The Association Between The Interval of Radioiodine Treatment and The Response and Adverse Effect in Patients with Non-Progressive Lung Metastases From Differentiated Thyroid Cancer

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Abstract

Purpose To assess the association between the interval of radioiodine treatment (RT) and short-term response and adverse effects in patients with non-progressive lung metastases from differentiated thyroid cancer (DTC).

Methods A total of 147 neighboring RT course pairs from 78 patients with ^{131}I -avid non-progressive lung metastases from DTC were retrospectively analyzed. The courses were categorized into two groups by interval of neighboring therapeutic ^{131}I administrations (≤ 12 months and >12 months). The short-term therapy response and adverse effects of the two groups were evaluated.

Results No significant differences were found between the two groups in the change rate of thyroid stimulating hormone (TSH) stimulated serum thyroglobulin ($\Delta\text{sTg}\%$) ($P=0.806$) or the change rate of metastasis lesion long diameter ($\Delta\text{LLD}\%$) ($P=0.246$). In the subanalysis considering the number of treatments (3 and >3 times), no significant difference was found ($P>0.05$). No difference was found in biochemical response (interval $\leq 12\text{m}$: $P=0.325$, interval $>12\text{m}$: $P=0.456$) or structural response (interval $\leq 12\text{m}$: $P=0.760$, interval $>12\text{m}$: $P=0.563$) between the former and latter courses with regard to different intervals. No difference was found in adverse events between former and latter courses with regard to different intervals ($P>0.05$).

Conclusions The interval of RTs is not associated with the short-term response or adverse effects in patients with non-progressive lung metastases from DTC. Appropriately prolonging the interval in specific patients seems to be feasible, and the interval of RT should be individually managed in clinical practice.

Introduction

Approximately 10% of patients with differentiated thyroid cancer (DTC) have distant metastases at presentation or during follow-up [1, 2]. The lungs are the most common organ of distant metastases, accounting for 70% of distant metastasis cases. DTC patients with lung metastases have a relatively poorer prognosis than those without metastases, with a median survival of < 10 years [3]. In the case of distant metastasis of DTC and continuous iodine uptake at the metastatic lesion, radioiodine (^{131}I) treatment (RT) is undoubtedly the most effective treatment [4]. However, no consensus is available to identify the treatment interval and influence of the interval of repeated RT on the therapeutic response. A wide selection of treatment intervals ranging from 3 to 12 months has posed challenges to clinicians when developing treatment strategies. The American Thyroid Association (ATA) [5] recommended that micrometastases (< 2 mm) should be treated with repeated RT every 6–12 m as long as the lesion continues to take up ^{131}I and respond clinically. For macronodular metastases (≥ 2 mm), the treatment intervals were suggested to be based on several factors. The benefits and possible adverse effects of repeated RT must be balanced to obtain a good therapeutic effect and improve the quality of life of patients [6, 7].

On the premise of ensuring the therapeutic effect, appropriately extending the interval might decrease the treatment frequency and incidence of adverse effects, with robust compliance of patients. However, reliable evidence about the potential association of longer intervals and outcomes is lacking. Thus, we performed this retrospective course-based study to assess whether the interval between neighboring therapeutic ^{131}I administrations is associated with short-term response and adverse effects in DTC patients with non-progressive ^{131}I -avid lung metastases, aiming at optimizing the management of DTC patients who need repeated RT.

Materials And Methods

Patients and RT course pairs

A retrospective analysis of DTC patients with lung metastases treated at the Nuclear Medicine Department of West China Hospital of Sichuan University from January 2009 to August 2018 was performed. The institution is a tertiary-care university teaching hospital in southwestern China and a referral center for thyroid cancer treatment. The study was approved by the local institutional review board, and the requirement for written informed consent was waived. The inclusion criteria were as follows: 1) patients who received total thyroidectomy or near-total thyroidectomy, and neck dissection was performed if any enlarged lymph node suspicious for malignancy was present in the preoperative radiologic examinations; 2) patients who were diagnosed with lung metastases demonstrated by initial Rx-WBS; and 3) first ^{131}I treatment performed within 6 m post-thyroidectomy. The exclusion criteria were as follows: 1) patients with other distant metastases; 2) patients with a concomitant second primary cancer; and 3) patients who underwent pulmonary lobectomy beyond RTs.

A course pair was constituted by neighboring two RTs (the former course and the latter course). If a patient underwent three courses of RT, the second course acted as not only the latter course of the first course pair but also the former course of the second course pair, and so on [8]. The exclusion criteria of course pairs were as follows: 1) a course pair constituted by the first and second RTs; 2) TSH levels after levothyroxine withdrawal of two RTs were comparable and anti-Tg antibody (TgAb) was > 40.0 IU/ml [9], 3) sTg and CT imaging was available for response evaluation, and 4) a course pair with an interval > 24 months due to poor compliance of patients.

Protocols of repeated ^{131}I treatment

All patients withdrew thyroid hormone medication 2-3wks and began a low iodine diet 3-4wks before RT. Repeated RT was performed with a ^{131}I dose of 3.7–7.4 GBq. The ^{131}I post therapeutic whole body scan (R-WBS) and/or ^{131}I single photon emission computed tomography/computed tomography (SPECT/CT) was performed 3-5d after ^{131}I administration. The RT stops once no ^{131}I uptake is present on a diagnostic WBS (D-WBS) or R-WBS, or metastases structurally progress despite ^{131}I uptake [5].

TSH-stimulated Tg measurements

Thyroid stimulating hormone (TSH)-stimulated (sTg) and anti-Tg autoantibody (TgAb) levels were measured with the same high-sensitivity electrochemiluminescence immunoassay after thyroid hormone withdrawal and just before the 131-I administration in the same laboratory. The assay used was the Roche Elecsys 2010 system (Roche Diagnostics GmbH, Mannheim, Germany) which was calibrated against the CRM-457 standard, with a sensitivity of 0.04 ng/mL and a reference range of 0.5–55 ng/mL. Quality control was ensured by assaying two levels of control sera in each series and by reassessing all sera showing a coefficient of variation exceeding 10%.

Computed tomography scan protocol

A chest computed tomography (CT) scan without iodinated contrast was performed extending from the lung apex to the adrenal glands at full inspiration just before 131-I administration. Patients underwent scanning with a multi-detector CT scanner (Somatom Definition Flash, Siemens Healthcare) with the following parameters: tube voltage, 100 kVp; tube current, 100 mAs; thickness, 1.00 mm; interval, 1.00 mm; pitch, 1.2.

Serologic and structural response evaluation

The comparison between the change rate of the sTg level (Δ sTg%) and the change rate of LLD (Δ LLD%) of the two groups with different intervals was performed. Δ sTg% was defined as follows: Δ sTg% = [sTg (the latter course) - sTg (the former course)]/sTg (the former course) × 100%. Δ LLD% was defined as follows: Δ LLD% = [LLD (the latter course) - LLD (the former course)] / LLD (the former course) × 100%.

The Δ sTg% results were further classified as serologic effectiveness and serologic non-effectiveness [10, 11]. Serologic effectiveness was defined as a reduction in the Tg level by at least 25% (Δ sTg% ≤ -25%). For serologic non-effectiveness, the Tg level decreased by less than 25% or increased (Δ sTg% > -25%). The Δ LLD% results were classified as structural complete remission (CR), structural partial remission (PR), structural stable disease (SD), and structural progressive disease (PD) according to the RECIST 1.1-like criteria (Supplemental Data) [12, 13]. The comparison of responses between former and latter courses with regard to different intervals was performed.

Adverse effect evaluation

The incidences of adverse effects were evaluated. The following indices were included: leukocytes, platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), calcium (Ca), and salivary gland imaging. Leukocytes, platelets, AST, ALT, and Ca were measured after thyroid hormone withdrawal and just before the 131-I administration in the same laboratory. The adverse effects were then graded and evaluated according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. The Grade 0 was recorded as normal, and grades 1–4 were recorded as abnormal. The salivary gland imaging scan protocol was shown in Supplemental Data. Salivary gland function was visually evaluated as normal or abnormal, by a nuclear medicine physician.

Statistical analysis

Continuous variables are expressed as the means $\pm$ standard deviations (SDs) or the medians (p25 to p75), and categorical variables are presented as numbers. The Chi-square test or Fisher's exact test and t test or Wilcoxon test were performed to compare the distributions of categorical and continuous variables, respectively. To evaluate the differences in response and adverse effects between the two groups with different intervals, the stratified Cochran-Mantel-Haenszel test was used. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics software (version 25.0; IBM Corporation, Armonk, NY, USA).

Results

Characteristics of patients and courses

A total of 234 patients with lung metastases were consecutively enrolled from May 1st, 2008 through December 31st, 2020. After the exclusion of patients and course pairs, 147 course pairs of 78 patients were finally established and utilized. The flowchart of inclusion and exclusion is shown in Fig. 1. Course pairs were then categorized into two groups based on the interval between neighboring two RTs: 1) ≤ 12 m (n = 81), and 2) > 12 m (n = 66).

The characteristics of 78 patients are shown in Table 1. The mean age at metastatic DTC diagnosis was 35.14 ± 15.88 years. Sixty-one (74.4%) patients were female, and 21 (25.6%) were male. At the time of the data lock (June, 2021), two patients were considered to have an excellent response to treatment (a suppressed Tg < 1 ng/mL and no structural evidence of disease) after undergoing 6 and 5 times RTs. Two patients had no structural evidence of disease after undergoing 5 and 8 times RTs. The RT was stopped in 7, 11, and 12 patients due to no I-131 uptake present on R-WBS, metastasis progression despite I-131 uptake, and personal reasons, respectively. Therefore, 30 (38.5%) patients underwent three times of RTs, and 48 (61.5%) underwent four or more times of RTs.

Table 1
Characteristics of 147 former courses from 78 patients.

Characteristics	78 patients	147 former courses		P value
		Interval $\leq$ 12 m (n = 81)	Interval > 12 m (n = 66)	
Age at metastases diagnosis (years), mean $\pm$ SD	35.14 $\pm$ 15.88	34.09 $\pm$ 15.25	32.69 $\pm$ 15.77	0.512
Gender, n (%)				
Male	21 (25.6)	20 (24.7)	41 (62.1)	0.319
Female	61 (74.4)	61 (75.3)	25 (37.9)	
Histology, n (%)				
Papillary	63 (80.8)	74 (91.4)	59 (89.4)	0.748
Follicular variant of papillary	13 (16.7)	3 (3.7)	6 (9)	
Follicular	4 (2.5)	4 (4.9)	1 (1.6)	
T stage, n (%)				0.755
T1b	4 (2.6)	4 (4.9)	4 (6.0)	
T2	3 (3.8)	3 (3.7)	3 (4.7)	
T3a	5 (6.4)	4 (4.9)	5 (7.6)	
T3b	8 (10.3)	2 (2.5)	7 (10.6)	
T4a	22 (28.2)	21 (26.0)	20 (30.3)	
T4b	3 (3.7)	3 (3.7)	4 (6.0)	
Tx	30 (38.5)	44 (54.3)	23 (34.8)	
N stage, n (%)				0.888
N0	4 (6.4)	2 (2.5)	3 (4.7)	
N1	62 (79.5)	63 (77.8)	56 (84.7)	
Nx	11 (14.1)	16 (19.7)	7 (10.6)	
ENE, n (%)				0.319
Yes	14 (17.9)	42 (51.9)	31 (47.0)	
No	40 (51.3)	12 (14.7)	14 (21.2)	
DTC, differentiated thyroid cancer; T, tumor; N, lymph node; ETE, extrathyroidal extension.				

Characteristics	78 patients	147 former courses		P value
		Interval $\leq$ 12 m (n = 81)	Interval > 12 m (n = 66)	
Missing	24 (30.8)	27 (33.4)	21 (31.8)	
Lesion size, n (%)				0.206
< 1 cm	72 (93.6)	74 (91.4)	63 (95.3)	
$\geq$ 1 cm	6 (6.4)	7 (8.6)	3 (4.7)	
Number of treatments, n (%)				0.510
3	30 (38.5)	30 (37.0)	21 (31.8)	
$\geq$ 3	48 (61.5)	51 (63.0)	45 (68.2)	
Cumulative dose (GBq), n (%)				0.623
< 22.2	13 (16.7)	11 (13.6)	0 (0.0)	
$\geq$ 22.2	65 (83.3)	70 (86.4)	66 (100.0)	
DTC, differentiated thyroid cancer; T, tumor; N, lymph node; ETE, extrathyroidal extension.				

Additionally, the characteristics of 147 former courses from 77 patients, grouped by interval, are shown in Table 1. Fifty-one (34.7%) former courses were second RTs, and 96 (65.3%) former courses were third or more RTs. Interval was ranged from 126 to 937 days. The median values of the interval in treatment times of former courses (second, third and more RTs) were 358 and 357 days, respectively. The median (P25, P75) interval was 287 days (211, 346) and 513 days (399, 710) in the two groups. We retrospectively analyzed how the interval of courses was decided clinically if the interval was > 12 m (n = 66), and the interval was prolonged in 47 (71.2%) and 17 (25.8%) courses due to patient personal reasons and physician advice, respectively. The decision method of the interval of 2 (3%) courses was unclear. No significant differences in characteristics were found between the two groups.

The Δ sTg% and the Δ LLD% of courses

Regarding the sTg levels of the 147 former courses, in the group with an interval of $\leq$ 12 m, the sTg levels just before RTs were 101.1 (29.0, 5000.0) ng/ml with a median TSH of 83.8 (51.4, 100.0) mIU/L. At the latter courses, the median sTg declined to 87.64 (23.83, 321.4) ng/ml with a median TSH of 88.0 (54.0, 100.0) mIU/L, yielding a median Δ sTg% of -29.0% (-44.2, -12.7). In the group with an interval of > 12 m, the sTg levels just before RTs were 134.0 (29.3, 592.9) ng/ml with a median TSH of 85.2 (47.1, 100.0) mIU/L. The median sTg declined to 95.5 (32.8, 247.0) ng/ml with a median TSH of 78.4 (55.6, 100.0) mIU/L at the latter courses, yielding a median Δ sTg% of -34.0% (-56.3%, -7.6%). We compared Δ sTg% of

the two groups in all pairs and in a subanalysis of number of treatments (latter course was third RTs, and fourth and more RTs). The median Δ sTg% of the two groups was -35.0% (-51.6%, -11.2%) and -31.0% (-56.5%, -12.6%) if the latter course was third RT. The median Δ sTg% of the two groups was -25.0% (-37.3%, -14.2%) and -34.0% (-55.8%, -6.6%) if the latter course was fourth and more RT. No significant differences in Δ sTg% were found between the two groups in any pairs ($P = 0.806$) or in a subanalysis of number of treatments ($P = 0.825$, $P = 0.548$) (Table 2).

Table 2
The Δ sTg% and the Δ LLD% of latter courses.

Median (p25, p75)	Interval		
	≤ 12 m (n = 81)	> 12 m (n = 66)	P value
Treatment times = 3			
ΔsTg%	-35.0 (-51.6, -11.2)	-31.0 (-56.5, -12.6)	0.825
ΔLLD%	0 (0, 0)	0 (0, 0)	0.240
Treatment times > 3			
ΔsTg%	-25.0 (-37.3, -14.2)	-34.0 (-55.8, -6.6)	0.548
ΔLLD%	0 (0, 0)	0 (0, 0)	0.267
Total			
ΔsTg%	-29.0 (-44.2, -12.7)	-34.0 (-56.3, -7.6)	0.806
ΔLLD%	0 (0, 0)	0 (0, 0)	0.246

Regarding the LLD value of the 147 former courses, in the group with interval of ≤ 12 m, the median LLD value just before RTs and at the latter courses were both 3mm (2mm, 5mm), yielding a median Δ LLD% of 0.0%. In the group with an interval of ≤ 12 m, the median LLD value just before RTs and at the latter courses both was 2mm (2mm, 4mm), with a median Δ LLD% of 0.0%. No significant differences in Δ LLD% were found between the two groups in any pairs ($P = 0.246$) or in a subanalysis of number of treatments ($P = 0.240$, $P = 0.267$) (Table 2).

The response evaluation of courses

The flow of patients in course pairs according to biochemical and structural response is shown in Fig. 2. No difference was found in biochemical response between former and latter courses with regard to different interval (interval ≤ 12 m: $P = 0.325$, interval > 12 m: $P = 0.456$). No difference was found in structural response between former and latter courses with regard to different interval (interval ≤ 12 m: P

= 0.760, interval > 12 m: P = 0.563). Representative patient who responded to repeated RTs and then underwent the next RT with an interval of > 12 m was illustrated in Fig. 3.

The adverse effect evaluation of courses

The adverse effects of the 147 Courses are shown in Table 3. No difference was found in adverse events between former and latter courses with regard to different intervals ($P > 0.05$).

Table 3
The adverse effect evaluation of 147 courses.

Former courses		Latter courses, n (%)		P value*
		Normal	Abnormal	
Salivary gland function				0.154
≤ 12 m	Normal	39	37	
	Abnormal	46	44	
> 12 m	Normal	26	23	
	Abnormal	40	43	
Leukocytes				0.187
≤ 12 m	Normal	64	39	
	Abnormal	17	42	
> 12 m	Normal	25	63	
	Abnormal	0	3	
Platelets				0.467
≤ 12 m	Normal	59	51	
	Abnormal	22	30	
> 12 m	Normal	65	65	
	Abnormal	1	1	
AST				0.761
≤ 12 m	Normal	65	67	
	Abnormal	16	14	
> 12 m	Normal	66	62	
	Abnormal	0	4	
ALT				0.986
≤ 12 m	Normal	71	70	
	Abnormal	10	11	
> 12 m	Normal	65	61	
	Abnormal	1	5	
AST, aspartate aminotransferase. ALT, alanine aminotransferase. *Cochran-Mantel-Haenszel test.				

Former courses		Latter courses, n (%)		
		Normal	Abnormal	P value*
Calcium				0.072
≤ 12 m	Normal	27	16	
	Abnormal	54	65	
> 12 m	Normal	54	53	
	Abnormal	12	13	
AST, aspartate aminotransferase. ALT, alanine aminotransferase. *Cochran-Mantel-Haenszel test.				

Discussion

Repeated RT has been widely implemented in treating of DTC with lung metastasis if the lesion continues to take up ¹³¹I and respond clinically. However, in patients with structural non-progressive lung metastases from DTC, especially after cumulative activities of 22.2 GBq. We may face one question: for patients who need to receive multiple RTs, what is the optimal timepoint for next RT considering of a balance of benefit and adverse effects? We performed this retrospective study to evaluate the association between the interval of RTs and short-term response and adverse effects in patients who underwent multiple RTs. We found that the interval of multiple RTs did not affect short-term biochemical response, structural response or adverse effects.

The ATA guideline [5] suggested that an interval that is too short (< 6 m) should be avoided because it frequently interrupts thyroid-stimulating hormone (TSH) inhibition therapy, which may stimulate follicular cells and increase the risk of tumor recurrence. Additionally, patients may receive more frequent RTs and more quickly achieve cumulative activity of 22 GBq if the interval is short. It is confirmed that RT efficacy is mainly associated with the expression of NIS in patients who had been treated with a cumulative activity of 22 GBq, and the impairment of iodine uptake may cause delayed curative effects or disease progression [4, 14]. One study reported that CR was more likely to be achieved when the metastatic lesion dose was > 80–100 Gy, but it was rare for dosimetry to show a dose > 20 Gy after cumulative activities of 20 GBq [15].

On the flip side, longer interval may decrease the number of stimulating follicular cells, reduce the frequency of multiple RTs, more slowly achieve a cumulative activity of 22 GBq, and minimize the risk of late effects of ¹³¹I in patients who had been treated with a cumulative activity of 22 GBq. In this retrospective study, courses were categorized into two groups by interval (≤ 12 m, > 12 m). Although a decline in sTg was observed in the two groups, no significant differences were found between the two groups in ΔsTg% and ΔLLD%, and no difference was found in biochemical or structural response between the former and latter courses with regard to different intervals. Additionally, we further performed a subanalysis of number of treatments (3 times, > 3 times), considering that patients usually achieve a

cumulative activity of 22 GBq after undergoing three RTs. No significant differences were found in the subanalysis. These results present primary evidence for the assumption above.

On the other hand, a low risk of early- and late-onset complications (salivary gland damage, dental caries, nasolacrimal duct obstruction, and secondary malignancies) is associated with the cumulative administered activity of ^{131}I and the total number of treatments [16–18]. We evaluated whether prolonging intervals prevent several early adverse effects, and no difference was found in salivary gland function, leukocytes, platelets, AST, ALT, and Ca between former and latter courses with regard to different intervals. With a consideration of a short-term observation window, the effect of interval on late-onset complications needs to be evaluated in the future.

Two issues urgently need to be discussed in this situation. First, how can candidates who may benefit from longer intervals be identified in clinical practice? In this cohort, if lung metastases were ^{131}I -avid, lesions were structurally stable or permissive and adverse effects were acceptable, patients would have an indication to receive repeated ^{131}I administrations. We did not exclude the former course of which patients were evaluated as serologic stabilization and non-effectiveness, because waiting at least 12 months for serologic progression would better establish a trend to ensure that the rise in the Tg or TgAb levels is not spurious or due to ^{131}I -induced tumor destruction [16]. Due to the limitation of the retrospective design, we did not identify a potential index for prolonging the interval. Second, what is the reasonable maximal length of time interval? The ATA recommended that the upper limitation value of the interval was 12 m for micrometastases, which is unclear for macronodular metastases. In this cohort, the median value of interval was 513 days (ranging from 126 to 937 days) in groups with > 12 m intervals, and number of treatments were not associated with intervals. This prolonged interval may not be enough to identify the maximal length of the time interval for multiple RTs.

Indeed, the interval of treatment for each patient should be individually managed in clinical practice, and several factors should be considered as well, such as age, the therapeutic response, cumulative dose, risk of complications, additional treatments, and patient desires [4, 5, 19], which need to be confirmed in prospective studies. As the 65-year-old male presented in Fig. 3, he had undergone three RTs with a cumulative dose of 600 mCi. Considering the good response, older age, and risk of pulmonary fibrosis, we prolonged the interval with close follow-up. After a longer interval (937 days), the patients still achieved remarkable serologic and structural responses. At the last follow-up (2 months after the fourth RT), the TSH-suppressed Tg showed a continuous decline.

Our study had some limitations. First, the small number of patients might cause an insufficient statistical power. Second, there may be a potential bias of patient selection (young patients, mostly PTC, lesion < 1 cm), because we focused on patients with non-progressive lung metastases, and older age, FTC, and lesion size of $\geq 1\text{cm}$ were associated with disease progression. Therefore, the generalizability of the results needs to be confirmed. Third, the effect of extending the interval time of RTs on the long-term outcomes and adverse effects of patients is unclear.

Conclusion

The interval of RT is not associated with the short-term response and adverse effects in patients with non-progressive lung metastases from DTC. Appropriately prolonging the interval in specific patients seems to be feasible, until further data are available. The interval for each patient should be individually managed in clinical practice, balancing the therapeutic response, cumulative dose, risk of complications, additional treatments and patient desires.

Declarations

Conflict of interest: The authors declare that they have no conflict of interest.

Informed consent: The study was approved by the Institutional Review Board of West China Hospital, Sichuan University and the requirement of written informed consent was waived.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Figures

Figure 1

The flowchart of the inclusion and exclusion of patients and courses.

Figure 2

Flow of patients in course pairs according to biochemical response and structural response (A, C: interval ≤ 12 m; B, D: interval > 12 m). No difference was found in biochemical response between former and latter courses with regard to different intervals (Cochran-Mantel-Haenszel test, $P=0.325$, $P=0.456$). No difference was found in structural response between former and latter courses with regard to different intervals (Cochran-Mantel-Haenszel test, $P=0.760$, $P=0.563$).

Figure 3

A 65-year-old male papillary thyroid cancer patient (T4aN1bM1) was evaluated for biochemical effectiveness and structural PR in the third course of RT, indicating a remarkable response to repeated RTs. Then, we prolonged the interval of the fourth RT (937 days), and the Δ sTg% and Δ LLD% just before the fourth RT were -77.2% and -58.5% (b, c), respectively. Local radioactivity was noted in the lungs on a posttherapeutic whole body scan (R-WBS) (a). At the last follow-up (2 months after the fourth RT), the TSH-suppressed Tg showed a continuous decline.

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