Am J Cancer Res 2026;16(1):255-267
www.ajcr.us /ISSN:2156-6976/ajcr0168329

Original Article

Analysis of the impact of Graves' disease on the efficacy of initial radioactive iodine therapy in patients with differentiated thyroid cancer

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Received August 25, 2025; Accepted January 13, 2026; Epub January 15, 2026; Published January 30, 2026

Abstract: This study aimed to assess the impact of Graves' disease (GD) on the clinicopathological characteristics and prognosis of patients with differentiated thyroid cancer (DTC) undergoing initial radioactive iodine (RAI) therapy, as well as to identify factors influencing RAI therapy outcomes. A retrospective analysis was conducted on 959 DTC patients who received initial RAI therapy at the Department of Nuclear Medicine, First Affiliated Hospital of Nanchang University, between January 2021 and December 2023. Patients were divided into two groups based on a history of GD: the GD group (n = 60) and the non-GD group (n = 899). Data on demographics, laboratory tests, clinicopathological features, and RAI-related parameters were collected. Univariate analysis was performed to identify variables associated with treatment response, followed by multivariate logistic regression to determine independent predictors of outcomes after initial RAI therapy. The distribution of treatment responses across the four categories was as follows: in the GD group, excellent response (ER) occurred in 71.67%, indeterminate response (IDR) in 16.67%, biochemical incomplete response (BIR) in 6.67%, and structural incomplete response (SIR) in 5.00%; in the non-GD group, the respective rates were 39.60% (ER), 29.37% (IDR), 17.80% (BIR), and 13.24% (SIR). Statistically significant differences were observed in dichotomous outcomes - ER versus non-excellent response (N-ER), and ideal/acceptable response versus incomplete response - between the two groups (both $P < 0.01$). Multivariate analysis identified several independent factors associated with favorable RAI outcomes, including younger age, GD ($P < 0.001$; OR = 0.16; 95% CI: 0.07-0.35), shorter interval between surgery and ^{131}I administration, fewer metastatic lymph nodes, negative pre-ablation thyroglobulin antibody (pa-TgAb), lower pre-treatment stimulated thyroglobulin (sTg) levels, and higher ^{131}I dose (all $P < 0.05$). In contrast, Hashimoto's thyroiditis (HT), maximum diameter of metastatic lymph nodes, body mass index (BMI), tumor multifocality, maximum tumor diameter, tumor location, and ATA recurrence risk stratification were not significantly associated with treatment response (all $P > 0.05$). Compared to non-GD DTC patients, those with GD exhibited more favorable pathological features and significantly better short-term prognosis following initial RAI therapy, with an 84% reduced likelihood of N-ER. Key predictors of favorable RAI response included GD status, younger age, shorter surgery-to-RAI interval, lower metastatic lymph node burden, pa-TgAb negativity, lower sTg levels, and higher ^{131}I dose. HT, metastatic lymph node size, BMI, tumor multifocality, tumor size, and tumor location did not significantly influence treatment outcomes.

Keywords: Graves' disease, differentiated thyroid cancer, radioactive iodine therapy, prognosis, influencing factors

Introduction

Thyroid cancer (TC) is the most common endocrine malignancy [1]. According to the latest statistics from the International Agency for Research on Cancer (IARC), TC ranks seventh in overall cancer incidence and fifth in women, with China accounting for more than half of the global burden [2]. Differentiated TC (DTC), comprising primarily papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), represents over 90% of all TC cases [1]. For nearly 80 years, radioactive iodine (RAI) therapy has been central to treating both hyperthyroidism and TC, continuing to play a vital role in the management of DTC [3]. Postoperative RAI

https://doi.org/10.62347/ACNT5059

treatment helps eliminate residual lesions, reducing recurrence rates and TC-related mortality [4]. Graves' disease (GD) is an autoimmune thyroid disorder and the most common cause of hyperthyroidism [5], characterized by hyperthyroidism and diffuse goiter. GD is primarily mediated by humoral immunity, where thyroid-stimulating antibodies (TSI) are elevated in response to B lymphocyte stimulation. TSI binds to the thyroid-stimulating hormone (TSH) receptor on thyroid cells, mimicking TSH, leading to thyroid follicular cell proliferation and the release of thyroid hormones *via* the cAMP pathway [5, 6]. Some studies [7, 8] suggest that TSI activates the TSH receptor on thyroid cells and upregulates various growth factors. The autoimmune nature and altered immune tolerance in GD also provide a theoretical basis for the increased cancer risk in GD patients. Chronic inflammation, oxidative stress, and dysregulation of TSH signaling are considered key factors in thyroid carcinogenesis [9].

The incidence of TC is higher in GD patients compared to the general euthyroid population [10]. Soares MN et al. [11] found a higher prevalence of thyroid nodules in GD patients, with an increased risk of TC correlating with the number and size of the nodules. Similar to normal thyroid cells, DTC tumor cells also express functional TSH receptors, and TSI-induced overstimulation of thyroid follicular cells may explain the higher incidence of DTC in GD patients [12]. Consequently, some scholars advocate for early diagnosis and more aggressive treatment of GD patients, including total thyroidectomy, lymph node dissection, and subsequent RAI therapy [13]. Although GD combined with DTC (GD-DTC) is relatively rare, several studies have analyzed the clinicopathological characteristics and prognosis of GD-DTC patients. However, due to factors like small sample sizes, broad study populations, and complex clinical environments, no consensus has been reached regarding the relationship between GD and DTC [14]. Furthermore, studies focusing on DTC patients undergoing ^{131}I treatment are limited [15], highlighting the need for further exploration in this area. This study aims to analyze the impact of GD on the clinicopathological features and prognosis of DTC patients undergoing ^{131}I therapy, explore factors influencing treatment outcomes, and enhance clinicians' understanding of these patients to inform clinical diagnosis and treatment strategies.

Materials and methods

Subjects

This study included 959 patients with DTC who underwent ^{131}I treatment at the Department of Nuclear Medicine, First Affiliated Hospital of Nanchang University, from January 2021 to December 2023. GD was diagnosed based on the 2016 American Thyroid Association (ATA) diagnostic criteria [16], including symptoms of thyrotoxicosis (e.g., palpitations, sweating, weight loss), diffuse goiter, and supportive evidence such as positive thyroid receptor antibodies (TRAb), elevated RAI uptake (RAIU), or increased blood flow on thyroid ultrasound. Patients were divided into two groups: the GD group (60 cases) and the non-GD (N-GD) group (899 cases), based on the presence of GD history before ^{131}I treatment. Inclusion criteria were as follows: (I) patients who underwent total thyroidectomy with pathological confirmation of DTC; (II) patients meeting the postoperative ^{131}I treatment criteria for TC according to the 2015 ATA guidelines for the management of adult thyroid nodules and DTC [17]; (III) patients who stopped taking thyroid hormone for at least 3 weeks with a TSH > 30 mIU/ml; (IV) a follow-up duration of ≥ 6 months. Exclusion criteria included: (I) a history of other malignancies or serious diseases; (II) multiple ^{131}I treatments; (III) incomplete follow-up data.

Postoperative management and follow-up

After total thyroidectomy, DTC patients began preparations for ^{131}I treatment once the surgical wound had healed. Preparation steps included: (I) discontinuation of levothyroxine for 3-4 weeks to achieve a TSH > 30 mU/L; (II) adherence to a low-iodine diet for 2 weeks, avoidance of iodine-containing contrast agents and medications, and routine urinary iodine level assessments; (III) measurement of thyroid function, serum stimulated thyroglobulin (sTg), and pre-ablation antithyroglobulin (pa-TgAb); (IV) risk stratification for recurrence, followed by determination of the ^{131}I treatment dose based on the results; (V) provision of safety education, including instructions for glucocorticoid, vitamin C, pantoprazole intake, adequate hydration, frequent urination, and pre-

vention of constipation during treatment. Patients were scheduled for follow-up visits at 2, 4, and 6 months post-^{131}I treatment, with intervals adjusted between 3 and 12 months based on treatment outcomes. Each follow-up visit involved measuring serum TSH, Tg, and TgAb levels, as well as routine neck ultrasound, chest CT, diagnostic ^{131}I whole-body scan (Dx-WBS), and single-photon emission computed tomography/computed tomography (SPECT/CT) for fusion imaging. If any tests or serum results were unsatisfactory, additional investigations, including fine-needle aspiration (FNA), washout Tg measurement, lymph node biopsy, and positron emission tomography-computed tomography (PET-CT), were performed to further clarify the situation. These diagnostic techniques were used to assess the presence of local recurrence and/or distant metastasis.

The 2015 ATA DTC guidelines [17] recommend that the efficacy of RAI treatment be assessed 6-12 months post-treatment. In this study, efficacy was evaluated after discontinuing levothyroxine tablets for 3-4 weeks, with four potential outcomes: satisfactory response (no tumor residual), indeterminate response, biochemical incomplete response, and structural incomplete response. The criteria for a satisfactory response include: (I) no clinical evidence of tumor presence; (II) no radiological evidence of tumor presence; (III) in the absence of antibody interference, Tg < 0.2 ng/mL under TSH suppression or serum sTg < 1 ng/mL. All other outcomes, excluding satisfactory response, were classified as non-satisfactory response (N-ER). In this study, the first follow-up occurred 6-8 weeks after iodine treatment, with a comprehensive assessment performed 6-12 months later, marking the final outcome of the treatment. During follow-up, serum Tg and TgAb concentrations were measured using electrochemiluminescence immunoassay (Roche, Switzerland, E801), with a detection range of 0.04-500.00 ng/mL and 10-4000 kU/L (normal reference range: 3.5-77.00 μg/L and 0-115 kU/L). TSH levels were assessed using chemiluminescence immunoassay (Bayer ADVIA Centaur, Germany), with a detection range of 0.04-100.00 mU/L (normal reference range: 0.27-4.20 mU/L).

Data collection

Electronic pathological records included general information, laboratory tests, clinical pathological results, and iodine treatment-related data. General information encompassed the patient's age, gender, body mass index (BMI), and thyroid disease history. Clinical pathological data included the tumor's location, size, number of tumor foci, histological type, presence of extrathyroidal extension (ETE), distribution, number, and maximum long diameter of metastatic cervical lymph nodes, presence of distant metastasis, and the American Joint Committee on Cancer (AJCC) 8th edition's primary tumor-node-metastasis (TNM) staging for TC. Iodine treatment-related data primarily covered the interval between surgery and RAI treatment, the iodine treatment dose, the time interval for comprehensive assessment post-RAI treatment, the initial recurrence risk (RR) stratification of DTC, and the AJCC 8th edition's prognostic staging for DTC.

Statistical analysis

Statistical analyses were performed using R (4.5.2.,https://cran.r-project.org). The analysis included the use of the broom, forestplot, and gt packages to generate forest plots, enabling subgroup analyses of the multivariable logistic regression model and clearly presenting the effect sizes (odds ratios) and their corresponding 95% confidence intervals for each variable. Additionally, the ggcorrplot function from the ggcorrplot package was employed to visualize the strength and direction of associations among all predictor variables, facilitating a clearer understanding of their interrelationships. Continuous variables with normal distribution are presented as mean ± standard deviation (SD) and compared between groups using the independent samples t-test. Non-normally distributed continuous variables are reported as median (interquartile range [IQR]) and compared using the Mann-Whitney U test. Categorical variables are expressed as frequency [n (%)] and compared between groups using the chi-square (χ^2) test. Univariate analyses were performed to identify variables associated with RAI treatment response, with candidate variables selected for multivariable modeling based on a significance threshold of $P < 0.05$. To assess potential multicollinearity among the 22 candidate clinical variables, Spearman's rank correlation analysis was conducted; all pairwise correlation coefficients were < 0.8, indicating no severe multicollinearity. The selected variables were subsequently

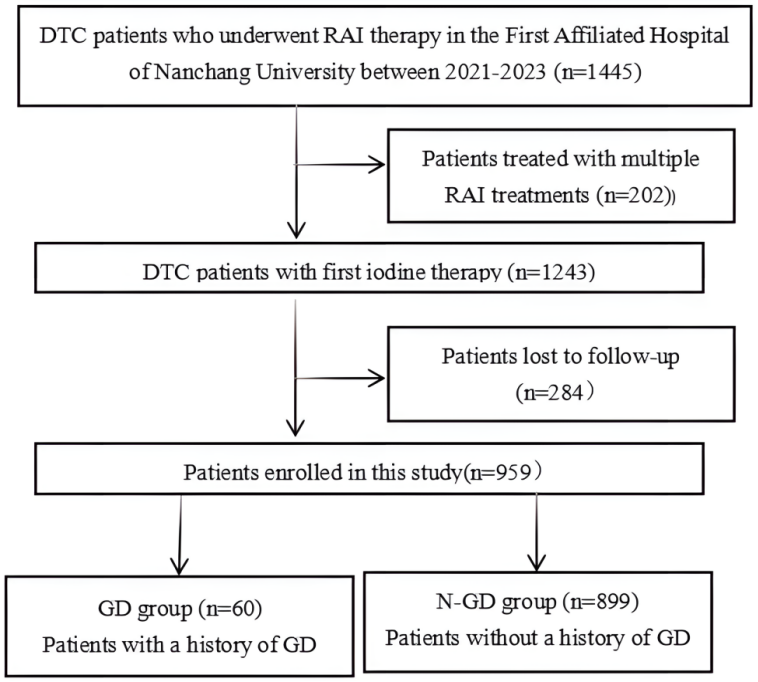

Figure 1. Flowchart. DTC, differentiated thyroid cancer; RAI, radioactive iodine; GD, Graves' Disease.

entered into a multivariable logistic regression model to identify independent predictors of RAI treatment efficacy in DTC patients. Based on our a priori hypothesis, interaction terms between GD status and key clinical variables were included in the multivariable model to assess potential effect modification by GD. The statistical significance of interactions was evaluated using likelihood ratio tests. All statistical tests were two-sided, and a *P* value < 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

A total of 959 patients with DTC were included in the final analysis (**Figure 1**). Based on the presence or absence of preoperative GD, 60 patients were assigned to the GD group, and 899 patients to the N-GD group (**Table 1**). The mean age of the patients was 40.93 years, with 69.03% being female. Preoperatively, 298 patients had Hashimoto's thyroiditis (HT). Approximately two-thirds of the patients underwent RAI therapy within 3 months post-surgery. According to the 8th edition of the AJCC prognostic staging for DTC, 84.24% were classified as stage I. Based on the initial RR stratification, 58.47% were classified as intermediate risk, while fewer than 15% were low risk. At the time of RIT, the median serum thyroglobulin (Tg) level was significantly lower in the GD group [0.54 μg/L (IQR: 0.02-4.01)] compared to the non-GD group [4.28 μg/L (IQR: 0.60-16.14)], with a between-group difference that was highly statistically significant (P < 0.001). The overall median Tg level across the entire cohort was 4.06 μg/L (IQR: 0.48-15.65). 16.37% had positive TgAb levels (> 115 IU/ml) at the time of RIT. Approximately 40% of patients received a dose greater than 150 mCi, while fewer than 10% received a dose below 100 mCi.

The distribution of clinical responses between the GD group and the Non-GD group

The distribution of clinical responses between the GD and N-GD groups is presented in **Table 2**. After RAI treatment, the median follow-up time was 7.23 months, with no significant difference between the groups (P = 0.109). Significant differences in therapeutic outcomes were observed between the GD and N-GD groups. When clinical outcomes were categorized into four groups, the distribution was as follows: GD group: ER (71.67%), IDR (16.67%), BIR (6.67%), and SIR (5.00%); N-GD group: ER (39.60%), IDR (29.37%), BIR (17.80%), and SIR (13.24%). When these four categories were combined into binary classifications (ER vs. N-ER or IR vs. N-IR), significant differences between the groups were observed (all P < 0.01).

Factors associated with clinical outcomes of RAI therapy

Table 3 presents the results of univariate and multivariate analyses for treatment outcomes, with ER/N-ER as the endpoint. Univariate analysis identified several factors positively correlat-

Table 1. Clinical characteristics according to the history of Graves' disease

	Total	Non-GD group	GD group	*P*-value
N	959	899	60	
Age (year)	40.93 ± 12.49	41.09 ± 12.55	38.55 ± 11.33	0.128
Female sex	662 (69.03%)	610 (67.85%)	52 (86.67%)	0.002
Therapy time interval (month)				0.539
≤ 3	653 (68.09%)	610 (67.85%)	43 (71.67%)	
> 3	306 (31.91%)	289 (32.15%)	17 (28.33%)	
Max tumor size (cm)	1.82 ± 1.07	1.85 ± 1.08	1.46 ± 0.96	0.009
Number of Metastatic Lymph Nodes	9.33 ± 9.14	9.56 ± 9.26	5.83 ± 6.17	0.002
maximum diameter of metastatic lymph node (cm)	0.97 ± 0.74	0.99 ± 0.75	0.71 ± 0.54	0.036
Pre-ablative Tg (μg/L)	4.06 (0.48-15.65)	4.28 (0.60-16.14)	0.54 (0.02-4.01)	< 0.001
BMI(kg/m^2)	24.03 ± 3.63	24.06 ± 3.62	23.64 ± 3.75	0.424
Hashimoto's thyroiditis				< 0.001
No	660 (68.89%)	633 (70.49%)	27 (45.00%)	
Yes	298 (31.11%)	265 (29.51%)	33 (55.00%)	
Recurrence risk				0.008
Low	140 (14.64%)	123 (13.73%)	17 (28.33%)	
Intermediate	559 (58.47%)	529 (59.04%)	30 (50.00%)	
High	257 (26.88%)	244 (27.23%)	13 (21.67%)	
Cancer position				0.525
Unilateral	390 (41.10%)	363 (40.83%)	27 (45.00%)	
Bilatera	559 (58.90%)	526 (59.17%)	33 (55.00%)	
Multifocal cancer				0.910
No	406 (44.03%)	380 (44.08%)	26 (43.33%)	
Yes	516 (55.97%)	482 (55.92%)	34 (56.67%)	
Positive lymph node distribution				0.016
None	69 (7.29%)	64 (7.19%)	5 (8.77%)	
Central	326 (34.42%)	297 (33.37%)	29 (50.88%)	
Lateral and central	552 (58.29%)	529 (59.44%)	23 (40.35%)	
Histological type				0.856
Papillary	939 (98.02%)	880 (98.00%)	59 (98.33%)	
Follicular	19 (1.98%)	18 (2.00%)	1 (1.67%)	
Pre-therapy TSH (mIU/mL)				0.842
< 60	242 (25.23%)	225 (25.03%)	17 (28.33%)	
60-90	326 (33.99%)	306 (34.04%)	20 (33.33%)	
> 90	391 (40.77%)	368 (40.93%)	23 (38.33%)	
TgAb positive at ablation	156 (16.37%)	133 (14.88%)	23 (38.98%)	< 0.001
AJCC stage*				0.772
I	802 (84.24%)	751 (84.19%)	51 (85.00%)	
II	104 (10.92%)	97 (10.87%)	7 (11.67%)	
III	30 (3.15%)	28 (3.14%)	2 (3.33%)	
IV	16 (1.68%)	16 (1.79%)	0 (0.00%)	
Tumor stage				< 0.001
T_x	42 (4.38%)	40 (4.45%)	2 (3.33%)	
T_{1a}	168 (17.54%)	145 (16.15%)	23 (38.33%)	
T_{1b}	175 (18.27%)	167 (18.60%)	8 (13.33%)	
T_2	127 (13.26%)	126 (14.03%)	1 (1.67%)	
T_{3a}	25 (2.61%)	24 (2.67%)	1 (1.67%)	
T_{3b}	291 (30.38%)	275 (30.62%)	16 (26.67%)	
T_{4a}	123 (12.84%)	115 (12.81%)	8 (13.33%)	
T_{4b}	7 (0.73%)	6 (0.67%)	1 (1.67%)	

Node stage				0.181
N_0	70 (7.31%)	63 (7.02%)	7 (11.67%)	
N_1	887 (92.69%)	834 (92.98%)	53 (88.33%)	
Distant metastases	30 (3.13%)	28 (3.12%)	2 (3.33%)	0.926
Dose of ^{131}I (mCi)				0.012
≤ 100	83 (8.65%)	73 (8.12%)	10 (16.67%)	
> 100	494 (51.51%)	459 (51.06%)	35 (58.33%)	
> 150	382 (39.83%)	367 (40.82%)	15 (25.00%)	

Note: GD group: preoperative presence of Graves' disease; non-GD group: preoperative absence of Graves' disease. BMI: body mass index. Continuous data are presented as mean ± SD for normal distribution or median (P25-P75) for non-normal distribution; categorical data are presented as frequencies (%). AJCC stage*: 8th edition of the AJCC prognostic staging for DTC.

Table 2. The distribution of clinical responses among GD group and non-GD group

	Total	Non-GD group	GD group	*P*-value
N	959	899	60	
Time of evaluating outcomes (month)	7.23 (6.33-9.08)	7.23 (6.30-9.02)	7.85 (6.52-9.85)	0.109
Quaternary outcomes				< 0.001
ER	399 (41.61%)	356 (39.60%)	43 (71.67%)	
IDR	274 (28.57%)	264 (29.37%)	10 (16.67%)	
BIR	164 (17.10%)	160 (17.80%)	4 (6.67%)	
SIR	122 (12.72%)	119 (13.24%)	3 (5.00%)	
Dichotomous outcomes based on ER				< 0.001
ER	399 (41.61%)	356 (39.60%)	43 (71.67%)	
N-ER	560 (58.39%)	542 (60.40%)	17 (28.33%)	
Dichotomous outcomes based on IR				0.001
IR	673 (70.18%)	620 (68.97%)	53 (88.33%)	
N-IR	286 (29.82%)	279 (31.03%)	7 (11.67%)	

Note: GD group: Preoperative presence of Graves' disease. Non-GD group: Preoperative absence of Graves' disease. Categorical data are presented as frequencies (%). Time of evaluating outcomes is given as median (P25-P75). N-ER: IDR + BIR + SIR; IR: BIR + SIR; N-IR: ER + IDR. Abbreviations: BIR, biochemical incomplete response; ER, excellent response; IDR, indeterminate response; IR, incomplete response; SIR, structural incomplete response.

ed with outcomes (all $P < 0.05$): age, GD, therapy time interval (TI), HT, number and maximum diameter of metastatic lymph nodes (NMLN, MDMLN), RR, maximum tumor size (MTS), positive lymph node distribution, sTg, pa-TgAb, tumor stage, node stage, and ^{131}I dose. However, multivariate analysis revealed that only age, GD, TI, NMLN, pa-TgAb, and ^{131}I dose remained significantly associated with RAI therapy outcomes (all $P < 0.05$). In contrast, the associations between HT, MDMLN, and RR with outcomes were not significant in the multivariate analysis (all $P > 0.05$).

Assessment of multicollinearity using spearman correlation

Spearman correlation analysis was performed on the 22 candidate clinical variables in the total cohort to assess potential multicollinearity before multivariate modeling. As shown in **Figure 2**, the correlation heatmap reveals generally low pairwise correlations across all variable combinations. All correlation coefficients had absolute values less than 0.8, indicating the absence of severe multicollinearity. This suggests that the variables contribute distinct, non-redundant information to the model. Notably, GD status showed minimal correlations with tumor size, nodal burden, and other conventional oncological parameters, emphasizing its statistical independence.

Forest plot visualization confirms the strong protective effect of GD and stability of predictors

Figure 3 visually supports the robust protective role of GD and the consistency of key predictors of excellent response to RAI therapy. The forest

Table 3. Risk factors influencing outcomes(ER/N-ER) in patients with DTC after RAI therapy

Covariate	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Sex (Ref: Male)				NA
Female	0.80 (0.61, 1.06)	0.124		
Age (year)	0.98 (0.97, 0.99)	< 0.001	0.98 (0.96, 0.99)	0.006
Graves' Disease (Ref: No)				
Yes	0.26 (0.15, 0.46)	< 0.001	0.16 (0.07, 0.35)	< 0.001
Therapy time interval (Ref: ≤ 3 month)				
> 3	1.51 (1.14, 2.00)	0.004	1.54 (1.07, 2.23)	0.021
Hashimoto's thyroiditis (Ref: No)				
Yes	0.68 (0.51, 0.89)	0.005	0.79 (0.53, 1.17)	0.243
Number of Metastatic Lymph Nodes	2.65 (2.02, 3.47)	< 0.001	1.86 (1.15, 3.01)	0.012
Recurrence risk (Ref: Low)				
Intermediate	1.71 (1.18, 2.49)	0.005	0.43 (0.22, 0.83)	0.012
High	3.74 (2.42, 5.78)	< 0.001	0.44 (0.21, 0.96)	0.040
Multifocal cancer (Ref: No)	1.34 (1.03, 1.74)	0.027	1.30 (0.93, 1.84)	0.128
Max tumor size (cm)	1.60 (1.39, 1.85)	< 0.001	1.10 (0.85, 1.41)	0.462
Positive lymph node distribution (Ref: None)				
Central	1.36 (0.80, 2.32)	0.261	0.79 (0.15, 4.20)	0.785
Lateral and central	3.59 (2.14, 6.02)	< 0.001	1.63 (0.31, 8.49)	0.561
maximum diameter of metastatic lymph node (cm)	1.75 (1.36, 2.24)	< 0.001	0.77 (0.55, 1.08)	0.128
Pre-ablative Tg (μg/L)	1.10 (1.08, 1.12)	< 0.001	1.11 (1.08, 1.14)	< 0.001
TgAb positive at ablation (Ref: No)				
Yes	2.76 (1.86, 4.11)	< 0.001	9.27 (5.35, 16.07)	< 0.001
Tumor stage (Ref: T_X)				
T_{1a}	0.30 (0.14, 0.63)	0.001	1.53 (0.55, 4.24)	0.411
T_{1b}	0.50 (0.24, 1.04)	0.062	2.03 (0.75, 5.50)	0.165
T_2	0.79 (0.37, 1.70)	0.547	1.65 (0.56, 4.87)	0.364
T_{3a}	2.93 (0.74, 11.66)	0.126	6.65 (1.12, 39.6)	0.037
T_{3b}	0.60 (0.30, 1.23)	0.163	2.24 (0.83, 6.05)	0.113
T_{4a}	0.56 (0.26, 1.21)	0.140	1.78 (0.61, 5.20)	0.295
T_{4b}	2.40 (0.26, 22.11)	0.440	19.12 (1.04, 352.38)	0.047
Node stage (Ref: N0)				
N_1	2.22 (1.35, 3.66)	0.002	2.49 (0.46, 13.45)	0.288
BMI (Ref: < 18.5 kg/m^2)				
18.5-23.9	0.50 (0.26, 0.94)	0.033	1.01 (0.44, 2.35)	0.973
24-27.9	0.50 (0.26, 0.96)	0.038	0.96 (0.40, 2.29)	0.929
≥ 28	0.61 (0.30, 1.25)	0.175	0.75 (0.29, 1.90)	0.540
Dose of ^{131}I (Ref: ≤ 100 mCi)				
> 100	2.34 (1.41, 3.89)	0.001	1.50 (0.76,2.95)	0.240
> 150	8.21 (4.83, 13.97)	< 0.001	2.66 (1.23, 5.76)	0.013

Note: Abbreviations: ER, excellent response; DTC, differentiated thyroid cancer; RAI, radioactive iodine; CI, confidence interval; OR, odds ratio; BMI, body mass index. Multivariate Analysis with Adjusted Model: Adjusted for age, BMI, Graves' disease, Hashimoto's thyroiditis, therapy time interval, Maximum diameter and number of metastatic lymph nodes, Positive lymph node distribution, T stage and N stage, Recurrence risk, Multifocal cancer, Maximum tumor size, TgAb positivity at ablation, Dose of ^{131}I, and Pre-ablative Tg.

plot includes all variables significantly associated with RAI outcomes in the multivariable model ($P < 0.05$), as well as several commonly referenced clinical factors. Interaction analy-

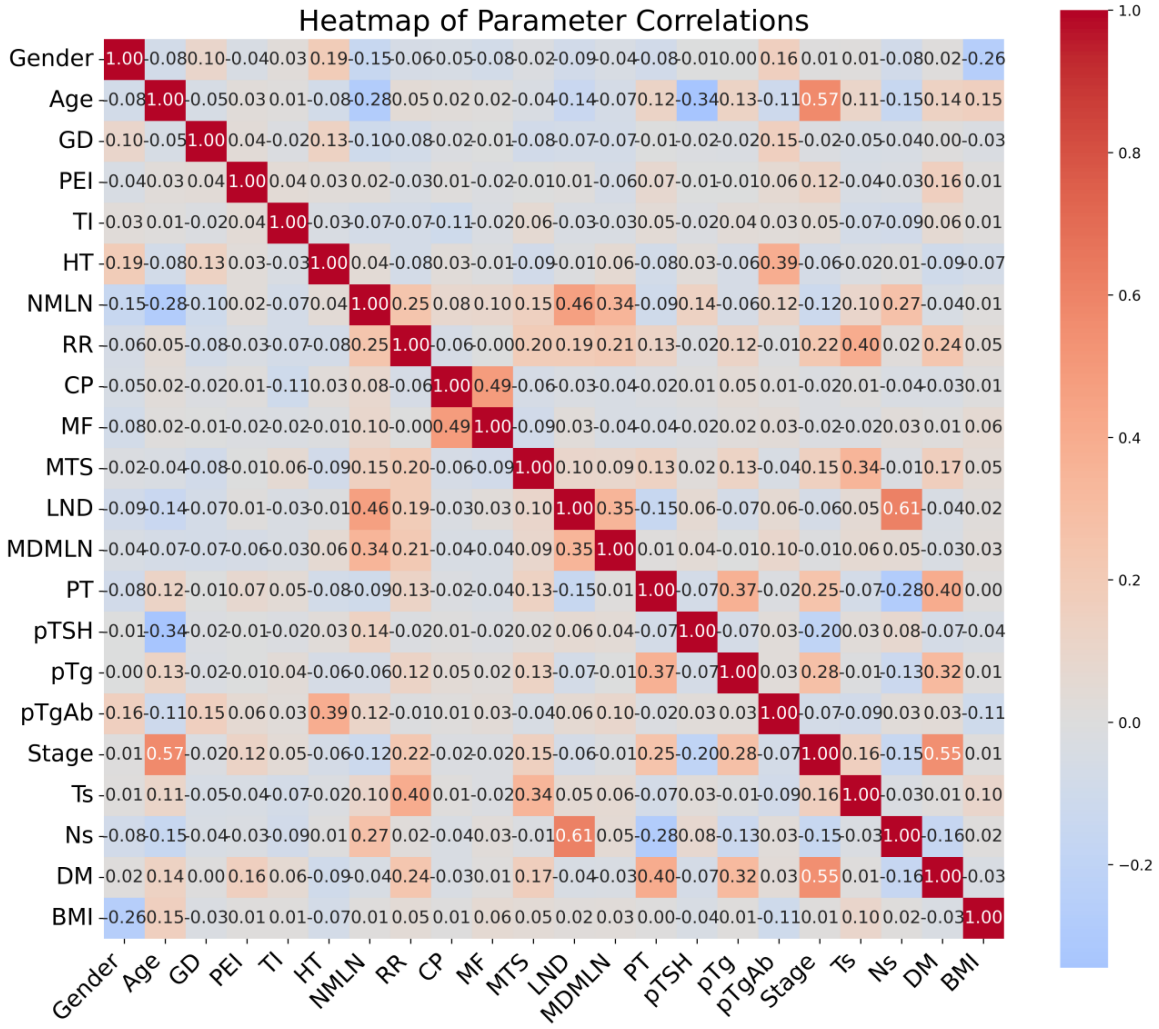

Figure 2. Heatmap of parameter correlations for factors influencing therapeutic efficacy after iodine treatment in DTC patients.GD, Graves' Disease; PEI, Post-treatment evaluation interval; TI, post-surgery iodine treatment interval; HT, Hashimoto's thyroiditis; NMLN, number of metastatic lymph nodes; RR, recurrence risk; CP, Cancer position; MF, multifocal tumor; MTS, maximum tumor diameter; MDMLN, maximum diameter of metastatic lymph nodes; PT, tumor pathological type; DM, Distant Metastasis; BMI, body mass index. Colors from blue (negative correlation) to red (positive correlation) indicate the direction and strength of correlations, with numerical values representing specific correlation coefficients (range: -1 to 1).

ses revealed no significant effect modification by GD status (all P for interaction > 0.05), indicating that the direction and magnitude of these associations remain stable across both GD and non-GD patients.

Discussion

This study included 959 DTC patients undergoing RAI treatment, with GD-DTC patients accounting for approximately 6.26% (60/959). Unfortunately, comparable data from previous studies are lacking. Statistics from the IARC [2, 15] indicate that the peak incidence age for TC is 50-54 years, with a female-to-male incidence ratio of about 3:1. The average age of patients in this study was 40.93 ± 12.49 years, with a female-to-male ratio of approximately 2.22:1, which closely aligns with the reported data. Age has been established as an important predictor of disease-free survival (DFS) [18], and the results of multivariate analysis in this study also showed that age was significantly associated with patient prognosis (P = 0.006).

Regarding the impact of GD on DTC prognosis, previous studies [19, 20] have yielded conflict-

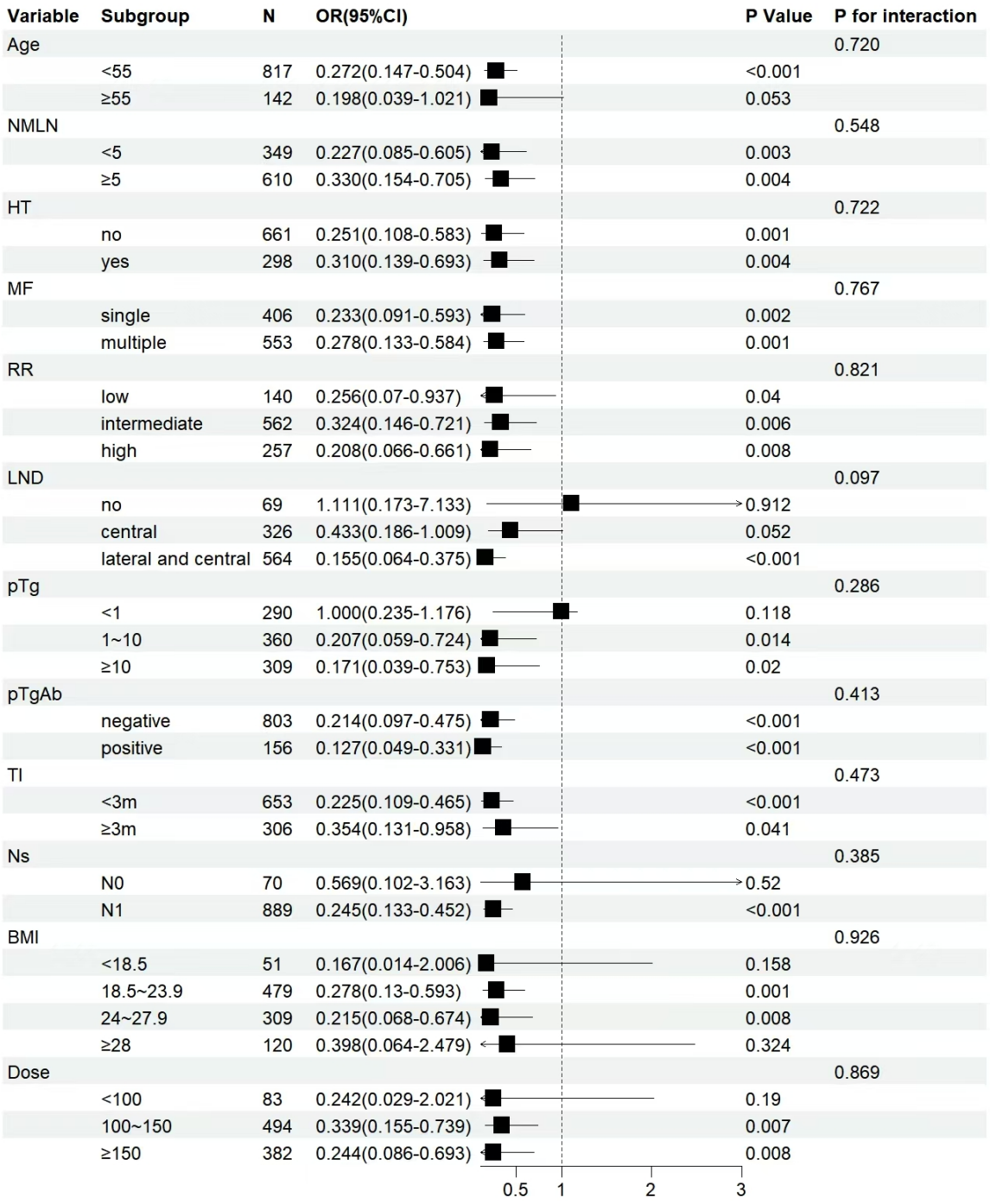

Figure 3. Forest plot of significant predictors and selected common clinical factors for excellent response to radioactive iodine therapy from multivariable analysis. This figure illustrates the associations between clinical factors that were statistically significant ($P < 0.05$) in the multivariable model, along with several commonly used clinical indicators, and RAI treatment outcomes (ER) in the entire cohort. Squares represent odds ratios (ORs); horizontal lines indicate 95% confidence intervals (CIs). The vertical dashed line denotes the null effect (OR = 1.0). NMLN, number of metastatic lymph nodes; HT, Hashimoto's thyroiditis; MF, multifocal tumor; RR, recurrence risk; LND, positive lymph node distribution; TI, post-surgery iodine treatment interval; BMI, body mass index.

ing results. Early GD was initially considered a protective factor for TC. However, since the 1990s, many researchers have found that TC is not only closely associated with hyperthyroid-

ism, particularly GD, but also exhibits more aggressive behavior [21]. A recent study by Marongiu et al. [8] demonstrated that GD-related PTC is more aggressive, with an increased metastasis risk and a less favorable prognosis compared to PTC without GD. A 2020 meta-analysis [22] suggested that GD could be a risk factor for adverse progression and survival in DTC, especially when accounting for factors such as geography, ethnicity, environment, incidental cancer, and surgical procedures. Another recent meta-analysis [23] reached a similar conclusion, indicating that GD is associated with an increased risk of recurrence or persistence in DTC, particularly in tumors ≥ 1 cm in diameter. The results of this study revealed significant differences in clinical pathological characteristics and outcomes following initial RAI ablation between GD-DTC patients and general DTC patients. Specifically, GD-DTC patients demonstrated more favorable pathological features and better short-term prognosis following initial iodine treatment, with an 84% reduced risk of N-ER ($P < 0.001$, OR = 0.16, 95% CI = 0.07-0.35). This finding contradicts some previous studies, and the reasons for this discrepancy remain unclear.

A study [7] including 3628 cases of total thyroidectomy for PTC found that GD did not affect the prognosis of PTC patients. The study summarized mechanisms that might explain a better prognosis in GD patients, including: GD activation of NK cells or an increase in M1-type macrophages, which triggers a humoral immune response that provides protective immunity for tumor cells and reduces the invasiveness of TC; GD patients tend to have goiter with relatively smaller TCs, making it difficult for tumors to invade the thyroid capsule or adjacent organs; surgery achieves immunological relief of TSI, eliminating the harmful effects of TSI; GD patients may undergo more meticulous surgical procedures, leaving fewer residual thyroid tissues. Additionally, the background of GD may influence RAI treatment outcomes. The sodium/iodide symporter (NIS) is known to be a key molecule for active iodide transport in the thyroid and some thyroid-extraneous tissues [24]. RAI treatment, the most successful targeted internal radiotherapy for ablating TC metastases and remnants after thyroidectomy, relies on the functional expression of NIS on the tumor cell plasma membrane [25]. It has been reported that 25-50% of TC patients exhibit weakened NIS absorption of RAI [26]. Yang et al. [27] confirmed that NIS protein expression is increased in GD thyroid tissue compared to normal thyroid tissue, suggesting that NIS expression in GD thyroid may be regulated by TRAb. Zhao et al.'s study [13] found that most primary hyperthyroidism patients with DTC achieve good clinical outcomes with ^{131}I treatment. These findings may help explain the better prognosis of GD-DTC patients after iodine treatment.

Tumor size and lymph node metastasis are well-established predictors of recurrence [7]. A study by Abidin Sayiner Z et al. [28] found that in patients with PTC coexisting with GD, tumor size was smaller, and multifocality was less common, suggesting a more favorable prognosis. In our study, although no significant difference in multifocality was observed, GD patients had a significantly smaller mean tumor diameter (1.46 cm vs. 1.85 cm, $P = 0.009$) and more favorable features of lymph node metastasis, including smaller maximum nodal diameter, fewer metastatic nodes, and predominant involvement of the central neck compartment (all $P < 0.05$). These results were consistent with the initial RR stratification of DTC as proposed by the 2015 ATA DTC guidelines, where GD patients had a significantly lower proportion in the low and intermediate risk categories (especially low risk) ($P = 0.008$). Additionally, a study indicated that GD is only associated with worse outcomes in coexisting PTC when the tumor diameter is ≥ 1 cm. Therefore, the better prognosis observed in GD patients may be related to these factors.

Since the discovery of the link between leukocytes and cancer development in 1893, the relationship between inflammation and carcinogenesis has gradually gained recognition. Literature [29] has reported that autoimmune and inflammatory conditions are risk factors for DTC, with GD and HT patients exhibiting oxidative DNA damage biomarkers that may promote DTC development. Evidence suggests that HT is associated with DTC, including papillary and FTC [30]. A recent meta-analysis by Xu et al. [31] demonstrated that HT increases the risk of PTC; however, PTC patients with HT exhibit more favorable clinical features and better prognosis than those without HT, espe-

cially in young females, suggesting a protective role of HT in PTC progression. Given that GD and HT share many similarities as autoimmune diseases with lymphocytic infiltration, this study found that GD patients were younger and had a higher proportion of females, which may contribute to earlier detection and treatment of TC during the management of GD.

The 2015 ATA guidelines did not specify the optimal timing for RAI treatment, and the timing of initial RAI treatment after surgery is often overlooked. It was previously believed that 3 months post-surgery was an appropriate time for RAI treatment. However, a 2022 meta-analysis [4] found that delaying the initial RAI treatment beyond 3 months but within 6 months does not adversely affect TC prognosis. This study did not further divide the timing of RAI treatment, but it did find that compared to RAI treatment within 3 months after surgery, the risk of N-ER was higher when the first RAI treatment occurred more than 3 months post-surgery ($P = 0.021$, OR = 1.54, 95% CI = 1.07-2.23), consistent with previous findings. In patients with confirmed DTC, Tg is a cornerstone tumor marker, providing specific, reliable information during long-term follow-up, especially after RAI therapy, for predicting persistent disease, recurrence, or distant metastasis [32]. Pre-ablation sTg is a significant predictor of incomplete treatment response in DTC, with higher sTg levels associated with poorer prognosis, highlighting its key role in guiding RAI ablation. This study confirmed this association ($P < 0.001$; OR = 1.11; 95% CI: 1.08-1.14) [33]. TgAb may be a response caused by the release of Tg, with approximately 25% of TC patients and 10% of the general population producing it [34]. Tg levels are easily influenced by TgAb, and TgAb positivity may lead to false-negative results in radioimmunoassays for Tg [35]. A recent study by Han et al. [35] found that sTg and pa-TgAb can predict the efficacy and prognosis of RAI treatment in TgAb-positive DTC patients. A 20-year follow-up study by Sanjari et al. [34] showed that high levels of TgAb in PTC patients predict a more severe course and worse prognosis and may signal disease recurrence. Multivariate analysis in this study also indicated that patients with pa-TgAb positivity had a worse prognosis ($P < 0.001$, OR = 8.86, 95% CI = 4.27-18.37).

This study has several notable strengths. First, to the best of our knowledge, this is one of the few studies specifically examining postoperative radioiodine therapy in patients with DTC complicated by GD, with a sufficiently large sample size. Additionally, a major strength lies in the comprehensive analysis of a broad range of potential influencing factors. However, several limitations must be acknowledged. First, being a retrospective, single-center study, it may introduce selection bias. Second, the relatively short follow-up period after radioiodine therapy limits the ability to assess long-term clinical outcomes, including mortality. Third, although the observed therapeutic benefit of GD history on radioiodine efficacy can be plausibly explained by clinical observations and prior literature, the retrospective nature of the study prevented the measurement of NIS protein or gene expression levels in tumor or residual thyroid tissues from both groups. This lack of direct evidence highlights the need for future research to adopt a prospective design, expand participant recruitment, extend the follow-up duration, and include mechanistic investigations to enhance the comprehensiveness and reliability of the findings.

In conclusion, compared to non-GD DTC patients, those with GD-DTC exhibited more favorable pathological features and a significantly better short-term prognosis following initial RAI treatment, with an 84% reduced risk of non-excellent response. Additional favorable factors included younger age, shorter surgery-to-RAI interval, fewer metastatic lymph nodes, negative pa-TgAb, and higher ^{131}I dose; Hashimoto thyroiditis, lymph node size, BMI, tumor multifocality, size, and location were not significantly associated with treatment outcomes.The primary significance of this study lies in its identification of GD history - an often-overlooked clinical factor - as significantly associated with RAI therapeutic efficacy, providing a valuable lead for future prospective mechanistic investigations.

Disclosure of conflict of interest

None.

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