ORIGINAL

Outpatient ablation treatment with two doses of 30 mCi of radioactive iodine for non-low-risk papillary thyroid cancer

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Abstract : Outpatient ablation therapy with low-dose radioactive iodine (RAI) is applied to non-low-risk papillary thyroid cancer patients due to a chronic shortage of inpatient RAI treatment wards in Japan. We used the maximum dosage available for outpatient therapy of 30 mCi of RAI for ablation and diagnostic (Dx) whole-body scintigraphy (WBS). This study aimed to examine the significance of the second dose of 30 mCi. DxWBS was performed 6 months after ablation, and assessment of success or failure was performed 12 months after ablation. A second WBS was performed in the remaining RAI accumulation cases in the neck on DxWBS. The criteria for successful ablation was negative cervical accumulation on WBS, thyroid stimulating hormone-suppressed thyroglobulin (sup-Tg) below 1.0 ng/mL, and no increase in thyroglobulin antibody (TgAb) level. At the time of DxWBS, 35/68 cases met the successful criteria, and 45 cases achieved success at assessment. Sup-Tg values decreased significantly after ablation and decreased further after DxWBS in successful ablation cases, whereas those were not changed in ablation failure cases. Findings indicated that RAI used in DxWBS had therapeutic effects. It makes sense to use 30 mCi for DxWBS, given the current difficulty of inpatient ablation therapy with high-dose RAI. J. Med. Invest. 70 : 17-21, February, 2023

Keywords **:** *radioactive iodine, papillary thyroid cancer, remnant ablation, 1110 MBq (30 mCi), thyroglobulin*

INTRODUCTION

Radioactive iodine (RAI) therapy for papillary thyroid cancer (PTC) includes remnant ablation, adjuvant therapy, and persistent tumor treatment, all of which were performed after total thyroidectomy. Ablation therapy uses 30 mCi (1110 MBq) of RAI to ablate normal thyroid remnants and facilitate the detection of recurrence by monitoring serum thyroglobulin (Tg) levels, which is indicated for cases considered to be at low-risk for recurrence. Adjuvant therapy uses 100–150 mCi (3,700–5,600 MBq) of RAI with the aim of destroying residual cancer cells that may be present, although unproven. Patients with incomplete surgical resection or those with distant metastases are treated with 100–200 mCi (3,700–6,400 MBq) of RAI (1, 2). However, there is a chronic shortage of inpatient radiotherapy wards in Japan, and high-dose RAI treatment should be reserved for patients in which residual or recurrent cancer is evident. As a result, 30 mCi therapy is widely applied in cases other than those with positive surgical margins or distant metastasis which can be used on an outpatient basis (3).

We have previously reported successful ablation in 30/43 patients (76.7%) as indicated by a negative diagnostic (Dx) whole-body scintigraphy (WBS) with 3 mCi RAI following 30 mCi ablation (4). This RAI may also be expected to have a therapeutic effect although the RAI dose commonly used for DxWBS is 3–10 mCi (3, 5-7). We have systematically used 30 mCi RAI for ablation and also for DxWBS since 2015. Here, the results of ablation defined by WBS and thyroglobulin (Tg) level are reported and the factors involved in ablation success or failure, and discussed the significance of the second dose of 30 mCi RAI.

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PATIENTS AND METHODS

Study population

From 2015–2019, 75 patients underwent ablation with 30 mCi RAI at the Osaka General Medical Center. A total of 68 patients were included in the analysis excluding cases with detected distant metastasis, cases without DxWBS, and cases without complete blood tests. Patient backgrounds were listed in Table 1. There are more female than male patients that range in age from 27–84 years (median 59 years). Clinical stages and risk assessment categories definitions are described below. Low-risk patients were not included in this study.

The Institutional Review Board of Osaka General Medical Center approved the present study (No. 2020-104).

Table 1. Patient Characteristics.

Characteristics	number
Gender : male/female	19/49
Age : </≥ 55 year old	23/45
T classification : T1ab/ 2/T3ab/4a	11/3/40/14
N classification : N0/1a/N1b	9/20/39
Stage : I/II/III	26/33/9
Risk classification : low/intermediate/high	0/43/15

Ablation protocol

Eligibility for ablation was determined after total thyroidectomy. Ablation was not applied to patients with postoperative pathological pT1aN0, pT1bN0, or pT2N0, positive resection margins, and known distant metastases diagnosis. Total thyroidectomy was not performed for cT1N0 and cT2N0 in preoperative evaluation.

Thyroid hormone replacement after total thyroidectomy was adjusted to thyroid stimulating hormone (TSH)-suppressive levels unless contraindicated after total thyroidectomy. After 3 months postoperatively, blood tests were performed to measure TSH-suppressed Tg levels (sup-Tg) and anti-Tg antibody levels (TgAb). Dietary iodine was restricted for 2 weeks from that day, followed by intramuscular injections of recombinant human TSH (rhTSH, Thyrogen TM, Sanofi Genzyme, Cambridge, MA, US) for 2 days to raise TSH. On the next day, 30 mCi of RAI was orally administered for ablation. On day 3 after RAI administration, WBS was taken and blood test was performed to measure TSH-stimulated Tg level (stim-Tg). Then, Dx WBS with 30 mCi RAI was performed 6 months later. Dietary iodine restriction, rhTSH administration, and blood tests were done as at the time of ablation. Blood tests were performed to measure sup-Tg and TgAb after another 6 months (1 year after ablation). A second Dx WBS was performed with 5 mCi of RAI in cases with residual cervical accumulation on DxWBS.

Staging and risk assessment

TNM classification and clinical stage was determined by the UICC TNM classification that was revised to the 8th edition in 2017 (8). Cases before 2017 were also revised according to the 8th edition. This study included 26 Stage I, 33 stage II, and 9 stage III subjects. Patients younger than 55 years are classified as stage I unless they have distant metastases.

Risk classification was determined based on the clinical practice guidelines for thyroid tumors published by the Japan Associations of Endocrine Surgeons in 2018 (2). Briefly, PTC is categorized into four groups. T1aN0M0 and T1bN0M0 PTCs are classified as very low-risk and low-risk, respectively. PTCs that meet at least one of the following criteria are classified as high risk : tumor size >4cm, a tumor with positive extra-thyroidal extension beyond the tissues or organs other than strap muscles, a metastatic lymph node >3cm, a metastatic lymph node of extranodal extension, or distant metastasis. PTCs that do not meet the very low-risk, low-risk, or high risk criteria are classified as intermediate risk. This study included 43 intermediate and 15 high risk patients.

Assessment of ablation

The American Thyroid Association (ATA) management guideline defined the categories of response to therapy in patients with differentiated thyroid cancer treated with total thyroidectomy and RAI ablation (1). Four categories and definitions are summarized below. "Excellent response" is defined by negative WBS and either sup-Tg <0.2 ng/mL or stim-Tg <1.0 ng/mL, and negative TgAb. The "indeterminate response" is defined by negative WBS and either sup-Tg level of 0.2 ng/ml ≤ sup-Tg <1.0 ng/mL or stim-Tg level of 1.0 ng/ml ≤stim-Tg <10ng/mL, and stable or declining TgAb level if TgAb positive. The "biochemical incomplete response" is defined by negative WBS and either sup-Tg ≥1.0 ng/mL or stim-Tg ≥10 ng/mL or rising TgAb level if positive. The "structural incomplete response" is structural or functional evidence of disease with any Tg level regardless of TgAb. Successful ablation in the present study corresponded to "excellent response" or "indeterminate response" of the ATA guideline. The Tg value was determined using the sup-Tg 1 year after ablation.

WBS was independently assessed by one otolaryngologist and one radiologist. RAI accumulation of the thyroid bed in the neck was classified into four categories : negative, weak, moderate, and strong in comparison with RAI accumulation in the oral cavity as described previously (4, 6). The strong RAI accumulation in the image was higher than oral accumulation and shows a star-shaped artifact.

Statistical analysis

The StatPlus : macPro software (AnalystSoft, VA, US) was used to perform the statistical analysis. Fisher's exact test was used to test the frequency distribution. Binomial logistic regression analysis was used for multivariate analysis. Parametric tests cannot be used because Tg values include values below the sensitivity limit (:0.04) in comparison with Tg values. A nonparametric Wilcoxon signed-rank test was used to test changes in Tg values. A nonparametric Mann–Whitney U test was used to compare the distribution of Tg values.

RESULTS

Figure 1 summarizes the WBS course, sup-Tg, stim-Tg, and TgAb tests. WBS at the time of ablation showed strong accumulation in 17 cases (25%). A total of 48 patients (70.6%) were negative for cervical RAI accumulation at DxWBS. Of the remaining 20 patients, 14 were negative at the second Dx WBS. Finally, 62 (91.2%) patients reached negative on WBS.

At the time of ablation, sup-Tg ranged from <0.04 to 66.8 ng/mL with a median of 0.44 ng/mL. A total of 24 cases were less than 0.2 ng/mL and 43 cases were less than 1.0 ng/mL. At the 6 month DxWBS timing, sup-Tg ranged from <0.04 to 33.1 ng/mL, with a median of 0.30 ng/mL ; <0.2 ng/mL in 30 cases and <1.0 ng/mL in 47 cases. At the time of assessment, 1 year after ablation, sup-Tg ranged from <0.04–33.9 ng/mL with a median of 0.15 ng/mL ; <0.2 ng/mL in 37 and <1.0 ng/mL in 47 cases. Sup-Tg decreased significantly during this period (from ablation to assessment, $p < 0.001$), and the number of <0.2 ng/mL and <1.0 ng/mL increased.

Stim-Tg values at ablation ranged from <0.04 to 183.6 ng/mL, with a median of 3.58. Stim-Tg at DxWBS ranged from <0.04–292, with a median of 1.10. Stim-Tg values decreased significantly ($p = 0.007$), and the number of both cases with <1.0 ng/mL and <10.0 ng/mL increased.

There were 14 TgAb positive cases (20.6%). Among them, there was one case where the value increased both at the times of DxWBS and assessment. In the other 13 cases, the values were stable or declined.

According to the criteria of the present study, 45 patients (66.2%) had successful ablation (WBS negative, sup-Tg <1.0 ng/mL, TgAb not rising). There were 24 cases (35.3%) that corresponded to the "excellent response" defined by the ATA guidelines. At the time of DxWBS, 35 cases (51.5%) had successful ablation and 21 cases (30.9%) had an "excellent response."

Table 2 shows comparisons between successful ablation and failed cases. No differences were detected in gender, age, T classification, N classification, or clinical stage. The following cases were significantly more frequent in successful ablation according to univariate analysis : intermediate risk (not high risk) by risk classification, weak or moderate (not strong) RAI accumulation on WBS at ablation, positive TgAb, sup-Tg at ablation <1 ng/mL and stim-Tg at ablation <10 ng/mL. Stim-Tg at ablation and WBS at ablation remained independent predictive factors after multivariate analysis.

Figure 2 shows changes in sup-Tg values for successful

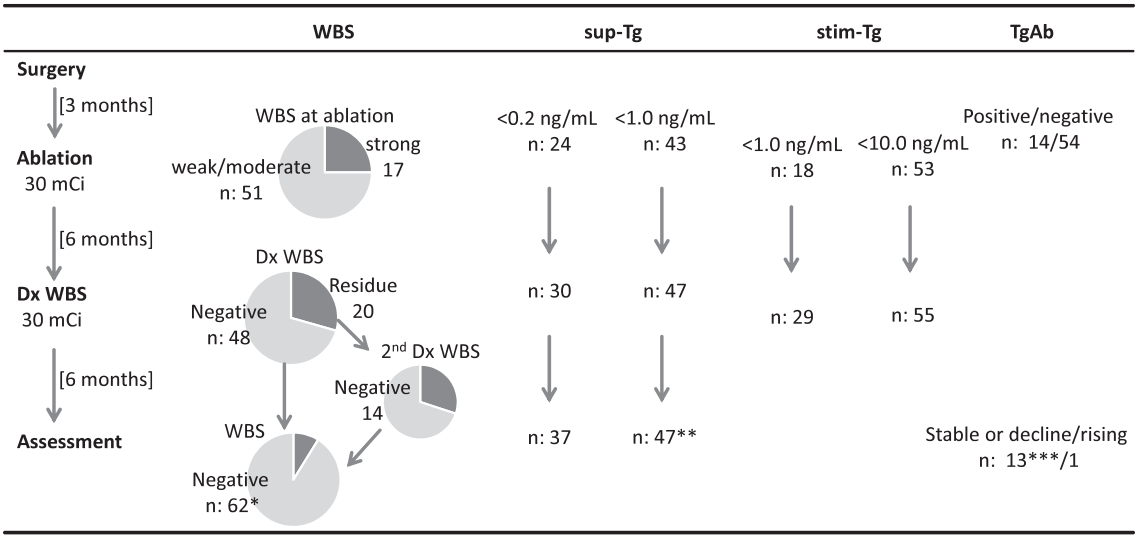

Figure 1. Treatment and assessment schedule and course of WBS, Tg level and TgAb.
The number of patients (n) in each examination at each timing is shown. Successful ablation was defined as negative WBS image*, sup-Tg <1.0ng** and no rising TgAb***, and was 45/68 cases.

Table 2. Clinical factors comparisons between successful ablation and failure cases.

Factors		Successful ablation (n : 45, 66.2%)	Ablation failure (n : 23, 33.8%)	Fisher's exact test (*p*)	Logistic analysis (*p*)
Gender	male	9 (20.0%)	10 (43.5%)	0.051	-
Age	< 55	13 (28.9%)	10 (43.5%)	0.283	-
T	T1–2 (not T3-)	9 (20.0%)	6 (26.1%)	0.555	-
N	N0 1a (not 1b)	23 (51.1%)	6 (26.1%)	0.070	-
Stage	I/II, III	15 (33.3%)	11 (47.8%)	0.296	-
Risk	intermediate (not high)	39 (86.7%)	13 (56.5%)	0.013*	0.084
WBS at ablation	weak moderate (not strong)	42 (93.3%)	9 (26.0%)	< 0.001*	0.034*
Tg Ab	positive	13 (28.9%)	1 (4.3%)	0.025*	0.624
sup-Tg at ablation	< 1 ng/mL	39 (86.7%)	5 (21.7%)	< 0.001*	0.119
stim-Tg at ablation	< 10 ng/mL	45 (100%)	8 (34.8%)	< 0.001*	< 0.001*

Factors, number of patients (%) and p-values of univariate analysis by Fisher's exact test and multivariate analysis by logistic analysis are listed. * : significant difference.

ablation cases and ablation failure cases. The Tg value decreased significantly from the time of ablation (range : <0.04–2.17, median : 0.20) to the time of DxWBS (range : <0.04–1.53, median : 0.11) (p <0.001) and from the time of DxWBS to the time of assessment (range : <0.04–0.73, median : 0.40) (p <0.001) in successful ablation cases. On the other hand, no significant changes were observed in the Tg values at these three timings (p = 0.681, p = 0.446) in the failed cases. The TSH values did not change at these three timings (p = 0.111, p = 0.197).

DISCUSSION

The successful ablation definition varies among studies. More studies used Tg values as a criterion in addition to WBS while some studies used WBS results alone as a criterion (4, 9). Tg cut-offs also varied among studies : sup-Tg or non-stimulated Tg <2 ng/mL (10,11), stim-Tg <5 ng/mL (5), stim-Tg <2 ng/mL (7, 12), stim-Tg <1ng/mL (13, 14) and others. As in this study, the Tg value should be included to determine the success or failure of

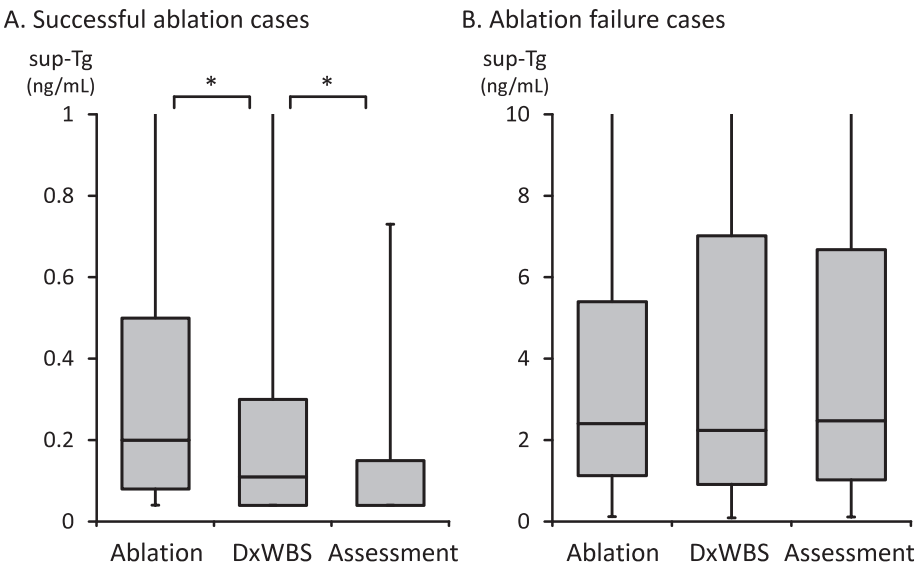

Figure 2. Changes in sup-Tg values from the time of ablation through the time of Dx WBS to the time of assessment. (A: successful ablation cases, B: ablation failure cases).
The boxplot consists of the lowest value, 25th percentile, median, 75th percentile, and highest value. But due to the broad and skewed distribution of the values, the highest values are off the chart, except for the A assessment. Since the lowest measured value is the detection limit (0.04 ng/mL), the lowest value and 25th percentile are the same for the A DxWBS and the A Assessment, and the median is also the same for the A Assessment.*: significant difference.

ablation when RAI was applied to thyroid cancer patients with a risk of recurrence and mortality. Tg value has been established as a tumor marker in follow-up after total thyroidectomy as it reflects the total amount of thyroid-derived tissue present in the body (15). In this study, the criteria for success was set as negative WBS and sup-Tg <1ng/mL and TgAb not rising assessed 1 year after ablation referring to the ATA guideline.

The ablation success rate with a low-dose RAI of 30 mCi reported from Japan (29.1%–73.5%) (5-7,1 0) was lower than that reported from other countries (85%–92%) (11, 12, 14) despite some differences in criteria. It is clear that the Japanese reports contain more cases with advanced-stage disease examining the case presentation of each report. The cases in the present study also included 42/68 (61.7%) of Stage II and III cases and did not include very low or low-risk cases. Japan has had a policy of not performing total thyroidectomy in low-risk cases consistent with recent global policy (1, 2). Therefore, low-risk cases were not eligible for RAI treatment.

This study reviewed the effect of 30 mCi RAI used for DxWBS, in addition to ablation. The effect of 30 mCi ablation in DxWBS images were negative in 48/68 (70.6%) and after 30 mCi DxWBS, 14/20 got negative, and finally 62/68 (91.2%) were negative. It was confirmed that RAI for DxWBS increased the number of WBS negative cases, although no comparison was made between 30 mCi and a lower dose of RAI. Similarly, the number of cases with sup-Tg <0.2 ng/mL was increased at the time of assessment, compared to that at the time of DxWBS. A total of 35/68 (51.5%) met the successful criteria and 21/68 (30.9%) the "excellent response" at the time of DxWBS, then at the assessment, successful ablation was achieved in 66.2% of cases, and "excellent response" in 35.3% of cases. RAI for DxWBS contributed to an increase in successful ablation cases and "excellent response" cases.

WBS and stim-Tg at the time of ablation were independent factors related to the final success or failure of ablation. A strong RAI accumulation in the neck at the time of ablation was also found as a predictive factor of ablation failure in our previous study (4). Stim-Tg at ablation would be a more potent predictive factor, which was also indicated by multiple previous studies (5-7, 16, 17). A large-scale meta-analysis by Webb *et al*. showed that stim-Tg at ablation is both a predictor of ablation and a prognostic factor of disease-free status, with stim-Tg <10 as a suitable threshold (16).

The sup-Tg values yielded contrasting results between the successful ablation and ablation failure groups. Sup-Tg levels decreased after 30 mCi ablation and decreased further after 30 mCi DxWBS in successful ablation cases. However, sup-Tg levels did not change after the first or second application of 30 mCi RAI in ablation failure cases. A second dose of 30 mCi was proved to be effective in cases with successful ablation but had no effect in cases of ablation failure. The range of sup-Tg at ablation (this value was measured before RAI administration) in successful ablation cases was <0.04–2.64 ng/mL in this study. Treatment with higher doses should be required in cases with Tg values above this range.

In summary, this study showed that after the second dose of 30 mCi RAI, the number of successful ablation cases was increased and sup-Tg levels in successful ablation cases were decreased. The findings indicated that RAI used in DxWBS had therapeutic effects, although differences between the effects of 30 mCi and lower doses of RAI had not been explored. It makes sense to use 30 mCi, the maximum available outpatient dose, for DxWBS given the current difficulty of inpatient ablation therapy with high-dose RAI. On the other hand, it was also shown that there were cases in which two doses of 30 mCi were ineffective. The Tg value before RAI therapy could be a predictor and patients with high Tg values should be considered for treatment with high RAI doses. The prognostic impact of two doses of 30 mCi had not been investigated and was left to future research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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