

# Clinical outcomes of low-dose and high-dose postoperative radioiodine therapy in intermediate-risk papillary thyroid carcinoma patients with low postoperative stimulated thyroglobulin (1-20 ng/ml) and non-structural or functional metastasis: study protocol for a randomized-controlled trial

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**Study protocol**

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# Abstract

**Background:** For some intermediate risk papillary thyroid carcinoma patients, if there are structural metastases, reoperation is preferred. If there are functional metastases ( $^{131}\text{I}$  avidity), they can be treated with high-dose radioactive iodine ( $^{131}\text{I}$ ). However, it is still controversial whether  $^{131}\text{I}$  ablation should be used and the determination of  $^{131}\text{I}$  dosage for another part of intermediate risk patients with non-structural or functional metastases, especially those with postoperative stimulated thyroglobulin (ps-Tg) 1-20 ng/ml. The aim of the present study is mainly to compare the 3-years disease-free survival between low-dose group (1.1 GBq) and high-dose group (3.7 GBq) in intermediate risk papillary thyroid carcinoma patients with non-structural or functional metastases and ps-Tg 1-20 ng/ml.

**Methods:** A single-center, randomized, double-blind parallel controlled study is designed at the Zhujiang Hospital of Southern Medical University. Participants will be randomized to low-dose group (1.1 GBq) or high-dose group (3.7 GBq) in a 1:1 ratio. After orally receiving different dosage of  $^{131}\text{I}$  once on an empty stomach, all patients will return to our hospital every 3-12 months to be performed related inspection items.

**Discussion:** We believe that the 3-year disease-free survival of low-dose group (1.1 GBq) may not be lower than that of high-dose group (3.7 GBq) in intermediate-risk thyroid papillary carcinoma patients with no structural or functional metastases and ps-Tg 1-20 ng/ml. Besides we expect to clarify whether there are apparent differences in successful remnant ablation, efficacy, progression-free survival, safety, and health economics evaluation between the two groups.

**Trial registration:** ClinicalTrials.gov (<https://clinicaltrials.gov/>), ID: NCT04354324. Registered on 16 April, 2020.

## Background

Thyroid cancer is the fastest growing and most prevalent endocrine malignancy worldwide. In 2018, the Cancer Center of China reported that thyroid cancer was the 8th in most common cancer and 4th in female malignant tumors [1]. Differentiated thyroid cancer (DTC) comprises the vast majority (> 95%) of all thyroid cancer, of which thyroid papillary cancer (PTC) accounts for up to 90% [2], with high 5-year survival rates of 90–95% [3] [4].

The 2015 version of American Thyroid Association (ATA) thyroid cancer guidelines proposed a three-tiered clinical-pathologic risk stratification system that classified patients as having low, intermediate, or high risk of recurrence, of which the proportion of intermediate risk is the highest. At present, the consensus of radioactive iodine ( $^{131}\text{I}$ ) ablation for low-risk, high-risk patients and intermediate-risk patients with structural metastases or functional metastases ( $^{131}\text{I}$  avidity) have been reached. However, whether  $^{131}\text{I}$  ablation should be used in another part of intermediate risk patients with non-structural or functional metastases and the choice of  $^{131}\text{I}$  dosage are still controversial [5]. Some studies showed that

there was no significant difference in the success rate of  $^{131}\text{I}$  remnant ablation and recurrence rate between low-dose radioactive iodine (1.1 GBq) and high-dose radioactive iodine (3.7 GBq) in non-high-risk DTC patients [6–17]. Recently, some scholars have proposed that low dose  $^{131}\text{I}$  can be used for intermediate risk of postoperative patients without metastasis, but there is no evidence from prospective research to support the effectiveness (disease-free survival, progression-free survival etc.).

For DTC patients with total/near-total thyroidectomy, low postoperative stimulated thyroglobulin (ps-Tg) indicates a lower recurrence rate and a better prognosis [18–21].  $^{131}\text{I}$  remnant ablation cannot be used in intermediate or low-risk DTC patients with ps-Tg  $\leq 1$  ng/ml or suppressed Tg  $\leq 1$  ng/ml [22, 23]; high ps-Tg usually indicates the presence of metastasis, and that is a clear indication of  $^{131}\text{I}$  therapy [24]. However, intermediate-risk PTC patients with intermediate ps-Tg level (1–20 ng/ml) account for the main proportion, and it is a difficult problem whether  $^{131}\text{I}$  therapy should be performed at present and  $^{131}\text{I}$  dose.

## Methods/design

### Hypothesis

We hypothesize that, for intermediate-risk thyroid papillary carcinoma patients with no structural or functional metastases and ps-Tg 1–20 ng/ml, the 3-year disease-free survival of low-dose  $^{131}\text{I}$  (1.1 GBq) may not be lower than that of high-dose  $^{131}\text{I}$  (3.7 GBq).

### Primary objective

Our main objective is to compare the 3-years disease-free survival between low-dose  $^{131}\text{I}$  (1.1 GBq) and high-dose  $^{131}\text{I}$  (3.7 GBq) in intermediate-risk thyroid papillary carcinoma patients with no structural or functional metastases and ps-Tg 1–20 ng/ml.

### Secondary objectives

The study will evaluate the efficacy, safety and health economics of low dose  $^{131}\text{I}$  (1.1 GBq).

### Trial design

This is a prospective, single-center, randomized, double-blinded (patient and researcher) parallel controlled, non-inferiority study. The trial is conducted at the Nuclear Medicine Department, Zhujiang Hospital of Southern Medical University. The follow-up period is 3 years. The study has been registered at ClinicalTrials.gov (ID: NCT04354324). Figure 1 shows an overview of the trial.

### Sample size

Eligible patients will be randomly assigned to low-dose (1.1 GBq)/intervention group and high-dose (3.7 GBq)/control group with a 1:1 ratio. According to literature reports and pre-clinical data [6–8], the disease-free survival of the control group is 92%, non-inferiority cut-off value is  $\delta = 7\%$ . A total of 254 subjects are generated from  $\alpha = 0.025$  (one-sided test), Power = 0.8, proportion = 0.5 (control group) and lost rate = 10% (two groups) by PASS 12.0 software (NCSS, US).

## Population

Subjects admitted to our department for  $^{131}\text{I}$  therapy are recruited by the research staff by means of propaganda, science popularization and so on. Eligible subjects who agree to participate in the study will have to sign a written informed consent that has been approved by the Ethics Committee before any screening process or evaluation. A total of 254 patients with PTC will be enrolled in the study from April 2020 to June 2024 at the department of Nuclear Medicine, Zhujiang Hospital of Southern Medical University.

## Inclusion criteria

1. Patients with histological confirmation of intermediate-risk PTC according to 2015 ATA Management Guidelines [5];
2. DTC patients who underwent total or near-total thyroidectomy according to 2015 ATA guidelines;
3. The level of serum ps-Tg at least 28 days after surgery is 1–20 ng/ml without or withdraw levothyroxine for 3 weeks at least;
4. Age is  $\geq 16$  years old;
5. Patients who volunteer to participate in the study and sign informed consent.

## Exclusion criteria

1. Image, for example ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) or  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography/computed tomography ( $^{18}\text{F}$ -FDG PET/CT) and so on, indicates the presence of metastases;
2.  $^{131}\text{I}$  whole body scan indicating the presence of metastases outside the thyroid bed;
3. Patients with positive Tg antibody (TgAb) ( $\geq 115$  Ku/L);
4. Patients who have other coexisting serious diseases or other factors that may affect the outcome of ablation;
5. Pregnant or breastfeeding women, or with birth planning within six months.

## Randomization

A simple randomization method is used in this study. A statistician uses SPSS 20.0 software (IBM, Armonk, NY) to generate 254 random numbers, which are then randomly divided into groups A and B in a 1:1 ratio to form a random distribution table. The statistician determines the dosage (1.1GBq or 3.7GBq) of group A and group B in advance, and retains the random distribution scheme in the form of a document, which is sealed and stored.

Sealed envelope method is used to realize grouping concealment. The statistician responsible for the grouping concealment distributes the results in 254 light-tight envelopes to the researchers. The researchers open the envelopes in the order of enrollment, according to the allocation scheme in the envelopes, and determine the group of patients (group A or group B), so as to avoid the possibility of

selectively deciding whether a certain study object should be included in the enrollment of patients because the researchers know the whole grouping order in advance.

### **Blinding**

The randomization will be performed using a code list created by the statisticians of Zhujiang Hospital of Southern Medical University. The trial staff will not know the arm of allocation (double-blind study). Technician in our department will prepare treatment kits assigning them the identification codes following the randomization lists. Only if necessary, for the safety of patients, the single kit code will be open by the investigators during the study period.

### **Interventions**

The test group and the control group will receive oral administration of 1.1 GBq and 3.7 GBq, respectively, once on an empty stomach. The interventions in this trial are one-time interventions. The researchers will stand by to see if the patients finish the drink while they take the medicine. The test drug and control drug are prepared (the radioactive activity is measured with instruments) by technician who are unblinded. The outer packing and volume of the two groups are the same, but the dosage forms are different, and the packing will be marked as A or B. Therefore, the products of the two groups cannot be distinguished with the naked eyes but measuring instruments. After the randomization is completed, drugs are distributed to participants according to their group number (A or B).

### **Research process**

The research process is divided into three phases: screening stage, treatment stage and following stage. Combined medications and adverse events record will be collected at every stage. Time schedule of the study is shown in Table 1.

Table 1  
Schedule of the study process.

Stage	Selection	Treatment	Follow-up							
Sequence	1	2	3	4	5	6	7	8	9	10
Time (m, month)	-1week	0	1m	3m	6m	12m	18m	24m	30m	36m
Basic information collection										
Signed informed consent	√									
Inclusion and exclusion criteria	√									
Demographic characteristics	√									
Medical and treatment history	√									
Combined disease and medication	√	√	√	√	√	√	√	√	√	√
Physical examination	√	√	√	√	√	√	√	√	√	√
Effectiveness observation index										
Neck ultrasound	√	√		√	√	√	√	√	√	√
Thyroid function tests <sup>a</sup>	√	√	√	√	√	√	√	√	√	√
Tg	√	√	√	√	√	√	√	√	√	√
TgAb	√	√	√	√	√	√	√	√	√	√
Neck and chest CT	√					√			√	

CT: computed tomography; MRI: magnetic resonance imaging; <sup>18</sup>F-FDG PET/CT: <sup>18</sup>F-fluorodeoxyglucose positron emission tomography/computed tomography.

a. Thyroid function tests including FT3, FT4 and thyroid stimulating hormone (TSH).

Stage	Selection	Treatment	Follow-up							
<sup>131</sup> I whole-body scan	√	√	It will be performed in 6–12 months after the initial treatment for patients who does not achieve excellent response.							
Optional examination										
Neck MRI	If the neck ultrasound indicates suspicious lymph nodes, but the diagnosis cannot be confirmed									
<sup>18</sup> F-DG-PET/CT	sTg ≥ 10 ng/ml in 6–12 months after the initial treatment.									
Disease-free Survival (primary)	√	√	√	√	√	√	√	√	√	√
Successful remnant ablation	√	√	√	√	√	√	√	√	√	√
Curative effect	√	√	√	√	√	√	√	√	√	√
Progression-free survival	√	√	√	√	√	√	√	√	√	√
Safety index										
Gastrointestinal side effect		√	√	√	√	√	√	√	√	√
Radiation thyroiditis		√	√	√	√	√	√	√	√	√
Salivary adenitis		√	√	√	√	√	√	√	√	√
Hematopoietic system adverse reactions		√	√	√	√	√	√	√	√	√
Reproductive system		√	√	√	√	√	√	√	√	√
Secondary cancer		√	√	√	√	√	√	√	√	√
Adverse event		√	√	√	√	√	√	√	√	√

CT: computed tomography; MRI: magnetic resonance imaging; <sup>18</sup>F-FDG PET/CT: <sup>18</sup>F-fluorodeoxyglucose positron emission tomography/computed tomography.

a. Thyroid function tests including FT3, FT4 and thyroid stimulating hormone (TSH).

Stage	Selection	Treatment	Follow-up
Health Economics Evaluation Index			
Hospital isolation date		√	
Hospital costs		√	
Others			
Random grouping		√	
CT: computed tomography; MRI: magnetic resonance imaging; <sup>18</sup> F-FDG PET/CT: <sup>18</sup> F-fluorodeoxyglucose positron emission tomography/computed tomography.			
a. Thyroid function tests including FT3, FT4 and thyroid stimulating hormone (TSH).			

## Outcomes

### Primary outcome

The primary outcome is disease-free survival, defined as the percentage of patients who achieve excellent responses during the 3-year follow-up period.

### Secondary outcomes

The secondary outcomes include:

#### 1. Effectiveness evaluation indexes [5]:

- Successful remnant ablation: subjects evaluated at 6–12 months after the initiation of treatment meet one of the following two conditions: (a) absence radioactive iodine uptake in the thyroid bed according to a diagnostic <sup>131</sup>I whole-body scan; (b) serum stimulated Tg is < 1 ng/ml or suppressed Tg is < 0.2 ng/ml.
- Efficacy: judged by response-to-therapy categories (see Table 2).
- Progression-free survival: subjects who meet any one of the following conditions are seen as progression survival: (a) Functional or structural metastases appear during follow-up; (b) when sTg > 1 ng/ml or suppressed Tg > 0.2 ng/ml, the serum Tg level increases by more than 25% compared to the previous; (c) TgAb was negative at the time of enrollment, and it is positive and persistently elevates during follow-up. The others are defined as progression-free survival.

2. Safety indexes: the incidence of short-term and long-term adverse reactions after <sup>131</sup>I treatment (Time points to distinguish short-term and long-term is 3 months), including gastrointestinal side effect, radiation thyroiditis, salivary adenitis, myelosuppression, secondary cancer, etc. (see Table 3).

3. Health economics evaluation indexes: average hospital isolation day and the cost of hospitalization when patients receive treatment. The hospital isolation day is determined by the radiation dose in the patient's body, and the national discharge standard must be met when discharged (400 MBq or 25 μSv/h).

Table 2  
Stratification of efficacy.

Excellent response	Biochemical incomplete response	Structural incomplete response	Indeterminate response
Negative image; met one of the following: 1) Suppressed Tg < 0.2 ng/ml <sup>a</sup> ; 2) sTg < 1 ng/ml <sup>a</sup> .	Negative image; meet one of the following: 1) suppressed Tg ≥ 1 ng/ml <sup>a</sup> ; 2) sTg ≥ 10 ng/ml <sup>a</sup> ; 3) TgAb persistently elevated during follow-up.	Evidence of structural or functional disease from image (suspicious lymph nodes on ultrasound); any level of Tg and TgAb.	Negative image; suppressed Tg detectable, but < 1 ng/ml; meet any one of following: 1) sTg detectable, but < 10 ng/ml; 2) TgAb stable or declining.
Tg: thyroglobulin; sTg: stimulated thyroglobulin; TgAb: anti-thyroglobulin antibody.			
a. When TgAb is negative.			

Table 3  
Adverse reactions after <sup>131</sup>I treatment.

Adverse Reactions	Details
Gastrointestinal side effect	Nausea, vomit, abdominal distension, constipation, decreased appetite, etc.
Radiation thyroiditis	Swelling and pain in the thyroid area, swallowing pain, dysphagia, etc.
Salivary adenitis	Pain and swelling of the salivary, dry mouth, taste alteration, dental caries, etc.
Hematopoietic system adverse reactions	Myelosuppression includes leukopenia, thrombocytopenia, erythrocytopenia, aplastic anemia
Reproductive system	Infertility, irregular menses, abortion, stillborn
Secondary cancer	Various secondary tumors

## Adverse event reporting and harms

It was reported in the literature that the incidence of adverse reactions was high when  $^{131}\text{I}$  dose exceeded 18.5–22.2 GBq. In this study, low and high doses of  $^{131}\text{I}$  (1.1 GBq and 3.7 GBq) are given in one time to treat differentiated thyroid cancer, which are relatively low and safe. The most common adverse reactions after  $^{131}\text{I}$  treatment, such as acute gastrointestinal reactions, radioactive thyroiditis and salivary adenitis, can be alleviated after general observation or symptomatic treatment. All adverse events reported by participants or detected by physicians will be recorded in the case report form (CRF), and all serious adverse events will be reported to the Ethics Review Committee.

### **Retention**

A coordinator will be assigned to each subject responsible for a CRF to ensure adequate recording of every participant's data. When the participant withdraws from the trial, record the reasons for withdrawal. Subjects will enjoy the following rights:

- (1) Enjoy a free thyroid function test once a year;
- (2) During the study, Emission Computed Tomography (ECT), bone density, thyroid iodine uptake test and urine iodine tests shall be free of charge according to the needs of the disease (the required drug fees will not be within the free range, only the cost of drugs will be charged);
- (3) Provide free internal radiation monitoring for individuals;
- (4) Free lifelong thyroid cancer consultation;
- (5) Enjoy priority medical services.

### **Data collection**

#### 1. Establishment of standard operating procedures

Prior to the start of the trial, the investigator and sponsor / Contract Research Organization (CRO) will discuss the formulation of standard operating procedures for clinical trials, in order to unify the operation methods, judgment standards and record forms during the trial process, so that researchers will strictly implement the protocol.

#### 2. Training of researchers

Prior to the start of the trial, the main investigators and monitors of each center will organize training for all medical staff participating in the trial, including clinical trial protocols, clinical trial manuals, standard operating procedures, special precautions, etc.

#### 3. Ensure the reliability and accuracy of the instrument

The various instruments, equipment, actuals, standards, etc. used in various inspection items in clinical trials should have strict quality standards and ensure that they work under normal conditions.

## **Statistical analysis**

SAS9.4 statistical software is used for statistical analysis. All statistical inferences are performed by two-sided test. The statistically significant test level is set to 0.05, and the confidence interval of the parameters is estimated to be 95% confidence interval. Use the parametric method as much as possible. When the data do not meet the conditions of the parameter method, it can be analyzed by the conversion method. If still not satisfied, consider using a non-parametric method.

A descriptive analysis of baseline data (including demographic indicators, etc.) will be performed. As for abnormal data, analysis of causes will be carried out to exclude objective and subjective reasons.

The integrity of the data is monitored in real time. If the patient is found not to be followed up in time, he will be notified by phone and the data will be filled in time. Withdrawal subjects do not fill in the data. The missing values are replaced by sequence averages.

## **Confidentiality**

In order to protect and respect the privacy of the participants, unless necessary, the names of them will not be used directly, but anonymous numbering. Prior consent is required for the use of a tape recorder, camera, etc. When the researcher needs to use the medical records or relevant documents, he/she shall obtain the prior consent of the relevant authorities and shall not use them without authorization. When the research results are published, the identity of the research subjects shall not be implied, and the rights and interests of them shall not be affected.

## **Dissemination plans**

The results of the trial will be published in medical journals and presented at conferences. Identification information about subjects will be kept confidential.

## **Ethics approval**

Written approval has been obtained from the Medical Ethics Committee of Zhujiang Hospital of Southern Medical University, China (approval number 2019-KY-050-02). Written, informed consent to participate will be obtained from all participants. Any modifications (eg, changes to eligibility criteria, outcomes, analyses) to the protocol will require a formal amendment to the protocol. The amendment will be submitted to the Ethics Committee for approval. In the event of any discomfort or new changes in the subject's condition or any unforeseen circumstances, whether drug-related or not, the subject should be notified promptly to the physician, who will make a judgment and medical treatment. If the study is determined to be related to the damage, we will bear the cost of treatment or give corresponding financial compensation to the subject in accordance with relevant regulations of China.

## **Discussion**

Most patients with differentiated thyroid cancer have thyroidectomy followed by  $^{131}\text{I}$  ablation and thyroid-stimulating hormone (TSH) suppression therapy. Some non-randomized studies have shown that  $^{131}\text{I}$  ablation reduces rates of death and recurrence [11, 25–27]. It is well established that  $^{131}\text{I}$  remnant

ablation is not routinely recommended after thyroidectomy for low-risk patients, and  $^{131}\text{I}$  adjuvant therapy is routinely recommended after total thyroidectomy for high-risk patients. Reoperation is recommended for intermediate risk DTC patients with structural metastases, while high-dose  $^{131}\text{I}$  is preferred for those who have functional metastases. In terms of intermediate risk patients with non-structural or functional metastases, especially ps-Tg 1–20 ng/ml, there are controversies about whether  $^{131}\text{I}$  ablation should be used and the choice of  $^{131}\text{I}$  dosage.

Two large non-inferiority trials (HiLo[8] and ESTIMABL[9]) have shown that a low administered  $^{131}\text{I}$  dose (1.1 GBq) for remnant ablation is as effective as the high dose (3.7 GBq) in low-risk and intermediate-risk patients with differentiated thyroid cancer[6, 7]. In a long-term results of an open-label, non-inferiority randomized controlled trial published in 2019, Dehbi et al.[8] compared recurrence rates between radioactive iodine doses in HiLo and showed that the recurrence rate among patients who had 1.1GBq radioactive iodine ablation was not higher than that for 3.7 GBq, consistent with data from large, recent observational studies [10–17]. On the contrary, the low-dose group had fewer adverse reactions, shorter lower cost and isolation days, which can relieve the tension in the beds of domestic  $^{131}\text{I}$  treatment. It is hoped that our study can further confirm the results in these variables.

Tg is important to monitor tumor recurrence and metastasis, which is widely used in the follow-up of DTC patients after total thyroidectomy and post-operative thyroid remnant ablation [28, 29]. Ps-Tg refers to postoperative serum Tg level measured when TSH elevated (more than  $30\ \mu\text{IU/mL}$ ) after without or withdrawing levothyroxine for at least 3 weeks, which is closely related to the postoperative residue of the tumor, as well as the remission, persistence and recurrence of the disease after initial therapy. For DTC patients with high ps-Tg, high dose of radioactive iodine is required [24]. Correspondingly, the low ps-Tg level is an indicator that the thyroid has been basically removed, which means a lower recurrence rate and a better prognosis [19–21, 28–31]. A study has shown that when  $\text{ps-Tg} \leq 1\ \text{ng/ml}$ , whether low-risk patients undergoing remnant ablation or not does not affect the recurrence, and can directly transit to TSH suppression therapy [22]. Ibrahim et al. showed suppressed  $\text{Tg} \leq 1\ \text{ng/ml}$ , low-risk and intermediate-risk patients may not be treated with  $^{131}\text{I}$  remnant ablation [23]. For intermediate risk DTC patients with non-structural or functional metastases, ps-Tg 1–20 ng/ml suggests there may be minute metastases with negative images. There is uncertainty over the dose of  $^{131}\text{I}$  required for survival in intermediate-risk PTC patients with non-structural or functional metastases and ps-Tg 1–20 ng/ml.

The main purpose of our research is to compare whether there is a difference in 3-years disease-free survival between the low-dose group (1.1 GBq) and the high-dose group (3.7 GBq) in intermediate risk PTC patients with non-structural or functional metastases and ps-Tg 1–20 ng/ml. Secondly, the successful remnant ablation, efficacy, 3-year progression-free survival and safety (short-term and long-term adverse reactions) are also compared. Two hundred and fifty-four subjects will be enrolled in the study, subsequently divided into two groups according to the randomization performed prior to recruitment. The evaluation variables are disease-free survival, successful remnant ablation, efficacy, progression-free survival, safety, and health economics evaluation.

If this research provides positive results, it will be possible to recommend that low-dose  $^{131}\text{I}$  be implemented in treatment protocols for intermediate risk PTC patients with non-structural or functional metastases and ps-Tg 1–20 ng/ml, to further reduce the radiation dose of  $^{131}\text{I}$  in these patients, to reduce adverse reactions, ineffective and excessive medical treatment, to shorten the isolating days in the hospital and alleviating the scarcity of isolation ward, to reduce the expenditure on radiation health protection and radioactive waste disposal of national departments and hospitals, and to reduce the radiation risk of the public and medical staff.

## **Trial Status**

This trial is at version 2.0, August 21, 2019. Participant recruitment has been started on 15 April 2020. The recruitment will be completed approximately on the end of the month of June 2024.

## **Abbreviations**

DTC: Differentiated thyroid cancer; PTC: thyroid papillary cancer; ATA: American Thyroid Association; ps-Tg: postoperative stimulated thyroglobulin; CT: computed tomography; MRI: magnetic resonance imaging;  $^{18}\text{F}$ -FDG PET/CT:  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography/computed tomography; TgAb: Tg antibody; CRO: Contract Research Organization; CRF: case report form; ECT: Emission Computed Tomography; TSH: thyroid-stimulating hormone.

## **Declarations**

### **Acknowledgements**

Thank numerous individuals participated in this trial.

### **Authors' contributions**

Prof. W-O and Prof. H-j F designed the trial and will supervise the entire study. J-x L drafted the article and P-C is responsible for the critical revision of the article. P-C and Y-y D organized the sample size and the statistical plan. J-q W and J-W are responsible for the quality control of different doses of  $^{131}\text{I}$ . L-q P and Y-y C are responsible for consulting the relevant literature. L-y Y and W-l Y collected and assessed the data. All authors read and approved the final manuscript. No professional writers were involved in this manuscript.

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The funder had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

### **Availability of data and materials**

Available from the corresponding author upon request.

### **Ethics approval and consent to participate**

Ethical approval has been confirmed from the Medical Ethics Committee of Zhujiang Hospital of Southern Medical University, China (approval number 2019-KY-050-02). This clinical trial must be conducted in accordance with the principles of the Declaration of Helsinki. After detailed explanations of the trial, written informed consent will be obtained from each participant.

### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare that there is no conflict of interest.

### **Authors' information**

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# Figures

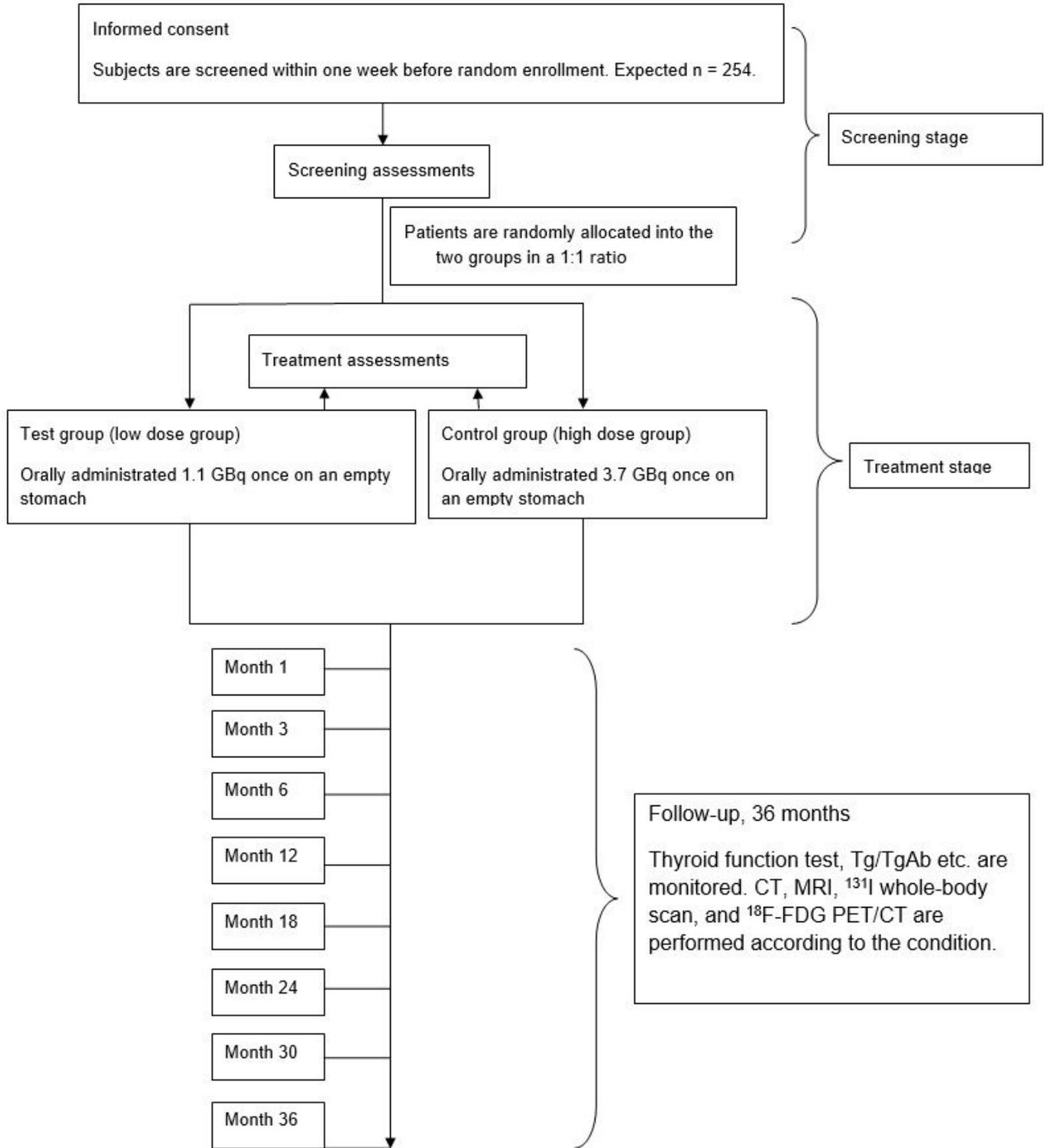


Figure 1

Study design.

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