy were recorded: one with colonic cancer diagnosed at 72 months, one with breast cancer diagnosed at 14 months, and one with acute leukemia diagnosed at 2 months. The mortality rate in our study according to the age group shows linear trend in the positive direction of age. The highest was

74-year-old (10.5 per 10,000 population). The average population mortality rate was 4.6 per 10,000 population, which is double the mortality rate in this study (2.2 per 10,000 population) (**Figure 3**).

Discussion. In this study, we found that the cumulative incidence of hypothyroidism was 55.5% at 6 months and 67.9% at one year. Thereafter, the annual incidence of hypothyroidism was 2% in the first 5 years and 0.5% between 5-10 years. Similar results and trends have been reported in the literature.[7] In our study, males and females showed similar response to RAI therapy. Allahabadia et al[8] found that a single dose of radioiodine cured hyperthyroidism is lesser in males (47%) than females (74%). There is considerable controversy regarding the most appropriate dose regimen for ^{131}I in the treatment of hyperthyroidism. The 2 commonly used protocols are dosimetry and fixed dose regimen. In our hospital we used dosimetry between 1984-1994, and fixed dose regimen since 1995 up to present. We grouped ^{131}I into different doses: 5-7 mCi, 7.1-9 mCi, 9.1-11 mCi, 11-13 mCi, and 13.1-15 mCi (**Table 2**), we did not find significant differences in the rate of response between subgroups. The overall incidence of hypothyroidism at 6 months ranged from 50-59%. The most frequently used dose was 9.1–11 mCi (36.1%) (**Figure 1**). Nordyke and Gilbert,[9] found that the effective dose of ^{131}I was between 5-10 mCi. Other reports disagree with our findings, a high dose of radioiodine 120-160 µCi/gm causes hypothyroidism in 90%,[1] while low dose radioiodine is more likely to result in treatment failure, necessitating another dose in 6-24 months.[10-12] Eighty percent of our patients had diffuse goiter, 13.5% had multinodular goiter, while 6.5% had a single autonomous nodule (**Table 1**). Our data did not show significant differences in the response rate: hypothyroidism at 6 months was 58%, 48.1% and 42.9 (**Table 4**). Other reports showed similar cure rates in the groups of diffuse goiter and those with toxic nodular goiter.[13] Eighty seven percent of our patients received antithyroid medications, prior to RAI treatment, most commonly carbimazole "73% versus 14.3% for PTU" (**Table 1**). The failure rate (TSH <0.2 miu/L at 6 months) was significantly higher in the group who received pre-treatment with antithyroid medication (19.1% versus 4.8%) (**Table 3**). Crooks et al[14] first noted the radioprotective effect of antithyroid drugs in Graves' disease in 1960.[14] This is a controversial issue, some reports showed radioprotective effects of antithyroid medications,[15-22] while others did not.[3,15,19] Imseis et al[4] found that pretreatment with propylthiouracil but not methimazole reduced the therapeutic efficacy of ^{131}I in hyperthyroidism. In our study, there was no significant difference in the response rate between PTU and carbimazole pretreatment. Fifty-nine patients (27.4%) in our study had some degree of ophthalmopathy in the follow-up period (2-12 years). We did not find significant worsening of ophthalmopathy post RAI treatment. None of the patients who did not have

Table 1 - Characteristics of patients.

Characteristics	%
Sex	
Male	38.7
Female	61.3
Age (years)	
12-30	21.3
31-50	67
51-74	11.7
Nationality	
Qatari	38.7
Non-Qatari	61.3
Exophthalmos	
Present	27.4
Absent	70.4
Not available	02.2
Co-morbidity conditions	
Hypertension	13.9
Coronary artery disease	03
Others	13
None	70.1
Etiology	
Diffuse	80
M. nodular	13.5
S. nodular	06.5
Pretreatment with anti-thyroid drugs	
Carbimazole	73
PTU	14.3
None	09.1
Not available	03.6

M. nodular - multiple nodular
S. nodular - single nodular
PTU -propylthiouracil

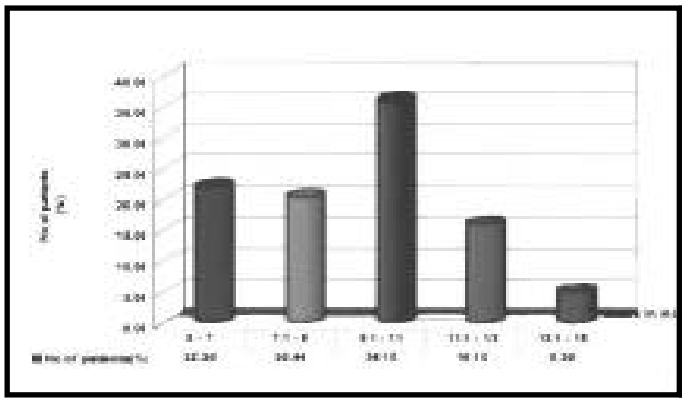

Figure 1 - Percentage distribution of patients by radioactive iodine treatment doses received.

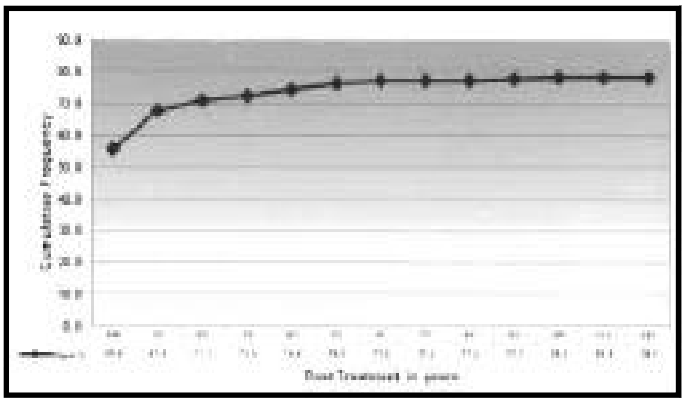

Figure 2 - Cumulative frequency (%) of hypothyroidism post radioactive iodine treatment.

Table 2 - Different doses of radioiodine and response rate.

Radioiodine dose	Thyroid stimulating hormone (6 months)			
	<0.2 n (%)	0.21 - 6 n (%)	>6.1 n (%)	Total n (%)
5.0-07 mCi	5 (11.4)	13 (29.5)	26 (59.1)	**44 (100)**
7.1-09 mCi	10 (22.7)	12 (27.3)	22 (50)	**44 (100)**
9.1-11 mCi	13 (16.7)	18 (23.1)	47 (60.3)	**78 (100)**
11.1-13 mCi	6 (16.2)	9 (24.3)	22 (59.5)	**37 (100)**
13.1-15 mCi	4 (33.3)	5 (41.7)	3 (25)	**12 (100)**
Total	**38 (17.7)**	**57 (26.5)**	**120 (55.8)**	**215 (100)**

Table 3 - Pretreatment with antithyroid medications and response after radioactive iodine treatment.

Pretreatment	Thyroid stimulating hormone		
	<0.2 %	0.21 - 6 %	>6.1 %
Anti-thyroid medications	19.1	23.7	57.2
Non anti-thyroid medication	4.8	52.3	42.9

Table 4 - Response rate to radioactive iodine treatment in relation to etiology.

Etiology group	Thyroid stimulating hormone (6 months)			
	<0.2 n (%)	0.21 - 6 n (%)	>6.1 n (%)	Total n (%)
Diffuse	32 (18.4)	41 (23.6)	101 (58)	**174 (100)**
Single nodule	3 (21.4)	5 (35.7)	6 (42.9)	**14 (100)**
Multiple nodule	3 (11.1)	11 (40.7)	13 (48.1)	**27 (100)**
Total	**38 (17.7)**	**57 (26.5)**	**120 (55.8)**	**215 (100)**

Table 5 - Exophthalmos post radioactive iodine treatment.

TSH (6 months)	Worsening exophthalmos		
	Yeas n (%)	No n (%)	Total n (%)
Exophthalmos TSH			
<0.2	2 (13.3)	13 (86.7)	**15 (100)**
0.21 - 6	0	14 (100)	**14 (100)**
>6.1	0	30 (100)	**30 (100)**
Total	**2 (3.4)**	**57 (96.6)**	**59 (100)**
Non-exophthalmos TSH			
<0.2	0	22 (100)	**22 (100)**
0.21 - 6	0	43 (100)	**43 (100)**
>6.1	0	88 (100)	**88 (100)**
Total	**0**	**153 (100)**	**153 (100)**

TSH - thyroid stimulationg hormone

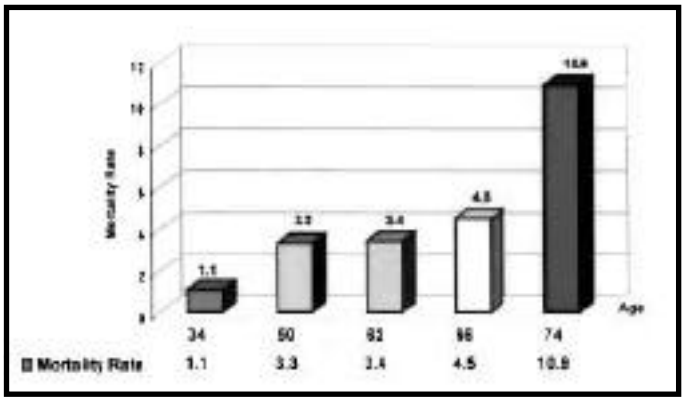

Figure 3 - Mortality rate per 100,000 population for thyrotoxicosis (post radioactive iodine treatment) in Qatar.

ophthalmopathy prior to RAI treatment developed it afterwards (**Table 5**). It is controversial whether radioiodine therapy affects the development or progression of Graves' ophthalmopathy.[23-25] In a subgroup analysis of our data we found that out of 15 patients, who failed to respond to the treatment and continued to be hyperthyroid post RAI treatment, 13.3% developed worsening ophthalmopathy. This probably corresponds with the finding by Bartelena et al[26] of exacerbation of ophthalmopathy post RAI treatment. None of our patients with ophthalmopathy who became euthyroid or hypothyroid had significant worsening of ophthalmopathy. This is in disagreement with the study by Tallstedt et al[27] who found that post-radioiodine hypothyroidism exacerbates ophthalmopathy.[28] Although radioiodine treatment for hyperthyroidism is safe and effective, recent reports have shown a slight, but statistically significant increase in mortality from all causes, cardiovascular, cerebrovascular disease and fracture.[29] Our data did not reveal any increase in mortality post RAI treatment in a follow-up period of approximately 10 years (**Figure 3**). There are also concerns on the subsequent risk of cancer in a population-based study recently published,[30] in conclusion, the absolute risk of cancers of small bowel and thyroid remain low, but the increased relative risk shows the need for long-term vigilance in those receiving radioiodine. Three of our patients developed malignancy post RAI treatment: colonic carcinoma (72 months), breast carcinoma (14 months), and acute leukemia (2 months) post RAI treatment. Obviously, our data did not show any increase in the incidence of thyroid or small bowel carcinoma.

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