Results of Long-term Follow-up After Compensated Fixed-dose Therapy for Thyrotoxicosis

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To evaluate the effects of simple compensated fixed-dose iodine-131 therapy for thyrotoxicosis, the long-term results for 74 patients treated with a fixed dose of iodine-131 ranging from 5 to 12 mCi (185 to 444 MBq) were evaluated in the first 2 years of a trial. The dose selected was loosely based on the gross size of the thyroid gland. Routine antithyroid drug therapy was given for a minimum of 3 months after iodine-131 therapy. The mean (± SD) duration of follow-up was 74.5 ± 42 months. The results indicated that roughly 25% of patients treated in this way will become hypothyroid after 5 years and that 85% are cured (need no further therapy during the follow-up period) using a single dose of iodine-131. Of those cured using a single iodine-131 dose, 81% were no longer receiving drugs after 6 months and 85% after 1 year. Such a regimen seems currently to be among the best available where prolonged periods of medication-free euthyroidism after therapy are sought.

KEY WORDS: IODINE-131; THYROTOXICOSIS; GOITRE; HYPOTHYROIDISM
INTRODUCTION

Although spontaneous remission of clinical thyrotoxicosis has been recorded, the vast majority of patients ultimately require surgery or iodine-131 therapy. There are two basic approaches to dosing in iodine-131 therapy—ablative and non-ablative. Ablative therapy usually aims at using a fixed dose near the upper limit of the therapeutic range and results in a high incidence of early hypothyroidism. This approach has not gained widespread acceptance because of uncertainty about the frequency of default, the numbers of non-compliant patients who later discontinue thyroxine, the adequacy and efficiency of follow-up, or possible complications, such as cancer of ischaemic heart disease. In non-ablative therapy, lower doses of iodine-131 are administered in an effort to minimize the occurrence of hypothyroidism, and reduced incidences of hypothyroidism result. This approach, however, has been associated with an increased incidence of treatment failure and prolonged morbidity due to hyperthyroidism. It is now known that lower rates of hypothyroidism and lower incidences of treatment failure are mutually exclusive, and that hypothyroidism is an inevitable consequence of iodine-131 therapy since it appears that the risk of thyroid failure continues for life, even with the lowest reported doses of iodine-131. The best approach, therefore, is to strike a balance between the two courses and offer the patient the maximum possible period of euthyroidism, which can be of great value, especially in the elderly.

Low-dose regimens have essentially either used fixed doses or have utilized various parameters to estimate an ideal delivered dose of radiation to the thyroid. Compensated delivered dose regimens have also been formulated in which the delivered dose is titrated for the size of the thyroid gland; however, the estimation of the radiation dose delivered to the thyroid gland is complicated and attempts to use estimates of these measurements in the individual patient have all suffered from the same basic flaw: the assumption that all the important differences between individuals regarding iodine-131 dosimetry can be predicted from the individual factors involved, usually gland mass and iodine-131 uptake.

Although some of the individual variability is generally ascribable to these factors, other factors may be more important. It has been shown, for example, that there is an uneven distribution of radiation through the thyroid gland and it has been calculated that there could be a 100-fold difference between the highest and lowest dose received in any one gland. Estimating the overall size of the thyroid is also thwart with difficulties and determining the cellular mass of a particular thyroid gland is even more problematical since amounts of fibrous and interstitial tissue, and the volume of relatively radio-resistant colloid all vary. As a consequence, the clinician cannot assume that the predicted delivered dose, based on the estimated thyroid gland mass and iodine-131 uptake, will be attained in a particular patient; in general, the dosage delivered by the various methods of individualizing therapy can be no more than an estimate. Furthermore, even if dosimetry were standardized, individual sensitivity to iodine-131 varies and is as yet unquantifiable.

A regimen was, therefore, introduced in the University Hospital, University of Malaysia, Kuala Lumpur in late 1979 that aimed to provide a reasonably good period of medication-free euthyroidism coupled with a reasonably low failure rate based on a rough estimate of the delivered radiation dose. Reported below are the preliminary results of long-term follow-up of the first group of patients treated with what may be termed a compensated fixed-dose regimen.
PATIENTS AND METHODS

PATIENTS
Hyperthyroid patients included in the present study were referred to the University Hospital, Kuala Lumpur, during the period 1979–1981 for further management of thyrotoxicosis. The diagnosis of hyperthyroidism was based on clinical findings in conjunction with elevated serum thyroxine concentrations, resin uptake and, in some cases, thyroid uptake studies.

STUDY DESIGN
Patients had, in general, first been treated with a full course of antithyroid medication (carbimazole or propylthiouracil for at least 1 year), being considered for iodine-131 therapy after they relapsed. The iodine-131 was delivered to patients in approximately euthyroid state, as far as possible. All medication was discontinued 7 days before therapy (since it is documented that antithyroid drugs decrease the amount of iodine in the thyroid gland?) and 7 days after therapy patients were recommenced on antithyroid medication for 3 months (10 mg/day carbimazole or 100 mg/day propylthiouracil), after which medication was stopped. Patients who still showed symptoms of thyrotoxicosis after stopping the drugs were given further drugs for up to about 24 months, when retreatment with iodine-131 was carried out.

The therapeutic dose of iodine-131 was based on the size of the gland alone. The uptake studies previously performed and the presence of nodularity in the gland on palpation were disregarded for dosage purposes. Goitres were classified on a grading scale of 0–III: grade 0, no clinically detectable (or just palpable) goitre; grade I, mild enlarged goitre; grade II, moderately enlarged goitre; and grade III, excessively enlarged goitre. The weight of the thyroid gland was roughly estimated based on the assumption that common clinically detectable goitres are in the range 20–100 g. It was, therefore, assumed that grade I goitres would weigh about 40 g and grade II goitres about 80 g. Fixed doses of 5, 7, 10 and 12 mCi, respectively, were given to grades 0, I, II and III goitres. Patients who were eventually given further treatment were treated with a different dose. Hypothyroidism was established on the basis of clinical signs in conjunction with an elevated serum concentration of thyroid-stimulating hormones.

The patients were followed up once every 3 months for the first year, thereafter, the patient was assessed every 6 months if he/she remained euthyroid.

STATISTICAL ANALYSIS
Data were analysed by the Kaplan–Meier product limit method, which indicates the probability of hypothyroidism during the follow-up years rather than the actual number of cases occurring in the group of patients treated in the individual years. This was preferred to the actuarial (life table) methods since it overcomes bias if there are a large number of withdrawals and if withdrawals do not occur mid-way in a time interval. Bivariate comparisons of nominal data were made using Fisher’s exact test because small sample sizes were encountered in the retreated group. Comparisons of continuous variables in two samples were made with the Mann–Whitney or Wilcoxon two-sample test.

RESULTS
A total of 74 patients were surveyed, of whom 16 (21.6%) were male and 58 (78.4%) female, and the mean (± SD) age was 46.9 ± 7.9 years. Of these patients, 64 (86.5%) required only a single dose of iodine-131, eight (10.8%) received two doses, one (1.4%) three doses and one (1.4%) four doses. The mean (± SD) duration of follow-up for the whole group was 74.5 ± 42 months. The numbers of patients

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with diffuse goitre, multinodular goitre, uninodular goitre and no goitre were 49 (66.2%), 15 (20.3%), two (5.4%) and one (1.4%), respectively; the remaining five patients were unclassified. A total of nine (12.2%) of the patients had undergone surgical treatment (sub-total thyroidectomy). The mean interval between diagnosis and first iodine-131 therapy was 45.6 ± 50.4 months (range < 1 - 204 months). The ethnic origins of the patients included in the study were 59 (79.7%) Chinese, 10 (13.5%) Malay and five (6.8%) Indian.

Bivariate comparisons of the single-dose and retreated patients showed that in the Malay patients there was a higher incidence of retreatment than in either the Chinese group alone, or the Chinese and Indians combined; the minimum follow-up period was 3 years. There was no statistically significant difference in the sex distribution, the sizes of goitres, or the surgical status of patients who did or did not need retreatment. Comparisons of the mean age, initial dose and interval between diagnosis and therapy also showed no statistically significant differences between the two treatment groups. The mean (± SD) initial doses of iodine-131 were 8.34 ± 1.8 mCi (308.6 ± 66.6 MBq) for the single-dose group and 8.6 ± 2.1 mCi for the repeated-dose group.

The proportion of the original group followed-up at each month after therapy and the corresponding probability of thyroid failure in that month are shown in Fig. 1 for the single-dose group. Overall, there was a consistent fall in the proportion of patients remaining in the study of about 80% per year ($n = 0.98$); the mean duration of follow-up was 69.9 months (median 68 months) in the group given one dose only. The mean (± SD) period of antithyroid drug therapy was 8.0 ± 15

**Figure 1**

Percentage of thyrotoxicosis patients (n = 74 initially) followed up after treatment with iodine-131 and percentage (of those followed up) that developed hypothyroidism during each month after therapy.

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months (median and mode, 3 months; 75 percentile, 5 months) for those given only one dose of iodine-131 (minimum follow-up period 1 year). The mean period of antithyroid medication following the second dose of iodine-131 (for those receiving two doses only) was 2.0 ± 1.7 months. Retreatment was carried out in a mean (± SD) of 23.2 ± 9.2 months after therapy range (8 – 40 months). Of those given two doses of iodine-131, five (62.5%) became hypothyroid in a mean (± SD) time of 16.8 ± 16.0 months; the remaining three (37.5%) were euthyroid for mean periods of up to 75.5 ± 27.0 months when they were lost to follow-up. Among patients with a minimum follow-up of 3 years the retreatment rate was 15% (cure rate, 85%). Cumulative incidences of hypothyroidism at 3.5 years and 5.5 years were 5.7% (95% confidence interval, 1 – 12%) and 22.2% (95% confidence interval, 9 – 35.4%), respectively, for those given only one dose of iodine-131 (Fig. 2). The percentages of patients that have survived without developing hypothyroidism are shown in Fig. 3.

**DISCUSSION**

The reasons for the considerable loss of patients to follow-up are unclear, although the drop-out rate was similar to that in a previously reported study in which the mean follow-up was 74 months and the median 60 months. It seems likely that patients who develop hypothyroidism are more likely to attend and those that do not are predominantly euthyroid. It cannot, however, be assumed that this is so, because other authors have attempted to relocate lost patients and reported that the incidence of hypothyroidism in this default group was the same as that in the patients who had been followed up.
Mean cumulative percentages of thyrotoxicosis patients treated with iodine-131 that had not yet become hypothyroid; the upper and lower plots represent the 95% confidence limits.

continuously. Attempts are currently being made to recall defaulters in the present study for further analysis.

The results of the present long-term study do not indicate any remarkable differences between the responses to therapy in patients with multinodular or diffuse goitres, although there has always been a wide variation of views about the appropriate treatment for toxic nodular goitre. The results of the present study are consistent with those of previous studies, in which patients with nodular goitres were more frequent and 1-year cure rates were relatively unaffected by gland type (impalpable, diffuse, or nodular) or post-operative status of the patients. Cure rates of 66 – 73% (overall 69%) have been reported in all these clinical groups following iodine-131 doses estimated to deliver 7000 rads to the thyroid. In the present study, four patients had a uninodular goitre, one of whom required three doses of iodine-131, one was cured with one dose (and remained euthyroid for 114 months) and the other two were not followed up sufficiently to determine their outcome.

Non-ablative therapy has commonly been administered in two forms, either as a fixed dose of radioiodine or as a dose estimated to deliver a predetermined amount of radiation. For the latter method, it has been suggested that the administered amount of iodine-131 given should ideally deliver a radiation dose of 6000 – 7000 rads (60 – 70 Gy), and 7000 rads has become regarded as a conventional dose. Following the administration of such iodine-131 doses in patients with thyrotoxicosis, 60 – 70% of patients have been reported to be euthyroid within 1 year after a single dose, the remaining patients needing retreatment. Within 6 months of the initial dose, roughly one-half of the patients can be expected to be rendered
euthyroid, with roughly 10 – 20% more achieving euthyroidism within the year.\textsuperscript{12,14,16} This cure rate is comparable to that of the present regimen where 81% of those receiving one dose of iodine-131 were receiving no medication and 69% were euthyroid after 6 months, and 85% were not receiving drugs and were euthyroid after 1 year. Rates of hypothyroidism after 1 or 2 years for patients given iodine-131 doses estimated to deliver 7000 rads have been reported to be approximately 10\%,\textsuperscript{11,12,14} which is comparable to an upper limit on the 95\% confidence interval of 5 – 9\% in the present study. The late incidence rate of hypothyroidism after 10 years has been reported to be relatively constant at about 2 – 4.5\% per year for iodine-131 doses ranging from 25 to 200 \(\mu\)Ci/g of thyroid.\textsuperscript{17,18} In this study, the rate in the first 5 years was 2.5\% per year and, in the subsequent 4 years, was 5.7\% per year. The rise in rates of hypothyroidism in the later years seems to be consistent with the suggestion that the patients lost to follow-up were predominantly euthyroid.

Compensated radiation dose therapy, as opposed to fixed-dose therapy, was originally developed following the finding that doses estimated to deliver a fixed amount of radiation to the thyroid resulted in rates of hypothyroidism that were highest in those with small goitres and decreased with increasing goitre size.\textsuperscript{10,11} An analysis of the response to first treatment in relation to the estimated weight of the thyroid gland in one of the previous studies did show a statistically significant rise in the percentage of patients remaining hyperthyroid with increasing gland mass\textsuperscript{11} and thus also supported the view that compensation for gland mass was required. Compensated doses, in general, delivered 3000 – 5000 rads since more than 90\% of the patients reported were estimated to have glands weighing less than 50 g, and these doses resulted in cure rates of approximately 66 – 76\% after about 1 year.\textsuperscript{10,20} Other compensated low-dose regimens (average dose probably in the same range as those above) reported cure rates of 83\% at 1 year (including the 10\% of patients who were hypothyroid at 1 year).\textsuperscript{20} Only 64\% of patients, however, were cured without the need for additional therapy; 19\% required supplementary antithyroid drug therapy before eventually becoming euthyroid at 1 year.\textsuperscript{20} Most patients given antithyroid medication will eventually no longer be hyperthyroid. There is, however, no advantage in giving regimens that require additional prolonged antithyroid medication as these patients will also eventually become hypothyroid (albeit over a longer period of time).\textsuperscript{10} Not much difference has been reported in the rates of hypothyroidism obtained with earlier compensated regimens compared with non-compensated regimens; both regimens resulted in 1-year rates of hypothyroidism of approximately 10\%.\textsuperscript{10,15,20} Neither compensated nor non-compensated estimated radiation dose therapy, therefore, showed superior results to the present study utilizing fixed doses (with compensation only for the approximate gland weight).

Although the lower rate of hypothyroidism expected for the compensated regimens compared with non-compensated ones was not discernible, non-compensated dosing regimens that on the average delivered similar doses to those compensated regimens have resulted in poorer outcomes. In one study where iodine-131 was given at a dose of 50 \(\mu\)Ci retained at 24 h/g of thyroid tissue (approximately 4000 rad anticipated dose), there was a 7.1\% incidence of hypothyroidism and a cure rate of 46\% at 1 year (i.e. 54\% of patients were still hyperthyroid at 1 year).\textsuperscript{21} Another study, in which roughly 3500 rads were delivered, similar results were observed, with 65\% of patients being hyperthyroid after 1 year and a rate of hypothyroidism of 4.3\%.\textsuperscript{12} Better outcomes have, however, been reported.
from other low-dose studies. In one such study where slightly higher doses were given (80 μCi per estimated g of thyroid tissue was given, mean radiation absorbed dose 5578 rads), 74% of patients were cured and 6% were permanently hypothyroid after a mean follow-up period of 19 ± 6 months. Higher cure rates were observed in this study possibly because of the routine administration of potassium iodide and, perhaps, the use of of higher iodine-131 dosages.

It may, therefore, be inferred that compensation for the size of the gland may increase the ability of a particular dose to bring about a cure. The reason why the rates of hypothyroidism induced by the consequent lower doses of iodine-131 are not lower is probably due to the fact that rates rise much faster for increases in doses above 7000 rads. This phenomenon has also been observed using fixed doses: after a iodine-131 dose of 2 mCi (74 MBq) 6% of patients were reported to be hypothyroid after 1 year and after a fixed 5 mCi (185 MBq) dose 15.5% were hypothyroid at 1 year. Following a 10 mCi dose, however, 61 – 69% were hypothyroid at 1 year. By contrast, as the radioactivity dose is varied, the cure rates at 1 year are less markedly affected. After the administration of 2 mCi (74 MBq) iodine-131, cure has been reported to be 55% at 1 year (excluding those that relapsed later, for whom the cure was 62%) and, among patients treated with fixed doses of 3 – 10 mCi iodine-131, 76.2% were cured, patients being considered to be cured if the functional status at 1 year was either euthyroid or hypothyroid without further treatment for hyperthyroidism during the year.

Classifying of these patients according to the dose administered resulted in no significant increase in the proportion cured by 3 – 5 mCi, but there was a significant increase with the administration of 5 – 10 mCi iodine-131 (5 mCi iodine-131, 70% cure rate; 10 mCi iodine-131, 87% cure rate). This is in agreement with other studies utilizing fixed iodine-131 doses of 5 mCi (185 MBq), in which the cure rate was 72% and following 10 mCi (370 MBq) iodine-131 81 – 88% of patients were reported to be cured at 1 year. Increasing the dose above 10 mCi did not result such big increases in cure rate as did the increase from 5 to 10 mCi iodine-131. A compensated fixed dose in the range 5 – 10 mCi thus seems to offer the best chance for lower rates of hypothyroidism combined with good cure rates. The results of the present study, and of parallel approaches to therapy, are consistent with this conclusion.

The vast number of different approaches to minimizing post-iodine-131 hypothyroidism, and the similarities of the results obtained, provides one of the primary reasons why there is still no conventionally accepted regimen for iodine-131 in the treatment of thyrotoxicosis. It seems that real progress in this field must await the methodological breakthroughs that will increase understanding of the biology of Graves’s disease and the interaction of that biology with radiation-induced aberrations at the subcellular level. In the meantime, the present therapeutic regimen offers a simple approach to therapy and may provide a good balance between hypothyroidism and treatment failure in patients with thyrotoxicosis where prolonged periods of euthyroidism are sought.
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