J HK Coll Radiol 2004;7:187-194

## ORIGINAL ARTICLE

# Standard-dose Prescription of Radioiodine Therapy for Thyrotoxicosis: the Queen Mary Hospital Experience

**C Kwok,[1] L Lui,[1] PM Wu,[1] M Law,[1] E Cheung,[2] A Cheng,[1] CC Yau[1]**

*[1]Department of Clinical Oncology and [2]Department of Medicine, Queen Mary Hospital, Hong Kong*

## ABSTRACT

***Objective:*** *To review the treatment outcome of a cohort of thyrotoxic patients treated with a standardised regimen of radioactive iodine.*

***Patients and Methods:*** *Between January and December 2000, a total of 177 patients with a diagnosis of thyrotoxicosis were referred to the Department of Clinical Oncology, Queen Mary Hospital, for radioactive iodine therapy. Patients' clinical records, thyroid function test results, and records of dispensed drugs were analysed to identify predictors of successful treatment outcome.*

***Results:*** *For the 149 patients who were eligible for analysis, the 1-year treatment success rate, defined as the proportion of patients who had become euthyroid or hypothyroid at 1 year after the first dose of radioactive iodine treatment, was 66%. Use of an antithyroid drug in the early post-treatment period was significantly associated with treatment failure. The cumulative rate of hypothyroidism at 1, 2, and 3 years after therapy was 57%, 66%, and 73%, respectively.*

***Conclusion:*** *The treatment results of the cohort of patients are comparable to those of patients treated in our institute using the prescribed absorbed dose method. Because the fixed-radioactivity method of prescription is much less resource-intensive and more user-friendly, we recommend its continued adoption as a routine practice.*

***Key Words:*** *Iodine radioisotopes/therapeutic use; Thyrotoxicosis/radiotherapy; Treatment outcomes*

## INTRODUCTION

Iodine 131 ($^{131}$I) is a radioisotope of iodine that produces high-energy electron particles that can be utilised for therapeutic effect. Called radioactive iodine (RAI) or radioiodine, $^{131}$I has been used as a simple, safe, inexpensive, and effective form of therapy for thyrotoxicosis for nearly half a century. However, there has been no general agreement as to the best approach to RAI dose selection.[1-5] (It should be noted that the term 'RAI dose' used in this context is quite loose and often refers to the radioactivity [in becquerels] of RAI prescribed, rather than the absorbed dose [in grays] in the thyroid tissue). There are 3 popular approaches to the selection of the optimal dose or radioactivity of RAI to be prescribed to patients with a diagnosis of thyrotoxicosis[6] — namely:

(1) Fixed administered radioactivity method, or the so-called fixed-dose method, in which a fixed radioactivity of between 110 and 185 MBq of RAI is given to all patients irrespective of the variables that affect the radiation effect to the thyroid, such as gland size, degree of uptake, or severity of disease. Some may make certain adjustments to the dose according to the degree of estimated thyroid gland size or the severity of disease.

(2) Prescribed radioactivity concentration method, in which a fixed radioactivity per gramme of thyroid is chosen — usually 55 to 110 μCi/g (or the equivalent in MBq/kg) — to deliver a dose of 50 to 100 Gy to the thyroid. The administered radioactivity is calculated according to the gland size and the percentage uptake of RAI at 24 hour in a tracer test, with the following formula:

$$\text{Administered activity } (\mu\text{Ci}) = \frac{\mu\text{Ci/g} \times \text{estimated gland mass (g)} \times 100}{\text{24-hour percentage uptake}}$$

***Correspondence:*** *Dr. C Kwok, Department of Clinical Oncology, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. Tel: (852) 2855 4225; Fax: (852) 2817 0056; E-mail: kwokch@ha.org.hk*

Submitted: 6 February 2004; Accepted: 26 November 2004.

(3) Prescribed absorbed dose method, in which the administered activity (μCi) is calculated according to the following equation[6]:

$$\text{Administered activity } (\mu\text{Ci}) = \frac{\text{Prescribed absorbed dose (rad) x gland mass (g) x 6.67}}{T_{1/2(eff)}\text{(day) x 24-hour percentage uptake}}$$

where $T_{1/2(eff)}$ is the effective (i.e., radioactive decay–uncorrected) half-life of RAI in the thyroid, which is given by the following equation:

$$\frac{1}{T_{1/2(eff)}} = \frac{1}{T_{1/2(phys)}} + \frac{1}{T_{1/2(bio)}}$$

where $T_{1/2(bio)}$ is the biological (i.e., radioactive decay–corrected) half-life of RAI in the thyroid, assuming a monotonically decreasing monoexponential time-activity curve and taking the 24-hour percentage uptake as the zero-time percentage uptake; $T_{1/2(phys)}$ is the physical half-life of $^{131}$I (8.04 days).

To determine the thyroid uptake of RAI for methods (2) and (3) above, the amount of RAI uptake in the thyroid is measured with a scintillation counter after the administration of RAI tracer dose. Because of the difficulty in measuring the absolute uptake, relative uptake is instead obtained by comparing the patient's uptake of RAI with a standard sample of RAI with usual radioactivity of 1 MBq. The 24-hour percentage uptake is the percentage of uptake in the patient, as measured at 24 hour after the administration of a tracer dose of RAI. By measuring the percentage uptake at 2 points along the uptake (time-activity) curve, the biological half-life over this period can be deduced. In clinical situations, however, even if the maximum uptake occurs at 24 hour, the biological decay may not exactly follow a monotonically decreasing mono-exponential function when successive data points for daily uptake are measured.

At the Queen Mary Hospital, the prescribed absorbed dose method had been conventionally used for prescribing the administered radioactivity of RAI in the treatment of patients with thyrotoxicosis. In applying this method for more precisely calculation of RAI radioactivity, medical physicists had derived elaborate equations to determine $^{131}$I biological half-life in order to take into account variations of the uptake curve. The corresponding effective half-life was then determined. Radioisotope thyroid scanning was also performed for gland mass estimation. On the basis of these measurements, the medical physicists calculated the radioactivity of RAI required to deliver an intended absorbed dose to the thyroid gland and recommended this to the radiotherapist for prescription. The whole process was time-consuming, as well as inconvenient to the patient, who needed to visit the clinic several times over several days for serial measurements of RAI tracer uptake. Furthermore, estimation of gland size by radioisotope thyroid scanning is highly inaccurate and has been reported to be no better than palpation performed by an experienced clinician.[7]

Since August 1996, a standard-dose prescription strategy has been adopted at the Queen Mary Hospital, in keeping with the global trend of using RAI in the management of hyperthyroidism[1,8,9] and with the Hong Kong Hospital Authority's objectives of productivity gain and service improvement in clinical departments. On the basis of the clinical assessment of the patient, a fixed radioactivity of RAI is prescribed to the patient, which usually ranges from 200 to 400 MBq, depending on the estimated gland size, disease status, and associated medical conditions. Higher radioactivities are given to patients with larger glands or nodular goitres, or to those for whom minimisation of the probability of recurrence is important, such as elderly patients with cardiac problems. Tracer testing is no longer performed routinely. In the case of suspected thyroiditis, however, a 4-hour tracer uptake measurement is performed.

The aim of this retrospective study was to analyse the treatment results of patients treated with RAI using the standard-dose prescription strategy and to assess the 1-year outcome after the first RAI treatment. From August 1996 to January 2003, a total of 1778 patients were treated with the standard dose regimen. Because of resource constraints in analysing the volume of data obtained during this period, a cohort of patients referred in the year 2000 was chosen for analysis. According to the literature, a 3-year follow-up duration is adequate to assess the early outcome of patients treated with RAI.[5]

## PATIENTS AND METHODS

A total of 177 patients with diagnoses of hyperthyroidism were referred to the Department of Clinical Oncology at the Queen Mary Hospital, from January to December 2000. Seven patients were not treated because either they refused treatment or they had normal thyroid function at the time of referral; an additional 7 patients underwent tracer testing only. Among the

remaining 163 patients who had undergone RAI treatment, 14 patients were lost to follow-up after therapy. Therefore, 149 patients were eligible for analysis.

Patients' clinical records, thyroid function test results, and records of dispensed drugs, all of which had been stored in the Clinical Management System, were reviewed. Basic clinical characteristics, the dose of RAI given, and the thyroid function status at follow-up were retrieved. Patients' thyroid function status was classified as follows:

(1) Hyperthyroid: increased free thyroxine ($T_4$) level and decreased thyroid-stimulating hormone (TSH) level;
(2) Borderline hyperthyroid: normal free $T_4$ level but suppressed TSH level;
(3) Euthyroid: both free $T_4$ and TSH levels are within the normal range; and
(4) Hypothyroid: low free $T_4$ level with normal or increased TSH level, and subsequent commencement of thyroxine replacement.

Patients who became euthyroid or hypothyroid at 1 year after the first dose of RAI were defined as having had a successful treatment outcome. Patients who remained hyperthyroid or borderline hyperthyroid, those who needed to continue antithyroid drug (ATD) therapy, and those who required a further dose of RAI within 1 year of the first dose were defined as having experienced treatment failure.

Chi-square tests were used to assess the difference in patients' baseline clinical characteristics between the success group and the failure group. Logistic regression analyses, both univariate and multivariate, were performed to identify the determinants of the treatment outcome. Statistical analysis was performed using the Statistical Package for the Social Sciences version 8.0 (SPSS Inc, Chicago, IL, United States). All statistical tests were two-tailed and p values of less than 0.05 were considered statistically significant.

## RESULTS

The baseline characteristics of the 149 patients are summarised in Table 1. The mean age of the patients was 51 years (range, 26-93 years). The female-to-male ratio was 2.5:1. The median follow-up duration was 31 months (range, 15-40 months).

Treatment before RAI therapy included an ATD for 64 patients, as follows: carbimazole for 52 patients, propylthiouracil for 10 patients, and methimazole for 2 patients. The ATD treatment was stopped 2 weeks before the start of RAI therapy. A total of 37 patients recommenced ATD treatment 5 days after RAI therapy. The mean and median durations of post-RAI ATD therapy were 91 days and 71 days, respectively (range, 19-316 days). The magnitude of RAI radioactivity that patients received during their first treatment is shown in Figure 1. The most commonly administered radioactivity was 300 MBq, followed by 250 MBq and 200 MBq.

In all, 24 patients became euthyroid and 74 became hypothyroid. Thus, treatment success was achieved in 66% of patients (Table 2). In addition, 32 patients remained hyperthyroid, of whom 21 needed further RAI therapy, and 19 had borderline cases of hyperthyroidism, of whom 5 received further RAI therapy. Thus, the treatment failure rate was 34%.

**Table 1.** Percentage distribution of patients undergoing radioactive iodine (RAI) therapy, by baseline characteristics.

| Characteristic | Patients, n = 149<br>No. (%) |
|---|---|
| Sex | |
| Male | 42 (28) |
| Female | 107 (72) |
| Status at referral | |
| 1st diagnosis | 80 (54) |
| Relapse | 69 (46) |
| Diagnosis | |
| Graves' disease | 85 (57) |
| Multinodular goitre | 6 (4) |
| Unclassified | 58 (39) |
| History of thyrotoxic related heart disease | |
| Yes | 18 (12) |
| No | 131 (88) |
| History of previous partial thyroidectomy | |
| Yes | 7 (5) |
| No | 142 (95) |
| Goitre | |
| Palpable | 70 (47) |
| Not palpable | 62 (42) |
| No record | 17 (11) |
| Exophthalmos | |
| Yes | 41 (27) |
| No | 89 (60) |
| No record | 19 (13) |
| Antithyroid antibodies (anti-thyroglobulin and/or anti-microsomal antibodies) | |
| Yes | 70 (47) |
| No | 17 (11) |
| Not done | 62 (42) |
| Pre-RAI antithyroid drug | |
| Yes | 64 (43) |
| No | 85 (57) |
| Post-RAI antithyroid drug | |
| Yes | 37 (25) |
| No | 112 (75) |

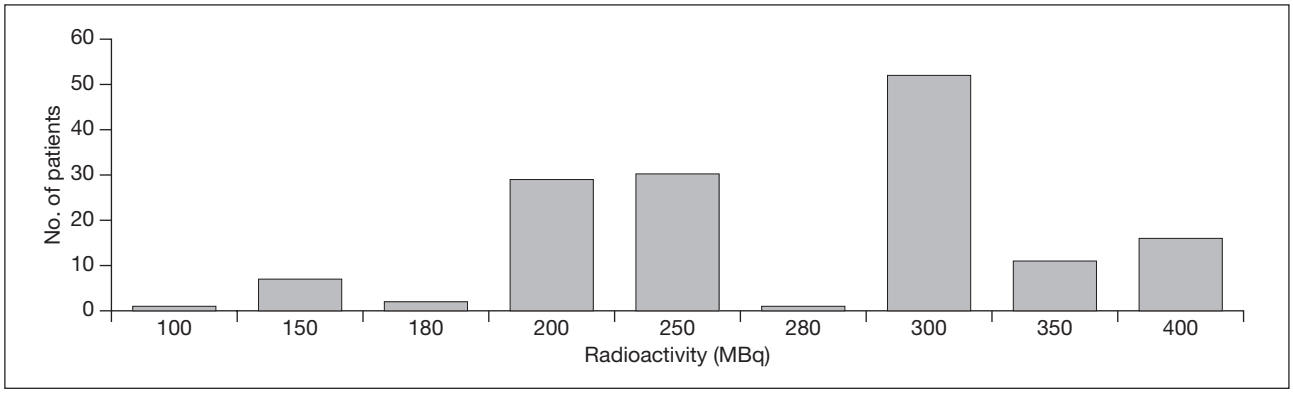


**Figure 1.** Number of patients by radioactivity of radioactive iodine used.

**Table 2.** Distribution of patients by treatment outcome at 1-year after radioactive iodine (RAI) therapy.

| Treatment outcome | Patients, n = 149<br>No. (%) |
|---|---|
| Success | 98 (66) |
| Euthyroid | 24 (16) |
| Hypothyroid | 74 (50) |
| Failure | 51 (34) |
| Hyperthyroid + further RAI | 32 (21) |
| Borderline hyperthyroid + further RAI | 19 (13) |

The distribution of patients by treatment outcome after 1 year of the first dose of RAI according to the administered radioactivity is shown in Table 3. Among the 149 patients, 26 (17%) patients received 2 doses of RAI treatment and 5 (3%) patients received 3 doses. The mean radioactivity that these patients received from RAI was 279 MBq. Notably, 13 hyperthyroid patients who underwent further RAI treatment within the first year subsequently became hypothyroid by the end of first year. Transient hypothyroidism occurred for 2 patients, who were noted to be hypothyroid at 1 year and then became euthyroid after a trial of 'off-thyroxine'. Of the 149 patients, 5 had further RAI therapy after the first year. One patient defaulted in the third half-year, 1 in the fourth half-year, and 1 in the fifth half-year. The number of patients who became hypothyroid at 1, 2, and 3 years was 85, 97, and 106; thus, the corresponding cumulative hypothyroid rates were 57%, 66%, and 73%, respectively (Table 4).

After categorisation of continuous data, chi-square tests showed that the only baseline characteristic that was significantly associated with treatment outcome at 1 year after the first RAI treatment was post-RAI use of ATD (Table 5). However, the large proportion of patients with missing data for thyroid antibody tests (42%; Table 1) could affect the validity of the test regarding this variable.

In logistic regression analyses, each selected variable was tested for its significance in predicting the treatment outcome; both univariate and multivariate analyses were used (with the forward stepwise method) [Table 6]. It was found that post-RAI ATD treatment significantly predicted treatment failure.

## DISCUSSION

The aim of optimal RAI therapy is to administer an amount of radioactivity of RAI that produces just enough damage to the thyroid gland to reduce the thyroid function to a normal state without causing hypothyroidism.[5] Despite more than half a century of experience in using RAI for the treatment of thyrotoxicosis, a universally agreed method to determine the optimal

**Table 3.** Number of patients by treatment outcome at 1 year, according to administered radioactivity of radioactive iodine at first treatment.

| Administered radioactivity (MBq) | No. of patients | | | |
|---|---|---|---|---|
| | Hyperthyroid | Borderline hyperthyroid | Euthyroid | Hypothyroid |
| 100 | 0 | 0 | 1 | 0 |
| 150 | 1 | 1 | 2 | 3 |
| 180 | 0 | 1 | 0 | 1 |
| 200 | 6 | 3 | 6 | 14 |
| 250 | 8 | 3 | 4 | 15 |
| 280 | 0 | 0 | 0 | 1 |
| 300 | 11 | 7 | 7 | 27 |
| 350 | 2 | 2 | 3 | 4 |
| 400 | 4 | 2 | 1 | 9 |

**Table 4.** Cumulative frequency of patients developing hypothyroidism after first radioactive iodine therapy, by follow-up duration.

| Follow-up (y) | Patients, n=149* Cumulative No. (%) |
|---|---|
| 0.5 | 66 (44.30) |
| 1.0 | 85 (57.05) |
| 1.5 | 93 (62.04) |
| 2.0 | 97 (65.99) |
| 2.5 | 102 (69.86) |
| 3.0 | 106 (72.60) |

*One patient each defaulted in the third, fourth, and fifth half-year.

**Table 5.** Chi-square analysis showing association between baseline characteristics and treatment outcome.

| Characteristic | Treatment outcome, n = 149 No. (%) | | p Value |
|---|---|---|---|
| | Success | Failure | |
| Sex | | | |
| Female | 75 (50.3) | 32 (21.5) | 0.076 |
| Male | 23 (15.4) | 19 (12.8) | |
| Age (y) | | | |
| 26-49 | 48 (32.2) | 29 (19.5) | 0.361 |
| 50-93 | 50 (33.6) | 22 (14.8) | |
| History of heart disease | | | |
| Yes | 11 (7.4) | 7 (4.7) | 0.657 |
| No | 87 (58.4) | 44 (29.5) | |
| History of thyroidectomy | | | |
| Yes | 5 (3.4) | 2 (1.3) | 0.747 |
| No | 93 (62.4) | 49 (32.9) | |
| Goitre | | | |
| Yes | 45 (34.1) | 25 (18.9) | 0.869 |
| No | 39 (29.5) | 23 (17.4) | |
| Exophthalmos | | | |
| Yes | 24 (18.5) | 17 (13.1) | 0.325 |
| No | 60 (46.2) | 29 (22.3) | |
| Thyroid antibodies | | | |
| Positive | 44 (50.6) | 26 (29.9) | 0.126 |
| Negative | 14 (16.1) | 3 (3.4) | |
| Pre-RAI antithyroid drug | | | |
| Yes | 39 (26.2) | 25 (16.8) | 0.281 |
| No | 59 (39.6) | 26 (17.4) | |
| Post-RAI antithyroid drug | | | |
| Yes | 12 (8.1) | 25 (16.8) | <0.01 |
| No | 86 (57.7) | 26 (17.4) | |
| Activity of RAI | | | |
| <300 MBq | 47 (31.5) | 23 (15.4) | 0.740 |
| ≥300 MBq | 51 (34.2) | 28 (18.8) | |

*Abbreviation:* RAI = radioactive iodine.

dose of RAI remains elusive.[1-5] Various dosing regimens have been practised, ranging from those based on high-precision dosimetry with ultrasound-guided volume determination of the thyroid gland, to those using large fixed-radioactivity of RAI intended to cause hypothyroidism soon after therapy.[10] Dosimetry of radioiodine therapy at the macroscopic level depends on 2 main factors: the radioiodine-avid component of the thyroid and the half-life of thyroidal iodine retention.[3] In an effort to optimise RAI therapy, complex formulae have been used to calculate the amount of radioactivity

**Table 6.** Significance levels from univariate and multivariate logistic regression analyses showing the association between selected variables and treatment outcome.

| Variables | p Value | |
|---|---|---|
| | Univariate | Multivariate |
| Sex (male vs female) | 0.078 | 0.234 |
| Age (<50 vs ≥50 years) | 0.937 | 0.995 |
| History of heart disease (yes vs no) | 0.657 | 0.226 |
| History of thyroidectomy (yes vs no) | 0.747 | 0.791 |
| Goitre (yes vs no) | 0.693 | 0.517 |
| Exophthalmos (yes vs no) | 0.326 | 0.452 |
| Pre-RAI antithyroid drug (yes vs no) | 0.281 | 0.650 |
| Post-RAI antithyroid drug (yes vs no) | <0.001 | <0.001 |
| 1st RAI radioactivity (<300 vs ≥300 MBq) | 0.581 | 0.527 |

*Abbreviation:* RAI = radioactive iodine.

needed, taking into account of the effective half-life of RAI in the thyroid and the size of the thyroid gland. The rationale is that there is a direct relationship between the radiation dose absorbed by the thyroid, the cure rate, and the amount of RAI-induced hypothyroidism.[2] However, the validity of these formulae has not been universally accepted.[11]

The equations that are used to calculate radioactivity according to the absorbed dose method make some assumptions — namely, the time-activity curve for RAI in the thyroid is expressed by a monotonically decreasing mono-exponential function and the radiation energy is uniformly distributed within the thyroid. However, kinetic studies show that RAI excretion does not usually follow a simple exponential curve.[6,11] The estimated thyroid mass, especially for very large or irregularly shaped glands, is a major source of error in determining the administered activity of RAI using the prescribed radioactivity concentration and the prescribed absorbed dose methods.[6] Although palpation results have been reported to correlate with findings from ultrasonography and surgery in estimating gland size,[7,12] palpation is highly dependent on the experience of the individual physician. Even if the accuracy of thyroidal volume can be further improved with advanced imaging techniques, such as ultrasonography, computed tomography, or magnetic resonance imaging, their limitation and accuracy to unifocal or multifocal areas of autonomy within the gland have to be established.[3]

The unpredictability of the therapeutic response to RAI therapy is also attributed to the difficulty in establishing the distribution of the absorbed dose at the cellular level and target-tissue sensitivity factors.[3] The calculated thyroid absorbed dose is regarded only as a good approximation, because of the difficulty in assessing the active mass of the thyroid in vivo and because of the

marked non-uniformity of uptake within the gland at the cellular level.[11] Thus, administering an optimal dose does not correspond with achieving an optimal treatment outcome. This issue has raised the question whether thyroid imaging and uptake measurements are a necessary prerequisite to RAI therapy.[3] Detailed volume estimation has not been shown to be beneficial in patient care; moreover, even in exact-dose calculations, outcome remains unpredictable to some extent.[2] Researchers have also commented that calculating dose prescriptions with complex formulae is not precise enough to justify its practice.[5] Therefore, effort should be directed not at unnecessary precision in volume estimation, but at dosage methods to improve patient convenience and to minimise the number of hospital visits, number of diagnostic procedures, and financial cost, while preserving the rate of successful treatment outcomes. For the purpose of RAI dose adjustment according to the thyroid volume, the categorisation of patients into volume groups is sufficient and can be performed conveniently by palpation.[2] Finally, there is also a reciprocal relationship between the incidence of hypothyroidism and the failure of initial therapy and hence the need for retreatment,[3] and it is well known that solitary nodules and multinodular goitres are more radio-resistant than Graves' disease and that large glands are less sensitive than small glands to the same dose of radioactivity administered.

Several studies have shown that calculated-dose methods do not have any benefit over the fixed-dose regimen, in terms of improving cure rates or of avoiding the development of hypothyroidism. In a prospective randomised study, Peters et al[13] directly compared the effectiveness of a standard radioactivity of 555 MBq with radioactivity calculated to deliver 100 Gy for treatment of Graves' disease. At 6 months after therapy, hyperthyroidism was eliminated in 71% (95% confidence interval, 61%-80%) of patients who had undergone the standard-radioactivity regimen and 58% (95% confidence interval: 48%-67%) of those randomised to the calculated-radioactivity regimen. Jarløv et al[4] reported another prospective randomised study comparing a fixed-dose regimen of 185, 370, or 555 MBq of RAI based on gland size as assessed by palpation only, with a calculated RAI dose based on the type of thyroid (diffuse, multinodular, solitary adenoma), accurate thyroid volume measurement, and 24-hour RAI uptake measurement. No significant difference in outcome was found between the 2 treatment regimens. The researchers concluded that a fixed-dose regimen was probably as good as the more elaborate calculated-dose approach; hence, the latter uses less time and has a higher cost-effectiveness. Kok et al[2] performed a 1-year follow-up study of 2 patient cohorts — those treated with a standardised regimen based on palpated thyroid volume and diagnosis, and those treated with a regimen based on an RAI uptake–adjusted dosimetric method. Overall outcome in patients with Graves' disease and multinodular goitre revealed similar results for both approaches, in terms of incidence of hypothyroidism, recurrent hyperthyroidism, and euthyroidism. These researchers concluded that patients with hyperthyroidism could be safely treated with a standardised method to minimise patient inconvenience and to improve procedure efficiency.

In a study by Kung et al[5] that analysed 827 patients with Graves' disease who were treated between 1968 and 1986 at our institution with the prescribed absorbed dose method, 56.7% of patients were euthyroid, 33.9% were still thyrotoxic, and 9.4% were hypothyroid at 1 year after RAI therapy. Our study found a combined euthyroidism and hypothyroidism rate of 66% at 1 year after therapy. Although the criteria for defining outcome status were somewhat different, the combined euthyroidism and hypothyroidism rate was comparable in these 2 studies. The much higher rate of hypothyroidism in our study could be explained by the generally higher radioactivity given in the present study — 272.6 MBq (standard deviation [SD], 68.7 MBq) for patients with treatment success — compared with that in the previous study — 218.3 MBq (SD, 103.6 MBq) for hypothyroid and 214.6 MBq (SD, 125.8 MBq) for euthyroid patients.

Many studies of the factors that may contribute to the outcome of RAI therapy have demonstrated that patients with larger-volume thyroid glands and severe hyperthyroidism are more likely to fail treatment with a single dose of radioiodine. Apart from the amount of RAI administered, these 2 clinical factors are widely regarded as the most reliable predictors of response to treatment.[1] Patients with toxic nodular hyperthyroidism have often been reported to be more resistant to RAI therapy than those with Graves' disease and have consequently required larger doses, presumably because of the reduced ability of suppressed normal extranodular tissue to concentrate radioiodine.[3,12,14] Allahabadia et al[1] analysed 813 hyperthyroid patients treated with 1 of 2 fixed-dose regimens and showed that male patients, younger patients, those with more severe hyperthyroidism, and

those with medium or large goitres were more likely than others to fail to respond to a single dose of RAI. The use of ATDs during the 2 weeks before or after RAI administration was significantly associated with failure of 1-dose RAI therapy. Logistic regression analysis revealed that radioactivity, sex, presence of medium or large goitres, and severity of hyperthyroidism were significant independent prognostic factors for cure after a single dose of RAI. That study, however, found almost identical cure rates among patients with toxic nodular hyperthyroidism and among those with Graves' disease. Alexander et al[10] found that young patients with larger thyroid glands, higher serum $T_4$ concentrations, higher 24-hour thyroid RAI uptake values, and ATD pretreatment for more than 4 months were at higher risk than others for treatment failure. The authors suggested that a higher radioactivity of RAI be given to these patients. Kung et al[5] also identified thyroid mass, free $T_4$ index at presentation, and 4-hour RAI uptake as the 3 variables that could predict early treatment outcome for Graves' disease; they suggested that patients with large goitres and severe disease might require higher radioactivities of RAI for treatment. The findings of all these studies provide the evidence to support the practice of using a 'sliding scale' of standardised doses.

The influence of ATDs on the outcome of RAI treatment has also received attention. Some studies have suggested that ATD treatment before or after RAI may provide a radioprotective effect for the thyroid and result in an increased failure rate of single-dose RAI treatment.[1,15-17] However, results have been conflicting, with some studies showing no effect,[18] or an effect confined to the use of propylthiouracil only.[19] The radioprotective effect of ATD has been postulated to act through various mechanisms, one of which is by altering radioiodine kinetics. Thiourea-group ATDs block the organification of iodine, thereby reducing the thyroidal iodine content and thus decreasing the absorbed dose to the thyroid.[20,21] Kung et al[21] prospectively studied the effect of adjunctive ATD and $T_4$ on the outcome of RAI therapy. Patients receiving methimazole were found to be underdosed by 22% ($p = 0.003$), and the biological half-life of RAI was also significantly shortened. In fact, some investigators have suggested increasing the delivered radioactivity of RAI empirically to compensate for the reduction in absorbed dose.[15] Others have proposed that thioureas confer radioprotection by virtue of their sulphydryl group, which acts as free-radical scavenger or inhibits peroxidase-catalysed synthesis, and hence inhibits the production of oxygen free radicals.[15,21] Contrary to the results of Kung et al, showing that ATD treatment did not affect the 1-dose cure rate with RAI, results of our study showed that post-RAI ATD treatment was significantly associated with therapy failure. Whether this failure was related to the fact that patients given ATD post-RAI generally had more severe disease thus needing ATD cover, or whether it was caused by a reduced absorbed dose as a result of decreased RAI uptake by ATD was not clear. This issue and the question of how long the interval should be between RAI dosing and ATD treatment so as not to affect the RAI absorbed dose perhaps need to be addressed in a prospective randomised study.

Although our study did not reproduce the findings described in other studies — namely, that patients with poor prognostic factors were more likely than others to experience treatment failure — our high rate of failure of the first RAI dose (34%) suggests that higher radioactivity is likely to be required for patients with larger glands or more severe disease for prompt control of their hyperthyroidism. We acknowledge several limitations of our study. There was uncertainty regarding the aetiology of thyrotoxicosis in some of the patients: the coding in the Clinical Management System was the same for thyrotoxicosis and Graves' disease. The diagnosis of Graves' disease can be made confidently only on the basis of the presence of Graves' eye signs, because clinical results from serum TSH-receptor antibody tests are not routinely available. Other clinical characteristics of Graves' disease, such as pretibial myxoedema and thyroid acropachy, were not mentioned in the patients' clinical notes. Thus, the diagnosis of Graves' disease was based mainly on the referral. The diagnosis of multinodular goitre or toxic adenoma was underestimated, because ultrasonography or radioisotope thyroid scanning was not performed for all patients. Consequently, 40% of the referred patients remained unclassified. Furthermore, some variables (i.e., thyroid gland size and pretreatment $T_4$ level) were incompletely or improperly documented, which limited further analysis of these variables with respect to the treatment outcome. These limitations highlight the importance of keeping a quality database for data analysis, which would allow the comprehensive study of factors that may contribute to treatment outcome.

## CONCLUSION

The treatment results of the present study that used fixed radioactivity of RAI in treating thyrotoxicosis are

comparable to those of studies of patients previously treated at our institution with RAI using the prescribed absorbed dose method. The standard-dose prescription strategy is therefore an efficient, cost-effective way of carrying out radioiodine treatment for thyrotoxicosis and is also convenient to the patient.

## ACKNOWLEDGEMENTS

We thank Ms Fidelia Wong for performing the statistical analyses and preparing the Figures, Mr James Luk for sorting the radioiodine therapy database, and Dr Rico Liu for assistance in the case reviews.

## REFERENCES

1. Allahabadia A, Daykin J, Sheppard JC, et al. Radioiodine treatment of hyperthyroidism — prognostic factors for outcome. J Clin Endocrinol Metab 2001;86:3611-3617.
2. Kok SW, Smit JW, De Craen, et al. Clinical outcome after standardized versus dosimetric radioiodine treatment of hyperthyroidism: an equivalence study. Nucl Med Commun 2000; 21:1071-1078.
3. Shapiro B. Editorial: Optimization of radioiodine therapy of thyrotoxicosis: what have we learned after 50 years? J Nucl Med 1993;34:1638-1641.
4. Jarløv AE, Hegedüst L, Kristensen LØ, et al. Is calculation of the dose in radioiodine therapy of hyperthyroidism worthwhile? Clin Endocrinol 1995;43:325-329.
5. Kung WC, Choi P, Lam KSL, et al. Discriminant factors affecting early outcome of radioiodine treatment for Graves' disease. Clin Radiol 1990;42:52-54.
6. Wagner HN, Szabo Z, Buchanan JW. Principles of nuclear medicine. 2nd ed. Philadelphia: Saunders; 1995:120.
7. Tannahill AJ, Hooper MJ, England M, et al. Measurement of thyroid size by ultrasound, palpitation and scintiscan. Clin Endocrinol 1978;8:483-486.
8. Royal College of Physicians of London. Guidelines on the use of radioiodine in the management of hyperthyroidism. London: Royal College of Physicians of London; Nov 1995.
9. Hedley AJ, Lazarus JH, McGhee SM, et al. Treatment of hyperthyroidism by radioactive iodine. Summary of a UK national survey prepared for the Royal College of Physicians Committee on Endocrinology and Diabetes. J R Coll Physicians Lond 1992;26:348-351.
10. Alexander EK, Larsen PE. High dose $^{131}$I therapy for the treatment of hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab 2002;87:1073-1077.
11. Watson B, Brownlie BEW, Frampton CM, et al. Outcome following standardized 185 MBq dose $^{131}$I therapy for Graves' disease. Clin Endocrinol 1988;28:487-496.
12. Nordmeyer JP, Simons M, Wenzel C, et al. How accurate is the assessment of thyroid volume by palpation? A prospective study of 316 patients. Exp Clin Endocrinol Diab 1997;105:366-371.
13. Peters H, Fischer C, Bogner U, et al. Radioiodine therapy of Graves' hyperthyroidism: standard vs. calculated $^{131}$iodine activity. Results from a prospective, randomized, multicenter study. Euro J Clin Invest 1995;25:186-193.
14. Farrar JJ, Toft AD. Iodine-131 treatment of hyperthyroidism: current issues. Clin Endocrinol 1991;35:207-212.
15. Sabri O, Zimny M, Schulz G, et al. Success rate of radioiodine therapy in Graves' disease: the influence of thyrostatic medication. J Clin Endocrinol Metab 1999;84:1229-1233.
16. Hancock LD, Tuttle RM, LeMar H, et al. The effect of propylthiouracil on subsequent radioactive iodine therapy in Graves' disease. Clin Endocrinol 1997;47:425-430.
17. Tuttle RM, Patience T, Budd S. Treatment with propylthiouracil before radioactive iodine therapy is associated with a higher treatment failure rate than therapy with radioactive iodine alone in Graves' disease. Thyroid 1995;5:243-247.
18. Marcocci C, Gianchecchi D, Masini I, et al. A reappraisal of the role of methimazole and other factors on the efficacy and outcome of radioiodine therapy of Graves' hyperthyroidism. J Endocrinol Invest 1990;13:513-520.
19. Imseis RE, Vanmiddlesworth L, Massie J, et al. Pretreatment with propylthiouracil but not methimazole reduces the therapeutic efficacy of $^{131}$I in hyperthyroidism. J Clin Endocrinol Metab 1998;83:685-687.
20. Ahmad AM, Ahmad M, Young ET. Objective estimates of the probability of developing hypothyroidism following radioactive iodine treatment of thyrotoxicosis. Euro J Endocrinol 2002; 146:767-775.
21. Kung WC, Yau CC, Cheng A. The action of methimazole and L-thyroxine in radioiodine therapy: a prospective study on the incidence of hypothyroidism. Thyroid 1995;5:7-12.