

Result of I-131-therapy for thyrotoxicosis at Songklanakarind Hospital 1991 to 1996

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ABSTRACT

B *ackground:* To evaluate the determinants dictating the outcome of RAI (radioactive iodine) therapy for patients referred with thyrotoxicosis.

Material and methods: Patients with thyrotoxicosis, previously medically treated and subsequently given RAI in single and multiple doses were traced and evaluated. The outcome was the thyroid status of those presently traceable or being followed. The patients were those first seen between 1991 and 1996.

Result: Out of a total of 615 patients, 387 had their thyroid status known up till the present (16,776 person-months of follow up from the time of the last dose). Fifty two percent of the patients needed multiple dosing (hence 48% was 'cured' with a single dose averaging 6.2 mCi). Of the multiple dosers, 62% needed only 2 doses averaging 10.4 mCi. Follow up found permanent hypothyroid at rates of 40-50%, 70 and 80% at 1, 1-3 and greater than 3 years. Corresponding euthyroid rates were 22 and 15% at 1-3 and greater than 3 years. The values of thyroid uptake did not appear to dictate the dose nor the eventual thyroid status.

Conclusion: The present report showed high rates of permanent hypothyroidism and as well high rates of intial persisting hyperthyroidism. These suggest poor or inability to use a proper dosage schedule of RAI for the treatment of thyrotoxicosis which had failed medical therapy. Also, it was thought that thyroid uptake may not be valuable in the large majority of RAI treatment.

INTRODUCTION

Radioactive iodine (RAI) therapy is an accepted mode of therapy for most forms of thyrotoxicosis and for most age group⁽¹⁻⁵⁾. It is safe and effective.

Different authorities used different RAI-dosages schemes for the treatment as reviewed by Kaplan et al⁽¹⁾. Fixed dose is popular^(4, 5) while others used arbitrary dosing which depends on gland size, eti-

ology of thyrotoxicosis and/or presence of complications particularly atrial arrhythmia and heart failures⁽⁵⁾. Others still, continued with formulating dose which depends on the accepted 3 factors: the amount of radiation wanted (rather than needed) per gram of thyroid tissue (this can vary 3 folds among different centers), the estimated size of the gland and lastly the RAI uptake at 24 hours⁽⁶⁾. As seen, aside from the uptake, the other two variables are approximations.

The radioactivity per gram rests on 2 concepts. Firstly whether one wants to achieve a high cure rate with a single dose of RAI inconsequential of the induction of hypothyroidism. Secondly, the biological half-life of the RAI in that particular gland. This varies for different subject perhaps depending on age, gland size, previous antithyroid drug^(7,8), the time interval these drugs were withheld prior to RAI^(7,8) and possibly the histological structure of the diseased glands (quoted off #1). The estimation of gland size is also fraught with inaccuracies as those familiar with the disease would be the first to agree. At the same time, it is noticed that rarely the tenseness of the gland is taken into account, so that in several instances, it is possible that a large gland can be less heavy because it is less dense.

It is hoped from this retrospective report of our experiences in treating thyrotoxicosis with RAI, that one may be able to extract information which may allow answering (if not fully, then partially) some of those queries:

- a) Should an uptake measurement of RAI be 'routinely' done on 'all' or majority of thyrotoxicosis when contemplating RAI therapy?

- b) What proportion of patients is 'cured' by a single dose RAI and the resultant rate of early and late hypothyroidism.

MATERIAL AND METHOD

The hyperthyroid clinic of the Nuclear Medicine division of this university hospital accepts patients from the surrounding provinces in Southern Thailand. These were referred specifically for RAI treatment mostly following relapse after stopping medical treatment. Some has had thyroid surgery followed by medical therapy. Very few were sent without initial ATD (antithyroid drugs). A small proportion was sent because of adverse reaction to ATD such as leucopenia, hepatitis, rash etc.

The procedures for RAI therapy is described. The ATD was always stopped and mostly about 10 days prior to oral RAI. The dose of I-131 utilised was 0.1 mCi pergram thyroid multiplied by the estimated gland weight in grams and divided by the fractional thyroid uptake at 24 hours. Often the ATD was restarted 2-4 days after the RAI and continued for 2 to 2.5 months prior to being reassessed at the third or fourth month when a repeat dose might be prescribed if indicated clinically and/or as dictated by the thyroid function test. As often however the patient did not return for follow up. If follow up showed hypo-functioning, then replacement therapy was instituted. Occasionally the replacement therapy was excessive and had to be curtailed. Betablockers were given according to the physician's preferences.

For the present review, consecutive charts of patients referred for RAI treatment for thyrotoxicosis were evaluated. Those few

not given RAI were discarded. We chose patients who attended from 1991 (the charts of earlier attendances often did not have all the information we needed) to 1996 (to allow adequate duration of follow up while presumably being treated under the same format). Pertinent data from the chart included date of birth, province of residence, gender, doses of I-131 and the following timings: dates of first and last doses, dates of blood test showing hypothyroidism and date when last seen. Aside from that, we also recorded the co-morbid conditions, the ATD, and the clinical and status of the thyroid function (as determined by us or by other physicians outside our division) at 3 month, 6-12 months, 12-36 and more than 36 months after the last RAI dose.

Those who were not followed by us or by our colleagues in the other department of the university hospital were contacted by mail. Over half responded and some were re-evaluated, often these were not aware of their hypothyroidism.

The diagnosis of late hypothyroid (late implying >6 months after the last RAI) was never difficult. However the early hypothyroid (i.e. early after RAI), in several instances, were only transient and in some these were given replacement and the hypothyroid not confirmed. Among the hypothyroid diagnosed by TSH levels (our normal level is 0.7-4.0 mIU/l) we separated out those with slightly elevated levels (4-8 mIU/l).

Data analysis

The tabulated data were subsequently analysed using EPI INFO 6. Descriptive data were presented as mean \pm 1 SD, or as median with the range between 25th to 75th percentiles.

During this 5.5 year of chart review, we noticed that there were 3 time periods whereby the I-131-thyroid uptake was persistently low for all patients and subsequently learnt that there were problems with the uptake measurement. Hence patients who had uptakes done during these 3 periods. [5 months in 1993, 10 months in late 1994, and 4 months in mid 1995] were arbitrarily assigned as the group with unreliable uptake. Their response in certain instances were evaluated different from those considered to have reliable values for thyroid I-131-uptake. This latter analysis was used for subsequent argument as to the value of doing routine uptake of iodine.

In the evaluation of percentage hypothyroidism we cross-sectionally calculated the prevalence at certain time periods (0-3 months, 1-3 years and greater than 3 years). But as is subsequently seen from the table, this incidence will be an approximation. It is obtained from the number of patients whose status is known at that point in time. Patients who were lost were not used in the denominator. We also evaluated patients who can be followed through the different time periods. Statistical differences were not performed.

RESULT

There were 615 consecutive patients in this report. The average (\pm SD) age was 46.8 \pm 12.6, ranging from 16-78 year old (median and 25th to 75th percentiles were 46, 35-57). Females composed of 73.5% of the total with similar age distribution as the males.

At the last evaluation in June 2000, 143 were lost and never replied the repeated communication by post-cards (several had left their initial residence), 178 were lost

but was traceable and most were re-evaluated. Two hundred had been discharged to be followed locally. Nine had died. The age when first seen of the ones who died was 60 ± 16 years and the interval to death was 2.2 ± 2.0 years. Two died from traffic accident at ages 31 and 40; 1 died with pneumonia on top of a chronic lung disease; 1 with heart failure; 1 with stroke and 1 with metastasis following cancer of the lung; one death was related to cirrhosis, one has had transient ischemic attack and in the last, we could not ascertain the cause. All died between 1992 and 1999.

Patients were sent from most provinces in the South but predominantly Songkhla, Nakorn-Sithamarat, Suratthani and Phatthalung. There was no particular reason for such distribution since we are the only I-131 provider for the Southern provinces.

Fifty eight has had previous thyroid surgery and 52 had it done once. At least 437 had been treated with propylthiouracil and 56 with methimazole. There were 12 patients who developed adverse reactions to the antithyroid drugs (eg. hematological and hepatic) that precluded pharmacologic therapy.

Congestive heart failure was reported in 34 patients of whom 12 had associated hypertension (HT), diabetes mellitus (DM), valvular heart diseases (pre-dominantly mitral) or chronic renal failure. We were not able to trace the final out-come of these heart failures. There were 20 patients with DM and 25 with HT and among these there were 5 with both (and as well, thyrotoxicosis). There were 12 with cancer, not site specific. There were 7 strokes of which 2 were hemorrhages.

With regards to the behavior in attending the follow-up, 8.3% did not return after the last dose of I-131, and 22% of the total attended up to 6 months only after the last dose. The lost to follow up was not necessarily related to distance travelled.

The variables, such as type of dosing (single or multiple), confidence in the uptake data (questionable or reliable uptake), thyroid status (euthyroid, probable or definite hypothyroid), and duration of follow up are summarised in the table.

There were only 387 patients who were followed and/or can be re-examined for greater than 12 months after their last dose. This represents 16776 person-months and the follow-up averages 43.3 ± 20.2 months per patient. The age of this 387 patient was 46.2 ± 11.9 years with ranges of 16-76 years and 76.8% were females. Two hundred and three patients belong to the multiple doses, given 2 to 7 times. Sixty two percent of the multiple doser were given 2 doses averaging a total of 10.4 ± 3.6 mCi for the 126 patients.

The table shows that when the uptake was questionable (abbreviated as "?UT"), the RAI dose tended to be higher as compared to when the UT was considered reliable. The same was seen with the multiple-dosing patients whether the total dose was examined (shown in the table) or whether the first dose (not shown) was evaluated [7.5 ± 3.2 vs 5.4 ± 2.1 mCi for the reliable UT]. The UT values for the non-reliable estimation of uptake were presented purely to illustrate that the malfunction resulted in very low values of UT perhaps providing the reason for the higher dosing. With regards to thyroid status among our patients, the percentage that became definitely hypothyroid at 1-3 years or after 3

Table Description of the RAI patients.

	Single dose			Multiple dose		
	all	?UT	reliable UT	all	?UT	reliable UT
N, subjects	184	81	103	203	76	127
Dose (mCi)	6.2±2.5	7.8±2.6	5.0±1.8	13.8±8.4	16.0±9.9	12.6±7.1
range	2-15	2-15	3-12	6-75	6-75	6-60
median	5.5	8	5	12	13	11
UT, %	50±26	26±10	69±17	56±25	30±17	71±15
Months followed, median	46	51	41	37	42	33
25-75 percentile	30-63	37-63	28-67	24-54	28-53	22-55
Yr 1-3 N-examined	168	73	95	180	71	109
N-status, subjects	126	50	76	145	54	91
Euthyroid, %	22	18	25	23	28	21
Hypothyroid, %	68	74	64	70	69	70
Probable hypothyroid, %	9	8	9	3	4	3
Yr > 3 N-status	119	61	58	104	48	56
Euthyroid, %	14	10	19	15	19	13
Hypothyroid, %	80	82	78	81	75	86
Probable hypothyroid, %	4	5	3	4	6	2

?UT = Uptake not reliable

N = number of patients

Dose = amount of RAI prescribed.

UT = percentage uptake of RAI by thyroid gland.

Follow up time = (median and 25th and 75th percentile) time in months starting from last dose of RAI to last seen in the division.

Yr 1-3 = patient examined or had blood tests done 1-3 years after last dose.

N-status = the number of patients whose thyroid status were known from blood tests.

Euthyroid, hypothyroid = percent of the N-status who were proven to be euthyroid, definite hypothyroid (TSH > 8 IU/l) or probable [TSH between 4 (our upper limits of normal) and 8 IU/l].

Yr > 3 = those whose thyroid status were known 3 years after the last RAI. The percentages may not add up to 100 because of decimal points, death or persisting mild hyperthyroidism.

years was about 70% and then about 80% respectively. It is reminded that the composition of the 1-3 year population versus the greater-than-3-year population was not exactly similar in that some of the patients in the 1-3 year-group were discharged or lost to follow up, while some of these previously lost returned after 3 years.

With regards to the percentage of hypothyroid among the different groups (as shown in the table) it did not appear that the groups which had questionable UT and also received higher doses of I-131, produced consistently higher percentages of hypothyroidism when compared to the groups with reliable UT.

We evaluated the change in status by examining cross-sectional-wise, a set group that can be followed for a certain duration. From the initial 387 patients who can be followed longer than 12 months after the last dose, 206 had evaluable status at 3 months. At this time, 55% were hypothyroid (note: some of these were only transiently hypothyroid) and 34% were euthyroid. The rest were either probable hypothyroid or mildly hyperthyroid. One hundred and fifty one could be followed to the 1-3 year set-up. Among the euthyroid at 3 months, 54% became hypothyroid at the 1-3 year mark, 12% were probable hypothyroid, leaving a third still euthyroid. Of the initially hypothyroid with TSH > 8 mIU/l (as stated, some may have been transiently hypothyroid), only 3% reverted to euthyroid state, the remainder became permanently hypothyroid. In summary then, this paragraph stated that if a group was euthyroid 3 months after RAI, over half (54%) will be hypothyroid about a year or so later.

Combined incidence of hypothyroid can be evaluated from the 271 out of possible 348 patients (N-status in the table) seen at 1-3 year during which time there were 69% with hypothyroid, 6% probable hypothyroid and 23% euthyroid [2% were still mildly hyperthyroid]. One hundred and forty nine could be followed past the third year. Among the euthyroid, 53% remained so while 40% became permanently hypothyroid. Those hypothyroid at 1-3 years, all remained, while those probable hypothyroid, 89% became permanently hypothyroid. Therefore, not unlike the previous paragraph, a group that was still euthyroid 1-3 years after RAI, 40% will be hypothyroid within the next few years.

DISCUSSION

We wish to re-iterate some results obtained from the present retrospective report. Examining only those who could be followed by us personally for greater than 1 year, those given single dose and multiple doses were equally divided in numbers hence it can be stated that half the hyperthyroid was 'cured' with only a single dose averaging 5-6 mCi, less so if reliance could be given to the measurement of thyroid uptake. Among those given only 2 doses, the total amount averaged 10.8 ± 4.0 for 182 patients. Hence relatively few need large doses.

With regards to the initial outcome, over half remained hyperthyroid after the first dose as seen by the proportion of patients needing multiple doses, but with further RAI eventually these became hypothyroid. Those found to be hypothyroid by TSH within the first 3 months, tended eventually to become permanently hypothyroid. About a third of those euthyroid at 3 months after the last dose remained so. The rest became definite or probable hypothyroid which add up finally to 70% hypothyroid at 1-3 years and 80% after 3 years. Similar percentages were obtained if one started with a group whose status could be followed throughout the 3-5 years. At 1-3 year, there will be about a fifth (22%) given I-131 for hyperthyroidism who remained euthyroid. This reduced to about 15%, 3 or more years after RAI.

The weaknesses of this study are many. It is retrospective. We were not able to follow every cases throughout. Each time period may consist of different patients. The distribution of thyroid status used denominator which did not take into account patients who were not followed

throughout. Hence an implicit assumption was that those lost or discharged had the same distribution of thyroid status as those remaining. Aside from this, there is no uniformity of data collection hence several of the co-morbid states could not be properly evaluated, such as, prevalence of exophthalmos, of atrial fibrillation, of heart failure and their eventual outcome. Last and most important is the lack of etiology of the hyperthyroid state. Evaluation according to the etiology may give a more useful information although with 80% eventual hypothyroidism perhaps this is not that vital. Franklyn⁽³⁾ and Bringmann⁽⁹⁾ reported different hypothyroid incidence after RAI, much higher in Graves than multimodular thyrotoxicosis.

Now to answer the objectives set forth.

Does the majority of RAI treatment need to have their thyroid uptake measured ?. If uptake measurement is absolutely essential we would expect a very high percentage needing only one dose of I-131, since uptake is part of denominator of the formula. One can argue that there are also other tangibles (e.g. size of gland, effective half-life of I-131 in any particular thyroid gland and previous antihyroid medication) in the formula. This is precisely the point why doing a routine thyroid uptake does not add precision to the regimen of treatment. Perhaps supportive but not directly so is the finding that when our uptake measurement was at fault (i.e.giving consistently too low readings) the incidences of hypothyroid and euthyroid (as shown in the table) were not different from those with reliable uptake whether RAI was given as a single or multiple doses. Franklyn⁽³⁾ prospectively evaluated an empirical 5 mCi dose among hyperthyroids and found that 34-56% re-

mained hyperthyroid not dissimilar to our data. As stated, empirical dosing of I-131 for treating hyperthyroid is frequently practised^(3-5, 9) and written up. Kaplan⁽¹⁾ listed 5 options for selecting I-131-dosage: small and repeated, large ablative, sliding scale, the formula similar to what we have used and precise dosimetry.

Franklyn⁽⁴⁾ went so far as to write "...no evidence that giving a calculated dose of radioiodine has any advantage over fixed dose of 5 or 10 mCi". There is always the argument that we may miss the case with low uptake if this is not done routinely. But how often were these seen and how often was RAI dose adjusted based on the uptake of say 20%. We further evaluated our data looking specifically at those whose uptake was considered reliable and separated the uptake less than 50% (mean $36 \pm 11\%$) versus greater than 80% (mean $87 \pm 5\%$) (N of 47 vs 108). The median first dose was similar at 5.5 and 5.0 mCi (means and standard deviations were 6.9 ± 2.4 and 4.9 ± 1.6). The median total doses for the multiple doses of I-131 for the 2 groups were 16 versus 11 mCi. The percentages of hypothyroid at 1-3 years were 66 and 69% in the low vs high uptake, and the percentages of euthyroid were 30% and 27% respectively. These results suggest that the low uptakes were given dosage schemes not related to the value of the uptake and the outcomes were also similar.

What are the proportions of thyrotoxic patients cured with RAI and how many developed hypothyroid ? Answers should be intuitively easy but on reflection, there are many factors involved, essentially, duration of follow up, dosage schemes [some studies actually aimed at hypothyroid state after the first RAI^(8, 9)] and, lastly,

the etiology of thyrotoxicosis^(3, 9). The present series, using different groups and different settings (i.e. not always the same individual in any groups), gave incidences of hypothyroidism to be about 50% in the first year (depending on when the estimation started), 70% in 1 to 3 years and 80% after 3 years. These appeared very high particularly among the single doser given an average of 5 mCi each (quoting only those with reliable uptake measurement). Low incidence of hypothyroid post RAI were quoted by Kaplan et al⁽¹⁾, 35% in 7.5 years to 50% after 10 years, and by Franklyn et al⁽⁸⁾ of 20% at 6 months following an empirical 5 mCi dose⁽³⁾. However, from the same study⁽³⁾ and looking at data from those with Graves thyrotoxicosis only and within 1 year, 59% became hypothyroid, albeit the persistent hyperthyroids were given a repeat of 10 mCi. Such high incidences were also reported by Bringmann et al⁽⁹⁾ and Sabri et al⁽⁸⁾ for Graves when given 'very' large fixed RAI (400-600 MBq). Lower incidences were seen with multinodular thyrotoxicosis when similarly treated^(3, 9). Perhaps the magnitude of the dose affects only the early incidence of hypothyroid because Sridama et al⁽⁶⁾ purposely gave a low formula-dictated dose averaging 4.9 mCi and found permanent hypothyroidism in 12% in the first year but this rose rapidly to 76% at 11 years. Another point of interest from previous reports is the persistently rising incidence of hypothyroidism at later times after RAI, 2-3% per year after 8-15 years^(1, 4, 10), and higher from Sridama et al (about 6.7% per year after 8 years). Interestingly, not too dissimilar rates were seen following surgery or with medical therapy alone^(4, 6). Perhaps the late incidence of hypothyroidism is just the natural history of the dis-

ease, if so, then a higher cumulative incidence should be seen in the medically treated Graves disease followed long term.

The high early hypothyroidism in our series then suggests a too aggressive dosage scheme, but against this was the greater than 50% failure rate. In favor of excessive dose was when we compared the patients with uptake of greater than 70% given an initial small dose (3 mCi, to represent small gland size) versus those given an initially large dose (6-8 mCi, representing large gland) and followed (some were given repeated RAI) 1-3 years or greater than 3 years. The hypothyroid rate at 1-3 year were 51 vs 41% for the presumed small versus large glands and 71 versus 53% after 3 years. Perhaps these meant a smaller gland need a disproportionately lower dosage scheme. It is also interesting that the UK guideline⁽²⁾ is fairly specific in stating that the amount of RAI for thyrotoxicosis should be such that the hypothyroid rate should not exceed 15-20% at 2 years. Perhaps, given our present lack of knowledge of the disease related to thyrotoxicosis, the dosage of RAI rests mainly on the philosophy of treatment, whether one would go for a high 'cure' rates or low 'hypothyroidism', as it is there is no precise RAI dose^(6, 10).

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