

Usage of a fixed dose of radioactive iodine for the treatment of hyperthyroidism: one-year outcome in a regional hospital in Hong Kong

Joyce SY Yau 丘思欣

KS Chu 朱競新

June KY Li 李錦燕

KW Chan 陳健華

IT Lau 劉業添

SW Yum 任紹榮

CW Chan 陳俊嶸

Loar KK Mo 巫家強

WK Kwan 關煒強

Objectives To evaluate the efficacy of a fixed dose of radioactive iodine (¹³¹I) in the treatment of thyrotoxicosis, and to identify risk factors associated with treatment failure.

Design Retrospective study.

Setting Thyroid Clinic of a regional hospital in Hong Kong.

Patients Patients receiving their first dose of radioactive iodine for the treatment of thyrotoxicosis during the inclusive period September 1999 to August 2004.

Main outcome measures Relapse rate and time to relapse.

Results A total of 113 patients received a fixed dose of 5 mCi (185 MBq), 6 mCi (222 MBq), 8 mCi (296 MBq), and 10 mCi (370 MBq) ¹³¹I in a proportion of 1:6:71:35. At 1 year, 42 (37%) of the patients had relapsed, of which 69% received a second ¹³¹I dose. The median time to relapse after first receiving ¹³¹I was 4 months. At 1 year, the remaining 71 (63%) of the patients were successfully treated; 46 (41%) were euthyroid, and 25 (22%) had become permanently hypothyroid. Basal free thyroxine level and goitre size were significantly associated with a relapse rate after a single dose of ¹³¹I; larger goitres showed a trend towards high rates of relapse. Patients pretreated with propylthiouracil had a higher rate of relapse during the first year after radioactive iodine than those pretreated with carbimazole, but the difference was not significant when combined with other pretreatment variables.

Conclusions A single fixed dose of radioactive iodine is a simple, safe, and effective treatment for hyperthyroidism. High basal free thyroxine concentration and large goitre size are associated with higher chance of relapse. Higher radioiodine doses may be considered to improve the cure rate.

Key words

Graves disease; Iodine radioisotopes;
Thyrotoxicosis; Treatment failure;
Treatment outcome

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Introduction

Radioactive iodine (¹³¹I) is increasingly used as first-line therapy for Graves' hyperthyroidism and is the treatment of choice for relapsed Graves' disease and toxic nodular hyperthyroidism. The aim of treatment is to cure the hyperthyroidism by rendering the patient either euthyroid or hypothyroid. Despite more than half a century of experience, there is still little agreement regarding the most appropriate dosage regimen.¹ Regimens used have included various fixed doses²⁻⁵ and calculated on the basis of thyroid size, the uptake of radioiodine, or the turnover of radioiodine (¹³¹I).^{2,5,6} Most dosimetric methods have the benefit of administering an amount of radioactive iodine that is proportional to the size of the gland, which theoretically increases the probability of cure. However, studies have failed to demonstrate either an improvement in cure rate or prevention of hypothyroidism in comparison to a fixed dose of radioiodine.^{5,7,8}

Moreover, the influence of pretreatment with anti-thyroid drugs on the efficacy of radioiodine therapy is controversial. Some studies suggest relative radio-resistance in those prescribed anti-thyroid drugs before or after radioactive iodine dose,⁹ but others have shown no effect,⁶ or an effect confined to propylthiouracil (PTU) only.¹⁰

In our study, we therefore aimed to evaluate the efficacy of fixed-dose radioiodine for the treatment of thyrotoxicosis and identify any risk factors predicting treatment failure.

Department of Medicine, Yan Chai Hospital, 7-11 Yan Chai Street, Tsuen Wan, Hong Kong

JSY Yau, FHKCP, FHKAM (Medicine)

JKY Li, FRCP (Edin), FHKAM (Medicine)

CW Chan, FHKCP, FHKAM (Medicine)

LKK Mo, FRCP (Edin), FHKAM (Medicine)

WK Kwan, FRCP (Edin), FHKAM (Medicine)

Nuclear Medicine Unit, Queen Elizabeth Hospital, Kowloon, Hong Kong

KS Chu, FHKCR, FHKAM (Medicine)

Department of Medicine and Geriatrics, Princess Margaret Hospital, Laichikok, Hong Kong

KW Chan, FRCP (Edin), FHKAM (Medicine)

Department of Medicine, Tseung Kwan O Hospital, Tseung Kwan O, Hong Kong

IT Lau, FRCP (Edin), FHKAM (Medicine)

Premicare Medical Practice, Hong Kong

SW Yum, MB, ChB

Correspondence to: Dr JSY Yau
E-mail: yauseeyun@yahoo.com.hk

回顧一所區域醫院在使用定劑量放射碘於治療甲亢一年後的結果

目的	評估定劑量放射碘對治療甲亢的成效，及找出治療失敗的高危因素。
設計	回顧研究。
安排	香港一所區域醫院的甲狀腺門診部。
患者	1999年9月至2004年8月期間，接受首次放射碘作治療甲亢的病人。
主要結果測量	復發率及復發時間。
結果	113名病人接受5、6、8、10 mCi (185、222、296、370 MBq)的定劑量放射碘（以1:6:71:35的比率分佈），42名病人（37%）在一年內甲亢復發，其中69%接受第二次放射碘治療。在接受放射碘後，復發時間的中位數為4個月。一年後，其餘71名病人（63%）成功治癒，當中46名病人（41%）甲狀腺素正常，25名病人（22%）長期甲狀腺素低。高fT4水平和甲狀腺腫大對接受單一放射碘治療後甲亢復發有明顯影響。甲狀腺越大對甲亢復發的影響越大。病人在接受放射碘治療前服食propylthiouracil跟服食carbamazole有較大機會於一年內甲亢復發，但當綜合其他治療前的變數作統計卻沒有明顯差別。
結論	單一劑量放射碘是一個簡單、安全和有效的甲亢治療方法。研究指出高fT4水平和大甲狀腺增加甲亢復發的機會。更高劑量放射碘或較能增加治療的成功率。

Methods

Patients

This was a retrospective review of patients treated with radioiodine for thyrotoxicosis in Princess Margaret Hospital from September 1999 to August 2004. All patients had clinical signs and symptoms of thyrotoxicosis with elevated thyroid hormone levels and suppressed thyroid-stimulating hormone (TSH) concentrations. Graves' disease was diagnosed on the basis of clinical and biochemical hyperthyroidism together with the presence of either a palpable diffuse goitre, a significant titre of thyroid microsomal and/or thyroglobulin autoantibodies, or the presence of dysthyroid eye disease. Toxic nodular goitre was defined as hyperthyroidism in the presence of a palpable nodular goitre. Patients who had a history of thyroidectomy or who had received radioiodine before September 1999 were excluded from our study. Patients lost to follow-up within 1 year of 131-I therapy or whose record was lost were also excluded.

Clinical data before radioactive iodine therapy

Baseline characteristics obtained included: age at diagnosis, gender, presence of eye disease, size of goitre, duration of hyperthyroidism, type of anti-

thyroid drug used before radioiodine, duration of anti-thyroid drug use, the period of time-off therapy before 131-I administration, and its indication. Goitre sizes were categorised on the basis of physical examination: none (gland impalpable or normal in size), small (thyroid palpably enlarged but not visible), and medium or large (palpable and visible goitre). Thyroid function tests included: TSH, free thyroxine (fT4) concentration, total thyroxine (TT4) concentration, free triiodothyronine (fT3) concentration, or total triiodothyronine (TT3) concentration. These were performed if applicable, at diagnosis and before taking 131-I.

Thyroid-stimulating hormone was measured by immunofluorometric assay (Delfia; Wallac Oy, Turku, Finland) before 2003, then changed to chemiluminescent microparticle immunoassay (CMIA) [Abbott Architect i2000; Abbott Diagnostics, Abbott Park (IL), US] after 2003. Free thyroxine level was measured by CMIA using the Abbott Architect i2000 kit before August 2002. Subsequently it was changed to a CMIA involving Immulite 2000 (Siemens Healthcare Diagnostics, Los Angeles, US). From August 2003, an enzyme immunoassay using the Abbott AxSYM kit (Abbott Diagnostics, Illinois, US) was used.

Treatment protocol

For patients referred for radioiodine treatment of hyperthyroidism, from September 1999 a standard protocol was implemented by the Nuclear Medicine Department in Princess Margaret Hospital. Anti-thyroid drugs and seafood were stopped at least 2 weeks before treatment. From October 2001, all patients underwent a 24-hour radioiodine uptake scan using 131-I 1 week before 131-I treatment. Thereafter, use of anti-thyroid drugs and intake of seafood were also stopped (for at least 3 weeks) prior to receiving any 131-I. Patients were assessed by the nuclear physician 1 week before 131-I therapy. A fixed dose of 8 mCi 131-I was given to all the patients. Some patients were also given a fixed dose of 6 mCi or 10 mCi, depending on the clinical and laboratory findings of that individual, including goitre size, severity of hyperthyroidism, thyroid uptake scan result, and thyrotoxic complications. Each patient was assessed within 7 to 10 days of radioiodine therapy, at which point adjuvant anti-thyroid drugs were started, if necessary. Thyroid function test results (for TSH, fT4 or TT4, fT3 or TT3) were monitored during subsequent follow-up.

Outcome after radioactive iodine therapy

In our study, the patient's thyroid status 1 year after radioiodine therapy was the primary outcome. Relapse was defined as clinical and biochemical

evidence of hyperthyroidism (elevated thyroid hormone concentration and suppressed TSH level) within 1 year, which triggered further radioiodine therapy or continuation of anti-thyroid medication 1 year later. Hypothyroidism was defined as persistent, low thyroxine concentration and an elevated TSH level within 12 months of therapy, and the initiation of levothyroxine replacement for the patient. Euthyroidism was defined as the patient having a normal thyroid hormone concentration and no anti-thyroid medication or a normal TSH concentration and no levothyroxine therapy at 1 year.

Statistical analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences (Windows version 13.0; SPSS Inc, Chicago [IL], US). A P value of less than 0.05 was taken as indicating statistical significance. The baseline characteristics of patients with and without relapse were compared using the Chi squared test for qualitative variables or by independent sample *t* tests for quantitative variables. Multivariate analyses of the baseline characteristics were reassessed using logistic regression. Survival analysis using Kaplan-Meier curves was used to estimate the time to relapse. Comparison of time to clinical outcome was assessed with the log-rank statistic.

Results

Between the inclusive period September 1999 and August 2004, a total of 145 patients had received radioactive ¹³¹I in the Nuclear Medicine Department in Princess Margaret Hospital. Among these, 17 patients had received prior ¹³¹I in another hospital, four had a history of thyroidectomy, nine were lost to follow-up, and the medical records of two were missing. The remaining 113 eligible patients were evaluated.

The pretreatment baseline characteristics of these patients are shown in Table 1. Their mean age at presentation was 39.9 years, and the male-to-female ratio 1:2.8. In all, 106 (94%) patients had Graves' disease. Most patients (48%) had small goitres. Twenty-four (21%) subjects were referred to have ¹³¹I as primary treatment, and 84 (74%) experienced toxic relapse. All the patients had received either carbimazole (81%) or PTU (18%) before ¹³¹I treatment.

In all, 71 (63%) of the patients received a fixed dose of 8 mCi ¹³¹I, whereas 35 (31%) received 10 mCi; only six patients received 6 mCi, and one patient received 5 mCi. At 1 year, 42 (37%) of the patients had persistent hyperthyroidism or relapsed (Fig 1). The median time to relapse was 4 months (interquartile range [IQR], 3-7 months) [Fig 2]. Among the toxic group, 29 (69%) of the patients received a second

TABLE 1. Pretreatment baseline characteristics of the 113 eligible patients

Demographic or clinical characteristic*	Data†
Age at diagnosis (years)	39.9±14.9
Gender (M/F)	30/83
Duration of hyperthyroidism before ¹³¹ I (months)	35±33 (interquartile range, 9-50)
Graves' disease:nodular goitre	106:4
Goitre size (none/small/medium or large)	36/54/23
Ophthalmopathy (nil/mild/moderate/severe)	81/27/4/1
Pretreatment with ATDs (CMZ/PTU/others)	92/20/1
Duration of ATD therapy before ¹³¹ I (months)	29.5±18.4
Indication of ¹³¹ I (primary/relapse/complication)	24/84/1
24-Hour ¹³¹ I uptake (%)	61.6±13.6
¹³¹ I Dose (5/6/8/10 mCi)	1/6/71/35
Free T4 at diagnosis (x upper limit of normal)	3.3±1.6
Total T4 at diagnosis (x upper limit of normal)	2.0±0.7

* ¹³¹I denotes iodine-131, ATD anti-thyroid drug, CMZ carbimazole, PTU propylthiouracil, and T4 thyroxine

† Data are shown as number of patients or mean±standard deviation, unless otherwise indicated

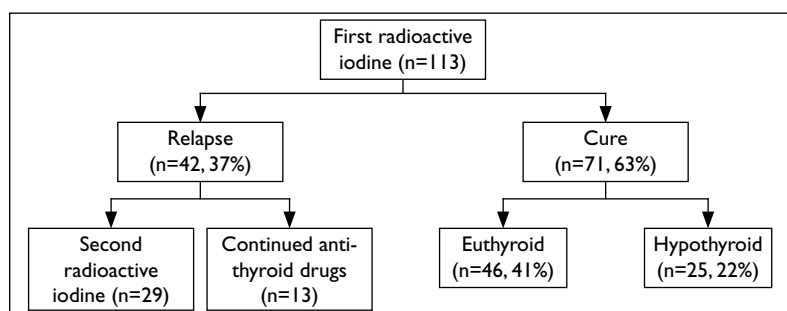


FIG 1. Schematic diagram of 1-year outcome after first radioactive iodine dose

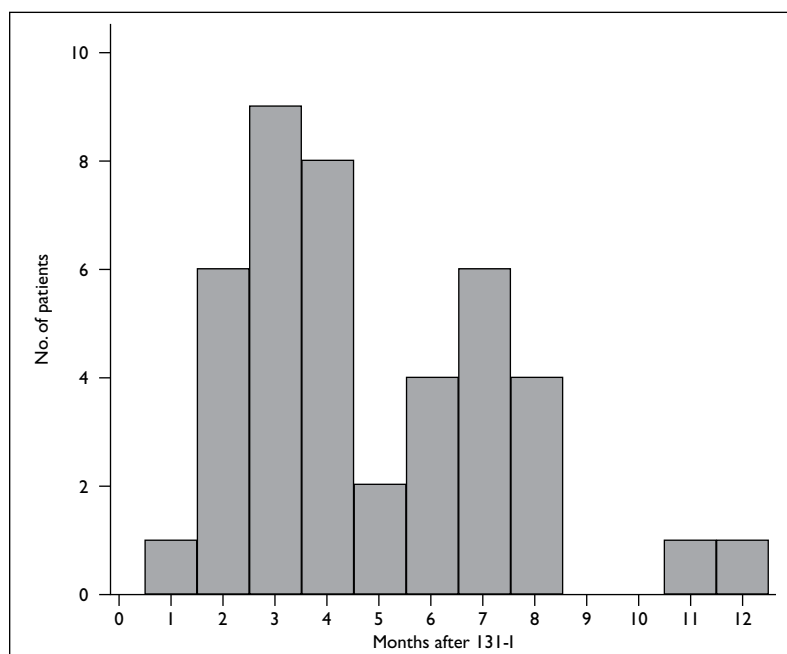


FIG 2. Time to relapse after first radioactive iodine dose (n=42)

TABLE 2. Univariate analysis of baseline characteristics in patients with hyperthyroidism and hypothyroidism/euthyroidism after first radioactive iodine dose

Characteristic*	Treatment failure (n=42)	Successful treatment (n=71)	P value
Gender (M/F)	12/30	18/53	0.71
Age at diagnosis (years)	39.9	40.1	0.83
Duration of hyperthyroidism before RAI (months)	37.6	33.6	0.55
Type of hyperthyroidism (Graves'/nodular goitre)	41/1	65/3	0.58
Goitre size (small/medium or large)	21/10	33/13	0.02
Ophthalmopathy (mild/moderate/severe)	11/2/1	16/2/0	0.49
Anti-thyroglobulin antibodies titre	1384	1380	1.0
Anti-microsomal antibodies titre	7310	17051	0.43
Pretreatment with ATDs (CMZ/PTU)	34/11	61/9	0.15
Duration of ATD (months)	32.5	27.7	0.18
Indication of RAI (primary/relapse)	7/31	17/53	0.60
24-Hour 131-I uptake (%)	64.7	60.0	0.19
Dose of 131-I (mCi [MBq])	8.3 (307)	8.6 (318)	0.23
Adjuvant ATD (yes/no)	16/26	30/41	0.66
Free T4 at diagnosis (x ULN)	4.5	2.8	0.001
Total T4 at diagnosis (x ULN)	2.1	1.9	0.29
Free T4 at RAI (x ULN)	1.2	1.0	0.31
Total T4 at RAI (x ULN)	0.9	1.0	0.67
TSH at RAI (x ULN)	0.64	1.7	0.56

* Biochemical test results given as means; ATD denotes anti-thyroid drug, CMZ carbimazole, 131-I iodine-131, PTU propylthiouracil, RAI radioactive iodine, T4 thyroxine, TSH thyroid stimulating hormone, and ULN upper limit of normal

dose of 131-I. For those successfully treated at 1 year, 46 (41%) of the patients remained euthyroid, and 25 (22%) became permanently hypothyroid (being in receipt of levothyroxine) [Fig 1].

Transient hypothyroidism was observed in seven (6%) of the patients. One patient received steroid cover during 131-I therapy for Graves' ophthalmopathy; there was no worsening of the condition after radioactive iodine. There was no other reported complication related to 131-I.

Table 2 compares the clinical and laboratory data of patients who were successfully treated with a single dose of radioiodine with those who remained thyrotoxic at 1 year. Treatment failure was not associated with age at diagnosis ($P=0.83$), gender ($P=0.71$), type of thyrotoxicosis ($P=0.58$), duration of hyperthyroidism ($P=0.55$), anti-microsomal antibodies titre ($P=0.43$), 24-hour 131-I thyroid scan uptake ($P=0.19$), or dose of radioactive iodine ($P=0.23$). Patients with therapy failure had taken anti-thyroid drugs before radioiodine for longer periods, but this difference was not statistically significant ($P=0.18$). These patients also had significantly higher basal fT4 levels ($P=0.001$) than those who were euthyroid or hypothyroid after a single dose of radioactive iodine. Goitre size was also significantly associated with treatment failure ($P=0.02$), and according to the logistic regression, there was a non-significant trend towards increasing size and relapse rate (odds ratio=1.65; 95%

confidence interval, 0.81-3.33; $P=0.166$). However, when these baseline variables were combined using multivariate logistic regression analysis, only fT4 level remained significantly associated with relapse 1 year after the first dose of 131-I ($P=0.029$).

Whilst all the patients had received anti-thyroid drugs before radioiodine therapy, during the first year there was a higher relapse rate after PTU than carbimazole pretreatment (P [log-rank]=0.038) [Fig 3]. When combined with other pretreatment variables, the Cox regression analysis demonstrated no significant association between anti-thyroid medication and radioiodine treatment failure within 1 year ($P=0.42$) [Table 3].

Discussion

Radioiodine was first used to treat patients with Graves' thyrotoxicosis in 1943, and since then it has been increasingly used for that purpose. After more than 50 years of radioiodine therapy, the optimal dosage is still debated. Regimens using fixed low or high doses, as well as those calculated according to the size of the thyroid gland, and the results of isotope uptake or turnover have been used.²⁻⁵ Dosimetric use of 131-I was popular in the past, but in terms of improving cure rates there is no evidence to suggest any advantage over fixed doses,^{5,7,8} nor was there any benefit with respect to the development

of hypothyroidism.⁶ A low fixed dose (185 MBq) was preferred by some clinicians, as it was associated with a reduced early incidence of hypothyroidism, but resulted in unacceptably low cure rates. It has also been suggested that the development of long-term hypothyroidism is inevitable, irrespective of the amount of radioiodine administered; the annual incidence being 2 to 3%.^{2,11} Some clinicians prefer administering a large ablative dose (555 MBq and upwards), which resulted in early hypothyroidism but minimised the need for retreatment.^{12,13} In one controlled trial, patients were randomised to one of four dose calculation methods: low-fixed, 235 MBq; high-fixed, 350 MBq; low-adjusted dose, 2.96 MBq (80 µCi)/g thyroid adjusted for 24-hour radioiodine uptake; and high-adjusted dose, 4.44 MBq (120 µCi)/g thyroid for the 24-hour radioiodine uptake. Clinical outcomes in terms of the proportions resulting in euthyroidism, hypothyroidism, or hyperthyroidism were almost identical in the four treatment arms.¹⁴ No advantage was demonstrated using adjusted dose methods, but those who used lower doses showed a trend towards development of recurrent or persistent hyperthyroidism. It was therefore inferred that for the treatment of hyperthyroid Graves' disease, fixed 131-I doses are effective and more economical to use, apart from being simpler to administer. The ideal fixed dose is still not defined, however.

In our study, most patients received a fixed dose of 8 mCi of 131-I. A higher dose of 10 mCi was given to patients who underwent ablative therapy, for example, patients with atrial fibrillation, thyrotoxic heart failure, thyrotoxic periodic paralysis, or patients suffering from severe anti-thyroid drug adverse effects (eg agranulocytosis, cholestasis, or hepatitis). In all, after 1 year of radioactive iodine, 63% of the patients were successfully cured, whereas 37% had relapsed. Up to 69% of those who had relapsed received a second dose of radioiodine. From the literature, after different doses of 131-I (5-12.3 mCi [185-455 MBq]) the cure rate varies from 67 to 86%.¹⁴⁻¹⁶ The reason for the lower cure rates in our cohort was unclear.

Several factors that influence the outcome of radioactive iodine treatment have been identified. In our study, large goitre and a high basal fT4 concentration were both associated with treatment failure. These findings were consistent with most other studies demonstrating larger-volume thyroid glands^{3,4,15-17} and severe hyperthyroidism^{4,6,15-18} were more likely in patients who do not respond to a single dose of radioiodine. A 24-hour radioiodine uptake of more than 90% is also considered predictive of treatment failure. It was recommended that empirical use of higher radioiodine doses could be prescribed for the first dose.¹⁹ Some studies have identified male gender²⁰ and age younger than 40 years¹⁵ as predictive of treatment failure, though others have

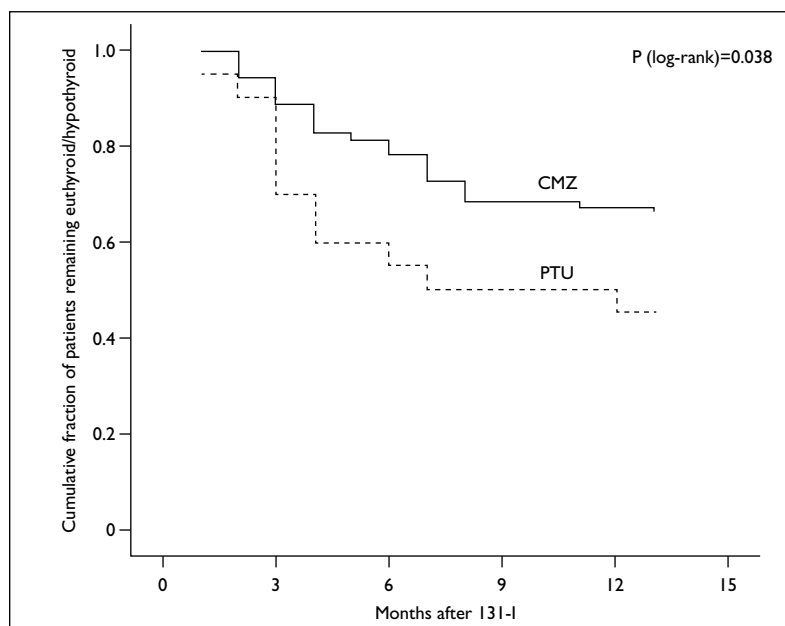


FIG 3. Kaplan-Meier estimates of the proportion of patients remaining euthyroid/hypothyroid within 1 year of a first dose of radioactive iodine in patients pretreated with carbimazole (CMZ) and propylthiouracil (PTU)

TABLE 3. Factors predictive of relapse after one dose of radioactive iodine based on Cox regression analysis

Factor*	Adjusted odds ratio to relapse	95% Confidence interval	P value
PTU	0.42	0.5-3.4	0.42
Free T4 at diagnosis	1.68	1.14-2.47	0.01
Larger goitre size	1.67	0.64-4.41	0.30
Duration of hyperthyroidism	1.0	0.97-1.03	0.94
Age at diagnosis	0.99	0.91-1.67	0.78

* PTU denotes propylthiouracil, and T4 thyroxine

not confirmed such findings.^{21,22}

It has been suggested that anti-thyroid drugs confer a radio-resistant effect resulting in radioiodine treatment failure,^{23,24} mostly following PTU therapy.^{25,26} One study noted that in patients pretreated with PTU, there was a cure rate of 24% to 8 months after 131-I therapy, compared to approximately 60% in those pretreated with methimazole (MMI) or not pretreated.¹⁰ A similar study also reported a 34% failure rate in patients pretreated with PTU compared to 4% among those who had not received anti-thyroid drugs.⁵ It was proposed that the radio-resistance associated with thiourea was due to the presence of a sulfhydryl group in PTU,²⁷ which is absent in MMI and carbimazole. Concerning the time interval between the last dose of anti-thyroid drug and radioiodine, Turton et al²⁸ demonstrated that the treatment failure rate was higher in patients whose last PTU dose was within 1 week of 131-I therapy as opposed to 7 to 14 days earlier (31% vs 15%). Cure rates in patients who

received their last dose more than 2 weeks before 131-I therapy and those who had never received PTU were no different. Hence the author recommended a PTU-free period of 2 weeks before 131-I therapy. A subgroup analysis was also performed in patients receiving PTU or MMI for various time periods, which suggested that a significant fraction of patients receiving PTU or MMI for 4 months or longer more commonly required repeated radioiodine treatment.

Our study demonstrated a higher rate of relapse in the first year after radioiodine therapy in patients pretreated with PTU as opposed to carbimazole. This result, however, was not confirmed by multivariate analyses. Most patients in our cohort had their anti-thyroid drugs stopped at least 2 to 3 weeks before radioiodine administration, so as to minimise radio-resistance to anti-thyroid drugs and enhance iodine uptake. This 2- to 3-week drug-free period may have minimised the radio-resistant effect of PTU, explaining the similar failure rates when the two groups were compared. Most of our patients had taken anti-thyroid drugs for a relatively long duration before receiving radioactive iodine (median, 30 months), which might also account for the higher failure rates in our study.

Hypothyroidism is inevitable post-radioiodine therapy.^{29,30} The ability to predict permanent hypothyroidism, however, remains poor, with an accuracy of only 60% in the presence of combination therapy with carbimazole, absence of ophthalmopathy, and a longer effective half-lives of 131-I.²⁹ Low dose of 131-I appears to delay the onset of hypothyroidism, but does not eliminate its ultimate development. In a Chinese retrospective study, the reported cumulative incidence of hypothyroidism at 1 year was 9.6%, with an average annual incidence of 3.3% thereafter.²⁹ Transient hypothyroidism also occurs in a proportion of Graves' disease patients treated with radioiodine, ranging from 9 to 17%. In one series, it comprised 58% of patients who developed hypothyroidism within 12 months of 131-I therapy.³¹ Our study reported an incidence of permanent hypothyroidism at 1 year as 22% and transient hypothyroidism 6%.

In our series, we did not encounter any patient with a thyroid storm or worsening of ophthalmopathy. Adverse effects of radioactive iodine are rare; thyroid storm having been reported to develop between 1 and 14 days after treatment in a small number of

patients.³² In a series of 7000 patients treated with radioactive iodine in one centre, none developed this complication.³³ Graves' ophthalmopathy may become worse after radioactive iodine treatment, particularly in those with severe eye signs.^{34,35} Rarely, severe neck swelling and tracheal compression have also been reported after 131-I administration to patients with very large goitres.³⁶ Other minor side-effects of 131-I therapy, which are usually self-limiting, include transient nausea and mild pain over the thyroid gland.

Our study provides information about the efficacy, safety, and ability to predict treatment failure after radioiodine, but has its limitations. Our definition of Graves' disease was based on the presence of a diffuse goitre and ophthalmopathy and in the presence of anti-thyroid antibodies. Some of these are subjective features open to misinterpretation, for example, multinodular goitre may be regarded as Graves' disease and vice versa. The 94% of patients labelled as Graves' disease in our study may therefore have been an overestimate. For a reliable diagnosis of Graves' disease, the demonstration of diffuse uptake by isotope scanning and the presence of TSH receptor antibody are necessary.³⁷ An isotope scan was not usually performed in our practice however, and the TSH receptor antibody testing is not available in Hong Kong. Therefore our cohort represents a heterogeneous group of thyrotoxic patients undergoing radioiodine in our centre, and our results may not be applicable to other populations. Also, the number of patients in our sample was small, limiting the power of our analysis. Moreover, we only looked at 1-year outcome after radioiodine retrospectively. A large prospective randomised control study is needed for further clarification of the effect of the dose of 131-I, pretreatment with different anti-thyroid drugs, and other predictive factors of treatment outcome.

Conclusions

Radioiodine therapy used for the treatment of hyperthyroidism is effective and safe. Fixed-dose 131-I is simple to administer. High initial thyroid hormone concentrations and larger goitre are poor prognostic factors, predicting liability to relapse. Higher doses of 131-I may be warranted to improve treatment outcomes in those with prognostic factors of a poor response.

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