Stimulated serum thyroglobulin but not RAIU level is a prognostic factor for ablation efficacy with a 3.7GBq (100mCi) fixed ^{131}I dose in patients with differentiated thyroid cancer

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Keywords: Differentiated thyroid cancer
- Radioactive iodine-131 uptake
- Ablation efficacy

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Received:
5 January 2021
Accepted revised:
26 March 2021

Abstract

Objective: The aim of this study was to determine prognostic value of radioactive iodine uptake (RAIU) and stimulated thyroglobulin (sTg) regarding the ablation efficacy in patients with differentiated thyroid cancer. **Subjects and Methods:** We studied 466 differentiated thyroid cancer (DTC) patients without distant metastases after thyroidectomy who underwent iodine-131 (^{131}I) ablation and were pre-therapy assessed by RAIU. The patients were divided into four groups according to the RAIU result, including: A) RAIU<2%, B) 2%≤ RAIU<5%, C) 5%≤RAIU<10% and D) RAIU≥10%. Every group was divided into four subgroups according to sTg levels, namely: 1) sTg<2ng/mL, 2) 2ng/mL≤sTg<5ng/mL, 3) 5ng/mL≤sTg<10ng/mL and 4) sTg≥10ng/mL subgroup. The ablation success was defined as a negative scan 6 months to 1 year and other imaging like US did not detect anything suspicious after ablation. Excellent response was considered as: sTg<1ng/mL with negative thyroglobulin antibodies (TgAb) and negative image scans. **Results:** The rate of successful ablation was 88.3%, 88.7%, 88.4% and 79% between group A to D, respectively (P=0.779). There was also no significant difference about the excellent response rate (64.5% vs 63.6% vs 48.8% vs 57.1%, P=0.256) between group A to D. The ablation success rate did not differ significantly between subgroups 1 to 4 in every group. However, the rates of excellent response were 86.8%, 52.1%, 25% and 15.2% between subgroups 1 to 4 for group A, respectively (P<0.001). Similarly, there was a significant difference about excellent response rate between subgroups 1 to 4 for groups B, C and D. **Conclusion:** After total thyroidectomy, not RAIU but sTg is a prognostic factor for ablation efficacy with a 3.7GBq (100mCi) fixed ^{131}I dose in patients with DTC.

Hell J Nucl Med 2021; 24(1): 53-59 *Epub ahead of print: 20 April 2021* *Published online: 30 April 2021*

Introduction

Radioiodine (^{131}I) remnant ablation (RRA) is an effective adjuvant treatment strategy for some patients with differentiated thyroid cancer (DTC) as a postsurgical targeted therapy. Radioiodine remnant ablation treatment is only used in patients with a history of total thyroidectomy and not hemithyroidectomy. The purpose of RRA therapy is to destroy residual, presumably benign thyroid tissue and tissue with suspected but unidentified remaining disease to facilitate initial staging and follow-up [1]. Successful remnant ablation contributes to a decreased recurrence rate, improves the sensitivity of ^{131}I scans and facilitates follow-up studies (serum stimulated thyroglobulin (sTg) as a specific tumor marker). Ablation success rates vary from approximately 30%-90% depending on the criterion used to evaluate the ablation success and the patient population [2]. Numerous clinical factors influence RRA efficacy. Some studies have reported that tumor size, higher sTg levels, lymph node capsular invasion, N1a classification, and distant metastases have a higher risk of ablation failure [3]. Serum sTg <2ng/mL is an essential and independent predictor for an excellent response [4]. Higher sTg levels before RRA treatment correlate with a greater likelihood of an incomplete response to initial treatment [5]. Thus, sTg levels predict ablation efficacy.

Radioactive iodine uptake (RAIU) is associated with thyroid remnant weight and expression of the sodium-iodine symporter [6]. Thyroglobulin is a macromolecular glycoprotein produced in normal thyroid tissue and DTC cells [7]. Higher sTg levels indicate more functioning thyroid tissue or DTC metastasis [8]. Although detectable Tg may be the result of distant metastases, RAIU and sTg can represent the extent of thyroid tissue remnant for DTC patients without distant metastasis after thyroidectomy. However, the effect of RAIU combined with sTg on ablation efficacy remains controversial. A few study results indicated an inverse correlation between RAIU levels and ablation efficacy [9-13]. However, another prospective study demonstrated that the rate of successful RRA was similar at different RAIU levels based on different radioactive ^{131}I therapeutic doses [14]. Similarly, some other reports indicated that RAIU levels did not influence ablation efficacy [15].

Therefore, the aim of this retrospective cohort study was to determine the prognostic value of RAIU and sTg regarding ablation efficacy in patients with differentiated thyroid cancer.

Subject and Methods

Patient

This cohort study was a retrospective analysis of records of 466 patients who underwent thyroidectomy and first RRA treatment for patients with DTC between January 2013 and December 2014 in our institution. To be included in the study, patients must have undergone thyroidectomy for DTC.

The exclusion criteria were as follows: distant metastasis observed by imaging modality such as computed tomography (CT), positron emission tomography/computed tomography (PET/CT), magnetic resonance imaging (MRI), ultrasonography (US); pregnancy or breast feeding women; severe coexisting conditions (including other cancers); previous ^{131}I ablation treatment; a recent history of ^{131}I contamination, such as iodine-containing drugs or iodine contrast agents within the previous 3 months; incomplete laboratory result; and positive TgAb.

Treatment protocol

^{131}I treatment

At our institution, therapeutic planning for patients with postoperative thyroid cancer was determined by a multidisciplinary thyroid cancer board on the basis of a patient risk profile, including surgical pathology findings, clinical parameters, baseline and stimulated Tg levels, preablation neck ultrasound, and other imaging studies (i.e., preoperative or preablation chest CT) if available. Iodine-131 ablation was initiated 1 to 6 months after surgery.

All the patients were staged according to TNM (tumor-node-metastasis) staging system of the American Joint Committee on Cancer (AJCC) 8th edition [16] and re-stratified into low, intermediate, high risk groups according to the 2015 American Thyroid Association (ATA) guidelines [17]. Before ^{131}I treatment, serum thyroid stimulating hormone (TSH) levels were greater than 30mIU/L in all patients after maintaining a low-iodine diet for 2 weeks and withdrawing from levothyroxine for 3 to 4 weeks (none of the patients were administered triiodothyronine). Thyroid stimulating hormone, Tg, and TgAb measurements were performed during hypothyroidism at ablation before ablative ^{131}I administration. The range of detection was 0.04-1000ng/mL for Tg and 10-4000IU/mL for TgAb. TgAb >115IU/mL was regarded as a positive standard. Next, RAIU was measured 24h after the administration of 0.185MBq of ^{131}I using a gamma counter during hospitalization. Then, technetium-99m pertechnetate ($^{99m}TcO_4^-$) thyroid imaging was performed. Thyroid imaging results were considered as positive or negative. Positive thyroid imaging showed $^{99m}TcO_4^-$ radioactive uptake in the thyroid bed area, and negative thyroid imaging indicated that no $^{99m}TcO_4^-$ uptake was found in the thyroid bed area. Time interval between RAIU measurement and RRA treatment was 2-3 days.

We selected DTC patients with dose of 100mCi of ^{131}I for simple remnant ablation and adjuvant therapy. Five days after oral administration of ablation activity of ^{131}I, postablation scintigraphy was performed to detect undefined or unexpected local and distant metastases.

Initial evaluation after ^{131}I therapy

Approximately 6 to 12 months after the initial application of RRA treatment, all the patients (n=466) underwent a second diagnostic WBS (Dx-WBS) with 5mCi of ^{131}I, and serum sTg and TSH levels together with TgAb were measured after withdrawal of levothyroxine replacement therapy for 2-4 weeks. We evaluated the ablation efficacy based on the ablation success rate and therapeutic response. Ablation success was defined as a negative scan 6 months to 1 year, and other imaging modalities, such as US, did not detect anything suspicious after ablation. Therapeutic response was divided into excellent response and non-excellent response according to ATA guidelines released in 2015 [17]. Excellent response was defined as the presence of sTg <1ng/mL (with negative TgAb) and negative image scans.

Late follow-up

Patients without apparent disease at the initial evaluation were followed-up by annual measurement of sTg and TgAb during levothyroxine replacement therapy and neck US. Imaging methods other than US (chest and mediastinal CT, fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT) were also performed in certain patients as needed when metastatic lesions were suspected. Diagnosis of a tumor in lesions detected by the imaging methods was made by cytology or histology and/or unequivocal ectopic uptake (excluding false-positive results) on Dx-WBS or ^{18}F-FDG PET/CT.

Patient group

A total of 466 DTC patients were collected. All the patients were divided into four groups according to RAIU levels: A, RAIU<2% group; B, 2%≤RAIU<5% group; C, 5%≤RAIU<10% group; D, RAIU≥10% group. Every group was divided into four subgroup according to sTg levels: 1, sTg <2ng/mL; 2, 2ng/mL≤sTg<5ng/mL; 3, 5ng/mL ≤ sTg <10ng/mL; 4: sTg ≥ 10ng/mL subgroup (Figure 1).

We compared the ablation success rate and excellent response rate between the A-D group and between subgroups 1-4 in the A-D group.

Statistical analysis

Continuous variables were reported as the mean±standard deviation (SD) for variables with normal distributions or as the median and 25th to 75th percentiles (P25-75) for variables without normal distributions. Categorical variables are expressed as absolute numbers and percentages. One-way ANOVA was performed to analyze continuous data between four groups. Comparative analyses were performed with an unpaired Student's t-test for variables with normal distributions, the Mann-Whitney U-test for variables without normal distributions and the Pearson chi-squared test for categorical variables. Receiver operating characteristic

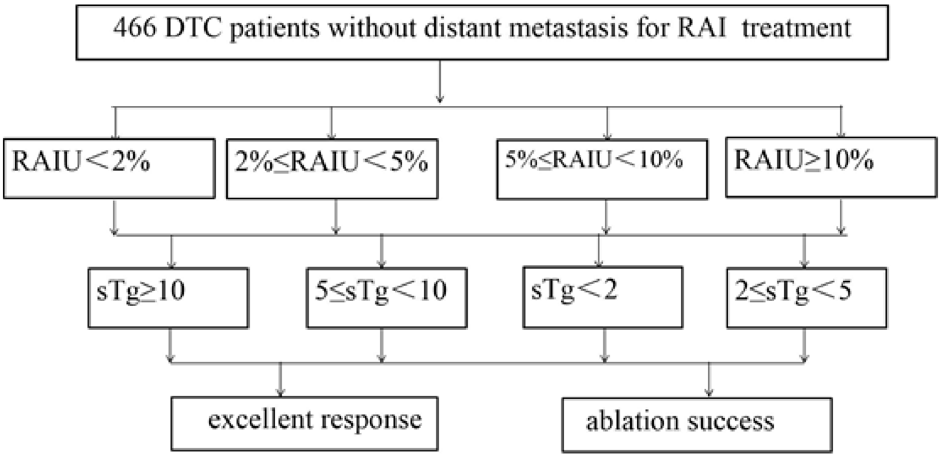

Figure 1. Patients without distant metastasis for radioactive iodine (RAI) treatment.

(ROC) was used to determine the optimal cut-off of sTg to predict ER and ablation success. Statistical analysis was performed with SPSS software (SPSS, version 21.0; SPSS Inc., Chicago, IL, USA). A P-value <0.05 was considered statistically significant.

Results

Baseline characteristics

We studied 466 patients with DTC for RRA treatment who did not have distant metastasis. Of the 466 enrolled DTC patients, 45.9% (214/466) were classified into the A group, 41.8% (195/466) were classified into the B group, and 9.2% (43/466) and 3% (14/466) were classified into the C and D groups, respectively. In the D group, the RAIU ranged from 10% to 30%. The mean sTg was the lowest in the A group and the highest in the D group (5.15±10.85 vs 26.40±23.04, respectively). There was a significant difference in the rate of positive $^{99m}TcO_4^-$ thyroid imaging between the A-D groups (52.8% vs 75.4% vs 81.4% vs 92.9%, P<0.001). The other baseline characteristics of the enrolled patients are shown in Table 1.

The relationship between RAIU and excellent response and ablation success

The rates of successful ablation were 88.3%, 88.7%, 88.4%, and 79% between groups A and D, respectively (P=0.779). There were also no significant differences in the excellent response rate (64.5% vs 63.6% vs 48.8% vs 57.1%, P=0.256) between the A-D groups (Figure 2). In group 4, 3 of 14 patients did not have ablation success, and their RAIU values were 14.5%, 22.3%, and 30%, separately. In Figure 3, we present a DTC patient who achieved ablation success and excellent response (RAIU: 21%).

The relationship between RAIU combined with sTg and excellent response and ablation success

Next, we performed subgroup analysis on the basis of different sTg levels. The ablation success rate was not significantly different between groups 1-4 in the A-D group. However, the rates of excellent response were 86.8%, 52.1%, 25%, and 15.2% between 1-4 in the A group, respectively (P<0.001). Similarly, significant differences in the excellent response rate were noted between groups 1-4 in the B, C, and D groups (Figure 4).

Receiver operating characteristic curve analysis was performed to evaluate the optimal cut-off to predict excellent response and ablation success. As shown in Figure 5A, the area under the curve (AUC) was 0.795 (95% confidence interval 0.753-0.836; P<0.001), and the optimal cut-off was 3.95ng/mL to predict an excellent response (with a sensitivity of 76.6% and specificity of 69.9%). Figure 5B shows the ROC curve for sTg levels to predict ablation success. The AUC was 0.632 (95% confidence interval 0.551-0.773; P<0.001), and the optimal cut-off was 2.51ng/mL, yielding a sensitivity of 47.4% and a specificity of 74.5%.

Late follow-up

The time of follow-up ranged from 5.2 to 7.1 years (median, 5.8 years). During follow-up, a total of 17 patients (3.6%) were confirmed to have structural recurrent disease. Among 17 patients, 4 patients (high risk) had pulmonary metastasis. Their RAIU and sTg levels were 1%, 1%, 2%, and 18.9% and 9.64ng/mL, 49.4ng/mL, 72.86ng/mL, and 84.46ng/mL, respectively. The other patients had lymphatic metastasis. The median RAIU level was 4.5%, ranging from 1 to 18.6%. The median sTg was 23.98ng/mL, ranging from 16.84 to 73.31 ng/mL.

Discussion

Thyroid carcinoma is an increasingly prevalent malignancy worldwide, and its incidence is gradually increasing [18]. Differentiated thyroid cancer is the main type of thyroid cancer. Successful RRA treatment can decrease the recurrence rate and disease-specific death rate [19]. Many clinical factors

Table 1. Patients baseline characteristics.

		RAIU<2%	2%≤RAIU<5%	5%≤RAIU<10%	RAIU≥10%	P
Age		42.4±11.4	44.9±11.5	38±12.3	47.9±11.4	0.624
Gender	Male/female	64/150	62/133	15/28	9/5	0.082
Pathology	PTC/FTC	211/3	190/5	42/1	13/1	0.605
T stage	T1/T2/T3/T4	147/16/32/19	128/15/25/27	28/5/7/3	8/2/1/3	0.662
N stage	N0/N1a/N1b	57/113/44	59/86/50	12/21/10	5/6/3	0.735
AJCC stage	I/II/III	193/18/3	168/24/3	42/1/0	12/1/1	0.066
ATA Risk stratification	Low/intermediate/high	68/123/23	58/110/27	11/28/4	3/8/3	0.732
Extrathyroidal invasion	No/yes	167/47	151/44	36/7	10/4	0.709
$^{99m}TcO_4^-$ Thyroid imaging	Positive %	113(52.8%)	147(75.4%)	35(81.4%)	13(92.9%)	<0.001
sTg	mean±SD	5.15±10.85	8.68±15.18	14.32±13.98	26.40±23.04	<0.001

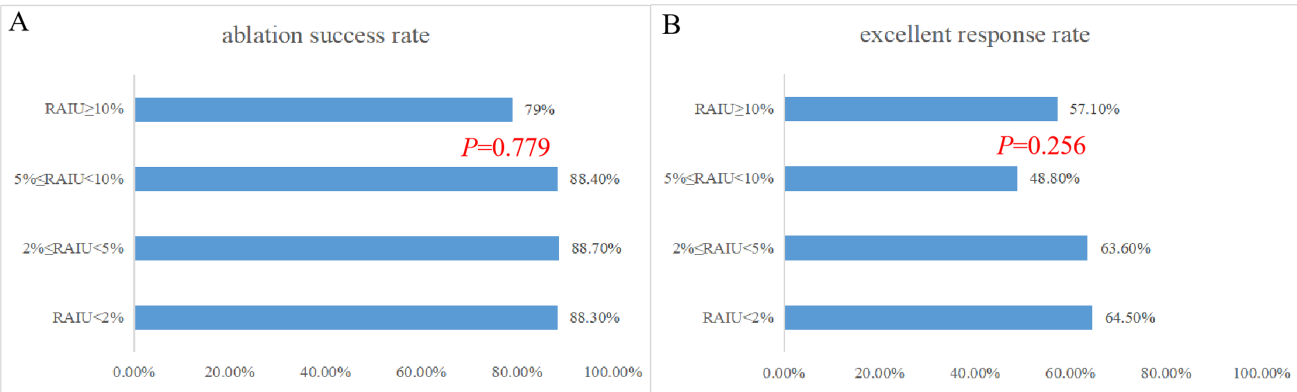

Figure 2. The relationship between RAIU and ablation success and excellent response.

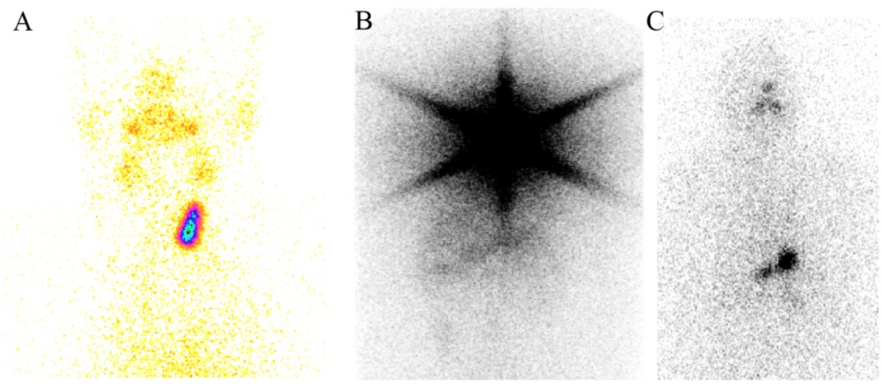

Figure 3. A 20-year-old man was admitted to our hospital for ^{131}I treatment (T1bN1aM0, I stage, intermediate-risk) after surgery for papillary thyroid carcinoma. The RAIU level was 21%, and the sTg level was 17.71ng/mL. $^{99m}TcO_4^-$ thyroid imaging showed the residual tissue of the left lobe. A total dose of 100mCi was administered for ablation treatment. Rx-WBS demonstrated apparent remnant thyroid tissue (RTT). Six months after ^{131}I treatment, the Dx-WBS showed no RTT (sTg: 0.04ng/mL), indicating an excellent response.

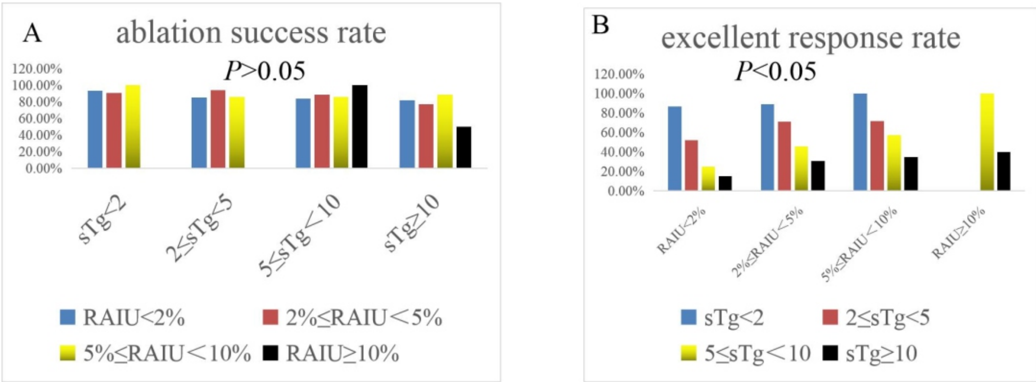

Figure 4. The relationship between RAIU combined with sTg and ablation success and excellent response.

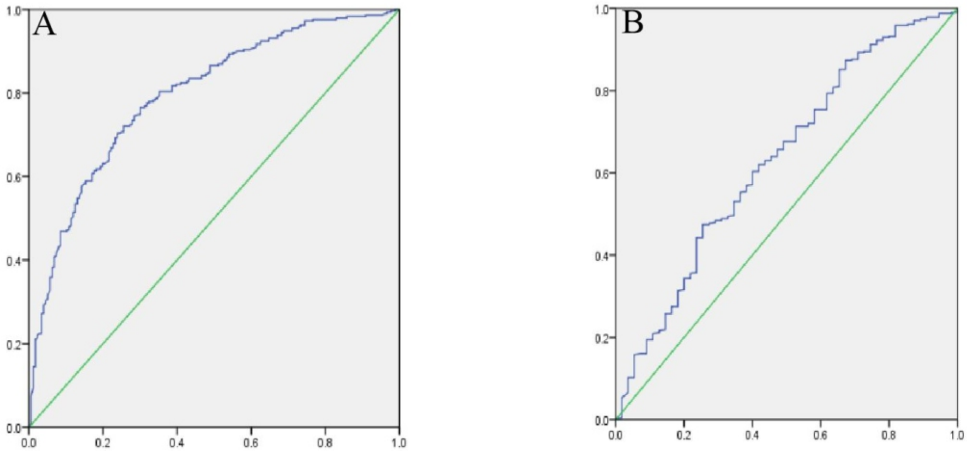

Figure 5. ROC curve to predict excellent response (A) and ablation success (B).

may influence ablation efficacy. However, there is no specific conclusion about the relationship between RAIU combined with sTg and ablation efficacy. This current study confirmed that RAIU had no influence on ablation efficacy after thyroidectomy with a dose of 100mCi for simple remnant ablation and adjuvant treatment. A recent meta-analysis showed that lobar ablation with ^{131}I is effective with a pooled rate of successful ablation of 69% and an ablation success rate ranging from 75% to 90% when a relatively high dose of ^{131}I (95-100 mCi) was used [20]. Lobectomy is associated with more residual thyroid tissue and higher RAIU levels than total thyroidectomy, thus indicating that high RAIU levels after lobectomy potentially have good ablation efficacy.

Several studies have been conducted to investigate the influence of RAIU levels on ablation efficacy, reporting that RAIU levels influence ablation efficacy [9-13]. The reason may be ascribed to the low dose of ^{131}I (less than 100mCi) for simple remnant ablation and adjuvant treatment. Rosario et al. (2004) reported an inverse correlation between RAIU levels and ablation efficacy with low-dose ablation treatment (30mCi) [9]. However, their results indicated that the ablation success rates using a ^{131}I dose of 100mCi in patients with RAIU levels <2%, 2-5%, and >5% were 92.5%, 86.6%, and 70%, respectively (P= 0.06). Similarly, a retrospective study including 235 DTC patients using low doses of ^{131}I (30-80mCi) according to RAIU levels for simple remnant ablation found that the ablation failure rate was 43% (presence of ^{131}I uptake in the neck region). The ablation success rate was only 60.6% when the RAIU level was greater than 10%. Based on our present study results, an RAIU less than 10% seems to be ideal considering the high success rate (88.4%). The ablation success rate with a ^{131}I dose of 100mCi was 79% when RAIU was greater than 10%, which was similar to the study results by van Wyngaarden et al. (1996) and Leung et al. (1992) [11, 21].

A prospective study including 277 DTC patients by Jin et al. (2019) compared the ablation efficacy between a fixed activity group (100mCi) and RAIU-Tg-based activity group (30-150mCi), which reported a higher success rate based on RAIU-Tg-guided dosimetry and showed that patients with RAIU >15% were administered a higher ablation dose (150mCi) with an ablation success rate of 88.7% [14]. A meta-analysis also indicated that a high dose of ^{131}I was significantly better than a low dose to achieve successful remnant thyroid ablation [22]. Nevertheless, as shown in Figure 3, a patient with a 21% RIAU based on an ablation dose of 100mCi eventually had ablation success. Whether higher RAIU levels require a higher ablation dose should be further explored. However, DTC patients with RAIU <5% may be given an individualized ablation dose of less than 100mCi for ablation success according to the results of Jin et al. (2019).

Furthermore, our results also showed that preablation sTg (pre-sTg) was one of the main prognostic factors for excellent response. At different RAIU levels, the higher the pre-sTg level was, the lower the excellent response rate was. Emerging literature has elucidated the good predictive value of pre-sTg for ablation efficacy [23, 24]. It has been reported that pre-sTg exhibits great performance in predicting excellent response. In the study by Zhang et al. (2018), the rate of excellent response was 92.2% when pre-sTg was less than 2ng/mL [4], which was similar to our research result. In an observational retrospective study of 1093 DTC patients, a pre-sTg cut-off of 10μg/L predicted an excellent response with a negative predictive value of 94% [25]. Another study by Mousa et al. (2017) including 393 low- or intermediate-risk DTC patients found that pre-sTg values greater than 5.6ng/mL before radioactive iodine ablation treatment were associated with a 2.38-fold risk of relapse [26]. In addition, Bernier et al. (2005) also showed that an increasing pre-sTg level during ablative radioiodine treatment in patients with DTC was associated with less efficacy for ^{131}I treatment [23]. The optimal pre-sTg cut-off to predict an excellent response in our research value was 3.95ng/mL. Considering the above literature report and our research, increasing pre-sTg levels were strongly predictive of ablation efficacy.

Our study has several limitations. First, it was retrospective study. Differentiated thyroid cancer patients in our study were enrolled between 2013 and 2014 in our institution, and we reperformed risk stratification based on the 2015 ATA guidelines. Thus, some low-risk patients underwent RRA treatment and were included in our research. According to the 2015 ATA and NCCN guidelines, low-risk DTC patients with no known or likely evidence of residual disease are not routinely recommended for RRA treatment [27]. Some study results also demonstrated that the survival rate was not different between low-risk patients receiving or not receiving RRA [28]. Further studies can be performed to identify low-risk patients for overtreatment, which may help impact practice patterns and improve the efficiency [29]. Second, all the patients used a dose of 100mCi for ablation treatment. A lower dose of 30mCi may be a reasonable dose for treating individuals with low-risk DTC patients [27, 30]. Third, only 14 DTC patients with RAIU >10% in our research were observed. The relatively small sample size may hint at an improvement in surgical methods. Based on the results in Figure 3, we recommend that DTC patients with RAIU<20% can receive ^{131}I treatment to achieve ablation success and avoid unnecessary surgery.

In conclusion, after total thyroidectomy, not RAIU but sTg is a prognostic factor for ablation efficacy with a 3.7GBq (100mCi) fixed ^{131}I dose in patients with DTC.

Funding
The research was supported by "1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYGD18016)".

The authors declare that they have no conflicts of interest.

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