Success Rate in Preparation of Patients with Thyroid Cancer for I-131 Total Body Scan by 3-Week Discontinuation of Thyroxine

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ABSTRACT

Objective: The purpose of this study was to evaluate the success rate in preparation of patients with thyroid cancer for I-131 total body scan by 3-week discontinuation of LT4 including clinical characteristics affecting the success.

Methods: Ninety-six patients with well-differentiated thyroid cancer on LT4 suppressive treatment were indicated for I-131 total body scan. After 3-weeks of LT4 withdrawal, T4 and TSH were measured whether TSH was ≥ 30 mIU/L. Then I-131 total body scan, Tg and TgAb measurements were performed upon achievement of TSH ≥ 30 mIU/L. If TSH was below 30 mIU/L, LT4 was still withheld and T4 together with TSH were evaluated weekly until TSH was ≥ 30 mIU/L. The percentage of success rate after 3-week withdrawal of LT4 was studied. Clinical characteristics between the success and failure rates after LT4 withdrawal for 3 weeks were compared.

Results: Success rate in preparation for I-131 total body scan was 54.2%, 81.3% and 93.8% by discontinuation of LT4 for 3, 4 and 5 weeks, respectively. Bivariate analysis indicated that factors which significantly affected the success were age (p-value = 0.0002), baseline TSH (p-value = 0.041) and cancer staging (p-value = 0.019). When multivariate analysis was used, only age and staging affected the success, independently. Patients who were older than 45 years old and stage I together with patients who were older than 45 years old and above stage I had more tendency to not achieve the target TSH after 3-week LT4 withdrawal as compared to the patients who were younger than 45 years old and stage I (Odd ratio, 9.281; 95% C.I., 2.269-37.957 and Odd ratio, 8.25; 95% C.I., 2.793- 24.366, respectively).

Conclusion: The success rate of 3-week discontinuation of LT4 was 54.2%. This method should be considered in patients under the age of 45 years old or being classified as stage I.

Keywords: Thyroid cancer, radioiodine ablation, total body scan

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INTRODUCTION

Standard monitoring of patients with well-differentiated thyroid cancer after thyroidectomy and radioactive iodine ablation includes I-131 total body scan and measurement of serum thyroglobulin level. Thyroid stimulating hormone (TSH) must be elevated, to stimulate the release of thyroglobulin and optimize the I-131 tumor cell uptake. The TSH concentration of 30 mIU/L or more is generally on optimal level to perform reliable I-131 total body scan and treatment. There have been many procedures for TSH elevation: discontinue thyroxine (LT4) for 4-6 weeks, reducing the dose of LT4 to 0.05 mg/day for 4 weeks and then discontinue LT4 for 2 weeks, substitute tri-iodothyronine (T3) for LT4 for 4 weeks and then withdraw T3 for 2 weeks.[1-3] These procedures, diminished patients' quality of life due to symptomatic hypothyroidism has been reported with the theoretical possibility that a prolonged period of high TSH could stimulate tumor cell growth.[4-6] Recombinant human TSH (rhTSH) has been introduced to replace thyroid hormone withdrawal, although its high cost has limited widespread use especially in the developing countries.

The aim of the present study was to determine the success rate of preparation of patients with thyroid cancer for I-131 total body scan by 3-week discontinuation of thyroxine, in order to reduce the period of hypothyroidism and improve patients' quality of life.

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MATERIALS AND METHODS

A descriptive prospective study was performed at the Division of Nuclear Medicine, Faculty of Medicine Siriraj Hospital between October 2009 and October 2010. There were 96 patients with well-differentiated thyroid cancer, following near-total or total thyroidectomy and I-131 ablation or treatment. All were on long-term suppressive thyroxine treatment with baseline serum TSH level below 0.1 mIU/L. They all had indications for I-131 total body scan such as follow-up after I-131 treatment, suspicion of recurrent tumor or abnormal serum thyroglobulin and/or antithyroglobulin levels. Serum levels of TSH and T4 were measured after 3 weeks discontinuation of thyroxine. If TSH was 30 mIU/L or more (success outcome), the patients underwent I-131 total body scan and measurement of serum thyroglobulin and antithyroglobulin. If TSH was below 30 mIU/L (failure outcome), the patient continued thyroxine withdrawal and measurement of serum TSH was done once a week until their TSH reached 30 mIU/L. The number of the patients whose serum TSH was 30 mIU/L or more after 3-weeks discontinuation of thyroxine were collected to determine the success rate of the procedure. Exclusion criteria were pregnancy and breast feeding. The study was approved by the Siriraj Institutional Review Board. Approval number was Si.No.456/2552 (EC3).

Statistical analysis

Data were analyzed using SPSS for Windows version 13.0. Continuous variables were summarized as mean (standard deviation) or median (range). Categorical variables were reported as counts and percentages. The differences in the continuous variables between the success and failure groups were tested using T-test or Mann-Whitney U test and the differences in categorical variables were tested using Pearson Chi-Square test or Fisher's exact test, as appropriate. Regarding the time to targeted TSH level, comparison of the success and failure groups was analyzed by Kaplan-Meier method. Multivariate analysis for factors affecting the success of preparation for I-131 total body scan, by 3-week discontinuation of LT4, by Logistic regression was performed. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patients' characteristic

Ninety-six consecutive patients were enrolled in the study. The demographic data of the patients have been shown in Table 1. There were 80 women (83.3%) and 16 men (16.7%). The mean age was 49.04 years (SD, 15.94 years; range, 21-87 years). Patients with papillary cancer were 85.3%, 13.5% with follicular cancer and 1% with mixed papillary and follicular cancer. Forty-six patients had locoregional or distant metastases seen on the last post-therapeutic I-131 total body scan.

Prior to LT4 withdrawal, the mean daily dose per body weight of LT4 was 3.68 µg (SD, 1.06 µg; range, 0.3-7.73 µg). Baseline TSH was found in the range of 0.007 to 0.075 mIU/L with a median of 0.014 mIU/L. The duration of LT4 suppressive therapy ranged from 1 to 20 years. The number of I-131 treatments ranged from 1 to 7 sessions. The duration between the last I-131 treatment and this TBS (The abbreviation TBS has not been defined.) ranged between 5.07 months and 17.73 years.

The indications for I-131 total body scan were as follows: one-year (82.3%) and 5-years or more (14.6%) after radioactive iodine treatment, suspicion of recurrent disease (2.1%) and having abnormal serum thyroglobulin (1%).

Success rate of preparation for I-131 total body scan by 3-week withdrawal of LT4

At 3 weeks after LT4 withdrawal, 52 out of 96 patients (54.2%) had TSH ≥ 30 mIU/L while 27.1% and 12.5% of patients had achieved this target after withdrawal of LT4 for 4 and 5 weeks, respectively.

The success rate of preparation for I-131 total body scan was 54.2%, 81.3% and 93.8% by discontinuation of LT4 for 3, 4 and 5 weeks, respectively.

The comparison of many factors which may possibly affect the success of preparation for I-131 total body scan by 3-week discontinuation of LT4 has been shown in Table 2. Patients who reached the target level of TSH after 3 weeks of LT4 withdrawal were significantly younger than the failure group; T-test, p = 0.0002 and Pearson Chi-square test, p = 0.001 as shown in Table 3.

Table 4 showed the comparison of baseline TSH levels between the success and failure groups. Although there was no significant difference in baseline TSH levels between the two groups, from Fisher's exact test, p = 0.371, the sum of ranks of baseline TSH level were significantly higher in the successful group than the other group, Mann-Whitney U test, p = 0.041 (Table 2).

Most of the patients who were in stage I of the disease achieved the target TSH at 3 weeks after LT4 withdrawal, whereas patients who were in other stages significantly required prolonged withdrawal of LT4 to meet the target level of serum TSH, Fisher's exact test, p = 0.019 (Table 5).

Thus three factors which significantly affected the successful outcome, by bivariate analysis, were age (t-test; p = 0.0002), baseline TSH levels (Mann-Whitney U test; p = 0.041) and staging (Fisher's exact test; p = 0.019).

Baseline TSH level was used to categorize the patients into two groups by the cut-off level of 0.05

TABLE 1. Demographic and clinical characteristics of all patients.

Clinical characteristics	
Gender: female, n (%)	80 (83.3)
Age, year[a]	49.04 ± 15.94
Histology, n (%)	
Papillary cancer	82 (85.4)
Follicular cancer	13 (13.5)
Mixed type	1 (1.1)
Staging, n (%)	
I	54 (64.3)
II	9 (10.7)
III	6 (7.1)
IV	13 (15.5)
IVB	-
IC	2 (2.4)
Metastasis, n (%)	46 (47.9)
Dose of LT4, µg/kg/day[a]	3.68 ± 1.06
Duration of LT4 suppressive therapy, year[b]	2
Baseline TSH, mIU/L[b]	0.014
Baseline T4, µg/dl[a]	12.06 ± 2.58
Number of I-131 treatment, session[b]	2
Duration from last I-131 treatment, month[b]	10.35

[a]Data are means ± SD, [b]Data are medians

TABLE 2. Clinical characteristics affecting the success of preparation for I-131 total body scan by 3-week withdrawal of LT4.

	TSH (mIU/L)		
Clinical characteristic	**≥30 (n = 52)**	**<30 (n = 44)**	**p-value**
Gender: female, n (%)	43 (82.69)	37 (84.09)	0.855*
Age, year[a]	43.62 ± 14.14	55.45 ± 15.71	0.0002**
Histology, n (%)			
Papillary cancer	45 (86.54)	37 (84.09)	0.945*
Follicular cancer	7 (13.46)	6 (13.64)	
Mixed papillary and follicular	-	1(2.27)	
Metastasis, n (%)			
Present	28 (53.85)	18 (40.91)	0.206*
Absent	24 (46.15)	26 (59.09)	
Dose of LT4, µg/kg/day[a]	3.58 ± 0.9	3.79 ± 1.24	0.374**
Duration of LT4 suppressive therapy, year[b]	2	3	0.221***
Baseline TSH, mIU/L[b]	0.014	0.014	0.041***
Baseline T4, µg/dl[a]	11.85 ± 2.82	12.29 ± 2.26	0.401**
Number of I-131 treatment, session[b]			
Once	21 (40.38)	19 (43.18)	0.782*
More than one time	31 (59.62)	25 (56.82)	
Duration from the last I-131 treatment, month[b]	10.13	11.35	0.372**

[a]Data are means ± SD, [b]Data are medians
*Pearson Chi-square test, **T-test, ***Mann-Whitney U test

TABLE 3. Number with percentage of patients achieved TSH ≥ 30 mIU/L after 3-week LT4 withdrawal based on age ranges.

	TSH (mIU/L)		
	≥30 (n = 52)	**<30 (n = 44)**	**p-value***
Age range, n (%)			
<45 year	34 (65.4)	9 (20.5)	0.00001
≥45 year	18 (34.6)	35 (79.5)	

*Pearson Chi-square test

TABLE 4. Number with percentage of patients achieved TSH ≥30 mIU/L after 3-week LT4 withdrawal based on baseline TSH level.

	TSH (mIU/L)		
	≥30 (n = 52)	**<30 (n = 44)**	**p-value***
Baseline TSH (mIU/L) n, (%)			
≥0.05	4 (7.7)	1 (2.3)	0.371
<0.05	48 (92.3)	43 (97.7)	

*Fisher's exact test

mIU/L. For the patients whose baseline TSH levels were 0.05 mIU/L or more, the duration of LT4 withdrawal to achieve a TSH level of 30 mIU/L was in the range of 20-28 days with a median of 21 days. For the patients whose baseline TSH was less than 0.05 mIU/L, the duration of LT4 withdrawal for the target level of TSH was in the range of 21-43 days with a median of 21 days. A significant difference of the duration of LT4 withdrawal between the two groups was observed; Kaplan-Meier method, P = 0.036. (Fig 1)

Age and staging were used for multivariate analysis to determine the exact factors which affect the success. Baseline TSH was disregarded because the data was not a Gaussian model. All of the 41 patients who were younger than 45 years old were stage I. Forty-three patients who were 45 years old or more were in not only stage I (13 patients), but also other stages (30 patients). Logistic regres-

TABLE 5. Staging of the disease and the success rate of preparation patients for I-131 total body scan by 3-week withdrawal of LT4.

	TSH (mIU/L)		
	≥30 mIU/L (n = 47)	**<30 mIU/L (n = 37)**	**p-value***
Staging, n (%)			
I	37 (78.72)	17 (45.95)	0.019
II	2 (4.26)	7 (18.92)	
III	2 (4.26)	4 (10.81)	
IVA	5 (10.64)	8 (21.62)	
IVB	0	0	
IVC	1 (2.12)	1 (2.70)	

*Fisher's exact test

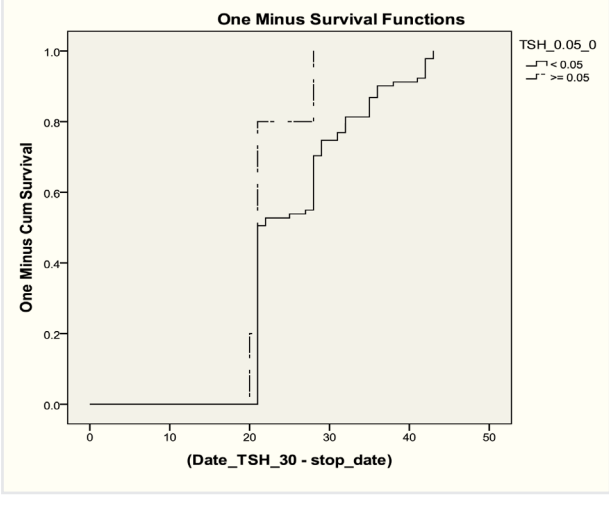

Fig 1. Duration of LT4 withdrawal for TSH achieving 30 mIU/L (Solid line: baseline TSH <0.05 mIU/L, Dash line : baseline TSH ≥0.05 mIU/L).

TABLE 6. Logistic regression for the factors affecting the success of preparation for I-131 total body scan by 3-week withdrawal of LT4.

Variable	B	S.E.	Wald	df	Sig.	Adjusted 95% C.I. for OR		
						OR	Lower	Upper
			17.633	2	0.0001			
Age ≥ 45 years old								
Stage I*	2.228	0.719	9.612	1	0.002	9.281	2.269	37.957
Other stage *	2.110	0.553	14.586	1	0.0001	8.250	2.793	24.366

2 Log likelihood = 94.711, Cox & Snell R^2 = 0.217, Nagelkerke R^2 = 0.291
Constant -1.417
Reference group: age <45 years old with stage I

sion analysis found that both age and staging independently affect the success. A patient who was 45 years old or more with stage I had a chance to fail by the procedure 19.218 times compared to a patient who was under 45 years old with stage I (odds ratio, 9.281; 95% C.I., 2.269-37.957). A patient who was 45 years old or more with other stages had a chance to fail by the procedure 8.25 times compared to a patient who was under 45 years old with stage I (odd ratio, 8.25; 95% C.I., 2.793- 24.366). (Table 6)

Logistic regression equations correctly predicted the success group 70.2% and the failure group 78.4%. Overall sensitivity, specificity and accuracy were 78.4, 70.2 and 73.8%, respectively. (Table 7)

DISCUSSION

In the present study the success rate of patient preparation for I-131 total body scan by withdrawal of LT4 for 3 weeks to accomplish serum TSH levels ≥ 30 mIU/L was 54.2%. This was much lower than the success rates reported by Sanchez[7], Grigsby[8] and Serhal[9] which were 90%, 96% and 98%, respectively. However, our result was in agreement with the unpublished results of 52.7% by Somboonporn at Khonkean University (personal communication). Compared with previous studies, our low success rate was primarily due to the different baseline TSH values. Our study demonstrated a baseline TSH level below 0.01 mIU/L while in another study these were 0.1-1.7 mIU/L[7] and 0.01-0.4 mIU/L.[10] In most of the cases, the baseline TSHs were below 0.014 mIU/L which was the lowest detectable level by electrochemiluminescence technique. Because of the lower baseline TSH levels, the hypothalamic-pituitary axis was more suppressed and responded slowly to LT4 withdrawal. Thus more time for LT4 withdrawal to achieve the target TSH level was needed as shown by the success rates of 81.3%, 93.8% and 100% at the 4th, 5th and 6th week, respectively. These results resembled the study by Somboonporn which found the success rate of 84.7% at the 4th week. Another possible explanation was the difference of hypothalamic-pituitary-thyroid axis response between Thais and foreign subjects of previous studies which were American[8,9], Mexican[7] and Israeli.[10] This slower response to LT4 withdrawal of Thais could be associated with genetics, food or environment which requires further study.

TABLE 7. Events prediction by logistic regression equation.

Observed	Predicted		
	TSH ≥30 mIU/L	TSH <30 mIU/L	Percentage correct
TSH ≥30 mIU/L	33	14	70.2
TSH <30 mIU/L	8	29	78.4
Overall Percentage (Accuracy)			73.8

Clinical characteristics which significantly independently affected the success were age and staging. Younger patients had more tendency to achieve the target TSH after 3 weeks LT4 withdrawal. Chow[11] and Over[12] showed that age affected the raising of TSH after LT4 withdrawal. They found that younger patients had higher levels of mean serum TSH than older patients after LT4 withdrawal. In older patients, serum TSH decreased because their pituitary glands produced lower levels of TSH. The mechanism of this process was unclear. It could be due to increased sensitivity of thyrotropes to negative feedback of LT4 or decreased thyrotropin-releasing hormone from their hypothalamus.[13] Staging was another significant contributing factor. Patients who were in stage I had more tendency to reach the target TSH after 3-week of LT4 withdrawal than other stages. Although all patients had received at least one session of I-131 treatment, patients who were not in stage I might have residual disease or distant metastasis which produced thyroid hormone to suppress TSH and subsequently responded slowly to LT4 withdrawal. A larger group of patients may be required to further evaluate the potential significance of this factor. Similar to the study of Chow[11], the baseline TSH levels of the success group were significantly higher than those of the failure group. Although the median TSH of both groups were the same at the level of 0.014 mIU/L, the sum of ranks of baseline TSH in the success group was more than the other group. Thus Mann-Whitney U test showed that baseline TSH was a significant contributing factor. This study also showed that patients whose baseline TSH level was 0.05 mIU/L or more needed a shorter duration of LT4 withdrawal to get the target level of TSH than the patients whose baseline TSH was less than 0.05 mIU/L. Revised American Thyroid Association management guidelines published in 2009 suggested a suppressive TSH level should be in the range of 0.1-0.5 mIU/L and 0.3-2 mIU/L in patients who were at high risk for recurrence, but free of disease and low risk for recurrence, respectively.14 The suggested TSH level was higher than the baseline TSH of patients in this study, so the success rate of preparation for I-131 total body scan by 3-week withdrawal of LT4 in the patients who obtained the suggested TSH level may be higher than the result of this study. However, the data of the baseline TSH was not a Gaussian model. Thus it was disregarded in multivariate analysis.

Distant metastasis was not found to be a significant contributing factor which resembled the study of Chow[11]. However in this study, there were only two patients with non-functioning distant metastases. Further study in a larger population may be needed.

In conclusion, the success rate in preparation of patients for I-131 total body scan by 3-weeks LT4 withdrawal was 54.2%. Age and staging were significantly independent affecting factors for the success. This method should be considered in patients under the age of 45 years old or being classified as stage I.

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Conflict-of-interest Notification Page

The authors declare there is no potential conflict of interest.

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