Factors Affecting Ablation Success After I-131 Radioactive Iodine Therapy in Low and Intermediate Risk Papillary Thyroid Cancer

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ABSTRACT

The study was to evaluate the effect of radioactive iodine (RAI) treatment application time and clinical, histopathological factors on ablation success in patients with operated papillary thyroid cancer (PTC) in low and intermediate-risk. One hundred sixty-one patients with PTC in the low and intermediate-risk were evaluated. Most patients (89.4 %) were in the low-risk, and 10.6 % were in the intermediate-risk. When the patients were divided into two groups according to the date of receiving RAI treatment after surgery, those who received early treatment (≤ 3 months) constituted the majority of the patients (72.7 %). Seventeen patients received 1.85 Gigabecquerel (GBq), 119 3.7 GBq, 25 5.55 GBq RAI. Most patients (82 %) achieved ablation success after the first RAI treatment. The time interval between surgery and RAI treatment did not affect ablation success. Stimulated Tg level measured on the RAI treatment day was an independent predictive factor for successful ablation ($p < 0.001$). The cut-off value of Tg found to predict ablation failure was 5.86 ng/ml. It was concluded that 5.55 GBq RAI treatment could predict ablation success compared to 1.85 GBq dose ($p = 0.017$). It was concluded that having a T1 tumor may predict treatment success compared to a T2 or T3 tumor ($p = 0.001$, $p < 0.001$, retrospectively). The time interval does not affect ablation success in low and intermediate-risk PTC. The ablation success rate may decrease in patients who receive low-dose RAI and have high Tg levels before treatment. The most crucial factor in achieving ablation success is giving enough doses of RAI to ablate the residual tissue.

Introduction

Thyroid cancer is the most common endocrine malignancy accounting for approximately 3 % of new cancer cases worldwide. It is among the slow-growing cancers, and the 10-year survival rate is over 95 % [1]. It is known that only 5 % of patients develop metastases during follow-up. The course of patients who develop metastases during follow-up is more aggressive, and their mortality increases [2–5].

Differentiated thyroid cancers (DTC), the majority of which are papillary (PTC) and follicular thyroid carcinoma (FTC) subtypes, account for approximately 90 % of all thyroid cancers. Current guidelines recommend total thyroidectomy (TT) with or without lymph node dissection, followed by radioactive iodine (RAI) therapy at varying doses and thyroid hormone suppressive therapy at varying levels according to risk classification [6–8]. The aim of first-dose ablation in the treatment of RAI after TT is to achieve an undetectable low serum thyroglobulin (Tg) level, to ablate the residual thyroid tissue, and to minimize the risk of recurrence by irradiating the undetected neoplastic focus with adjuvant therapy [7, 9].

While deciding whether to apply RAI treatment after TT, the decision is made by considering other prognostic factors, such as the age and gender of the patients, in addition to the American Thyroid Association (ATA) risk classification. ATA guidelines divided DTC patients into three groups according to the risk categories of dis-

ease recurrence. These groups are as follows: low, intermediate, and high risk [8]. The decision to apply RAI therapy to the patient and the dose to be given is determined by risk assessment and staging [8, 10]. Although postoperative RAI treatment is generally not strictly necessary in low-risk patients, it is recommended to be given in intermediate and high-risk patients. There is still much debate about which patients should be used in treating RAI and at what dose it should be administered. High radioactivity [more than 1.85 Gigabecquerel (GBq)] is effective for the ablation of high-volume residual thyroid tissue and destruction of micrometastases; however, low radioactivity (1.1 GBq) may be effective in destroying small amounts of thyroid tissue, whereas high-volume residual thyroid tissue may not be sufficient to ablate [11, 12].

Another factor affecting the success of ablation is the application time of RAI treatment. Studies show that the RAI therapy application time affects ablation success [13, 14].

Given the excellent prognosis in low and intermediate-risk groups, successful ablation of the residual focus with RAI therapy is essential in preventing recurrent disease [8, 15]. Therefore, in this study, we aimed to evaluate the effect of RAI treatment application time on ablation success and the factors affecting ablation success in patients with papillary thyroid cancer in the low and intermediate-risk groups.

Patients and Methods

Patients and study design

A total of 407 patients diagnosed with thyroid cancer in a tertiary university training and research hospital between 2014 and 2021 were evaluated retrospectively. Patients diagnosed with papillary subtype DTC and in low-to-intermediate risk groups that received RAI therapy for remnant tissue ablation after TT with or without lymph node dissection were included in the study.

The patients with high risk according to the ATA-2015 and had distant metastases according to TNM (AJCC-8), who were not screened for iodine-131 (I-131) RAI given with five millicurie (mCi) after 9–12 months to RAI therapy, patients aged 18 years or younger, and patients with incomplete clinical and laboratory data were not included in this study. When all inclusion and exclusion criteria were evaluated, a total of 161 papillary DTC patients who received I-131 RAI therapy in low and intermediate-risk groups for ablation could be included in the study.

All patients were staged according to TNM (AJCC-8), and risk classification was made according to the ATA-2015 guidelines. Demographic and clinical data, laboratory parameters, histopathological diagnosis, surgical method, thyroid scintigraphy imaging after surgery, and post-therapy whole body RAI scanning of the patients were obtained from the hospital information system and radiology-nuclear medicine imaging archive.

The patients' serum Tg and Anti-Tg values were measured from blood tests performed when the thyroid stimulating hormone (TSH) level was above 30 mU/l on the day of RAI treatment and diagnostic RAI screening with five mCi after 9–12 months to initial RAI therapy. Patients received an iodine-poor diet ten days before RAI treatment and diagnostic RAI screening with five mCi.

Based on the current literature, the time interval between TT and RAI treatment for all patients was calculated [13]. Patients were divided into two groups for this period of three months or less as Group A and patients with more than three months as Group B.

Criteria for successful ablation were determined as follows: Absence of I-131 uptake on the neck or any part of the whole body on diagnostic RAI screening with the five mCi RAI stimulated Tg level less than one ng/ml after 9–12 months to RAI treatment (when TSH level > 30 mU/l) and a low Anti-Tg level [in the normal range (0–4.5 IU/ml) or undetectable level].

Ethical approval was obtained from the local ethics committee of our university and hospital before starting this retrospective study (2021/183).

Imaging procedures

Postoperative thyroid scintigraphy imaging, whole body scanning after 7–10 days to RAI therapy, and whole body diagnostic RAI scanning with five mCi I-131 were performed with Mediso AnyScan SPECT Dual Detector Gamma Camera. Diagnostic or post-treatment I-131 whole-body scans were taken with a high-energy parallel collimator on a double-headed gamma camera. I-131 whole-body imaging was performed by selecting an energy peak of three hundred and sixty-four kiloelectronenvolt (keV) with a 20 % window interval. While the patient was lying on their back, anterior and posterior whole-body images were imaged in a 256 × 1024 matrix with a scanning speed of 70 mm/minute.

Postoperative thyroid scintigraphy imaging was taken with a low-energy high-resolution parallel collimator on a double-headed gamma camera by selecting an energy peak of one hundred and forty keV with a 20 % window interval. Imaging was done in a 256 × 256 matrix until the number of counts collected from the thyroid bed was three hundred thousand.

Statistical analysis

All statistical analyzes were performed using the SPSS version 25 software (IBM Corp., Armonk, New York, USA). Whether the quantitative variables were normally distributed or not was checked with the Kolmogorov – Smirnov test. In independent group comparisons, the independent samples t-test was used for normally distributed variables, and the Mann–Whitney U-test was used for non-normally distributed variables. Descriptive statistics for normally distributed variables were given as mean ± standard deviation and median (25th–75th percentile) for non-normally distributed variables. Relationships between categorical variables were determined by Chi-square independence analysis. Descriptive statistics for categorical variables were given as frequency (percentage). Cut-off values for stimulated Tg (before RAI ablation therapy) and Anti-Tg (before RAI ablation therapy) variables were determined by Receiver Operating Characteristic (ROC) analysis in the diagnosis of treatment success. The effects of independent variables on treatment success were determined by multivariate logistic regression analysis (forward). p-Values < 0.05 values were considered statistically significant.

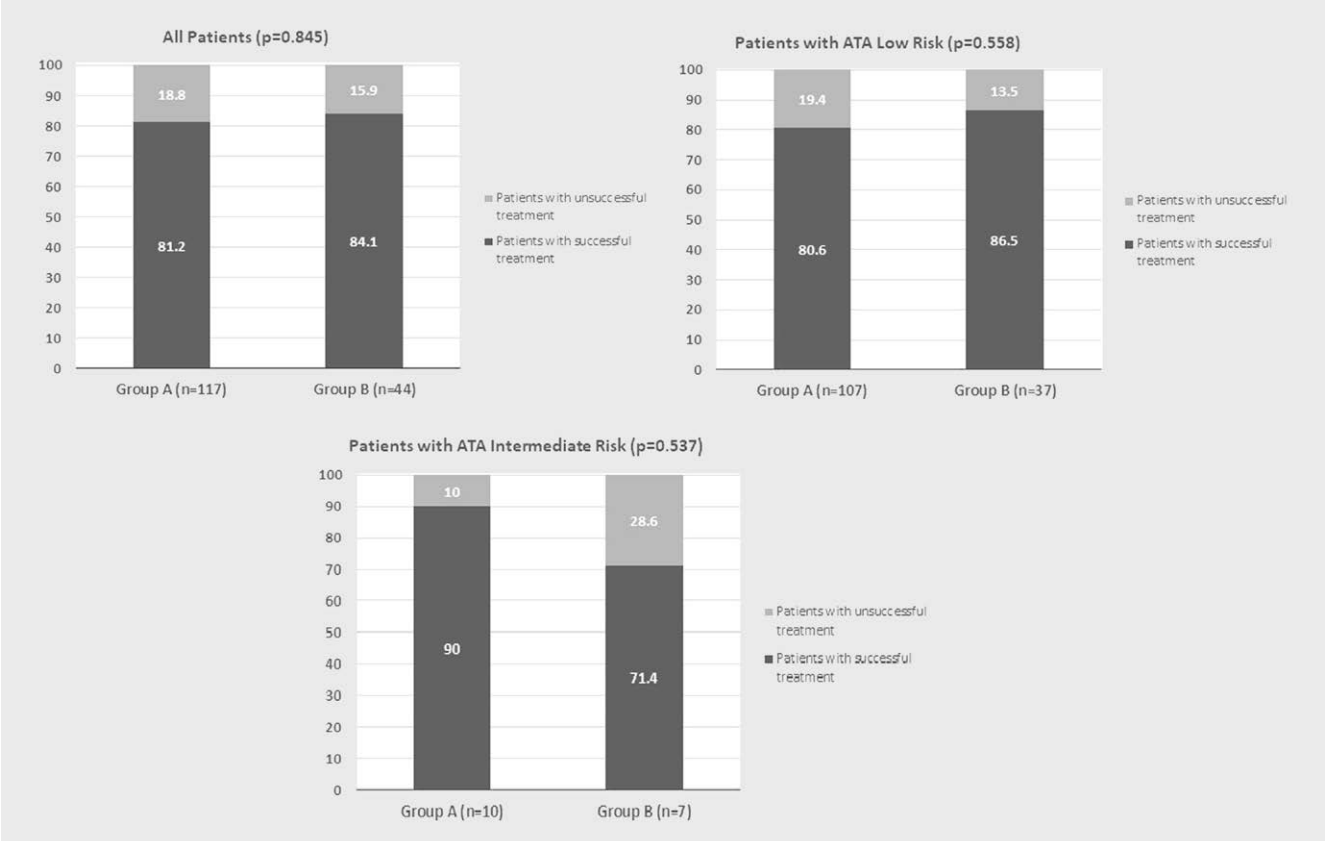
Results

A total of 161 patients with papillary subtype DTC were evaluated retrospectively. Most patients were females (82.6 %), and the mean age was 48.87 ± 11.50 years (min-max: 19–76). The mean follow-up period of the patients was 60.0 (46.0–73.0) months. Fifty patients (31.1 %) were diagnosed with papillary microcarcinoma, and 111 (68.9 %) had papillary carcinoma. Nineteen (11.8 %) patients had aggressive variant histopathological subtype (tall cell, insular, solid variant). Six of 161 patients underwent lobectomy first and followed by complementary thyroidectomy surgery. While central lymph node dissection was performed in 97 (60.24 %) patients, central and lateral lymph node dissection was performed in only two patients.

All patients received RAI treatment in the range of 1.85–5.55 GBq. When the patients were divided into two groups according to which month they received RAI treatment after surgery, most received RAI treatment in less than three months. One hundred seventeen patients (72.7 %) received RAI treatment in the first three months or less after TT, while others (29.3 %) received longer than three months. When patients who received RAI treatment in the first three months or less and those who received RAI treatment longer than three months were compared, only perineural invasion was found to be different among all parameters. Perineural invasion was detected in only eight patients; most (62.5 %) received RAI treatment in more than three months after TT ($p = 0.04$). Half of the eight patients had tall cell histopathological subtype, and these patients were in the intermediate risk group. All these patients received RAI treatment at 3.7 GBq dose and above; ablation success was 87.5 %. No other relationship was found between the time interval of receiving RAI treatment and any clinical-laboratory parameter with ablation treatment success. The graphs showing the success of treatment in low and intermediate risk groups and all patients according to the time interval of RAI treatment are given in ▶ **Fig. 1**.

In the whole-body planar scannings, taken after 7–10 days of RAI treatment, RAI uptake of the residual thyroid tissue on the thyroid lodge of all patients was observed. Uptake intensities could not be rated due to the image quality of the gamma camera.

Ablation success was observed in most of the patients (82 %) in the 9–12 month follow-ups after the RAI treatment. Ablation success was found to be significantly higher in T1 tumors compared to T2 and T3 ($p < 0.001$). Ablation success was found to be statistically significantly lower in patients with microscopic extrathyroidal spread, receiving low-dose RAI treatment, high stimulated Tg and Anti-Tg values in blood tests taken on the day of RAI treatment, and 9–12 month follow-ups, significant residual tissue on the thyroid scintigraphy image before the RAI treatment ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.013$, $p < 0.001$, respectively). Demographic-clinicopathological characteristics, TNM stage, risk classification according to ATA, and ablation success rates of all patients are summarized in ▶ **Table 1**.



▶ **Fig. 1** The relationship between time interval of TT and RAI treatment with the success of ablation RAI therapy in low (**b**) and intermediate (**c**) risk papillary thyroid cancer (**a**). Group A: patients receiving RAI therapy in the first three months or less after surgery, Group B: patients receiving RAI therapy in more than three months after surgery.

The effects of all clinical-laboratory-histopathological features and imaging modalities in predicting the success of RAI ablation were evaluated by multivariate logistic regression analysis. Patients with T2 and T3 tumors have a 7.610 and 24.022 times greater risk of failure of ablation therapy than T1 tumors ($p = 0.001$, $p < 0.001$, respectively). Patients who took of 1.85 GBq RAI dose have a 14.434 times greater risk of RAI ablation treatment failure than those with 5.55 GBq ($p = 0.017$). Patients with a stimulated Tg (before RAI treatment) value > 5.86 ng/ml have a 12.022 times greater risk of ablation failure than patients with ≤ 5.86 ng/mL ($p < 0.001$). We did not find any other significant factors in predicting the success of RAI ablation therapy. Multivariate logistic regression analysis is given in ▶ **Table 2**.

Discussion

The time interval between TT and RAI therapy may be longer, especially for patients requiring higher doses and additional imaging or reoperation. Since patients in low and intermediate-risk groups were included in our study, most of our patients received RAI therapy in the first three months after the surgery. The effect of this time interval on treatment success and surveillance is still unclear. In the literature [16], a retrospective study found that patients with DTC who received the first RAI treatment 180 days after TT had a 4.22 times higher risk of death than those who received the first RAI treatment within 180 days. Another study [17] found that this time interval did not affect the 6-month remission rates in patients with low-risk DTC. Our study evaluated the ablation success after the first RAI treatment in patients with low and intermediate-risk papillary thyroid cancer. We found that the time interval between TT and RAI treatment did not impact the ablation success. In our study, only the rate of perineural invasion was statistically significantly higher in patients who received RAI therapy more than three months after TT. The fact that half of these patients are in the intermediate-risk group may have caused a delay in additional tests. This result supports the data that this time interval is prolonged in high-risk patients or patients who need additional tests, scanning, or reoperation.

A study [17] determined that the time of RAI treatment given to ablate remnant tissue in low-risk differentiated thyroid cancer did not make a difference in the clinical course. Although we included both low and intermediate-risk groups in our study, the effect of this time interval on our remnant tissue ablation success was similar to the literature. In another study [13], ablation success was significantly higher in DTC patients who were given RAI treatment over three months after TT than those treated in three months or less. In our study, on the contrary, we did not detect the effect of the time interval on ablation success, although we took three months cut-off level as the time interval. This difference may be because we only included patients with papillary subtype DTC in our study. Again, the absence of T4 tumors according to the TNM stage in our study group and the fact that no patients received RAI treatment at a dose of more than 5.55 GBq may be the reasons for the different results with the literature [14, 17–20].

Diagnostic whole-body RAI screening is essential in predicting recurrence or persistent disease in the follow-up of DTC [21]. In a study [22], it was reported that additional metastatic focus was detected in 10–20 % of patients compared to pre-treatment, and the stage of the disease changed. In addition, the involvement rate in the residual thyroid tissue indicates the success of primary thyroid surgery. Our study detected significant RAI uptake in residual tissue on the thyroid lodge in all patients' post-treatment whole-body RAI scans. We did not classify RAI uptake rates in predicting treatment success because our gamma camera could not rate uptake intensities due to image quality. But we concluded that pre-treatment stimulated Tg values of the patients were determinant in predicting treatment success. Tg values are proportional to the amount of residual tissue, and according to the results of our study, high Tg values (> 5.86 ng/ml) will negatively affect the ablation success. This result we found was compatible with the current literature [23]. The fact that ablation success was significantly lower at high stimulated Tg values before treatment supports the result we found in our study. In the literature, they reported that the stimulated Tg cut-off value before RAI was nine ng/mL in predicting the success of ablation therapy. We found this value as 5.86 ng/ml. This difference may be because we included patients with low and intermediate-risk papillary thyroid cancer in our study. In contrast, Abe et al. [23] included intermediate and high-risk patients in their study. This may be why we found the cut-off Tg value to be low.

In our study, according to the thyroid scintigraphy taken before RAI treatment, it was observed that the success of ablation therapy given at high doses (> 1.85 GBq) was low in patients with significant residues in the thyroid lodge. Therefore, treatment failure should be considered when administering low ablation doses to patients with significant residual tissue. Each patient should be evaluated individually regarding the need for follow-up without RAI treatment or a relatively high dose before giving RAI treatment. We know that the recurrence rate is very low in DTCs in low and intermediate-risk groups. A recent study in the literature [24] stated that the ablation dose did not affect the success of treatment in patients with DTC in low and intermediate-risk groups. However, our study found the ablation success of low RAI treatment dose to be low. We know that the residual tissue volume after the surgery and the iodine-restricted diet adherence to the patients before the RAI treatment and the duration of the diet affect the ablation success. This difference, which we have seen in the literature, may be due to these factors or may be due to the primary tumor characteristics of the patient. Dong et al. [24] did not include T3 tumors and aggressive variant histopathological subtypes in their studies. Our study included T3 tumors and aggressive variant papillary thyroid cancers, although their patient group was small. Again, in recent literature, it was found that low and high-dose RAI treatment did not affect ablation success in patients with intermediate and high-risk groups. Unlike ours, this study did not include low-risk patients but instead included high-risk patients [25]. In another similar study [26], it was reported that the RAI treatment dose applied affected the ablation success. In the study, the patients who received 1.1 GBq RAI treatment in the patient group who received 3.7 GBq RAI treatment were compared, and the treatment success was found to be significantly higher in patients who received high ablation dose. Our study found that the ablation success of the patients who received 1.85 GBq RAI treatment was significantly lower than those who received 3.7 and 5.55 GBq. Our result is compatible with the literature. As a result, we should emphasize that

▶ **Table 1** Characteristics of patients.

	All patients (n = 161, 100 %)	Patients with successful treatment (n = 132, 82 %)	Patients with unsuccessful treatment (n = 29, 18 %)	p
Age ± means (years)	48.87 ± 11.50	48.95 ± 11.82	48.48 ± 10.08	0.842
Sex				0.805
Female	133 (82.6)	110 (83.3)	23 (79.3)	
Male	28 (17.4)	22 (16.7)	6 (20.7)	
TNM (AJCC 8)				
T1	104 (64.6)	104 (78.8)	0 (0)	**< 0.001**
T2	45 (28)	24 (18.2)	21 (72.4)	
T3	12 (7.4)	4 (3)	8 (27.6)	
N0	147 (91.3)	122 (92.4)	25 (86.2)	0.177
N1	14 (8.7)	10 (7.6)	4 (13.8)	
Aggressive histopathological subtype				1.000
(+)	19 (11.8)	16 (12.1)	3 (10.3)	
(–)	142 (88.2)	116 (87.9)	26 (89.7)	
Lymphatic invasion				1,000
(+)	20 (12.4)	17 (12.9)	3 (10,3)	
(–)	141 (87.6)	115 (87.1)	26 (89.7)	
Parenchyma invasion				0.821
(+)	33 (20,5)	28 (21,2)	5 (17.2)	
(–)	128 (79.5)	104 (78.8)	24 (82.8)	
Vascular invasion				1.000
(+)	13 (8.1)	11 (8.3)	2 (6.9)	
(–)	148 (91.9)	121 (91.7)	27 (93.1)	
Perineural invasion				1.000
(+)	8 (5)	7 (5.3)	1 (3.4)	
(–)	153 (95)	125 (94.7)	28 (96.6)	
Surgical margin positivity				0.395
(+)	29 (18.1)	26 (19.7)	3 (10.7)	
(–)	131 (81.9)	106 (80.3)	25 (89.3)	
Extrathyroidal spread (microscopic)				**< 0.001**
(+)	7 (4.3)	0 (0)	7 (24.1)	
(–)	154 (95.7)	132 (100)	22 (75.9)	
Multicentric tumor				0.726
(+)	118 (73.3)	98 (74.2)	20 (69)	
(–)	43 (26.7)	34 (25.8)	9 (31)	
ATA Risk classification				1.000
Low Risk	144 (89.4)	118 (89.4)	26 (89.7)	
Intermediate Risk	17 (10.6)	14 (10.6)	3 (10.3)	
RAI Dose (mci/GBq)				**< 0.001**
50/1.85	17 (10.6)	6 (4.5)	11 (37.9)	
100/3.7	119 (73.9)	104 (78.8)	15 (51.8)	
150/5.55	25 (15.5)	22 (16.7)	3 (10.3)	
Follow Up (months)	60 (46–73)	60 (43.3–73)	64 (52.5–77)	0.172
Time interval				0.845
≤ 3 months	117 (72.7)	95 (72)	22 (75.9)	
> 3 months	44 (27.3)	37 (28)	7 (24.1)	
Time interval (months)	2 (2–4)	2 (2–4)	2 (2–3)	0.593

▶ **Table 1** Continued

	All patients (n = 161, 100 %)	Patients with successful treatment (n = 132, 82 %)	Patients with unsuccessful treatment (n = 29, 18 %)	p
Stimulate Tg value (before RAI ablation) (ng/ml)	2.2 (0.4–6.4)	1.3 (0.3–3.3)	9.4 (7.8–12.1)	**<0.001**
Stimulated Tg Value at 1st Year Screening (ng/ml)				**<0.001**
<1	126 (78.3)	126 (95.5)	0 (0)	
≥1	35 (21.7)	6 (4.5)	29 (100)	
Anti-Tg (before RAI ablation) (IU/ml)	2.6 (1.2–12.1)	2.2 (1.1–5.5)	12.2 (1.8–24.6)	**0.013**
Residual tissue on scintigraphy				**<0.001**
(+)	94 (58.4)	66 (50)	28 (96.6)	
(–)	67 (41.6)	66 (50)	1 (3.4)	

* TNM: Tumor-Node-Metastases; AJCC: The American Joint Committee on Cancer; ATA: American Thyroid Association; RAI: Radioactive iodine; mCi: Millicurie; GBq: Gigabecquerel; Tg: Thyroglobulin.

▶ **Table 2** Multivariate logistic regression analysis.

Patient Characteristics	Multivariate Analysis OR (95 % CI)	p
TNM (AJCC 8)		
T1	1	
T2	7.610 (2.471–23.438)	**0.001**
T3	24.022 (3.918–67.303)	**<0.001**
RAI Dose (mci/GBq)		
50/1.85	1	
100/3.7	4.486 (0.979–20.552)	0.053
150/5.55	14.434 (2.608–49.585)	**0.017**
Stimulated Tg (ng/ml) (before RAI ablation)		
≤5.86	1	
>5.86	12.022 (3.959–36.505)	**<0.001**

* TNM: Tumor-Node-Metastases; AJCC: The American Joint Committee on Cancer; RAI: Radioactive iodine; mCi: Millicurie; GBq: Gigabecquerel; Tg: Thyroglobulin; OR: Odss Ratio; CI: Confidence interval.

many factors may affect ablation success, and these factors should be reviewed and compared to similar studies.

As for the limitations of our study, an important limitation is that we could not evaluate the volume of residual thyroid tissue by ultrasonography and its effect on treatment success due to the retrospective design. Another limiting factor is that we could not group the RAI uptake by the intensity of the post-treatment whole-body imaging due to the acquisition quality of the gamma camera. Therefore, we could not evaluate the effect on the success of the ablation treatment according to the intensity of RAI uptake on the thyroid lodge after the RAI treatment. One of the crucial limitations that reduced the number of our patients is the exclusion of these patients because most of the low-risk patients did not undergo diagnostic RAI screening after the 9–12 months of RAI treatment.

Conclusion

In conclusion, we can say that the timing of RAI treatment after TT does not affect ablation success in low and intermediate-risk papillary thyroid cancer. Primarily, whether RAI treatment is indicated in patients should be evaluated by considering the recommendations of current guidelines. More important than the application time of the RAI treatment to be given for ablation is to decide which dose to give. The success of low-dose RAI therapy in ablating the remnant tissue may be low in large tumors and patients with high stimulated Tg values that give essential information about the postoperative residual tissue before the treatment. How many doses should we give to which patients? Or which patients should we give RAI treatment to? These questions still need to be clarified. Therefore, considering the long survival times of DTC, there is a need for well-designed studies that require long-term follow-up.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] James DL, Ryan ÉJ, Davey MG et al. Radioiodine remnant ablation for differentiated thyroid cancer: a systematic review and meta-analysis. JAMA Otolaryngol Head Neck Surg 2021; 147: 544–552

[2] Harris PE The management of thyroid cancer in adults: a review of new guidelines. Clin Med 2002; 2: 144–146

[3] Haymart M, Banerjee M, Stewart AK et al. Use of radioactive iodine for thyroid cancer. JAMA 2011; 306: 721–728

[4] Segal K, Shpitzer T, Hazan A et al. Invasive well differentiated thyroid carcinoma: effect of treatment modalities on outcome. Otolaryngol Head Neck Surg 2006; 134: 819–822

[5] Siegel R, Ma J, Zou Z et al. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9–29

[6] Rosario PW, Ward LS, Carvalho GA et al. Thyroid nodules and differentiated thyroid cancer: update on the Brazilian consensus. Arq Bras Endocrinol Metabol 2013; 57: 240–264

[7] Cooper DS, Doherty GM, Haugen BR et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009; 19: 1167–1214

[8] Haugen BR, Alexander EK, Bible KC et al. American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and ifferentiated thyroid cancer. Thyroid 2015; 2016: 1–133

[9] Pacini F, Schlumberger M, Dralle H et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006; 154: 787–803

[10] Tuttle RM, Ahuja S, Avram AM et al. Controversies, consensus, and collaboration in the Use of 131I therapy in diferentiated thyroid cancer: a joint statement from the American thyroid association, the European association of nuclear medicine, the society of nuclear medicine and molecular imaging, and the European thyroid association. Thyroid 2019; 29: 461–470

[11] Hackshaw A, Harmer C, Mallick U et al. 131I activity for remnant ablation in patients with differentiated thyroid cancer: a systematic review. J Clin Endocrinol Metab 2007; 92: 28–38

[12] Albano D, Bonacina M, Durmo R et al. Efficacy of low radioiodine activity versus intermediate-high activity in the ablation of low-risk differentiated thyroid cancer. Endocrine 2020; 68: 124–131

[13] Özdoğan Ö, Aksu A, Doğan E et al. Applying postoperative radioiodine therapy before 3 months seems to decrease ablation success in patients with differentiated thyroid carcinoma. Ann Nucl Med 2021; 35: 223–231

[14] Li H, ZhangY-Q WC, Zhang X et al. Delayed initial radioiodine therapy related to incomplete response in low- to intermediate-risk diferentiated thyroid carcinoma. Clin Endocrinol 2018; 88: 601–606

[15] Lamartina L, Cooper DS Radioiodine remnant ablation in low-risk differentiated thyroid cancer: the “con” point of view. Endocrine 2015; 50: 67–71

[16] Higashi T, Nishii R, Yamada S et al. Delayed initial radioactive iodine therapy resulted in poor survival in patients with metastatic differentiated thyroid carcinoma: a retrospective statistical analysis of 198 cases. J Nucl Med 2011; 52: 683–689

[17] Tsirona S, Vlassopoulou V, Tzanela M et al. Impact of early vs late postoperative radioiodine remnant ablation on final outcome in patients with low-risk well-differentiated thyroid cancer. Clin Endocrinol 2011; 80: 459–463

[18] Krajewska J, Jarzab M, Kukulska A et al. Postoperative radioiodine treatment within 9 months from diagnosis significantly reduces the risk of relapse in low-risk differentiated thyroid carcinoma. Nucl Med Mol Imaging 2019; 53: 320–327

[19] Scheffel RS, Zanella AB, Dora JM et al. Timing of radioactive iodine administration does not influence outcomes in patients with differentiated thyroid carcinoma. Thyroid 2016; 26: 1623–1629

[20] Suman P, Wang CH, Moo-Young TA et al. Timing of adjuvant radioactive iodine therapy does not affect overall survival in low-and intermediate-risk papillary thyroid carcinoma. Am Surg 2016; 82: 807–814

[21] Schneider DF, Ojomo KA, Chen H et al. Remnant uptake as a postoperative oncologic quality indicator. Thyroid 2013; 23: 1269–1276

[22] Araz M, Küçük NÖ Should the place of radioactive iodine whole body scintigraphy in follow-up of ifferentiated thyroid cancer reevaluated in the era of SPECT/CT? Nucl Med Semin 2021; 7: 70–79

[23] Abe K, Ishizaki U, Ono T et al. Low-dose radioiodine therapy for patients with intermediate- to high-risk differentiated thyroid cancer. Ann Nucl Med 2020; 34: 144–151

[24] Dong P, Wang L, Qu Y et al. Low- and high-dose radioiodine ablation for low-/intermediate-risk differentiated thyroid cancer in China: Large randomized clinical trial. Head Neck 2021; 43: 1311–1320

[25] Iizuka Y, Katagiri T, Ogura K et al. Comparison between the different doses of radioactive iodine ablation prescribed in patients with intermediate-to-high-risk differentiated thyroid cancer. Ann Nucl Med 2019; 33: 495–501

[26] Mallick U, Harmer C, Yap B et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. N Engl J Med 2012; 366: 1674–1685