Development of hypothyroidism over 13 years of follow-up of patients with hyperthyroidism after radioiodine therapy

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Abstract

Objective: To analyze the incidence and associated factors of hypothyroidism after radioiodine treatment for hyperthyroidism during a 13-year follow-up period. **Subjects and Methods:** This was a retrospective study of consecutive patients with hyperthyroidism who were treated using a single dose of radioactive iodine (RAI) with a calculated dose regimen from 07/2005 to 12/2012. Univariate and multivariate Cox regression models were used to examine the factors that are associated with the occurrence of hypothyroidism after RAI therapy. Kaplan-Meier analysis was used for confirming associations between these models. **Results:** A total of 182 patients were included during a 7.5-year median follow-up (range: 6-13 years). They were 36.4±11.1 years. The mean radioactive iodine dosage was 308.2±104.3 (range: 129.5-740.0) MBq. The rates of euthyroidism, early hypothyroidism, improvement, and ineffective treatment at 6 months were 48.4%, 37.9%, 8.8%, and 4.9%, respectively. The cumulative incidence of hypothyroidism in all patients with hyperthyroidism was 45.6% at 1 year, 48.9% at 5 years, and 52.3% at 10 years. Thyroid weight >46g (HR=0.643, 95%CI: 0.422-0.981, P=0.040) and a course of disease of 0.5-3 years (HR=0.592, 95%CI: 0.358-0.981, P=0.042) were identified as independent factors associated with an increased risk of hypothyroidism after radioactive iodine therapy. **Conclusion:** Radioactive iodine treatment with a calculated dose has a high cure rate for hyperthyroidism and has a low annual increase of hypothyroidism. Hypothyroidism after radioactive iodine treatment is more likely to occur in patients with small thyroid and a short disease course.

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Introduction

Hyperthyroidism is a form of thyrotoxicosis resulting from an inappropriately high synthesis and secretion of thyroid hormone by the thyroid gland [1, 2]. Patients with hyperthyroidism are categorized into three diagnostic groups as Graves' disease (GD), toxic nodular hyperthyroidism, and hyperthyroidism of indeterminate etiology [3, 4]. Complications of hyperthyroidism include thyroid storm (a life-threatening condition), cardiovascular complications such as heart failure and atrial fibrillation, and osteoporosis and fractures [1, 2]. Subclinical hyperthyroidism may be associated with cardiovascular and other complications similar to overt hyperthyroidism [1, 2]. The prevalence of hyperthyroidism is 3% in China, or 4.1% in women and 1.6% in men, and 88%-90% of the patients have GD [5].

For decades, the management options for hyperthyroidism have remained unchanged, consisting of antithyroid drugs, radioactive iodine (RAI), and surgery [1, 6]. The RAI has been used for over 70 years as a treatment for hyperthyroidism [7]. This therapy is safe with a very low risk of long-term side effects [8]. It leads to remission with one course of treatment in most patients, and it has been considered the first-line treatment in most patients presenting with solitary autonomous thyroid nodules, toxic nodular goiter, or GD [9, 10]. Hypothyroidism is the main side effect of RAI treatment and is, therefore, a common finding in patients treated with RAI [1, 6-10]. Hypothyroidism can occur from weeks to months and even years after RAI therapy [11]. Nevertheless, the pathogenesis and incidence of hypothyroidism after RAI therapy remains unclear, several studies reporting different incidence of hypothyroidism [7, 12-16]. One study showed that the incidence of hypothyroidism is up to 80% at 6 months [17] or 80.9% at 1 year [18], or with a cumulative rate increasing by 1%-4.8% per year during long-term follow-up [19-22]. Patients with permanent hypothyroidism induced by RAI require a lifetime follow-up to optimize levothyroxine treatment. Many patients, especially in rural China, do not comply with lifelong levothyroxine replacement [23, 24].

There are many studies exploring the factors involved in early hypothyroidism [11, 25-28]. Boelaert et al. (2009) [7] showed that a 600MBq dose, female sex, younger age, ab-

sence of a palpable goiter, and presence of ophthalmopathy are independent factors predicting the probability of development of hypothyroidism at 1 year. There is an increased risk of early hypothyroidism in patients with lower 24-h iodine uptake and treated with a lower total dose of iodine and a higher iodine dose per gram of thyroid tissue [29].

Nevertheless, the factors associated with hypothyroidism occurrence during long-term follow-up are uncertain. There is an ongoing debate regarding the optimal regimen for RAI therapy to minimize the risk of hypothyroidism while maximizing the cure rate of hyperthyroidism. Therefore, this study aims to analyze the incidence and associated factors of hypothyroidism retrospectively after RAI therapy in patients with hyperthyroidism during 13 years of follow-up in China. The results might help improve the management of patients with hyperthyroidism.

Subjects and Methods

Patients

This is a retrospective study of consecutive patients with hyperthyroidism who were treated using a single dose of RAI with a calculated dose regimen from July 2005 to December 2012 at the Department of Nuclear Medicine of the Third Affiliated Hospital of Sun Yat-Sen University. This study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University. The requirement for informed consent was waived by the committee.

The inclusion criteria were: 1) diagnosed hyperthyroidism, 2) thyroid function serum tests confirmed hyperthyroidism, 3) 24-h uptake of RAI ≥40%, 4) underwent RAI therapy, and 5) >18 years of age. The exclusion criteria were: 1) more than one dose of RAI therapy, 2) incomplete data, or 3) lost to follow-up or refused follow-up.

RAI therapy protocol

As per routine procedure, all patients were advised to maintain a low iodine diet for 4-6 weeks prior to RAI uptake testing and treatment. If antithyroid drugs were administered, these drugs were withdrawn 1 week before RAI therapy. Intake of iodine-rich food and contrast-enhanced imaging protocols were avoided. Prior to RAI therapy, the patients undergo routine eligibility examinations: RAI uptake test, thyroid weight estimated by thyroid scintigraphy, free T3 (fT3), free T4 (fT4), thyroid-stimulating hormone (TSH). Clinical hyperthyroidism was defined as suppressed TSH and elevated fT3 and/or fT4. Euthyroidism was defined as normal TSH and normal fT3 and fT4. Subclinical hypothyroidism was defined as elevated TSH and normal fT3 and fT4. Clinical hypothyroidism was defined as elevated TSH and low fT3 and fT4. RAI was administered orally. The dose was calculated according to the formula:

$$A = \frac{W \times D(\frac{MBq}{g})}{U24}$$

Where A is the RAI dose, D (MBq/g) is the RAI dose of per gram of thyroid tissue (range: 1.78-6.74MBq), U24 is the RAI uptake rate at 24h, and W is the thyroid weight. The final RAI dose was administered once according to the calculated dose and the patient's condition. The mean dose of RAI in all patients was 308.2±104.3 (range: 129.5-740.0) MBq.

Follow-up

Follow-up was censored in December 2018. All patients were routinely followed by outpatient visits or telephone every 3-6 months for the first year, and then yearly. The median follow-up period after RAI therapy was 7.5 years (interquartile range [IQR]: 7-11; range: 6-13). Thyroid function tests before and after therapy and during follow-up were performed by chemiluminescence methods. Treatment success was determined using laboratory testing of TSH, free T4, free T3, and other biochemical measurements. Post-therapeutic hypothyroidism was confirmed according to elevated TSH levels with or without levothyroxine therapy, or normal TSH levels with levothyroxine treatment. Euthyroidism was assumed when the TSH levels were within the normal range in patients not taking levothyroxine or antithyroid medicine.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 (IBM, Armonk, NY, USA). Continuous data are expressed as means±standard deviation (SD) or median (IQR), Categorical data are presented as n (%). Univariate and multivariate Cox regression models were used to examine the factors that are associated with the occurrence of hypothyroidism after RAI therapy. Kaplan-Meier analysis was used for confirming associations. Two-sided P-values <0.05 were considered statistically significant.

Results

Characteristics of the patients

Among the included patients, 58 patients were males and 124 patients were females. The mean age of those patients was 36.4±11.1 years (range, 18 to 64 years). Finally, there were 182 patients in this study, and their characteristics are presented in Table 1.

Effect of RAI therapy and the occurrence of hypothyroidism

At 6 months after single-dose RAI therapy, the overall effective rate was 95.1% (48.4% for euthyroidism rate, 37.9% for early hypothyroidism rate, 8.8% for improvement rate), and the ineffective rate was 4.9%. Furthermore, the cure rate (including the euthyroidism and early hypothyroidism rates) at 6 months was 86.3%, 82.8% for male and 87.9% for female. The cumulative incidence of hypothyroidism in all patients with hyperthyroidism was 45.6% at 1 year, 48.9% at 5 years, 52.3% at 10 years (Figure 1). An average rise of 1.5 % per year was observed for 13 years.

Factors associated with hypothyroidism

Table 2 presents the multivariable analysis. Sex (female vs. male), age (≤35 vs. >35 years, based on the median), course of the disease (≤0.5 vs. >0.5 and ≤3 vs. >3 years), texture of the thyroid gland (soft vs. medium vs. hard), thyroid weight (≤46 vs.

>46g, based on the median), 24-h RAI uptake (≤63% vs. >63%, based on the median), the dose of RAI (≤296 vs. >296MBq, based on the median), and RAI dose per gram of thyroid (≤3.8 vs. >3.8MBq, based on the median) were included into the Cox Regression Analysis (Forward: LR). Thyroid weight >46g (HR=0.643, 95%CI: 0.422-0.981, P=0.040) and a course of disease of 0.5-3 years (HR=0.592, 95%CI: 0.358-0.981, P=0.042) were identified as independent protective factors, which meant thyroid weight <46g and a course of disease of ≤0.5 years were associated with an increased risk of hypothyroidism after RAI therapy. Those associations were confirmed using the Kaplan-Meier analysis (Figure 2).

Table 1. *Characteristics of the patients.*

	All
Age (years), mean±SD	36.4±11.1
Sex, n (%)	
Male	58(31.9%)
Female	124(68.1%)
Course of disease (years)	2.6±3.5
Texture of thyroid, n (%)	
Soft	60(33.0%)
Medium	116(63.7%)
Hard	6(3.3%)
Thyroid weight (g), mean±SD	50.9±22.4
24-h RAI uptake, mean±SD	61.7%±11.5%
Dose of RAI (MBq) , mean±SD	308.2±104.3
RAI dose per gram of thyroid (MBq) , mean±SD	3.8±0.6

RAI: radioactive iodine.

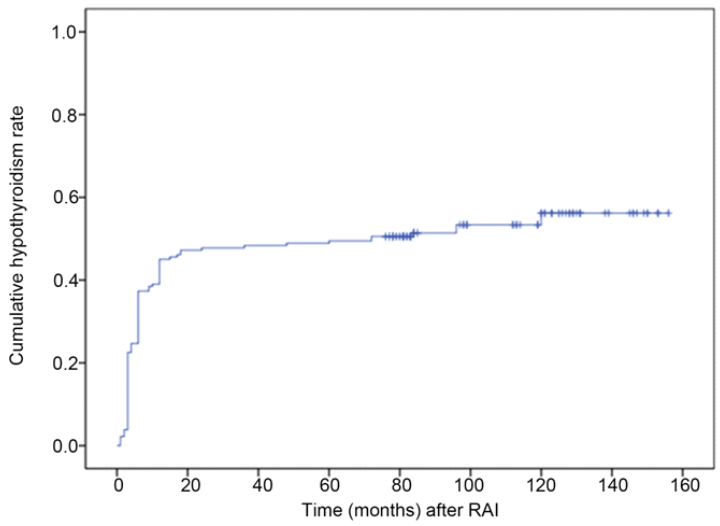

Figure 1. At the end time of follow-up (December 2018), 182 of the 182 patients in this study survived, and 0 died. The incidence of hypothyroidism in 1, 5, and 10 was 45.6%, 48.9%, and 52.3%.

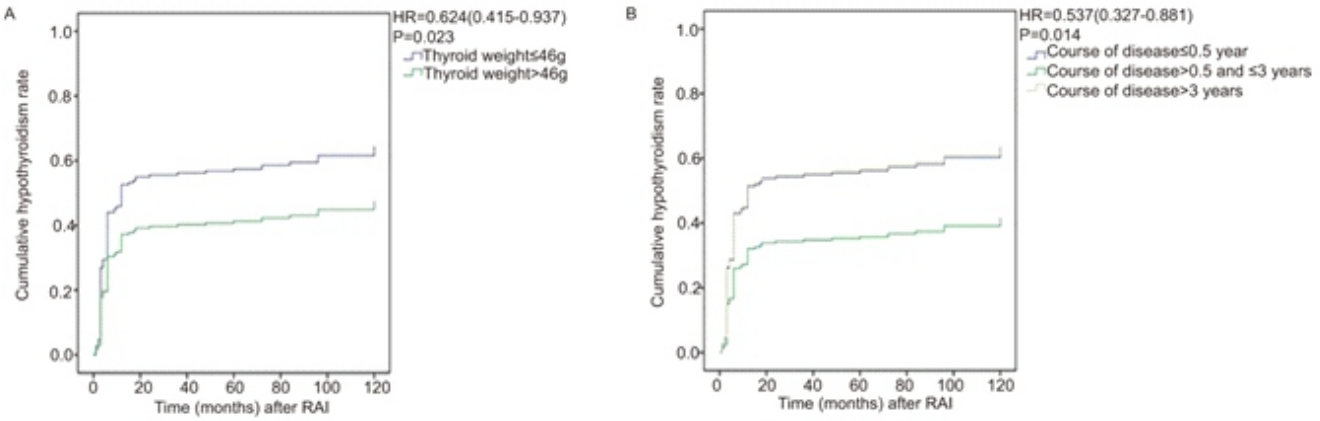

Figure 2. Comparison of the (A) thyroid weight and (B) course of disease in hypothyroidism rate after RAI with the log-rank test in Kaplan-Meier method.

Table 2. *Factors associated with the development of hypothyroidism after RAI therapy with Univariate analysis and Multivariate COX regression analysis.*

Risk factors	Univariate analysis			Multivariate analysis		
	HR	95%CI	P	HR	95%CI	P
Age						
≤35years	ref					
>35 years	0.783	0.499-1.228	0.286			
Gender						
Male	ref					
Female	0.923	0.619-1.377	0.695			
Course of disease						
≤0.5 year	ref			ref		
>0.5and ≤3 years	0.537	0.327-0.881	0.014	0.592	0.358-0.981	0.042
>3 years	1.019	0.629-1.651	0.939	1.163	0.707-1.914	0.552
Texture of thyroid						
Soft	ref					
Medium	1.217	0.786-1.887	0.379			
Hard	1.227	0.374-4.032	0.736			
Thyroid weight						
≤46g	ref			ref		
>46g	0.624	0.415-0.937	0.023	0.643	0.422-0.981	0.040

(continued)

24-h RAI uptake			
≤63%	ref		
>63%	1.074	0.721-1.599	0.727
Dose of RAI			
≤296MBq	ref		
>296MBq	0.739	0.480-1.137	0.169
RAI dose per gram of thyroid			
≤3.8MBq	ref		
>3.8MBq	1.147	0.768-1.713	0.502

OR: odds ratio; CI: confidence interval; RAI: radioactive iodine.

Discussion

The factors associated with hypothyroidism occurrence during long-term follow-up are uncertain. Therefore, this study aims to analyze the incidence and associated factors of hypothyroidism after radioiodine treatment for hyperthyroidism during a 13-year follow-up period. The results suggest that RAI treatment with a calculated dose has a high cure rate for hyperthyroidism and has a low annual increase of hypothyroidism. Hypothyroidism after RAI treatment is more likely to occur in patients with small thyroid and a short disease course.

Radioactive iodine therapy has been confirmed to be a safe, well-tolerated, and cost-effective option in patients with hyperthyroidism [1, 6-10]. In this study, the euthyroidism rate, early hypothyroidism rate, improvement rate, and inefficient rate at 6 months are 48.4%, 37.9%, 8.8%, and 4.9% after a single-dose RAI therapy. Furthermore, the cure rate (i.e., including euthyroidism and early hypothyroidism) at 6 months was 86.3%. These are supported by the literature. Indeed, Kahraman et al. (2012) [30] showed that hyperthyroidism is cured in 85% of patients at 3 months after RAI therapy [30]. In other studies, hyperthyroidism was no longer present in 159/206 patients (77.2%) at 3-4 months [25], and the cure rate at 6 months after RAI therapy of GD is 76.0% [29].

Definitive hypothyroidism may occur after RAI therapy of GD. The cumulative hypothyroidism rate at 1 year in patients with hyperthyroidism was 45.6%, and an average rise of 1.5% per year is observed over 13 years. Similar results were reported by Tavintharan et al. (1997) [22], who showed that 47.4% of their patients were clinically hypothyroid at 1 year. In previous studies, the occurrence of hypothyroidism at 1 year is variable, ranging from 4% to 81% [16, 18, 20, 30, 31], because of several limitations such as the heterogeneity of the studies included, the different formulas used for the estimation and calculation of the thyroid activity, and the different causes of hyperthyroidism. Nevertheless, the average rise per year of hypothyroidism is only 1.5%, less than 2% observed in previous studies [16, 18, 20, 30, 31], which might be because individual RAI dose is routinely performed at the study center. Another reason is that late hypothyroidism found during long-term follow-up is a likely consequence of RAI therapy if the patient lives long enough [19].

The individual RAI therapy using the calculated dose regimen is still the main method used in China. The concern of Chinese doctors is to optimize RAI therapy in patients with hyperthyroidism and to reduce the hypothyroidism rate. The aim of this study is also to analyze the factors associated with hypothyroidism after RAI therapy. Cox regression analysis showed that light thyroid weight is an independent factor associated with hypothyroidism, in agreement with previous a finding that showed that the absence of a palpable goiter is an independent factor predicting the probability of hypothyroidism at 1 year [7]. In addition, in this study, a short course of the disease is also an independent factor associated with hypothyroidism. One reason may be that the RAI therapy doses are more likely to be overestimated in patients with light thyroid weight and a short course of the disease.

The strength of this study is the long follow-up and the analysis of independent factors of hypothyroidism after RAI therapy. We nevertheless acknowledge the following limitations. First, hyperthyroidism was not categorized according to the etiology because routine evaluation by ultrasound was not performed. Second, thyroid antibodies such as TGAb, TPOAb, and TRAb are not routinely performed at this hospital. Finally, this is a retrospective study limited to the data available in the charts.

In conclusion, RAI treatment with a calculated dose has a

high cure rate for hyperthyroidism and has a low annual increase of hypothyroidism. Hypothyroidism after RAI treatment is more likely to occur in patients with small thyroid and a short course of the disease.

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The authors declare that they have no conflicts of interest.

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