Predictive factors for the efficacy of ^{131}I therapy with formulated dosage calculation on Graves' disease

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Abstract

Objective: To analyse predictive factors to ensure the efficacy of iodine-131 (^{131}I) therapy on Graves' disease (GD). **Subjects and Methods:** Graves' disease patients from three tertiary medical centers were enrolled. Serological data, thyroid mass estimation, thyroid radioactive iodine uptake, thyroid texture and thyroid murmurs (bruits) were recorded. Iodine-131 treatment was performed by applying a formulated calculation method. After one year of follow-up, GD patients with euthyroidism and hypothyroidism were classified as the cured group, and the other thyroid function status refers to the uncured group. These analyses were performed by using SPSS17.0 software. A P value of less than 0.05 was considered statistically significant. **Results:** A total of 970 GD patients, of which 540 patients (55.7%) belonged to the cured group, and 430 patients (44.3%) belonged to the uncured group, participated in the current analyses. Multivariate logistic regression analysis was performed. Moreover, estimated thyroid mass, thyroid murmurs (bruits), prescribed ^{131}I dosage, FT3 and FT4 have independent prognostic value for ^{131}I efficacy, and their odds ratios are 1.368, 2.283, 1.326, 1.467 and 1.419, respectively. **Conclusions:** Graves' disease patients who are undergoing ^{131}I therapy using the formulated dosage calculation could be influenced by thyroid mass, thyroid murmurs, ^{131}I dosage and thyroid function.

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Introduction

The prevalence of hyperthyroidism in the general population is approximately 1.2% to 1.6% [1, 2], with 0.5% to 0.6% as overt hyperthyroidism and 0.7% to 1.0% as subclinical hyperthyroidism. The most common causes of hyperthyroidism are Graves' disease (GD), toxic nodular goitre and toxic adenoma. Approximately 3% of women and 0.5% of men develop GD during their lifetime, with the peak incidence of GD occurring among patients aged 30 to 60 years [3, 4]. Graves' disease can be treated by decreasing thyroid hormone synthesis with anti-thyroid drugs or by reducing the amount of thyroid gland tissue with iodine-131 (^{131}I) or thyroidectomy [5, 6].

In the US, Europe and Asia, 59.7%, 13.3% and 29.4% of GD patients use ^{131}I therapy, respectively [2]. Multiple factors affect the efficacy of ^{131}I therapy. For instance, Zheng et al. (2012) [7], showed that the higher the maximal radioactive uptake of thyroid (RAIUmax) and (or) the longer the effective half-life, the higher the possibility of a one-time cure. Liu et al. (2014) [8] displayed high failure rates in patients who presented higher 2-hour RAIU, particularly those with 2-hour RAIU of more than 58.5%. In another approach, higher ^{131}I dosage, longer effective half-life time ($T_{1/2eff}$) and higher thyroid antibody will increase the hypothyroidism possibility by analysing post-therapeutic hypothyroidism from Wang et al. (2010) [9]. At present, the influencing factors of ^{131}I treatment are still unclear. Therefore, in this study, we intended to perform a comprehensive analysis on a much higher number of recruits from three centers to provide more solid statistical evidence to solve the aforementioned controversy.

Subjects and Methods

Inclusion and exclusion of patients

This work is a retrospective study from three tertiary medical centers (i.e. two in Nanchang and one in Tianjin) from China. We reviewed the data archive of the departments from March 2012 to June 2017. The patients were given comprehensive physical examinations and serological tests before their ^{131}I treatments to review their family history.

Graves' disease was diagnosed based on having criteria (1) to (3), and/or one or several of criteria (4) to (7). Specifically: (1) typical symptoms of elevated metabolism, (2) sign of goitre (or in some cases normal thyroid volume), (3) laboratory findings of elevated thyroid hormones and suppressed thyrotropin level, (4) increased thyrotropin receptor antibodies (TRAb) concentration (or in some cases normal TRAb), (5) increased uptake in RAIU or thyroid scintigraphy, (6) with Graves' ophthalmopathy (GO) (or in some cases without) and (7) with Graves' dermopathy or pretibia edema (or in some cases without). Inclusion criteria were patients with a confirmed diagnosis of GD. Exclusion criteria were: (1) patients younger than 16 years of age, (2) pregnant or breastfeeding female GD patients, (3) clinical evidence of invasive Graves' ophthalmopathy, especially, with moderate or severe active GO or vision threatening active GO, (4) giant compressive goiter or intrathoracic goiter, (5) with thyroid nodule of suspected or confirmed malignancy. The Institutional Review Board of Tianjin Medical University General Hospital, the First Affiliated Hospital of Nanchang University and Jiujiang No.1 People's Hospital approved the ethical, methodological and protocol aspects of this investigation. All GD patients provided their written informed consent.

Serological data measurement, thyroid imaging and thyroid texture assessment

Serum thyroid hormones, including total triiodothyronine (T3), total thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4) and sensitive thyroid-stimulating hormone (TSH) were determined with chemiluminescence microparticle immunoassay (Abbott Ireland Diagnostics Division, Lisnamuck, Longford, Ireland). Thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TpoAb) were measured with chemiluminescent reaction principle assay (ADVIA Centaur analyser, Siemens Healthcare Diagnostics, New York City, New York, USA). Thyrotropin receptor antibodies was measured with electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics GmbH, Sandhofer Strasse, Mannheim, Germany). Thyroid imaging was performed in all patients. Thirty minutes after intravenous administration of 10mCi of $^{99m}TcO_2$, thyroid imaging was performed to observe the distribution of radioactivity, determine the functional status of thyroid nodules and exclude the diagnosis of thyroiditis. Patients were positioned in a supine position with the neck hyper-extended and imaged using a single photon emission computed tomography/computed tomography (SPECT/ CT) machine (Discovery NM/CT 670; General Electric Medical Systems, Milwaukee, Wisconsin, USA) with a low-energy parallel hole high-resolution collimator, peak 140keV and a window width of 20%. Thyroid texture and thyroid murmurs (bruits) were assessed. Two or more experienced doctors put a stethoscope on the thyroid for auscultation to determine if there is a murmurs. With palpation, the clinician can sense the texture , in order to distinguish between soft and hard texture.

Thyroid mass estimation

Thyroid size measurements were performed by using a GE Logiq C9 Premium Ultrasound machine (GE Healthcare, Wauwatosa, WI) with a linear 10-MHz transducer. Optimal longitudinal and transverse scans were conducted to allow the measurement of the depth (D), width (W) and length (L) of each thyroid lobe. The volume of each thyroid lobe (V) was calculated on the basis of ellipsoid formula: $V(cm^3)= 0.479\times D\times W\times L$ (cm). The thyroid volume was the sum of the volumes of both thyroid lobes. Then, considering the density of thyroid tissue to be approximately $1.0g/cm^3$, the thyroid mass [M (in grams)] was calculated by multiplying the volumetric data by $1.0g/cm^3$ [10].

Thyroid radioactive iodine uptake measurement

All patients underwent 2-, 6-, 24-, 48- and 72-hour RAIU measurements before ^{131}I therapy. The time interval between the uptake measurement and the ^{131}I treatment is generally not more than one week. Patients were administered a 3.7×10^4MBq (100μCi) dose of sodium iodide ($Na^{131}I$) on an empty stomach. All patients were also required to withdraw antithyroid drugs or drugs that may affect the thyroid gland (e.g., methimazole, propylthiouracil, compound iodine solution and amphetamine) 3 to 7 days before measuring the iodine uptake rate. Radioactive iodine uptake was measured 2, 6, 24, 48 and 72 hours after the administration using a MN-6110 Thyroid Function Instrument (Anhui USTC ZONKIA Scientific Instruments Co. LTD, Hefei, Anhui, China). Briefly, a NaI crystal scintillation probe (3cm in diameter) was positioned at the site of the thyroid for 2min at a fixed distance of 25cm. Then, the probe was also positioned at the site of the thigh at the same distance for 2min to obtain background correction. After the background correction, the activity in counts per minute over the thyroid region was compared with the activity measured from a standard source that contained 3.7MBq (100μCi) $Na^{131}I$. Maximum ^{131}I thyroid uptake value and $T_{1/2eff}$ were then calculated.

^{131}I treatment

Patients were instructed to avoid seaweed, seafood and nutritional supplements that contained iodine for the past month before ^{131}I treatment. In addition, the patients were asked to withdraw anti-thyroid drugs or drugs that can affect the thyroid (e.g. methimazole, propylthiouracil, compound iodine solution and propantheline) for 3 to 7 days before ^{131}I treatment. Iodine-131 doses were calculated on the basis of the following formula [11]: ^{131}I (mCi)=[estimated thyroid mass (g)×absorption dose (Gy/g)×0.67] / [$T_{1/2eff}$ (days)×maximum ^{131}I thyroid uptake value (%)]. Absorption dose=100Gy/g, and 0.67 is a rectified factor. All GD patients took the calculated dose of ^{131}I orally. They all fasted for at least 2 h before and after the administration of ^{131}I to achieve higher absorption and avoid food intervention.

Follow-up and efficacy of ^{131}I treatment

We measured the serum levels of thyroid function indices on GD patients at 1, 3, 6, and 12 months after ^{131}I therapy to evaluate the efficacy of the treatment. At the end of 12 months, we defined complete remission (euthyroidism) and hypothyroidism as 'cure' (cured group) and partial remission, inefficacy or recurrence as 'uncured' (uncured group). Hypothyroidism was defined as persistent, low thyroxine consen-

tration, elevated TSH levels, and beginning to replace levothyroxine for the patient within 12 months of treatment. Hyperthyroidism was defined as patients with normal thyroid hormone concentration at 1 year, no antithyroid drugs or normal TSH concentration and no levothyroxine treatment.

Statistical analysis

Data were presented as mean±standard deviation (SD) or case number (percentage). T-test and analysis of variance were used to evaluate differences between continuous variables. Data with a non-normal distribution were tested using the Mann-Whitney U-test. Chi square-test was used to evaluate differences between categorical variables. Logistic regression analysis was conducted to measure the prognostic factors between variables. Unconditional multivariate logistic regression was used to analyse whether any of these factors can be related to an uncured outcome, and the odds ratio (OR) with 95% confidence interval (CI) was then calculated. These analyses were performed by using SPSS 17.0 software. A P value of less than 0.05 was considered statistically significant.

Results

A total of 970 patients with a confirmed diagnosis of GD, who received ^{131}I therapy, participated in the current analyses. Altogether, 540 patients (55.7%) belonged to the cured group [310 euthyroidism cases (32.0%) and 230 hypothyroidism cases (23.7%)] whilst 430 patients (44.3%) belonged to the uncured group (Table 1). No significant differences in gender, age, family history, maximum ^{131}I thyroid uptake, TSH, TgAb, TRAb, TpoAb levels, thyroid texture, as well as blood cells, hepatic function and renal function were observed between the two groups (P>0.05). The proportions of patients with huge goiter and having thyroid murmurs (bruits) in the uncured group were significantly higher than those in the cured group (P<0.05). The dosages of ^{131}I, as well as levels of FT3 and FT4 in the uncured group, are significantly higher than those in the cured group (P<0.05).

The results of univariate logistic regression analysis showed that thyroid mass, having thyroid murmurs, prescribed ^{131}I dosage and the levels of FT3 and FT4 were associated with disease outcome. Then, unconditional multivariate logistic regression analysis was performed by using the above indices with significances (Table 2), The calculated results showed that each one of the included factors had an independent prognostic value for the GD patients (P<0.05).

Discussion

Ever since the first two pioneer papers about radioactive iodine therapy in hyperthyroidism were published by Hertz and Roberts [12] and Chapman and Evans [13], the effectiveness and safeness of this treatment have been acknowledged and proposed by several thyroid societies as a cornerstone therapy [13-15]. Historically, the therapeutic strategy of RAI in the US is to completely ablate the thyroid, thereby rendering permanent hypothyroidism [15]. In China, nevertheless, the critical doctor-patient relationship [9, 16] still requires that the therapeutic goal is balanced to achieve euthyroidism and avoid hypothyroidism; thus, personalised dosage is adopted in most hospitals [8, 17]. If factors affect the outcome of the RAI, the calculated dose should be modified according to these characteristics. This study aimed to analyse the factors that could have a potential influence on the effects of therapy with ^{131}I.

In our study, some parameters, such as large thyroid mass and a high level of basal FT3 and FT4, could affect the efficacy of ^{131}I therapy, and a high level of ^{131}I dosage is associated with treatment failure.

Firstly, similar to many previous studies [18, 19], the treatment failure rate in patients with larger thyroid mass is higher than those with smaller glands. In Danrong Yang et al. (2018) [20], the thyroid volume was treated as a negative predictor, and its threshold was 35cm^3. Markovic et al. (2007) [21] reported that the chances of treatment failure for the patients with thyroids larger than 62g were much greater. However, some studies [22] show no statistical difference between thyroid mass and the outcome of ^{131}I therapy. Differences amongst various studies may result from a lack of unified and objective methods to measure thyroid size and a clear standard definition of thyroid size threshold. Secondly, our study also showed that the higher the levels of FT3 and FT4, are the higher the incidence of being uncured will be. This finding is consistent with some studies, in which free thyroid hormone (FTH) levels had a negative impact on the RAI success rate [20]. Lower serum FTH level, which can reflect the severity of hyperthyroidism, may suggest that the patient's condition is milder and may lead to improved therapeutic effect. However, some studies have found that FTH level does not affect the success rate of RAI. The different results may be due to the effect of the duration of the ATD withdrawal on the serum levels of thyroid hormones. Thirdly, a lower level of ^{131}I dosage is associated with ^{131}I treatment success in this study. This result may be due to the milder condition in the low-dose group. Lastly, in our report, thyroid murmur was identified as one factor that was associated with treatment failure. In the hyperthyroidism status, thyroid vascularity and blood flow increases are also reported to be associated with the activation of thyroid-stimulating hormone receptors by TSH or TRAb [23]. Thyroid murmurs (bruits) occur in several GD patients, reflecting the diffuse toxic status of thyroid function [24]. However, this result is easy to be influenced by subjective factors. In our observation, the rate of iodine absorption and thyroid-associated antibodies did not affect the outcome treatment significantly, which is consistent with some other studies [20, 25]. However, many studies showed that higher thyroid uptake [8] or high level of TRAb may be the cause of ^{131}I treatment failure [26, 27]. Hence, more samples are needed to confirm this finding.

This study had limitations that are worthy of attention. Firstly, only three tertiary medical centers are included in

Table 1. *Data comparisons between the cured group and the uncured group.*

	Cured group		Uncured group		Statistics	
	Number or mean ± SD	%	Number or mean ± SD	%	χ^2/t value	P value
Total case number	540		430			
Males/Females	80/460	14.81/85.19	70/360	16.28/83.72	χ^2=0.153	>0.05
Age (y)	33.8±3.1		31.5±1.9		t=0.633	>0.05
Having family history	110	20.37	84	19.53	χ^2=0.175	>0.05
Estimated thyroid mass (g)	55.17±2.31		72.23±5.19		t=2.355	<0.05
Having thyroid murmurs (bruits)	51	9.44	123	28.60	χ^2=5.156	<0.05
Maximum ^{131}I thyroid uptake (%)	56.27±1.85		59.52±3.72		t=1.072	>0.05
Prescribed ^{131}I dosage (mCi)	4.64±1.45		7.39±2.15		t=5.853	<0.05
FT3 (pmol/L)	23.19±4.40		39.62±5.64		t=3.972	<0.05
FT4 (pmol/L)	53.41±3.28		67.95±1.68		t=2.004	<0.05
TSH (mIU/L)	0.015±0.007		0.018±0.010		t=1.070	>0.05
TgAb (IU/ml)	451.09±11.57		433.75±9.86		t=0.182	>0.05
TpoAb (IU/ml)	365.74±9.51		386.62±12.63		t=0.165	>0.05
TRAb (IU/ml)	45.29±1.61		43.36±1.06		t=0.561	>0.05
Soft/firm thyroid texture	110/430	30.37/79.63	90/340	20.93/79.07	χ^2=1.269	>0.05
WBC (10^9/L)	5.14±0.63		4.91±0.54		t=0.562	>0.05
ALT(U/L)	20.17±1.75		21.49±2.45		t=0.254	>0.05
AST（U/L)	19.35±1.46		20.89±1.79		t=0.262	>0.05
BUN(mmol/L)	10.25±1.06		9.78±0.94		t=0.187	>0.05
Cr (umol/L)	57.41±2.19		56.27±2.06		t=0.162	>0.05

Table 2. *Factors relating an uncured outcome in multivariate logistic regression.*

Variables	OR	95%CI	P value
Estimated thyroid mass (g)	1.368	1.246-1.385	0.021
Having thyroid murmurs (bruits)	2.283	1.783-5.693	0.006
Prescribed ^{131}I dosage (mCi)	1.326	1.125-1.458	0.032
FT3 (pmol/L)	1.467	1.369-1.569	0.013
FT4 (pmol/L)	1.419	1.036-1.659	0.027

this study. Thus, a multi-centered study with more recruits is needed to reduce selection bias. Secondly, long-term (exceeding one year) follow-up to observe the therapeutic efficacy is also necessary to verify the current findings. Thirdly, the individualised ^{131}I dosage method should be compared with other dosage methods to check whether the prognostic factors are the same. Fourthly, some parameters, such as thyroid murmurs (bruits) and thyroid texture determination, thyroid lobe measurement of depth, width and length (optimal longitudinal and transverse scans in ultrasonography can be determined differently by various doctors), rely on subjective determinants to some extent.

In conclusion, estimated thyroid mass, thyroid murmurs (bruits), prescribed ^{131}I dosage, FT3 and FT4 are the most influential parameters with independent prognostic values for GD patients who are undergoing ^{131}I therapy with formulated dosage calculation.

Limitations

This study had limitations that are worthy of attention. Firstly, only three tertiary medical centers are included in this study. Thus, a multi-centered study with more recruits is needed to reduce selection bias. Secondly, long-term (exceeding one year) follow-up to observe the therapeutic efficacy is also necessary to verify the current findings. Thirdly, the individualised ^{131}I dosage method should be compared with other dosage methods to check whether the prognostic factors are the same. Fourthly, some parameters, such as thyroid murmurs (bruits) and thyroid texture determination, thyroid lobe measurement of depth, width and length (optimal longitudinal and transverse scans in ultrasonography can be determined differently by various doctors), rely on subjective determinants to some extent.

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The authors declare that they have no conflicts of interest.

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