

## COMPARISON OF CLINICAL OUTCOME OF TWO DOSE GROUPS OF RADIOACTIVE IODINE<sup>131</sup> THERAPY IN HYPERTHYROID PATIENTS

Emerson M. De Jesus, M.D.\* and Leilani B. Mercado-Asis, M.D., PhD\*\*

### ABSTRACT

**Objective:** To compare clinical outcome of two doses of radioactive iodine<sup>131</sup> therapy given to hyperthyroid patients.

**Method:** We reviewed records of hyperthyroid patients who consulted at an endocrine referral clinic from 1995 to 2005. Diagnosis of hyperthyroidism was based on compatible clinical manifestations and/or suppressed TSH (n=373, N.V. 0.3-4.0uIU/ml) and/or elevated FT4 (n=91, N.V. 10.0-25.7 pmol/l). We compared two dose groups of radioactive I<sup>131</sup> therapy, group 1 (<10 mCi) vs group 2 (≥10 mCi) in terms of requirement for second and/or third radioactive I<sup>131</sup> therapy.

**Results:** Four hundred sixty four patients were diagnosed to have hyperthyroidism and all were treated with radioactive I<sup>131</sup>. Patient ages ranged from 14 to 79 years with a mean of 38 of which 397 were females 67 were males. The patients were divided into two groups based on the radioactive I<sup>131</sup> doses given to them, group 1 (<10 mCi) vs group 2 (≥10 mCi). Four hundred forty four patients were included in group 1 and 23 patients were included in group 2. Baseline thyroid function tests showed mean TSH 1.6, mean FT4 89 for group 1 and mean TSH 0.31, mean FT4 41.21 for group 2. Fifty patients in group 1 (11%) required 2nd and/or 3rd radioactive I<sup>131</sup> therapy with a mean FT4 of 23.35 on average follow-up of 12.9 months while only 2 patients in group 2 (8.7%) required 2nd and/or 3rd radioactive I<sup>131</sup> therapy with a mean FT4 of 23 on average follow-up of only 2 months.

**Conclusion:** Significant number of hyperthyroid patients treated with low-dose radioactive I<sup>131</sup> therapy (<10 mCi) required 2nd/3rd dose of I<sup>131</sup> re-treatment and longer duration of achieving euthyroid state post-therapy compared to patients who received high-dose radioactive I<sup>131</sup> therapy (≥10 mCi).

**Keywords:** Thyroid, Radioactive Iodine,<sup>131</sup> Hyperthyroid

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\*Resident, Department of Internal Medicine, University of Santo Tomas Hospital, España, Manila, Tel. No. 7494012, Email: maverickemer@yahoo.com

\*\*Chief, Section of Endocrinology and Metabolism, Department of Medicine, University of Santo Tomas and University of Santo Tomas Hospital, España, Manila, 1608, Philippines, Suite 6001, Medical Arts Building, UST Hospital, España, Manila, Email: leilanimercadoasis@endo-society.org.ph

Reprint request to: Emerson M. De Jesus, M.D.St. Thomas Diabetes Center, 2nd Floor University of Santo Tomas Hospital, España, Manila, 1608, Philippines, Telefax: +632- 7810802

### INTRODUCTION

Radioiodine therapy has enjoyed increasing popularity since its use in the 1960s for hyperthyroidism because of its efficacy and few side effects. The primary goal of radioiodine therapy in Graves' disease is to cure the hyperthyroidism. It is controversial, however, whether radioiodine should be given in sufficient dose to induce hypothyroidism or in a lower dose in an attempt to achieve a euthyroid state.

A number of dosing regimens have been proposed ranging from those based on high precision dosimetry and ultrasound-guided volume determination, to large, fixed doses of RAI<sup>131</sup> intended to cause hypothyroidism soon after treatment. Controversy exists regarding the optimal dosing regimen of radioiodine to ablate the thyroid gland. However, it is clear that most patients ultimately develop hypothyroidism after therapy. Administration of relatively low doses of RAI<sup>131</sup> designed to restore euthyroidism, but not cause hypothyroidism, may simply delay this or fail to cure the hyperthyroidism. Additionally, unless a program of annual contacts with the euthyroid group of patients is maintained, undiagnosed hypothyroidism may occur years later, thus necessitating additional treatment, which may entail additional expenses in time and finances.

Although attempting to lower thyroid function to normal with a low dose of radioiodine may appear desirable, this approach has several disadvantages. In particular, only less than one-third of patients are euthyroid 10 years after therapy.<sup>1</sup> Low-dose radioiodine therapy is more likely to result in treatment failure, necessitating another dose in 6 to 24 months.<sup>2,3</sup> Many patients will have subclinical hyperthyroidism after low-dose radioiodine therapy, with its associated risks of atrial fibrillation and reduced bone density. Most patients who become euthyroid soon after radioiodine therapy will eventually develop hypothyroidism at a rate of 2 to 3 percent per year.<sup>4</sup>

## MATERIALS AND METHODS

This is a retrospective observational study of hyperthyroid patients treated with radioactive iodine. Out-patient records/data at a specialty endocrine clinic of all hyperthyroid patients (>18 years old) based on compatible clinical manifestations of hyperthyroidism and/or suppressed TSH (n=373, N.V. 0.3-4.0 uIU/mL) and elevated FT4 (n=91, N.V. 10.0-25.7 pmol/L) from 1995 to 2005, who were treated with radioiodine therapy, were collected and reviewed.

Subjects were divided into 2 groups based on the fixed radioiodine dose given (Group 1 less than 10 mCi; Group 2 greater than/equal to 10 mCi).

Subjects in the two groups were compared according to the number of patients who required re-treatment with radioiodine and the time interval from administering radioactive iodine to developing euthyroidism and/or hypothyroidism.

## RESULTS

Two hundred fifty six patients were diagnosed to have hyperthyroidism and all were treated with radioactive I.<sup>131</sup> Patients aged from 19 to 79 years with a mean age of 37.8 year old, of which 47 were males and 209 were females. The patients were classified into two groups based on the radioactive I<sup>131</sup> doses given to them, group 1 (<10 mCi) and group 2 (≥10 mCi). Two hundred thirty six patients were classified under Group 1 and twenty patients under Group 2. There was no statistically significant difference in terms of the age and sex distribution, (age p=.71 and gender p=.27) Overall, the baseline thyroid function tests showed mean TSH 0.68 (n=214), mean FT4 108.145 (n=233) for group 1 and mean TSH 0.31 (n=20), mean FT4 43.29 (n=14) for group 2. Baseline T3 values were statistically higher among those received ≥ 10 mCi of I<sup>131</sup>. (mean 37 versus 20.6; p=.034) Conversely, free T4 was statistically higher among those who received <10 mCi of I<sup>131</sup>. (mean 122 versus 43.7; p=.014) There was no significant difference in the baseline T4 and TSH among those who previously received the fixed doses of radioactive iodine. (p=0.26 and p=0.18 respectively) (see Table-I)

## DISCUSSION

Radioactive iodine (RAI) is effective in treating hyperthyroidism. In a study by Tarantini, RAI was

effective in 93.7% for toxic adenoma, 81.1%, toxic multinodular goiter and 87.1% for Grave's disease.<sup>5</sup> Although it was not noted as to what type of hyperthyroidism do the patients in this study have, all of them converted to hypothyroid state at cumulative mean follow-up period of 2.4 years and 1.7 years for Group 1 and Group 2, respectively.

Fixed doses of 5, 10, or 15 mCi (185, 370, or 555 MBq) are commonly given to patients with Graves' hyperthyroidism. According to Nordyke's study, the optimum dose in treating hyperthyroidism is 10 mCi. As such, this dose was used as the cut off value for this study.<sup>6</sup> In the study of Allahabadia, patients given 5 mCi (185 MBq) had a 67 percent cure rate and a 41 percent incidence of hypothyroidism, while those given 10 mCi (370 MBq) had an 85 percent cure rate and a 61 percent incidence of hypothyroidism.<sup>7</sup> In our study, there was no significant difference between the two dose groups in terms of rendering patients hypothyroid i.e. in terms of requirement for additional radioiodine doses. Possible reason for this finding could be the relatively small sample of Group 2 patients resulting to skewness of the study results.

The percentage of patients who become hypothyroid within the first year after treatment varies directly with the dose of radioiodine. Thereafter, the annual incidence of hypothyroidism is 2 to 3 percent per year and is independent of the dose. Most studies show that hypothyroidism occurs at a much later date. In the study of Tamai, the cumulative incidence of hypothyroidism in patients with Graves' disease and toxic multinodular goitre at 1, 10 and 25 years was 24% vs. 4%, 59% vs. 15% and 82% vs. 32%, respectively.<sup>8</sup> A significant finding obtained from this study is the lesser time interval to developing hypothyroidism for patients given high dose of radioiodine.

### Analysis

Descriptive statistics include mean and standard deviation for continuous numerical data and percentage frequency distribution for categorical variables.

Due to the inherent skewed distribution of the two groups, non-parametric statistics apply. To compare for independent continuous data, Mann Whitney U was used, while Chi-square was used to compare the distribution of categories.

Repeated measures analysis of variance was used to compare thyroid function values across doses of RAI. Cox proportional hazards analysis was used

to determine the mean and median time lapsed to develop euthyroid and hypothyroid state .

All statistical tests of significance were carried out at 0.05 alpha level of significance, 95% confidence interval using the Statistical Package for the Social Sciences (SPSS Version 14) as licensed software.

**Table I. Comparative Profile of Patients Treated with < 10 mCi and > 10mCi of I<sup>131</sup>, Endocrine Clinic 1995-2005**

Characteristic	<10 mCi Group n= 236, (%)	≥10 mCi Group n=20, (%)	p-value*
Age			
Mean ± SD	37.8 ± 12	38.1 ± 11	.71*
Median	36	39	
Gender			
Male	41 (17)	6 (30)	.27**
Female	95 (83)	14 (70)	
Baseline TSH			
Mean ± SD	0.87 ± 3	.01 ± .014	.18
Range	0 - 29.6	0 - .02	
Baseline Free T4			
Mean ± SD	122 ± 108	43.7 ± 55	.014*
Range	0 - 442	4.48 - 82.9	

\*Significant difference in ranks if p-value is <.05, Mann Whitney U Test

\*\*Chi-square

*Requirement for 2nd and 3rd Dose of I131*

Twenty nine patients in group 1 (12%) required 2nd and/or 3rd radioactive I<sup>131</sup> therapy after an average follow-up of 350 days while 2 patients in

group 2 (10%) required 2nd radioactive I<sup>131</sup> therapy after follow-up of 71.5 days.

There was no statistical association between the initial dose of fixed dose radioactive iodine and the need for succeeding doses. (OR =1.26, 95% CI, 0.26 – 8.3, p=0.76). (The chances of requiring a 2nd dose of RAI when the initial dose given was <10 mCi was only 1.26)

**Table IIA. Relationship of Initial I<sup>131</sup> Fixed Dose and Requirement for Succeeding Doses of I<sup>131</sup>, Endocrine Clinic 1995-2005**

Group	Required 2nd /3rd dose	No Requirement for 2nd /3rd dose	OR 95% CI p-value
< 10 mCi Group n, (%)	29 (93)	207 (92)	1.26
≥ 10 mCi Group n, (%)	2 (7)	18 (8)	0.26 – 8.3 p=0.76
Total	31	225	256

After the initial therapy, there was no statistically observable difference in the percentage of subjects who were hyperthyroid, euthyroid and hypothyroid in both groups of subjects (p=0.96, p=0.93, p=.80 respectively). Likewise, no observable difference in the proportion of subjects who are hyperthyroid, euthyroid and hypothyroid after the 2nd and third doses. (all p-values >.05)

**Table IIB. Actual Number of Patients With Specific Outcomes After the Initial, 2nd and 3rd Dose of RAI Using Two Fixed Doses, Endocrine Clinic 1995-2005**

Group	After 1st Dose			After 2nd Dose			After 3rd Dose		
	Normal N (%)	Hyperth N (%)	Hypoth N (%)	Normal N (%)	Hyperth N (%)	Hypoth N (%)	Normal N (%)	Hyperth N (%)	Hypoth N (%)
<10 mCi	38 (16)	29 (12)	169 (72)	2 (1)	3 (3)	231 (96)	5 (2)	0 --	231 (98)
> 10 mCi	3 (15)	2 (10)	15 (75)	0 --	0 --	20 (100)	0 --	0 --	20 (100)
p-value*	.96	.93	.80	--	--	.36	.77	--	.39

Percentages reflect horizontal sum

\*Z –test of two proportions, significant difference if p-value is <.05

Trend Analysis of Thyroid Function in 2 Fixed-Doses of RAI

From baseline, TSH values of Group 2 patients showed a decreasing trend after the 1st dose of RAI<sup>131</sup> approaching a value of less than 0.8 IU/L when compared with Group 1. The two groups did not differ significantly in terms of the decreasing trend in between doses ( $p=.74$  –between groups). In each group, the drop of TSH values were not statistically different in between doses ( $p=.89$ -within groups). (See figure 1)

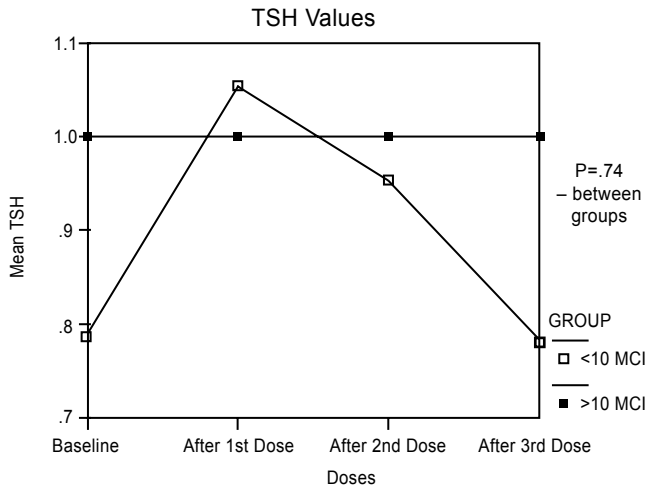


Fig. 1. Mean TSH Values Measured at Baseline, Post 1st Dose and Succeeding Doses, Endocrine Clinic 1995-2005

In terms of free T4 values, both groups showed a statistically significant decreasing trend from baseline ( $p=.003$ - within groups), however, the two groups was no superior than the other (lines converging) ( $p=.89$ -between groups). (See figure 2)

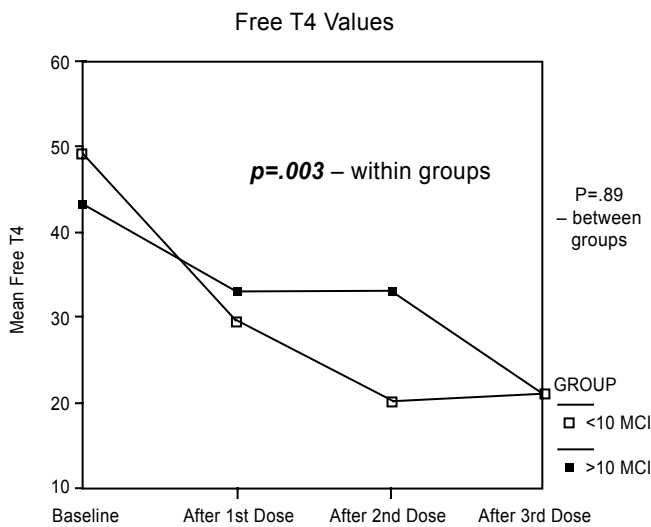


Fig. 2. Mean Free T4 Values Measured at Baseline, Post 1st Dose and Succeeding Doses, Endocrine Clinic 1995-2005

*Time to Develop A Hypothyroid State After the First and Succeeding Doses of RAI*

Cox-proportional hazards analysis reveal that the mean time for the total cumulative incidence of hypothyroidism in patients who received < 10mCi was at 2.4 years (95% CI 2.13; 2.17 years) with a median time of 1 year.

After the first dose the mean time to develop hypothyroidism was at 0.8 years or 9.6 months with the <10mCi group. After the second dose, the mean time to develop hypothyroidism using this dose was 0.5 years or roughly 6 months. No further observations after the third dose were made. All patients who received >10mCi except for 2 subjects became hypothyroid after the 1st dose (hence plot is not shown). The mean time to develop hypothyroidism at this dose is 7.4 months (median 7.6 months). >10mci mean time was at 1.7yrs (95%ci 1-2.6yrs.) p value .031 statistically significant.

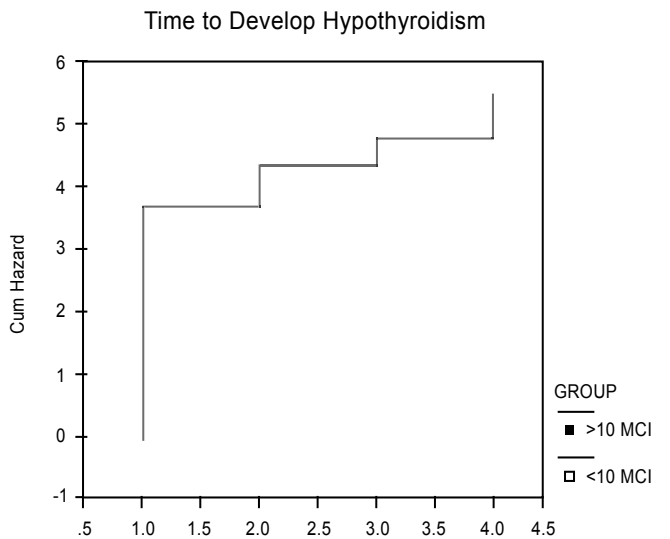


Fig. 4. Cox Proportional Hazards Plot of the Cumulative Incidence of Hypothyroidism Using the Two Doses of RAI, Endocrine Clinic 1995-2005

*Time to Euthyroid State*

The range of time to convert to a euthyroid state after the first dose was at 1 year for Group 1 (range 6.3 months – 13 months) and Group 2 ( 4 months – 9 months).

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