Factors predicting cure at one year after administration of radioactive iodine to patients with Graves' disease

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Abstract

Objective: To investigate the determinants of cure after radioactive iodine (RAI), a treatment frequently used to treat Graves' thyrotoxicosis. **Materials and Methods:** We conducted a retrospective analysis of data from 160 consecutive patients with Graves' thyrotoxicosis who received 370MBq of iodine-131 (^{131}I) at one centre between 2009 and 2018. Data included gender, age, cause of thyrotoxicosis, and number of RAI doses administered. Free thyroxine (fT4) and triiodothyronine (fT3) level at diagnosis, thyroid stimulating hormone (TSH), fT4 and fT3 levels on the day of RAI, and TSH, fT4 and fT3 at 3, 6, and 12-months post RAI treatment were reviewed. Cure was defined as achieving a euthyroid or hypothyroid state within one year of RAI administration. **Results:** Eighty one percent of the total cohort achieved cure at one year. Sixty one point eight percent of patients developed hypothyroidism within one year necessitating lifelong thyroxine replacement. fT4 at diagnosis (P=0.02), fT3:fT4 ratio at diagnosis (P=0.05) and the ratio of fT4 at diagnosis to fT4 pre-RAI ratio (P=0.05) and fT4 pre-RAI (P=0.002) were independent variables associated with cure after one year. **Conclusion:** Radioactive iodine is a highly effective treatment for Graves' thyrotoxicosis. It is more likely to be successful in patients with lower fT4 at diagnosis and pre-RAI.

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Introduction

Antithyroid drugs, radioactive iodine or thyroidectomy are the three main modalities of choice to treat Graves' thyrotoxicosis. Radioactive iodine (RAI) (iodine-131 (^{131}I)) is a safe and cost-effective treatment with minimal side effects that has been used in the management of benign thyroid disease for more than 80 years [1, 2]. The main indications in hyperfunctioning glands are Graves' disease, toxic multinodular goitre, or toxic adenomas.

The precise RAI dose that results in cure and eliminates the chance of long-term hypothyroidism is a subject of debate and several studies with various doses have been carried out [3-5]. The Royal College of Physicians guidelines for radioiodine in the management of benign thyroid disease recommend a wide range of ^{131}I doses to treat Graves' and toxic nodular hyperthyroidism which vary between 400 to 800MBq [6].

The decision to administer RAI is taken after a consultation with patients and relies on their ability to follow the necessary radiation precautions post-treatment. In our country, an 18-month course of anti-thyroid medication such as carbimazole or propylthiouracil is the first line treatment for Graves' patients. Subsequently, if patients relapse, they are offered RAI as a definite treatment option. All patients who agree to proceed with RAI are rendered euthyroid using either carbimazole or propylthiouracil prior to RAI administration.

We administered RAI at a fixed dose of 370MBq to a series of consecutive patients in a well-defined population in Malta where patients are referred to one central National Health Service. The primary objective of the study was to assess their clinical response within the first year and the secondary objective was to explore clinical factors that may predict a successful outcome.

Materials and Methods

A retrospective analysis of data from 160 consecutive patients diagnosed with Graves'

disease who received ^{131}I from 2009 till 2018 was performed. Data were collected from our online patient database, iSOFT clinical manager, and patient's case notes.

The information recorded included patient name, gender, age, clinical diagnosis, dose of ^{131}I administered, number of doses received, free thyroxine (fT4) and free triiodothyronine (fT3) levels at diagnosis of hyperthyroidism and fT4 and fT3 levels on the day of RAI treatment.

Carbimazole was stopped 10 days before and propylthiouracil (PTU) was discontinued 14 days prior to administration of RAI. Antithyroid drugs were not restarted routinely post RAI. Free thyroxine and fT3 levels at 3, 6 and 12-months post RAI treatment were recorded. Normal values at our lab for, for fT4 between 11.9-20.3pmol/L, and for fT3 between 2.76-6.45pmol/L.

All patients received a first RAI dose of 370MBq. A repeat dose of 555MBq was given to patients who remained hyperthyroid after six months following the initial dose. A euthyroid state was defined as having normal fT4, fT3 and thyroid stimulating hormone (TSH) levels. Hypothyroidism was defined as low fT4 and high TSH or being on thyroxine replacement. Hyperthyroidism was defined as high fT4 and/or fT3 and low TSH or receiving antithyroid medication. Subclinical hyperthyroidism was defined as low TSH and normal fT4 and/or fT3.

Cure was defined as achieving either a euthyroid or hypothyroid state within one year of RAI administration. Persistent hyperthyroidism or subclinical hyperthyroidism within one year post treatment was recorded as not cured.

Results

Our cohort included 41 male and 119 female patients with Graves' disease. One hundred and forty three patients received one dose whilst 17 patients received two doses of RAI. Patient's ages at RAI administration varied between 18 to 83 with a median age of 56 years (interquartile range, IQR: 43-66). The median fT4 at diagnosis was 31pmol/L (IQR: 20-42). The median fT3 at diagnosis was 11pmol/L (IQR: 7-15).

Cure

Eighty one percent of the total cohort achieved cure at one year. Sixty nine percent of them achieved cure early on at 3 months, an additional 8% achieved cure at 6 months and 4% at 12 months. Seventeen patients received a second treatment dose as they were persistently hyperthyroid at 6 months. Eighty two point three percent of these patients achieved cure at 3 months, 11.8% at 6 months and 6% at 12 months.

Permanent hypothyroidism post RAI

Sixty one point eight percent of patients were hypothyroid at one year necessitating lifelong thyroxine replacement.

Identification of factors associated with cure at 12 months post RAI

Free thyroxine at diagnosis and fT4 pre-RAI were strongly associated with cure at twelve months; fT3 at diagnosis and pre-RAI were not associated with cure. The ratio of fT4 at diagnosis to fT4 on the day pre-RAI was associated with cure (P= 0.05) in univariate analysis. (Table 1) The ratio of fT3 to fT4 at diagnosis was associated with cure on univariate analysis (P= 0.05).

Patients with severe hyperthyroidism, i.e. a high fT4 at diagnosis and pre-RAI (Tables 2 & 3), are less likely to achieve cure with RAI. The need for multiple doses of RAI was strongly associated with lower likelihood of cure in univariate analysis (Table 1). We did not include this in multivariate analysis since it highly correlates with fT3 and fT4 at diagnosis and pre-RAI therapy and because we wanted to investigate the determinants of cure at baseline i.e. before the administration of RAI.

Table 1. *Univariate analysis of parameters analysed to predict cure at one year post RAI administration.*

Parameter	Odds ratio	95% CI	P value
Age	0.98	0.95-1.01	0.21
Female gender	4.22	0.94-18.99	0.06
No of doses	0.01	0.001-0.07	**0.00**
fT4 at diagnosis	0.98	0.96-0.99	**0.02**
fT3 at diagnosis	0.93	0.86-1.00	0.06
fT4/pre-RAI fT4 ratio	0.97	0.94- 0.99	**0.05**
fT3/fT4 ratio at diagnosis	1.47	1.01-2.17	**0.05**
fT4 pre-RAI	0.97	0-95-0.99	**0.002**
fT3 pre-RAI	0.99	0.94-1.03	0.55
fT3/fT4 ratio pre-RAI	4.92	0.43-56.3	0.20

Table 2. *Multivariate analysis of parameters analysed to predict cure at one year post RAI administration (model 1).*

Parameter	Odds ratio	95% CI	P value
Female gender	1.59	0.69-3.65	0.28
fT4 at diagnosis	0.97	0.97-0.99	<0.001
fT3:fT4 at diagnosis	9	0.69-3.65	0.28

Table 3. *Multivariate analysis of parameters analysed to predict cure at one year post RAI administration (model 2).*

Parameter	Odds ratio	95% CI	P value
Female gender	1.59	0.65-3.87	0.32
fT4 pre-RAI	0.97 (0.95-0.99)	0.96-1.09	0.003
fT3:fT4 pre-RAI	2.92	0.23-37.7	0.41

Relationship between fT3 and fT4

The scatterplot relating circulating levels of fT3 and fT4 at diagnosis, shown in Figure 1, does not show a clear trend towards decreased deiodination at high circulating fT4.

Discussion

We demonstrate that a single dose of 370MBq ^{131}I is successful in treating hyperthyroidism in a consecutive series of 160 patients suffering a relapse of Graves' thyrotoxicosis after 18 months of antithyroid drugs. Eighty one percent of patients achieved cure within one year. This finding is consistent with studies performed previously [7, 8].

In univariate analysis, we found that low fT4 levels at diagnosis and high ratios of fT3 to fT4 at diagnosis, low fT4 pre RAI and low ratio of fT4 at diagnosis to fT4 pre RAI, were predictors of cure at twelve months [9].

Only the fT4 at diagnosis and pre-RAI were significant predictors of cure in multivariate analysis. In our study patients diagnosed with severe hyperthyroidism as determined by a high fT4 level at diagnosis or immediately pre-RAI were less likely to achieve cure with a single dose of RAI. High pre-treatment fT4 levels may be an indicator that RAI will not be immediately successful. High fT4 levels suggest a high rate of iodine turnover in the thyroid gland. Thus, the residence time of radioiodine within the gland is shorter. This results in a lower success rate. Furthermore, RAI is more likely to be effective when administered to patients who are euthyroid. Past studies have identified pre-treatment fT4 as an independent predictor for cure of Graves' hyperthyroidism [4], and other causes of thyrotoxicosis [2]. Aung et al. (2019) [11] followed-up 655 patients treated with RAI for Graves' thyrotoxicosis and reported that higher fT4 at diagnosis in Graves' disease patients is independently associated with treatment failure. This finding is in keeping with other preceding studies [2, 4, 10, 11].

Even though fT3 is the biologically active thyroid hormone, we found that fT4, but not fT3, is associated with cure. This may be because fT4 is the main output from the thyroid, whilst the level of fT3 largely depends on the rate of peripheral deiodination. Free thyroxine is therefore a better indicator of thyroid gland hyperactivity. One should note that there is evidence that the rate of peripheral deiodination decreases with high circulating fT4 [12], although this is not apparent from our data (Figure 1), so that it remains questionable whether this relationship could explain why high fT3:fT4 ratios at diagnosis predict cure in our univariate analysis.

Patients had a high rate of hypothyroidism at one year at 61.8%. Previous authors reported similar findings [4, 13, 14]. A possible explanation may be that in patients with Graves' disease radioiodine is distributed throughout the whole thyroid tissue thus leading to long term hypothyroidism [10]. Hypothyroidism is dependent on the dose of RAI administered and seems to be unavoidable in the long term with an annual incidence of 2%-3% many years after treatment [4]. Patients need lifelong follow-up as hypothyroidism may develop at any time [13].

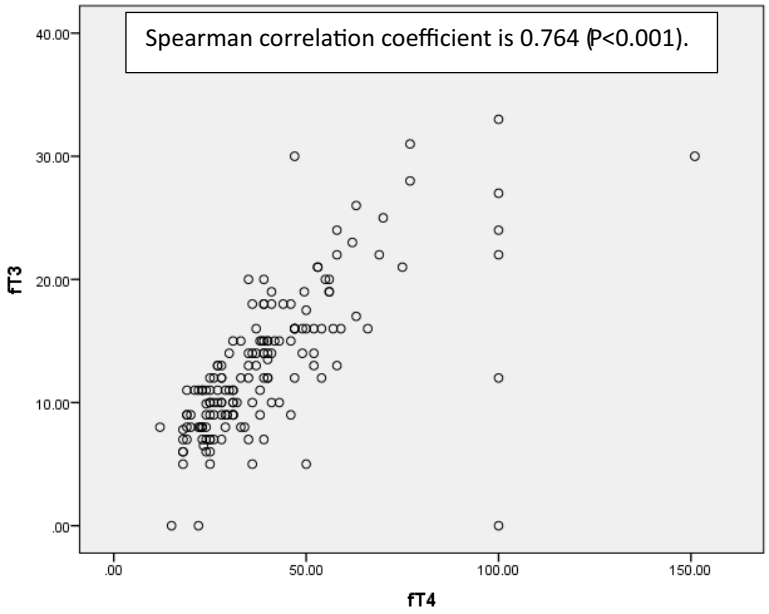

Figure1. Scatter plot of fT3 and fT4 at diagnosis in our study population.

The PRAGMA study followed 812 patients in the UK for one year post RAI. It reported a high frequency of dysthyroidism in the first 12 months post RAI. Hypothyroidism occurred in 80.7% and was more frequent in the first six months [15]. The study found that when 400-800MBq of RAI is administered, the probability of developing permanent hypothyroidism in the first 6 months is 90%. The authors suggest that the first 6 months post RAI are crucial, and patients must be followed up frequently so that hypothyroidism is timely diagnosed, and levothyroxine replacement is initiated as soon as possible [15].

There is no single method to establish a dose of radioiodine that will not cause hypothyroidism. There are many different independent variables that may contribute to development of long-term hypothyroidism. These include age, comorbidities, gender, severity and duration of underlying thyroid disease, radiation delivered to the gland and prior drug treatment with antithyroid medication [16].

Indeed, hypothyroidism may be a good outcome as it improves cardiovascular mortality. In a study by Boelaert et al. (2013) [17], mortality was increased in patients above the age of forty who received radioiodine but failed to achieve hypothyroidism. Overt hyperthyroidism was associated with an increase in all-cause mortality and mortality from cardiovascular causes in patients over 40 years [17]. This increase in mortality persists for several years after diagnosis. On the other hand, all-cause mortality was not increased in patients without serious comorbidities who developed

Strengths & Limitations

The strength of our study is the considerable number of patients who were all followed-up for one year post treatment. Our cohort included a sequential series of patients from a well-defined population who received radioiodine at a single centre from 2009 till 2018. Thus, we are confident we have included all patients who were administered RAI during this period consequently limiting selection bias.

On the other hand, we should recognize that all patients have initially been treated for 18 months with antithyroid drugs, and that RAI was only offered as a second line treatment in case of relapse. This limits our findings to patients relapsing after antithyroid drug treatment. We acknowledge that other possible variables which were not included in our study may affect treatment success. These include the details pertaining to type and dose of anti-thyroid drug prescribed prior to RAI and the presence of thyroid goitre or Graves' ophthalmopathy.

In conclusion, our findings confirm the efficacy of the proposed RAI scheme in patients relapsing after antithyroid drug treatment. Patients who remain biochemically hyperthyroid pre-RAI might benefit from more careful surveillance and treatment reviews prior to considering RAI administration.

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