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ORIGINAL ARTICLE

The Success Rate of Initial ^{131}I Ablation in Differentiated Thyroid Cancer: Comparison Between Less Strict and Very Strict Low Iodine Diets

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Abstract
Purpose To decrease the risk of recurrence or metastasis in differentiated thyroid cancer (DTC), selected patients receive radioactive iodine ablation of remnant thyroid tissue or tumor. A low iodine diet can enhance uptake of radioactive iodine. We compared the success rates of radioactive iodine ablation therapy in patients who followed two different low iodine diets (LIDs).
Materials and Methods The success rates of postsurgical radioactive iodine ablation in DTC patients receiving empiric doses of 150 mCi were retrospectively reviewed. First-time radioactive iodine ablation therapy was done in 71 patients following less strict LID and 90 patients following very strict LID. Less strict LID restricted seafood, iodized salt, egg yolk, dairy products, processed meat, instant prepared meals, and multi-vitamins. Very strict LID additionally restricted rice, freshwater fish, spinach, and soybean products. Radioactive iodine ablation therapy was considered successful when follow-up ^{123}I whole body scan was negative and stimulated serum thyroglobulin level was less than 2.0 ng/mL.
Results The success rate of patients following less strict LID was 80.3% and for very strict LID 75.6%. There was no statistically significant difference in the success rates between the two LID groups (p=0.48).
Conclusions Very strict LID may not contribute to improving the success rate of initial radioactive iodine ablation therapy at the cost of great inconvenience to the patient.

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Introduction

Although well-differentiated thyroid carcinoma shows relatively good prognosis, some higher risk patients have a high tendency of disease recurrence [1]. To decrease risk of disease recurrence, patients undergo ablation of remnant thyroid tissue after total thyroidectomy with ^{131}I.

To enhance the uptake of radioiodine, the plasma inorganic iodide pool should be depleted before administrating radioiodine. The depletion of plasma iodide can be achieved with a low iodine diet (LID) that limits iodine intake [2].

The goal of a low iodine diet is a daily iodine intake of under 50 μg [3, 4]. LID is widely used at many hospitals for the pre-ablation process. In general, sea salt, seafood, and seaweed are prohibited. The detailed list of prohibited food in LID is different for each hospital.

Since ^{131}I ablation therapy was started at our medical center, the LID guideline has changed a few times after reviewing various references regarding iodine content of numerous food items. The main prohibited foods such as sea salt have been maintained, but some foods were additionally prohibited. Therefore, we describe our old LID guidelines as the "less strict low iodine diet" and the new revised version as the "very strict low iodine diet."

Numerous studies have suggested that LID appears to increase radioiodide uptake and radiation dose [2, 3, 5, 6]. However, Morris et al. concluded there was no statistical difference in radioiodine ablation rates between a regular and a stringent type of LID [7]. Korean diet usually consists of relatively high iodine content due to great intake of sea salt and soybean products. Limited studies have compared the ablation success rates according to different low iodine diets. As a result, we speculated that a stricter LID correlated with a higher success rate, and we compared the results following both types of LID methods.

Materials and Methods

Treatment and Management of Differentiated Thyroid Cancer (DTC)

The Catholic Medical Center (CMC) is a large referral hospital for the treatment and management of DTC in Korea. The initial therapy of DTC was total thyroidectomy, followed by high dose ^{131}I ablation therapy. The patients received thyroid hormone replacement (T4, thyroxine) after total thyroidectomy. Before the ^{131}I ablation therapy, thyroxine was discontinued for at least 4 weeks, with triiodothyronine (T3) replacement for the first 2 weeks. The patients underwent LID for at least 2 weeks. After thyroid hormone withdrawal and LID, patients had ^{123}I whole body scan and serum TSH, thyroglobulin (Tg), and anti-thyroglobulin antibody (anti-Tg) titer measured. The administered dose of ^{131}I was based on post-operative pathology results, ^{123}I whole body scan findings, and serum Tg levels, ranging from 100 to 250 mCi. Six to twelve months after initial ablation, follow-up ^{123}I whole body scan was obtained, and serum TSH, Tg, and anti-Tg were again measured (Fig. 1). We only included patients who received 150 mCi in this study to eliminate ^{131}I dose as a confounding factor.

Types of Low Iodine Diet

The CMC LID guidelines were revised in September 2005.

Less Strict Low Iodine Diet

The less strict LID guidelines were used from January 2004 until August 2005 at CMC. The guidelines included restriction of following items: sea salt, all seafood, dairy products, egg yolk, processed meat, iodine-containing multivitamins, and instant prepared meals (Table 1).

Very Strict Low Iodine Diet

The very strict LID was used from September 2005. Restricted items from the previous guidelines were continued, and further food items were restricted [8–10]. The additional restricted items were rice, freshwater fish, spinach, and soy products such as soy sauce, soybean paste, soy milk, and tofu (Table 1).

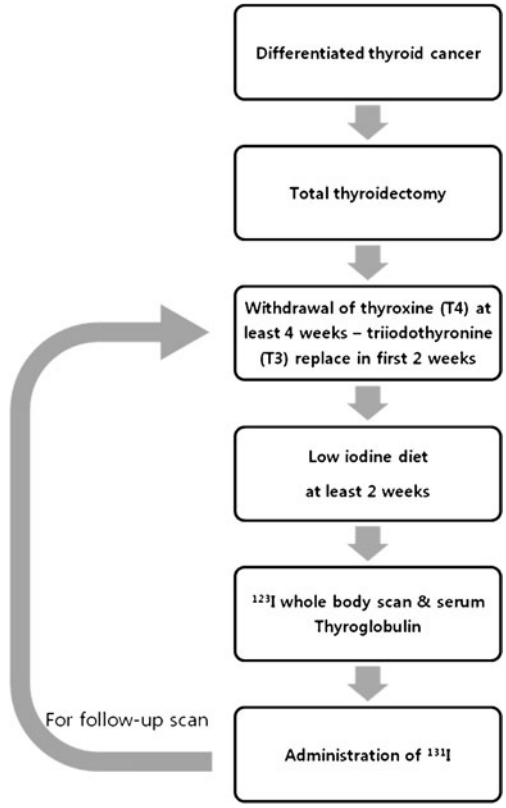

Fig. 1 CMC protocol of ^{131}I ablation

Both LIDs were explained in detail by nuclear medicine physicians, and the patients were given handouts indicating the allowed and restricted food items prior to starting the diets.

Patients

A total of 161 thyroid cancer patients undergoing initial ^{131}I ablation therapy were included in this retrospective study. Seventy-one patients followed the less strict LID. The very strict LID was followed by 90 patients between January 2006 and April 2007. Because patients received LID education in the months prior to ablation, patients who

Table 1 Restricted items of each low iodine diet

Less strict low iodine diet	Very strict low iodine diet (additional restrictions)
Sea salt	Rice
All seafood	Freshwater fish
Dairy products	Spinach
Egg yolk	Soy products: soy sauce, soybean paste, soy milk, and tofu
Processed meat	
Iodine-containing multivitamins	
Instant prepared meals	

received treatment during the overlap period between the two methods of LID (from September 2005 to December 2005) were excluded.

Inclusion criteria were as follows: patients with histologically confirmed differentiated thyroid cancer, who had undergone total thyroidectomy, and who received 150 mCi of ^{131}I for initial ablation after sufficient TSH stimulation by hormone withdrawal and follow-up whole body scan with ^{123}I and serum TSH, Tg, and anti-Tg.

The patients with distant metastases based on histologic results or imaging findings were excluded from this study. Other exclusion criteria were as follows: an interval between total thyroidectomy and ablation of over 1 year, TSH stimulation by recombinant human TSH (thyrotropin alpha) injection, no pre-ablation ^{123}I whole body scan, or no follow-up tests.

Analysis of ^{123}I Whole Body Scan, Serum Tg, and Anti-Tg

Pre-ablation

Pre-ablation ^{123}I whole body scans were visually analyzed, and the remnant uptake of the scan was categorized into three grades. Grade I indicated faint or focal uptake in thyroid bed, grade II large or multiple uptake areas, and grade III the appearance of star artifact.

Follow-up

Analysis of the ablation result was based on ^{123}I whole body scan, serum Tg, and anti-Tg. On follow-up ^{123}I whole body scan after initial ablation therapy, a negative scan was defined as no perceptible uptake in the thyroid bed. Serum Tg and anti-Tg antibody titer were also considered. Stimulated Tg and anti-Tg titer were considered as negative when stimulated Tg titer was under 2.0 ng/mL and anti-Tg titer under 70 IU/mL, while TSH was stimulated to above 30 mIU/L. Successful ablation was defined as a negative scan and negative stimulated serum Tg and anti-Tg titers. Unsuccessful ablation was defined as follows: perceptible uptake in thyroid bed on follow-up ^{123}I whole body scan [1]; or no perceptible uptake in thyroid bed, but elevated stimulated serum Tg or elevated anti-Tg [2].

Some guidelines or studies have defined successful ablation by different criteria [11, 12]. Our results were also analyzed by considering only a follow-up ^{123}I whole body scan negative finding as well as various stimulated Tg thresholds (Tg<1, Tg<5, and Tg<10 ng/mL) as defining successful ablation.

Statistical Analysis

Chi-squared analysis was used to test differences in success rates between the two LIDs. Variables that could affect

Table 2 Epidemiology and clinical features

	All (n=161)	Less strict LID group (n=71)	Very strict LID group (n=90)	p
Age (years)	47.8±11.2	45.1±10.1	50.0±11.5	0.005
Males/females, n (%)	28/133 (17.4/82.6)	12/59 (16.9/83.1)	16/74 (17.8/72.2)	0.884
Interval from op to ablation (months)	4.0±1.7	4.2±1.8	3.9±1.6	0.385
Remnant uptake on pre-ablation scan (n)				
Grade I	58	26	32	0.310
Grade II	43	15	28	
Grade III	60	30	30	
Pre-ablation TFT				
TSH	71.1±24.8	69.9±27.4	77.3±22.2	0.061
Tg	7.5±21.1	7.0±21.2	7.8±21.2	0.801
Anti-Tg	20.7±30.7	17.8±27.6	22.9±32.8	0.294
Tumor size (cm)	1.3±0.9	1.3±0.9	1.3±0.9	0.536
T stage				
T1	94	46	48	0.139
T2	6	4	2	
T3	43	13	30	
T4	18	8	10	
Capsular invasion, positive (n)	109	48	61	0.981
Extrathyroidal extension, positive (n)	58	20	38	0.065
Home-cooked meals only (n)	98	46	52	0.365

LID Low iodine diet, *TFT* thyroid function test

Table 3 Result of ablation

Result of ablation	Less strict LID (n=71)	Very strict LID (n=90)	p
Successful	57 (80.3 %)	68 (75.6 %)	0.475
Unsuccessful	14 (19.7 %)	22 (24.4 %)	

LID Low iodine diet

successful ablation were analyzed. Categorical variables were presented as proportions and analyzed between the two LID groups and also between the successful and unsuccessful ablation groups. Continuous variables were tested with *t*-test. Logistic regression analysis was performed for multivariate analysis. These statistical analyses were performed using SPSS 13.0 for Windows (SPSS, Chicago, IL, USA).

The institutional review board of our institution approved this retrospective study, and informed consent was waived.

Results

Patient Characteristics

A total of 161 patients were divided into the less strict LID (n=71) and the very strict LID groups (n=90). Patient characteristics did not differ statistically between the less strict LID group and the very strict LID group except for age (Table 2).

Success Rates of Each Low Iodine Diet

Fifty-seven patients (80.3%) in the less strict LID group and 68 patients (75.6 %) in the very strict LID group had successful initial ablation. The success rates of the two LID groups were not statistically different (Table 3).

Variables That Affect Thyroid Ablation

Variable factors that influence outcome of ^{131}I ablation were analyzed for the two LID groups (Tables 4 and 5). Age, visual grade of remnant uptake on pre-ablation ^{123}I whole body scan, pre-ablation stimulated anti-Tg titers, T stage from surgical specimen, capsular invasion (negative versus positive) on histologic exam, extrathyroidal extension (negative versus positive) on histologic exam of primary differentiated thyroid carcinoma, and occupation status (currently working versus not working) showed no significant differences between successful and unsuccessful patients groups, and between the two LID groups. Pre-ablation Tg titers showed a significant difference between

Table 4 Clinical data of the ablation results for two types of low iodine diets

	All (n=161)			Less strict LID (n=71)			Very strict LID (n=90)		
	Successful	Unsuccessful	p	Successful	Unsuccessful	p	Successful	Unsuccessful	p
Age (years)	47.9±10.6	47.6±13.2	0.907	45.9±9.8	41.6±11.3	0.160	49.5±11.0	51.5±13.1	0.502
Males/females (n)	19/106	9/27	0.172	10/47	2/12	0.771	9/59	7/15	0.048
Remnant uptake									
Grade I	42	16	0.467	19	7	0.493	23	9	0.756
Grade II	34	9		13	2		21	7	
Grade III	49	11		25	5		24	6	
Pre-ablation TFT									
TSH	74.8±24.8	72.4±24.8	0.474	70.8±28.4	66.6±23.2	0.610	78.2±21.0	74.6±26.1	0.505
Tg	3.1±4.6	22.5±40.8	<0.001	3.0±4.4	23.3±44.4	0.001	3.3±4.9	21.9±39.3	<0.001
Anti-Tg	20.6±30.6	21.1±31.5	0.929	18.0±26.4	17.2±33.0	0.926	22.7±33.6	23.6±31.1	0.917
Tumor size (cm)	1.2±0.8	1.8±1.0	<0.001	1.2±0.8	1.8±1.2	0.060	1.1±0.8	1.8±0.9	0.001
T stage									
T1	77	17	0.401	38	8	0.684	39	9	0.347
T2	5	1		3	1		2	0	
T3	30	13		9	4		21	9	
T4	13	5		7	1		6	4	
Capsular invasion, negative/positive (n)	45/80	7/29	0.061	19/38	4/10	0.733	26/42	3/19	0.032
Extrathyroidal extension, negative/positive (n)	84/41	19/17	0.112	41/16	10/4	0.970	43/25	9/13	0.065
Home-cooked meals only, no/yes (n)	44/81	19/17	0.057	17/40	8/6	0.055	27/41	11/11	0.395

LID Low iodine diet, *TFT* thyroid function test

Table 5 Multivariate logistic regression analysis of variables

	All		Less strict LID group		Very strict LID group	
	Odds ratio	*p*	Odds ratio	*p*	Odds ratio	*p*
Age	1.012	0.600	0.950	0.288	1.021	0.523
Sex	1.052	0.945	0.134	0.255	1.710	0.572
Remnant uptake		0.068		0.226		0.298
Pre-ablation TFT						
TSH	0.989	0.330	0.983	0.380	0.988	0.451
Tg	1.213	<0.001	1.378	0.004	1.190	0.002
Anti-Tg	1.008	0.288	1.019	0.203	1.005	0.536
Tumor size	2.440	0.011	1.431	0.573	2.853	0.032
T stage		0.816		0.591		0.930
Capsular invasion	1.616	0.466	12.644	0.076	0.784	0.790
Extrathyroidal extension	0.396	0.599	0.175	0.438	0.0	1.0
Home-cooked meals only	1.741	0.331	4.880	0.134	1.268	0.776

LID Low iodine diet, *TFT* thyroid function test

successful and unsuccessful groups ($p<0.001$). The tumor size was significantly different between the successful and unsuccessful groups in the total study population (1.2±0.8 versus 1.8±1.0 cm, $p<0.001$) as well as in the very strict LID group alone (1.1±0.8 versus 1.8±0.9 cm, $p<0.001$).

Success Rates by Other Definitions

We defined successful ablation as negative ^{123}I whole body scan plus negative serum Tg and anti-Tg titer. When we re-defined successful ablation according to following requirements: (1) negative ^{123}I whole body scan only, (2) Tg titer under 1 ng/mL, (3) Tg titer under 2 ng/mL, (4) Tg titer under 5 ng/mL, and (5) Tg titer under 10 ng/mL, no statistical difference in success rate was noted between the two LID groups (Table 6).

Discussion

We investigated the influence of two different LIDs on initial remnant ablation of DTC using very strict and less strict LIDs. Ablation results showed no statistical difference in success rates between the two types of LID. Instead, in our study, large tumor size and high pre-ablation Tg levels were closely related to the results of radioactive iodine ablation.

In DTC, the outcome of ablation is closely related to the effective dose delivered to the tumor [13]. Effective tumor dose is associated with serum TSH level and iodide pool [14, 15], and the iodide pool is reduced by LID. In a previous study by Morris et al., different ablation results were seen between patients who were instructed about the diet verbally (mostly via telephone) and patients who had a copy of a food list. The success rate was higher in the patients with a list of restricted food items, but there was no significant difference (68.2 versus 62.0%, $p=0.53$). Although our success rates were higher than that of Morris et al., this was not statistically significant. The lower success rates of Morris et al. may be due to diversity in characteristics of the study population (such as the administered dose, which ranged from 100 to 200 mCi).

A few studies measured urine iodine excretion or urine iodine-to-creatinine (I/Cr) ratio. Tomoda et al. contrasted

Table 6 Results of ablation for two low iodine diet (LID) types according to other definitions of success

Successful ablation definition	Less strict LID (%)	Very strict LID (%)	*p*
Negative ^{123}I whole body scan only	91.5	90.0	0.737
Any whole body scan finding and Tg (ng/mL)			
<1	77.5	71.1	0.362
<2	85.9	81.1	0.418
<5	91.5	88.9	0.575
<10	94.4	94.4	0.983
Negative ^{123}I whole body scan and Tg (ng/mL)			
<1	71.8	67.8	0.579
<5	85.9	82.2	0.527
<10	87.3	85.6	0.746

urine I/Cr ratio between a conventional restricted iodine diet and a stringent LID [16]. A more ideal urine I/Cr ratio appeared in those using the stringent LID. Similar results were shown in a study of Roh et al. [17]. Two types of LID, stringent LID for 1 week and less stringent LID for 2 weeks, were investigated, and the more stringent LID was found to be more desirable. Choi et al. reported that urine iodine excretion was significantly lowered after LID [18]. However, Tala Jury et al. presented dissimilar results [19]. They evaluated the association between urine iodine excretion and outcome of ablation. No significant difference in urine iodine excretion was seen in groups with successful versus unsuccessful ablation. They concluded that body iodine content may not be an important determinant of ablation.

On the other hand, Pluijmen et al. reported significantly higher success rates of ablation after 4 days of LID than standard diet [20]. In addition, comparison of 24 h urine iodine excretion and 24 h neck uptake of ^{131}I were made. In the LID group, 24 h urine iodine excretion showed significantly lower levels, and 24 h uptake test of ^{131}I showed significantly higher levels.

Our two types of LID showed no statistical difference in outcome of ablation, contrary to our expectation. Compliance of the patients on LID may be another important factor, as carrying out strict LID is very difficult [15, 17, 18, 21]. As dietary restrictions become more difficult to follow, compliance may decline. For example, rice and soybean products, the additionally restricted foods in our very strict LID, are commonly used ingredients in Korean diet, and some patients may have strayed from the LID occasionally.

In this study, the two sexes had different success rates in the very strict LID group. The success rate of radioactive iodine ablation in males was lower than the rate in females in the very strict LID group.

We thought that those who work and thus cannot cook every meal according to the LID might have a lower radioactive iodine ablation success rate, but there was no difference between actively working patients and stay at home patients.

One important limitation of this study is that we could not assess patients' body iodide pools. Urine iodine excretion or I/Cr ratio are not routinely measured in our hospital. Given these conditions, it is difficult to evaluate the actual compliance. Furthermore ablation therapy cannot be rejected or delayed even in patients with low compliance. Therefore, proper education on LID may prove to be more important than arbitrary compliance.

In our medical center, at present, empiric ablation for remnant thyroid tissue is available in doses of 100 and 150 mCi, and only those administered with 150 mCi were included in this study. However, according to NCCN guideline and other studies, an ablation dose of less than 100 mCi is more commonly given. Therefore, another limitation of our study is the use of 150 mCi for remnant ablation dose.

On the basis of our results, although rice and soybean products were prohibited items according to very strict LID guidelines, they are currently allowed in the CMC protocol.

In conclusion, very strict LID and less strict LID showed no statistical difference in success rates of ablation. Very strict LID may cause great inconvenience to the patients without additional benefit in ablation outcome.

Disclosure Statement We declare that we have no conflict of interest.

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