Scientific Research Publishing

Journal of Biosciences and Medicines, 2023, 11, 103-113
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Effect of Hashimoto's Thyroiditis on Efficacy of ^{131}I Ablation Therapy in Intermediate- and High-Risk of Thyroid Papillary Carcinoma

Lu Zhou, Gang Cheng*

Department of Nuclear Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
Email: zl06015223@163.com, *chg05@163.com

How to cite this paper: Zhou, L. and Cheng, G. (2023) Effect of Hashimoto's Thyroiditis on Efficacy of ^{131}I Ablation Therapy in Intermediate- and High-Risk of Thyroid Papillary Carcinoma. *Journal of Biosciences and Medicines*, **11**, 103-113.
https://doi.org/10.4236/jbm.2023.114008

Received: March 14, 2023
Accepted: April 11, 2023
Published: April 14, 2023

Abstract

Objective: The purpose of this study was to investigate the effect of Hashimoto's thyroiditis on efficacy of ^{131}I ablation in intermediate- and high-risk of thyroid papillary carcinoma patients. The findings will help to develop a personalized treatment plan for patients with thyroid papillary carcinoma complicated with Hashimoto's thyroiditis. **Material and Methods:** From January 2016 to December 2020, patients who were diagnosed with intermediate- and high-risk PTC with lymph node metastasis were analyzed retrospectively, excluding patients with incomplete clinical data, distant metastasis, positive TGAb, TSH < 30 mIU/L. The baseline data of sex, age, and biochemical information were collected before admission. All patients included had radioactive iodine (RAI) with 3.70 GBq. The treatment response of patients was evaluated 6 - 8 months after discharge. By means of univariate and multivariate analysis, including excellent response (ER) and non-excellent response (NER) groups of clinical data, we assessed the impact of ^{131}I on patients outcome. **Results:** A total of 525 patients (166 males and 359 females) were included in the study, including 368 patients in ER group (70.1%) and 157 patients in NER group (29.9%). Eleven factors including combining Hashimoto's thyroiditis, pre-ablative Tg levels, sex, tumor diameter, extraglandular invasion, multifocal, bilateral lesions, central lymph node metastasis, lateral lymph node metastasis, lymph node metastasis rate, thyroglobulin were statistically different between ER group and NER group with significance at $P < 0.05$. Further multivariate analysis showed that Hashimoto's thyroiditis, Ps-Tg levels and lateral lymph node metastasis could be used as independent factors. And patients with HT had significantly superior outcomes compared with patients without HT. **Conclusion:** Hashimoto's thyroiditis, Ps-Tg level and lateral lymph node metastasis are potential predictors for short-term efficacy of ^{131}I treatment in intermediate- and high-risk thyroid papillary carcinoma. Ha-

shimoto's thyroiditis, high Ps-Tg level and increased number of lateral lymph node metastasis reduce the efficacy of ^{131}I therapy in patients with intermediate and high risk thyroid papillary carcinoma.

Keywords

Papillary Thyroid Carcinoma, Hashimoto's Thyroiditis, ^{131}I Therapy, Curative Effect

1. Introduction

Thyroid carcinoma (TC) accounts for less than 1% of all malignant tumors and 0.5% - 10% of thyroid nodules develop to thyroid carcinoma. Previous findings indicate that in countries high iodine intake 80% of thyroid cancer cases comprise well-differentiated thyroid cancer, of which 60% are papillary thyroid cancers (PTC), and about 70% of the tumor cases are detected in clinical [1] [2] [3] [4] [5]. Hashimoto's thyroiditis (HT) is the most common inflammatory disease of the thyroid. HT is the leading cause of hypothyroidism in countries with high iodine intake. The thyroid gland grows larger in HT subjects; then it gradually shrinks and progresses to hypothyroidism. Previous findings show that the peak age of HT onset is between 30 and 50 years old, and the ratio of incidence in male to female is 8 - 9:1 [6]. HT is a chronic inflammatory disease but its effect on the occurrence or progression of thyroid cancer, especially the effect on the therapeutic effect of ^{131}I therapy in PTC patients, has not been fully elucidated.

The recurrence rate and risk of death in most differentiated thyroid carcinomas, especially papillary thyroid carcinomas, are significantly reduced with a 5-year survival rate more than 95% after thyroidectomy, radioactive iodine and TSH inhibition [7] [8]. Previous studies report that age, surgical resection method, tumor pathological characteristics, thyroglobulin and recurrence risk stratification affect the therapeutic effect of ^{131}I therapy [7] [8] [9]. Low-dose ^{131}I treatment is less expensive and is associated with fewer side effects compared with high-dose ^{131}I treatment [10] [11] [12]. Therefore, it is imperative to administer effective treatment to patients with poor response, and avoid higher doses in people with good response to ^{131}I treatment. Therefore, the purpose of this study was to explore the effect of HT on efficacy of ^{131}I therapy in PTC patients.

2. Data and Methods

2.1. Clinical Data

Patient data extracted from the clinical electronic medical record system were de-identified so that all private information of patients was not included. The Institutional Review Board of the First Hospital, Chongqing Medical University approved the use of medical records and allowed us to obtain written consent from each patient (2022-K248). All procedures complied with the Declaration of

Helsinki for research involving human subjects. All the patients signed informed consent before RAI.

From January 2016 to December 2020, a total of 525 patients treated with ^{131}I for the first time after total thyroidectomy surgery and neck lymph node dissection were retrospectively reviewed. The inclusion criteria were as follows: 1) subjects with postoperative pathology confirmed PTC, and the risk stratification was intermediate- and high-risk patients; 2) patients with complete clinicopathological data; 3) subjects who had undergone total thyroidectomy plus central and/or lateral lymph node dissection; 4) level of thyroid stimulating hormone (TSH) ≥ 30 ulU/ml. 5) serum level of anti-thyroglobulin antibody (TgAb) below 115 IU/ml to alleviate the effect on the results of thyroglobulin. The pathological evaluation was performed by the same group of pathologists. Data on the tumor size (if the tumor was multifocal, the maximum diameter of the largest nodule was recorded), multifocal (yes/no), central lymph node metastasis (yes/no), lateral lymph node metastasis (yes/no), thyroid extracapsular invasion (yes/no) and BRAF600E mutation (yes/no) were recorded. The patients were grouped into stages I, II and III according to the TNM staging guidelines for differentiated and undifferentiated thyroid carcinoma recommended by the American Joint Commission on Cancer.

2.2. Treatment Methods

All patients were required to eat a low-iodine diet for 4 weeks, stop taking levothyroxine tablets for 3 weeks, and were not supposed to undergo enhanced CT and other examinations before receiving ^{131}I treatment. The acclimatization period was extended for 2 weeks if the TSH level was still less than 30 mIU/L. Routine examinations and evaluation of related items were performed, including stimulated thyroglobulin (Ps-Tg), TgAb, TSH, abdominal and neck ultrasound, cervicothoracic computed tomography CT, thyroid iodine uptake rate, thyroid static imaging, renal GFR imaging and salivary gland imaging, were performed before iodine treatment. Physicians gave the patients iodine doses according to the recurrence risk stratification, Ps-Tg levels and clinicopathological factors. Whole-body post-treatment scans (Rx-^{131}I-WBS) were performed 72 hours after iodine administration. Patients were monitored for serological indicators (Ps-Tg, TgAb, TSH, etc.), and neck ultrasonography, and whole body diagnostic ^{131}I imaging (Dx-^{131}I-WBS) were performed during 6 - 8 months after discharge.

2.3. Evaluation Criteria and Grouping

The outcomes were classified as excellent response(ER) and non-excellent response (NER) after 6 months according to the imaging results obtained at 6 months and the stimulation/inhibition Tg levels, Dx-WBS examination, neck ultrasonography and other imaging examinations performed during the follow-up period as recommended in the 2015 edition of ATA guidelines. Imaging examination with no clear lesions, inhibitory Tg < 0.2 ng/L or irritant Tg < 1.0 ng/L

represented excellent response, whereas other all other outcomes were classified as NER. Three nuclear medicine physicians independently evaluated the results of the follow-up tests after treatment and reached an agreement through discussion in the event of discrepancies.

2.4. Statistical Methods

Data obtained in this study were statistically analyzed using SPSS25.0 software. Continuous numerical variables were presented as means ± standard deviation or median and quartile, and categorical variables were presented as frequency (percentage). T test, Chi-square test and rank sum test were performed to compare the differences between two groups of patients. Logistic regression analysis was performed for multivariate analysis. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Comparison of Clinical Features of Thyroid Cancer Patients between the Two Groups

A total of 525 patients were enrolled in the study. The average age of patients was 39.87 years old. The proportion of patients under 55 years old was relatively higher than patients above 55 years. The ratio of male to female was 1:2.2. Most of the primary lesions in the subjects were single, unilateral and microcarcinoma, and only a few lesions invaded the capsule. In this study, 367 cases of thyroid papillary carcinoma without Hashimoto thyroiditis (HT) and 158 cases of thyroid papillary carcinoma with HT were confirmed by postoperative pathological diagnosis. The results showed that the curative effect of the first ^{131}I therapy was ER in 368 cases. There was no significant difference in sex, age, tumor diameter, lymph node metastasis and ^{131}I therapy of subjects in the two outcome groups ($P > 0.05$) (Table 1).

3.2. Factors Affecting the Efficacy of ^{131}I Therapy in Patients with Thyroid Cancer

Univariate analysis showed that extraglandular invasion, multifocal, bilateral lesions, central lymph node metastasis, lateral lymph node metastasis, lymph node metastasis rate, Ps-Tg and HT affected the efficacy of PTC^{131}I therapy. Multivariate analysis showed that the number of lateral lymph node metastasis, Ps-Tg and HT were independent factors that affected the efficacy of PTC^{131}I therapy (Table 2).

3.3. Comparison of the Efficacy of ^{131}I Therapy in Patients with and without Hashimoto's Thyroiditis

The results showed that the proportion of ER outcomes based on ^{131}I therapy effect of the Non-HT group was significantly higher than that of the HT group (Table 3, Figure 1).

Table 1. Clinicopathological characteristics of patients with papillary thyroid cancer in the ER group and the NER group.

Category	ER group (n = 368)	NER group (n = 157)	*P*
Gender			0.98
Male	117 (31.8%)	49 (31.2%)	
Female	251 (68.2%)	108 (68.8%)	
Age	51 (13.9%)		0.69
<55	317 (86.1%)	138 (87.9%)	
≥55	51 (13.9%)	19 (12.1%)	
Tumor size (cm)	1.06 ± 0.51	1.12 ± 0.59	0.09
Extragrandular invasion			0.07
Yes	75 (20.4%)	44 (28%)	
No	293 (79.6%)	113 (72%)	
Multifocality			0.76
Yes	143 (38.9%)	64 (40.8%)	
No	225 (61.1%)	93 (59.2%)	
Minuteness			0.72
Yes	101 (27.4%)	40 (25.5%)	
No	267 (72.6%)	117 (74.5%)	
Bilateral lesions			0.69
Yes	109 (29.6%)	50 (31.8%)	
No	259 (70.4%)	107 (68.2%)	
HT			0.64
Yes	108 (29.3%)	49 (31.8%)	
No	260 (70.7%)	108 (68.2%)	
$BRAFV^{600E}$ mutation			0.10
Yes	197 (53.5%)	97 (61.8%)	
No	171 (46.5%)	60 (38.2%)	
Number of central lymph node metastases	5.58 ± 4.51	5.29 ± 3.81	0.74
Number of lateral lymph node metastases	2.53 ± 3.29	2.92 ± 3.59	0.13
Total lymph nodes resected	26.47 ± 18.09	27.9 ± 17.59	0.30
Lymph node ratio metastasis	0.35 ± 0.22	0.36 ± 0.24	0.98
Ps-Tg	13.81 ± 53.33	15 ± 55.51	0.22
TPOAb	22.89 ± 82.5	27.73 ± 82.59	0.16
TgAb	16.02 ± 78.32	36.45 ± 218.54	0.27

Table 2. Logistic regression analysis of factors that affect ^{131}I treatment efficacy in patients with thyroid cancer in the training group (n = 525).

Factors	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	P	OR (95% CI)	*P*
Gender	1.518 (1.019 - 2.261)	0.06		
Age	1.278 (0.745 - 2.191)	0.27		
Tumor size	0.803 (0.572 - 1.126)	0.09		
Extragrandular invasion	1.601 (1.037 - 2.473)	0.02*	1.448 (0.801 - 2.619)	0.17
Multifocality	0.623 (0.424 - 0.914)	0.02*	0.913 (0.377 - 2.212)	0.14
Microcarcinoma	0.999 (0.651 - 1.533)	0.76		
Bilateral lesions	1.664 (1.114 - 2.485)	0.03*	1.636 (0.648 - 4.126)	0.57
HT	1.286 (0.172 - 0.475)	<0.0001*	0.488 (0.255 - 0.934)	0.04*
BRAFV^{600E} mutation	0.727 (0.496 - 0.1064)	0.1		
Central lymph node metastasis	0.939 (0.900 - 0.980)	0.05*	0.982 (0.922 - 1.045)	0.7
Lateral lymph node metastasis	0.863 (0.816 - 0.913)	0.0001*	0.887 (0.817 - 0.963)	0.04*
Total nodes resected	0.997 (0.987 - 1.008)	0.65		
Lymph node ratio	0.978 (0.970 - 0.986)	0.0003*	0.988 (0.977 - 0.999)	0.08
Ps-Tg	0.838 (0.803 - 0.876)	<0.0001*	0.857 (0.820 - 0.896)	<0.0001*
TPOAb	1.004 (1.000 - 1.009)	0.34		
TgAb	1.005 (0.999 - 1.010)	0.41		

Note: HT represents Hashimoto's thyroiditis; * indicates a statistically significant difference.

Table 3. Comparison of the efficacy of ^{131}I nail clearance in patients with thyroid cancer grouped according to Hashimoto's thyroiditis.

	HT Group	Non-HT Group	*P*
ER	134	234	<0.0001*
NER	23	134	<0.0001*

Note: HT Group represents PTC with Hashimoto's thyroiditis group; Non-HT Group represents without Hashimoto's thyroiditis group; * indicates a statistically significant difference.

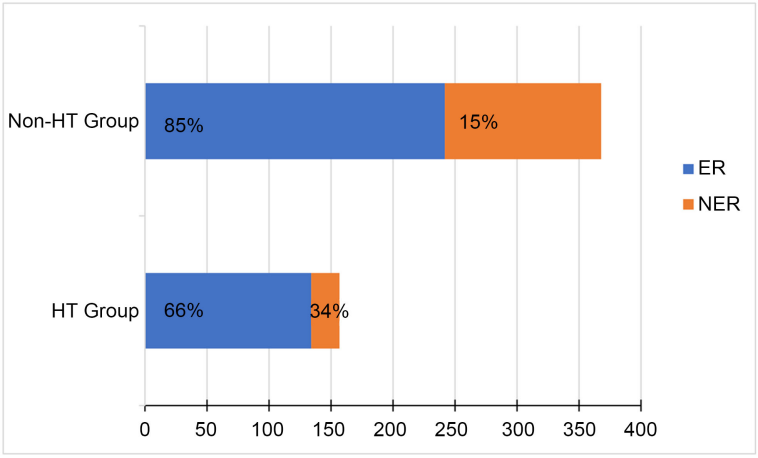

Figure 1. A histogram showing the distribution of ^{131}I treatment efficacy between the HT Group and Non-HT Group.

4. Discussion

The relationship between Hashimoto's thyroiditis and thyroid papillary carcinoma has been extensively studied. A significant increase in the incidence of co-existence of these two diseases had been reported in the past 20 years, and the two conditions was reported to be between 10% and 58% [13] [14]. In the present study, the incidence of PTC cases presenting with HT was 30.1%. PTC ^{131}I treatment after total thyroidectomy results in good prognosis of patients. The results in this study shows that 70.1% of patients with papillary thyroid cancer in the achieved ER status. Previous findings indicated that 63.2% - 70% of PTC patients who had received ^{131}I treatment for the first time achieved ER status, which is a relatively consistent with the present finding [15] [16] [17]. The male to female ratio of patients included in this study is 1:2.2, indicating that papillary thyroid carcinoma has higher incidence in female subjects, but male have a higher risk for thyroid cancer recurrence. Previous results showed that age is an independent risk factor affecting the postoperative staging of differentiated thyroid cancer, with higher the age associated with worse prognosis of thyroid cancer patients [18]. In this study, gender and age were not associated with the therapeutic effect of radioactive iodine, which was consistent with the results from previous studies [19] [20] [21].

Xu *et al.* [13] reported that tumor diameter, regional lymph node metastasis status, and extrathyroid invasion were correlated with the prognosis of thyroid cancer. Pathological characteristics of tumors are associated with efficacy of ^{131}I treatment. The present findings indicated that multi-focal, capsule invasion, maximum tumor diameter and tumor location did not affect the efficacy of intermediate-high risk papillary carcinoma. Grani *et al.* [22] reported similar results after exploring the efficacy of radioiodine therapy administered to intermediate-low risk papillary carcinoma. These findings indicate that the pathological features of all risk stratification PTC may not affect the efficacy of ^{131}I treatment. Lymph node is the most common site of a cancer metastasis, and the main types include central lymph node and lateral lymph node metastasis. The number of lymph node metastases, the total number of lymph nodes cleared, and the ratio of metastatic lymph nodes were included in the multivariate analysis in this study. The results showed that the number of lateral lymph node metastases was an independent risk factor for predicting treatment response, which was different from findings reported in previous studies [23]. This observation indicates that iodine dose should be increased in patients with lateral lymph node metastasis to increase the efficacy of RAI treatment and reduce the recurrence rate among this group.

Hashimoto's thyroiditis (HT) is the most common autoimmune disease reported in humans HT is associated with high risk of occurrence and poor prognosis of thyroid papillary carcinoma patients [13]. Previous findings showed that HT could reduce the efficacy of ablation with low dose radioactive iodine [24]. In this study, a multivariate analysis of HT is carried out and the results showed that HT was an independent risk factor for the therapeutic effect of ^{131}I for PTC.

The expression level of sodium iodine transporters (NIS) in the basement membrane of thyroid follicular epithelial cells with HT is lower compared with normal thyroid tissue, which may affect the uptake of ^{131}I by residual thyroid tissue [25]. BRAFV^{600E} mutation is an indicator of intermediate recurrence risk, which leads to decreased expression of sodium iodine transporter (NIS) and promotes downregulation of genes and proteins involved in iodide metabolism [26]. The mutation rates of BRAFV^{600E} were 56%. The results of this study showed that mutation of the gene had no significant effect on the efficacy of radioactive iodine therapy in PTC patients. The sample size was not large enough and the data in this study was from a single center so studies with a higher number of patients should be conducted and data from multiple centers should be used to verify the present findings.

Thyroglobulin (Tg) is produced by thyroid tissue and is proportional to the volume of thyroid [25]. Tg has a biological half-life of 65 hours. Tg is undetectable 4 - 6 weeks after total thyroidectomy in the absence of levothyroxine supplement and without metastasis [27] [28] [29] [30]. This implies that the concentration of Tg in serum can be used to estimate the volume of residual thyroid gland and predict the efficacy of radioactive iodine ablation. A higher level of Ps-Tg is associated with poor therapeutic effect of radioactive iodine therapy. High level of Ps-Tg is also correlated with poor prognosis of patients and a higher risk of recurrence. Liu *et al.* reported that Ps-Tg (cutoff value 9.05 ng/mL) can be used as an independent factor to predict satisfactory efficacy (ER) of radioactive iodine therapy. Previous findings showed that Ps-Tg < 9.05 ng/mL was associated with ER in 87.5% of patients. These findings indicate that Ps-Tg combined with tumor size is an effective marker to predict the response to the first ^{131}I treatment. The results on the levels of Ps-Tg in the present study were consistent with previous finding. However, the cutoff value of Ps-Tg in our study was 3.75 ng/mL. The difference in cutoff value is observed mainly because intermediate-high risk thyroid cancer is explored in the present study, whereas the study by Liu *et al.* comprised patients at three risk levels. Moreover, the follow-up time in this study was shorter, 6 - 8 months compared with the 5 - 10 years follow-up time reported in the study by Liu *et al.* The ATA guidelines indicate that the optimal Tg cutoff value for predicting ^{131}I treatment response has not been determined, and more experiments should be conducted to evaluate the effective cut off value. A previous study reported 3.2 ng/mL as the critical value for Ps-Tg among intermediate-risk patients, which was effective in predicting the progression-free survival of patients. The dose of radioactive iodine should be increased when the biochemical level is high. The level of Ps-Tg can be used as a guiding factor for increasing the dose of radioactive iodine in patients with PTC [30]. Studies should be conducted to explore the optimal dose of radioactive iodine for ^{131}I therapy.

5. Conclusion

Our data suggest that coexisting Hashimoto's thyroiditis, Ps-Tg and lateral

lymph node metastasis are independent risk factors for poor clinical prognosis for patients with moderate and high-risk thyroid papillary carcinoma after ^{131}I treatment. The efficacy of ^{131}I treatment significantly decreases when papillary thyroid carcinoma is complicated with Hashimoto's thyroiditis. Similarly, the efficacy of ^{131}I therapy decreases significantly with the increase of the number of lateral lymph nodes and the increase of Ps-Tg level.

Funding/Support

There is no fund support for this study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Pacini, F., Chiofalo, F. and De Groot, L.J. (2016) Chapter 92: Thyroid Neoplasia. In: Jameson, J.L., *et al.*, Eds., *Endocrinology*: *Adult and Pediatric*, Seventh Edition, Elsevier B.V., Amsterdam, 1601-1628. https://doi.org/10.1016/B978-0-323-18907-1.00092-5

[2] Haugen, B.R., Alexander, E.K., Bible, K.C., *et al.* (2016) 2015 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 Differentiated Thyroid Cancer. *Thyroid*, **26**, 1-133. https://doi.org/10.1089/thy.2015.0020

[3] Gupta, S., Harper, A., Ruan, Y., *et al.* (2020) International Trends in the Incidence of Cancer among Adolescents and Young Adults. *JNCI*: *Journal of the National Cancer Institute*, **112**, 1105-1117. https://doi.org/10.1093/jnci/djaa007

[4] Bray, F., Ferlay, J., Soerjomataram, I., *et al.* (2018) Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **68**, 394-424. https://doi.org/10.3322/caac.21492

[5] Li, M., Dal Maso, L. and Vaccarella, S. (2020) Global Trends in Thyroid Cancer Incidence and the Impact of Overdiagnosis. *The Lancet Diabetes & Endocrinology*, **8**, 468-470. https://doi.org/10.1016/S2213-8587(20)30115-7

[6] Repplinger, D., Bargren, A., Zhang, Y.W., *et al.* (2008) Is Hashimoto's Thyroiditis a Risk Factor for Papillary Thyroid Cancer? *Journal of Surgical Research*, **150**, 49-52. https://doi.org/10.1016/j.jss.2007.09.020

[7] Ciarallo, A. and Rivera, J. (2020) Radioactive Iodine Therapy in Differentiated Thyroid Cancer: 2020 Update. *AJR*: *American Journal of Roentgenology*, **215**, 285-291. https://doi.org/10.2214/AJR.19.22626

[8] Kwon, S.Y., Lee, S.W., Kong, E.J., *et al.* (2020) Clinicopathologic Risk Factors of Radioactive Iodine Therapy Based on Response Assessment in Patients with Differentiated Thyroid Cancer: A Multicenter Retrospective Cohort Study. *European Journal of Nuclear Medicine and Molecular Imaging*, **47**, 561-571. https://doi.org/10.1007/s00259-019-04634-8

[9] Seib, C.D. and Sosa, J.A. (2019) Evolving Understanding of the Epidemiology of Thyroid Cancer. *Endocrinology and Metabolism Clinics of North America*, **48**, 23-35.

https://doi.org/10.1016/j.ecl.2018.10.002

[10] Horvath, E., Skoknic, V., Majlis, S., *et al.* (2020) Radioiodine-Induced Salivary Gland Damage Detected by Ultrasonography in Patients Treated for Papillary Thyroid Cancer: Radioactive Iodine Activity and Risk. *Thyroid*, **30**, 1646-1655. https://doi.org/10.1089/thy.2019.0563

[11] Sparano, C., Moog, S., Hadoux, J., *et al.* (2022) Strategies for Radioiodine Treatment: What's New. *Cancers*, **14**, Article 3800. https://doi.org/10.3390/cancers14153800

[12] Palot Manzil, F.F. and Kaur, H. (2022) Radioactive Iodine for Thyroid Malignancies. StatPearls Publishing LLC, Treasure Island.

[13] Xu, S., Huang, H., Qian, J., *et al.* (2021) Prevalence of Hashimoto Thyroiditis in Adults with Papillary Thyroid Cancer and Its Association with Cancer Recurrence and Outcomes. *JAMA Network Open*, **4**, e2118526. https://doi.org/10.1001/jamanetworkopen.2021.18526

[14] Battistella, E., Pomba, L., Costantini, A., Scapinello, A. and Toniato, A. (2022) Hashimoto's Thyroiditis and Papillary Cancer Thyroid Coexistence Exerts a Protective Effect: A Single Centre Experience. *Indian Journal of Surgical Oncology*, **13**, 164-168. https://doi.org/10.1007/s13193-022-01515-9

[15] Liu, J.R., Liang, J. and Lin, Y.S. (2019) Relationship between Preablative Stimulated Thyroglobulin and the Excellent Response in Differentiated Thyroid Carcinoma. *Journal of China Cancer*, **29**, 125-130.

[16] Iizuka, Y., Katagiri, T., Ogura, K. and Mizowaki, T. (2019) Comparison between the Different Doses of Radioactive Iodine Ablation Prescribed in Patients with Intermediate-to-High-Risk Differentiated Thyroid Cancer. *Annals of Nuclear Medicine*, **33**, 495-501. https://doi.org/10.1007/s12149-019-01357-6

[17] Jin, M., Ahn, J., Lee, Y.M., *et al.* (2021) Clinical Implications of Age and Excellent Response to Therapy in Patients with High-Risk Differentiated Thyroid Carcinoma. *Clinical Endocrinology*, **95**, 882-890. https://doi.org/10.1111/cen.14543

[18] Kitahara, C.M. and Sosa, J.A. (2020) Understanding the Ever-Changing Incidence of Thyroid Cancer. *Nature Reviews Endocrinology*, **16**, 617-618. https://doi.org/10.1038/s41574-020-00414-9

[19] Özdoğan, Ö., Aksu, A., Doğan, E., *et al.* (2021) Applying Postoperative Radioiodine Therapy before 3 Months Seems to Decrease Ablation Success in Patients with Differentiated Thyroid Carcinoma. *Annals of Nuclear Medicine*, **35**, 223-231. https://doi.org/10.1007/s12149-020-01555-7

[20] Abe, K., Ishizaki, U., Ono, T., *et al.* (2020) Low-Dose Radioiodine Therapy for Patients with Intermediate- to High-Risk Differentiated Thyroid Cancer. *Annals of Nuclear Medicine*, **34**, 144-151. https://doi.org/10.1007/s12149-019-01432-y

[21] Jeong, J.H., Kong, E.J., Jeong, S.Y., *et al.* (2017) Clinical Outcomes of Low-Dose and High-Dose Postoperative Radioiodine Therapy in Patients with Intermediate-Risk Differentiated Thyroid Cancer. *Nuclear Medicine Communications*, **38**, 228-233. https://doi.org/10.1097/MNM.0000000000000636

[22] Grani, G., Lamartina, L., Alfò, M., *et al.* (2021) Selective Use of Radioactive Iodine Therapy for Papillary Thyroid Cancers with Low or Lower-Intermediate Recurrence Risk. *The Journal of Clinical Endocrinology & Metabolism*, **106**, e1717-e1727. https://doi.org/10.1210/clinem/dgaa973

[23] Cao, J., Yun, C., Zhu, X., *et al.* (2021) Clinical Analysis of the Short-Term Outcome of Papillary Thyroid Micro Carcinoma after ^{131}I Treatment. *Cancer Management and Research*, **13**, 4691-4698. https://doi.org/10.2147/CMAR.S308012

[24] Kwon, H., Choi, J.Y., Moon, J.H., *et al.* (2016) Effect of Hashimoto Thyroiditis on Low-Dose Radioactive-Iodine Remnant Ablation. *Head Neck*, **38**, E730-E735. https://doi.org/10.1002/hed.24080

[25] Ma, Y., He, J., Shen, N., *et al.* (2019) Expression of NIS, VEGF-A and Thyroid Autoantibody in Papillary Thyroid Carcinoma with or without Hashimoto's Disease. *ORL*: *Journal for Otorhinolaryngology and Its Related Specialties*, **81**, 281-286. https://doi.org/10.1159/000501620

[26] Bastos, A.U., Oler, G., Nozima, B.H., *et al.* (2015) BRAF V600E and Decreased NIS and TPO Expression Are Associated with Aggressiveness of a Subgroup of Papillary Thyroid Microcarcinoma. *European Journal of Endocrinology*, **173**, 525-540. https://doi.org/10.1530/EJE-15-0254

[27] Zhang, L., Zhou, L., Feng, Q., Li, Q.L. and Ge, M.H. (2021) Mutation of Hashimoto's Thyroiditis and Papillary Thyroid Carcinoma Related Genes and the Screening of Candidate Genes. *Frontiers in Oncology*, **11**, Article ID: 813802. https://doi.org/10.3389/fonc.2021.813802

[28] Jollant, F, Lawrence, N.S., Olie, E., *et al.* (2010) Decreased Activation of Lateral Orbitofrontal Cortex during Risky Choices under Uncertainty Is Associated with Disadvantageous Decision-Making and Suicidal Behavior. *Neuroimage*, **51**, 1275-1281. https://doi.org/10.1016/j.neuroimage.2010.03.027

[29] Huang, S., Qi, M., Tian, T., *et al.* (2022) Positive BRAFV600E Mutation of Primary Tumor Influences Radioiodine Avidity but Not Prognosis of Papillary Thyroid Cancer with Lung Metastases. *Frontiers in Endocrinology*, **13**, Article ID: 959089. https://doi.org/10.3389/fendo.2022.959089

[30] Nóbrega, G., Cavalcanti, M., Leite, V., Vilar, L. and Brandão, S.C.S. (2022) Value of Stimulated Pre-Ablation Thyroglobulin as a Prognostic Marker in Patients with Differentiated Thyroid Carcinoma Treated with Radioiodine. *Endocrine*, **76**, 642-647. https://doi.org/10.1007/s12020-022-03021-y