



Predictive Value of Clinical and Pathological Characteristics for Metastatic Radioactive Iodine-Refractory Differentiated Thyroid Carcinoma: A 16-year Retrospective Study

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Purpose: To assess predictive value of clinical and pathological characteristics for metastatic radioactive iodine-refractory differentiated thyroid carcinoma (RAIR-DTC) in early stage retrospectively.

Methods: We studied 199 metastatic DTC patients who were divided into two groups (TgAb negative and TgAb positive). The stimulated Tg (Sti-Tg) at the first and second radioiodine therapy (RIT) were defined as Sti-Tg1 and Sti-Tg2, the suppressed Tg (Sup-Tg) were designated as Sup-Tg1 and Sup-Tg2, while the TgAb were defined as TgAb1 and TgAb2, respectively. Univariate analysis and Logistic regression were used to investigate the effects of 13 observed factors to predict RAIR-DTC.

Results: In TgAb negative group, ROC curve analysis showed that cut-off values of age, Sti-Tg2/Sti-Tg1 and Sup-Tg2/Sup-Tg1 to predict RAIR-DTC were 40 years old, 57.0% and 81.0%, respectively. Age, extrathyroid invasion, Sti-Tg2/Sti-Tg1, Sup-Tg2/Sup-Tg1 and BRAF gene mutation were proved to be independent factors predicting RAIR-DTC. In TgAb-positive group, ROC curve analysis showed that cut-off values of age, TgAb1 and TgAb2/TgAb1 to predict RAIR-DTC were 55 years old, 297 IU/ml (14.8 times higher than the upper limit) and 53.6%, respectively.

Conclusions: For TgAb-negative DTC, age over 40, extraglandular invasion, mutated BRAF gene, Sti-Tg decreased less than 43%, and Sup-Tg decreased less than 19% after the first two courses of RIT were independent predictors for RAIR-DTC. For TgAb-positive DTC, age over 55, extraglandular invasion, mutated BRAF gene, distant metastasis before RIT, TgAb level 14.8 times higher than the upper limit, TgAb dropped less than 46.4% after two courses of RIT were influencing factors.

Keywords: radioiodine therapy (RIT), radioactive iodine-refractory differentiated thyroid carcinoma, receiver-operating characteristic curve (ROC), thyroglobulin, thyroglobulin antibody (TgAb)

BACKGROUND

Thyroid carcinoma is the most common endocrine malignancy, most of which are differentiated thyroid carcinoma (DTC). For decades, “thyroidectomy + radioiodine therapy (RIT) + L-T₄ suppression therapy” has been considered as standard treatment, the clinical efficacy is well documented (1, 2). However, about 30% of patients with distant metastases become radioactive iodine-refractory DTC (RAIR-DTC) (3, 4), and the 10-year survival rate is less than 10%. Patients would benefit little from RIT if they do not respond or become refractory to ¹³¹I. Therefore, timely diagnosis of RAIR-DTC can avoid unnecessary RIT and allow patients to move towards other relatively effective treatments. Till now, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸FDG-PET/CT) is recommended in clinical guidelines for the identification of RAIR-DTC, combining with ¹³¹I-whole body scan (¹³¹I-WBS), computed tomography (CT) and serum thyroglobulin (Tg) level after multiple RIT (3). How to early evaluate, diagnose, and timely adopt effective therapy for metastatic DTC (m-DTC) is a great clinical challenge. This study analyzed the detailed clinical and pathological characteristics of such patients, and proposed a prediction methodology for RAIR-DTC at an early stage.

MATERIALS AND METHODS

Study Conduct

Each patient was provided with written information about the principles of the therapy and regulations of radiological protection. Further, written informed consent was obtained from all patients for participating the study. The selection and drop outs of study participants were shown in Flowchart Figure (Figure 1).

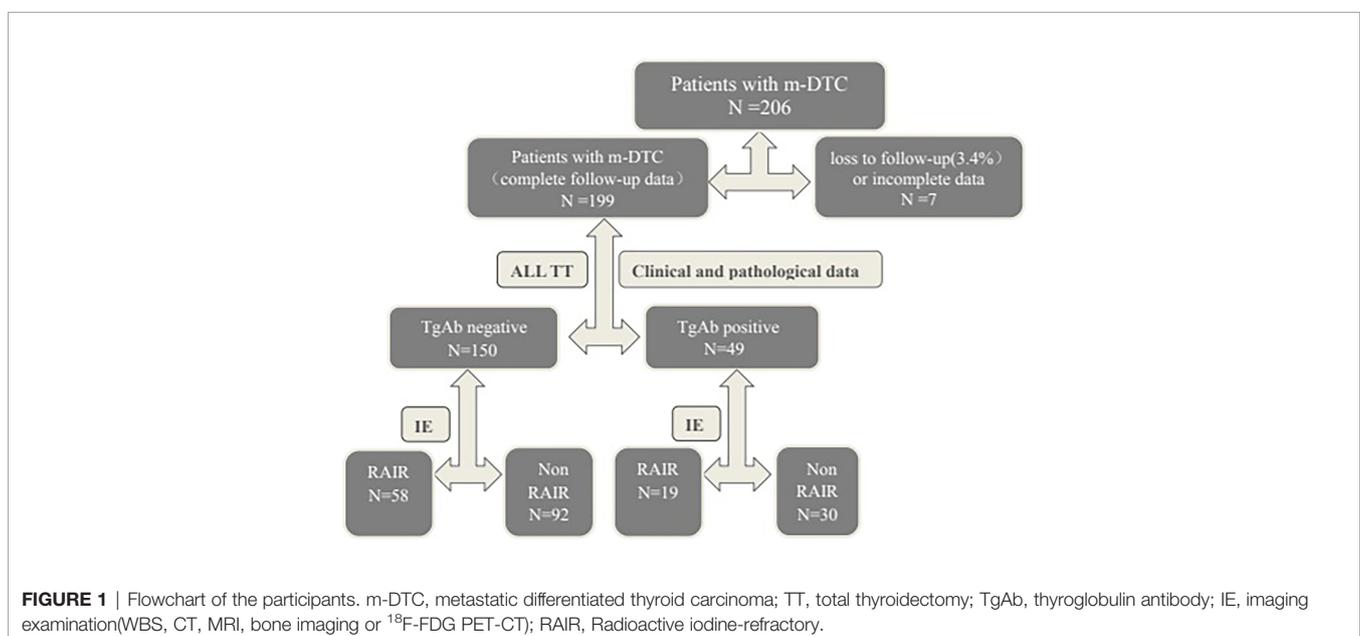
Patients

This retrospective study was conducted between January 2003 and October 2019. There were 199 of 206 cases with complete follow-up data. Loss to follow-up rate was 3.4%. Collectively, 199 m-DTC patients (71 males and 128 females; age range: 11-73 years) were enrolled. The average follow-up time was (50.2 ± 20.3) months. The inclusion criteria were as follows: (1) received total or near total thyroidectomy, (2) metastatic lesions existed, (3) received at least two courses of RIT, (4) both Tg and thyroglobulin antibody (TgAb) measured at the same time and scored according to the results. Patients were divided into TgAb negative group and TgAb positive group.

Patients were defined as lung, lymph node, bone or other site of metastasis with the following facts (3): (1) metastasis site confirmed by histopathology, (2) ¹³¹I-WBS showed focal or diffuse lung, lymph node, bone or other metastatic uptake, with or without other positive findings (by chest CT, X-rays, MRI, bone imaging or ¹⁸F-FDG PET/CT) and with or without Tg (TgAb) level elevation, (3) m-DTC patients diagnosed with different metastases site by post-therapeutic or diagnostic ¹³¹I-WBS after thyroid remnant ablation.

Clinical and Pathological Data

The clinical and histopathological data evaluated in this study included gender, age, primary tumor size, extrathyroid invasion, single or multiple primary tumors, AJCC TNM staging (4), BRAF gene mutation, lung metastasis size, and lymph nodes metastases size. Among them, lung metastasis, and lymph node metastasis were all divided into <1cm and ≥1cm; AJCC T staging was divided into T4 and T3 or below; AJCC N staging was divided into N0 and N1; AJCC M staging was divided into M0 and M1; BRAF gene mutations were detected by PCR.



Postoperative RIT and Follow-Up Strategy

A serum thyroid stimulating hormone (TSH) level of higher than 30 μ IU/mL was achieved by thyroid hormone withdrawal (THW) before RIT. All patients were instructed with a low iodine diet from the beginning of THW till 3 weeks after RIT. Patients were administrated with a radioactive iodine dose of 3.7–7.4GBq (100–200mCi) according to the Chinese guideline (5). The second RIT was performed about 6 months after first therapy (5). All patients were under TSH suppressive therapy by using sodium levothyroxine with TSH <0.1 μ IU/mL.

The functional detection sensitivities of Tg and TgAb by electrochemiluminescence immunoassay (Abbott Laboratories, Chicago, IL, USA) were 0.2 ng/mL and 20 IU/mL. TSH was determined by chemiluminescence immunoassay (Abbott Laboratories, Chicago, IL, USA), with a measuring range from 0.35 to 4.94 μ IU/mL. A serum stimulated or suppressed Tg, TSH, TgAb were usually followed 1 day before RIT and 2–3 months after RIT.

¹³¹I-WBS was obtained by using Discovery NM/CT 670 (General Electric Medical Systems, Milwaukee, Wisconsin, USA) equipped with high-energy parallel-hole collimators, and a 20% energy window was centered at 364 keV, at a table speed of 14 cm/min for a total time of 20 min (256 \times 1024 matrix). Post-therapeutic whole-body scan (Rx-WBS) was performed 3–6 days after RIT (5).

Tg and TgAb Assessment Profiles

The patients were divided into TgAb negative group and TgAb positive group. The stimulated Tg (defined as Sti-Tg) at the first and second RIT were defined as Sti-Tg1 and Sti-Tg2, the suppressed Tg (defined as Sup-Tg) were designated as Sup-Tg1 and Sup-Tg2, while TgAb were defined as TgAb1 and TgAb2, respectively.

Assessment of Radioactive Iodine-Refractory Thyroid Carcinoma

Till the last time of follow-up, RAIR-DTC was defined if the patient met any of the followings criteria (3): (1) the malignant/metastatic tissue did not ever concentrate RAI, (2) tumor tissue lost the ability to concentrate RAI after previous evidence of RAI-avid disease (absence of ¹³¹I contamination), (3) RAI was avidly concentrated in some lesions but not in others, and (4) metastatic disease progressed despite avidity of RAI.

Statistical Analysis

Univariate analysis, t test and Mann-Whitney test were used for qualitative variables, and chi-square test was used to compare categorical data. Logistic regression was used for multivariate analysis. ROC (Receiver operating characteristic) curve analysis was used to determine the critical value for predicting RAIR-DTC. Statistical analysis was carried out using SPSS (version 22.0; SPSS Inc, Chicago, Illinois, USA). A p value of less than 0.05 was considered significant.

RESULTS

Patient Clinical and Pathological Characteristics

A total of 199 m-DTC patients (71 males and 128 females; age range: 11–73 years) were involved in this study, 150 were in the TgAb negative group and 49 in the TgAb positive group. Among them, 4 cases were follicular thyroid carcinoma (FTC) and 195 cases were papillary thyroid carcinoma (PTC). A total of 77 patients were considered as RAIR-DTC. The average follow-up time was (50.2 \pm 20.3) months. The clinical and pathological characteristics of the included patients were shown in **Table 1**.

Univariate Analysis

Univariate analyses on the factors to predict RAIR-DTC were given in **Tables 2, 3**. The results of TgAb negative group showed that cases with older age, extrathyroidal invasion, higher AJCC T stage, BRAF V600E mutation positivity, lower Sti-Tg2/Sti-Tg1 and lower Sup-Tg2/Sup-Tg1 after the first two courses of RIT would lead to poorer prognosis ($P=0.000, 0.000, 0.002, 0.000, 0.000$ and 0.000 , respectively). However, we found no statistically significant differences in gender, primary tumor size, multifocality, AJCC N stage, AJCC M stage, lung metastasis size and lymph node metastasis size.

The results of TgAb positive group showed that cases with older age, extrathyroidal invasion, higher AJCC M stage, higher TgAb1 level, BRAF V600E mutation positivity, and lower TgAb2/TgAb1 would more likely progress to RARI-DTC ($P=0.005, 0.000, 0.000, 0.004, 0.003$ and 0.000 , respectively). However, we found no statistically significant differences in gender, primary tumor size, primary tumor multifocality, AJCC T stage, AJCC N stage, lung metastasis size, and lymph node metastasis size. In specific, cases over 55 years old, with extraglandular invasion, positive BRAF gene mutation, distant metastasis before the first RIT, TgAb level 14.8 times higher than the upper limit, TgAb dropping less than 46.4% after the first two courses of RIT were influencing factors for becoming RAIR DTC.

ROC Curve Analysis and Diagnostic Performance

Data with statistical significance in the above univariate analyses were further assessed by ROC curve.

In TgAb negative group, ROC curve showed that age, Sti-Tg2/Sti-Tg1 and Sup-Tg2/Sup-Tg1 had good performances in predicting RARI-DTC (**Figure 2**). A cut-off value of age was 40 years old, with a sensitivity of 81.0% and specificity of 60.9% and an area under the curve (AUC) of 0.772. Cut-off value of Sti-Tg2/Sti-Tg1 was 57.0%, with a sensitivity of 98.3% and specificity of 80.4% and AUC of 0.921. Cut-off value of Sup-Tg2/Sup-Tg1 was 81.0%, with a sensitivity of 82.8% and specificity of 65.2% and AUC of 0.740.

In TgAb positive group, ROC curves were drawn regarding age, TgAb1 level and TgAb2/TgAb1 in predicting RARI-DTC (**Figure 3**). The cut-off values of age, TgAb1 level and TgAb2/TgAb1 were 55 years old, 297 IU/ml (14.8 times higher than the

TABLE 1 | Clinical and pathological characteristics of the included patients.

Characteristics	Case number (%) or value
Gender	
Female	128(64.3)
Male	71(35.7)
Age	
Mean \pm SD(years)	45.27 \pm 15.23
>55	60(30.2)
\leq 55	139(69.8)
Tumor size	
Median (IQR) (cm)	1.0(0.8,2.6)
Multifocality/Unifocality	
Multifocality	88(44.2)
Unifocality	111(55.8)
Extra-thyroid extension	
Yes	110(55.3)
No	89(44.7)
AJCC T Stage	
T1	74(37.2)
T2	32(16.1)
T3	36(18.1)
T4	57(28.6)
AJCC N Stage	
N0	46(23.1)
N1a	113(56.8)
N1b	40(20.1)
AJCC M Stage	
M0	98(49.2)
M1	101(50.8)
Before treatment TSH level (μ U/mL)	
First	82.0 \pm 37.5
Second	87.4 \pm 34.4
RIT dose (mCi)	
First	123.6 \pm 29.3
Second	145.3 \pm 35.0
Metastasis region	
Pulmonary Only	17(8.5)
Lymph node Only	98(49.2)
Pulmonary and Lymph node	44(22.1)
Pulmonary and Bone	22(11.1)
Pulmonary and other organs	18(9.1)
Lung Node size(cm)	
>1cm	12(6.0)
\leq 1cm	187(94.0)
Lymph Node size (cm)	
>1cm	11(5.5)
\leq 1cm	188(94.5)
RAIR	
Yes	77(38.7)
No	122(61.3)
Detection of Non- ¹³¹ I-avid Lesions	
CT combined with Tg	69(89.6)
PET combined with Tg	8(10.4)
Follow-up time	
Mean \pm SD(month)	50.2 \pm 20.3

TSH, thyroid stimulating hormone; RIT, radioiodine therapy; RAIR, radioactive iodine-refractory.

upper limit) and 53.6%, with corresponding sensitivities of 68.4%, 73.7% and 94.7%, specificities of 86.7%,70.0% and 86.7%, and AUC values of 0.712, 0.747 and 0.974, respectively.

Multivariate Logistic Regression Analysis

In TgAb negative group, multivariate logistic regression (Table 4) revealed that age (OR: 6.285, 95% CI: 1.256–31.446,

$P=0.025$), extrathyroid invasion (OR: 8.299, 95% CI: 1.521–45.269, $P=0.014$), Sti-Tg2/Sti-Tg1 (OR: 53.337, 95% CI: 8.630–329.660, $P=0.000$), Sup-Tg2/Sup-Tg1 (OR: 11.404, 95% CI: 2.270–57.288, $P=0.003$) and BRAF gene mutation (OR: 7.292, 95% CI: 1.603–33.167, $P=0.010$) were independent factors in predicting RAIR-DTC. Specifically, age over 40 years old, with extraglandular invasion, BRAF gene mutation positivity, Sti-Tg decreased less than 43% and Sup-Tg decreased less than 19% were independent predictors for RAIR-DTC.

Due to small number of cases in TgAb positive group, the logistic regression analysis was not conducted.

DISCUSSION

Currently, RIT is the mainstay treatment for m-DTC, especially for patients with lung, lymph node, bone or other metastases, while its efficacy depends on the ability of radioiodine uptake in the metastatic lesions. Non-avidity of the lesions usually indicates a tendency towards RAIR and less favorable outcome. The prognosis of patients with m-DTC is affected by many factors, and the loss of iodine uptake capacity in metastases will eventually transform into RAIR-DTC leading to a poorer prognosis (6–8). And the increasing risk of adverse effect and the progression during THW each time from repeated high-dose RIT limited its benefits. The current advancements in RAIR-DTC diagnosis are made according to post-¹³¹I therapy evaluation, under which circumstance the patients may have been exposed to unnecessary RAI and missed the opportunity to receive more effective interventions (such as targeted drug therapy). There is a need to be able to predict RAIR-DTC before ¹³¹I therapy and direct to a more individualized treatment (9). How to quickly evaluate and diagnose RAIR-DTC in an early stage, and timely adopt more effective methods for m-DTC is an important issue that needs to be solved urgently (10–12). In the current study, we envision whether metastatic RAIR-DTC can be early predicted by analyzing the clinical and pathological characteristics of these patients.

Multiple studies have confirmed Tg as a specific biomarker of DTC metastasis (13, 14). Song et al. (8) reported that the decline of Tg levels after RIT could link to the efficacy of ¹³¹I. Serum Tg level is the most sensitive and easily available bio-marker, and an indicator of recurrence or metastasis during the follow-up monitoring after thyroidectomy and ¹³¹I ablation in DTC patients. The quantitative changes of Tg could provide the basis for tumor response to RIT, and could be used as an index to predict RAIR-DTC (15). Miyauchi et al. (16) found that Tg-doubling time (Tg-DT) was a prominent independent predictor of RAIR-DTC prognosis. Patients with Tg-DT shorter than 1 year showed a 10-year-survival rate of 50%, which was significantly less than 95% of those with Tg-DT for 1–3 years. However, some patients with positive TgAb would hamper the accuracy of Tg determination and makes serum Tg level unreliable. In these patients, Tg cannot be used as DTC marker (17, 18).

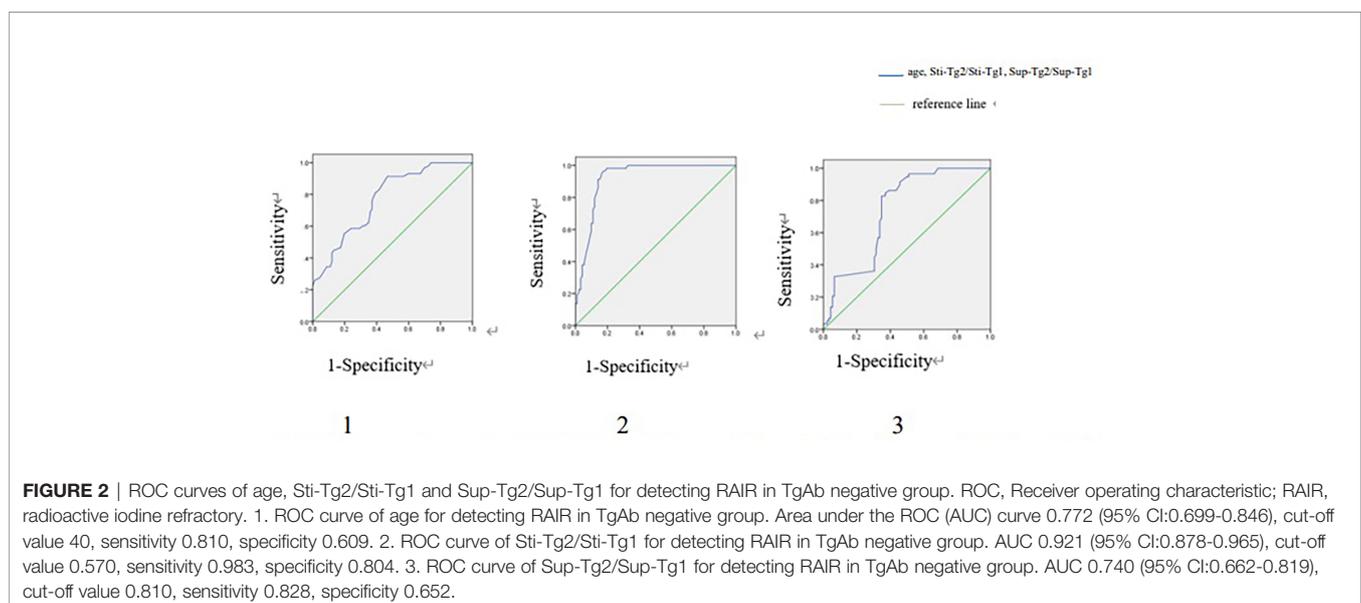
In the current management guideline (3), the concept of using TgAb as DTC marker has not been taken into account with a full

TABLE 2 | Univariate analysis of the factors in the TgAb negative group.

Baseline factors	Univariate			
	RAIR	non-RAIR	t/Z/X ²	P
Gender (Male/Female)	24/34	29/63	1.513	0.226
Age	52.190 ± 13.093	37.978 ± 13.937	6.224	<0.001
Tumor Size	1.5(0.9-2.6)	1.0(0.7-1.7)	-1.900	0.057
Extra-thyroid extension (+/-)	55/3	34/58	49.375	<0.001
Multifocality/Unifocality	30/28	40/52	0.9727	0.401
AJCC T Stage(T4/≤T3)	27/31	21/71	9.202	0.002
AJCC N Stage(N1/N0)	50/8	66/26	3.248	0.056
AJCC M Stage(M1/M0)	36/22	51/41	0.643	0.498
Sti-Tg2/Sti-Tg1	1.121 ± 0.484	0.465 ± 0.288	9.337	<0.001
Sup-Tg2/Sup-Tg1	0.967 ± 0.258	0.665 ± 0.397	5.639	<0.001
BRAF (+/-)	47/11	16/76	59.149	<0.001
Lung Node size(>1/≤1cm)	6/52	2/90	4.704	0.056
Lymph Node size(>1/≤1cm)	3/55	3/89	0.339	0.677

TABLE 3 | Univariate analysis of the factors in the TgAb positive group.

Baseline factors	Univariate			
	RAIR	non-RAIR	T/Z/X ²	P
Gender (Male/Female)	4/15	14/16	2.274	0.132
Age	54.105 ± 16.289	42.367 ± 11.559	2.951	0.005
Tumor Size	1.2(0.8-2.5)	0.9(0.7-1.3)	-1.611	0.107
Extra-thyroid extension (+/-)	15/4	6/24	14.186	<0.001
Multifocality/Unifocality	10/9	8/22	3.375	0.066
AJCC T Stage(T4/≤T3)	6/13	3/27	3.613	0.057
AJCC N Stage(N1/N0)	17/2	20/10	2.155	0.142
AJCC M Stage(M1/M0)	12/7	2/28	15.527	<0.001
TgAb1	528.000 (262.000-1652.000)	160.000 (72.750-681.500)	-2.894	0.004
TgAb2/TgAb1	1.046 ± 0.400	0.353 ± 0.199	7.030	<0.001
BRAF (+/-)	11/8	4/26	8.878	0.003
Lung Node size(>1/≤1cm)	2/17	2/28	0.231	0.631
Lymph Node size(>1/≤1cm)	3/16	2/28	0.296	0.587



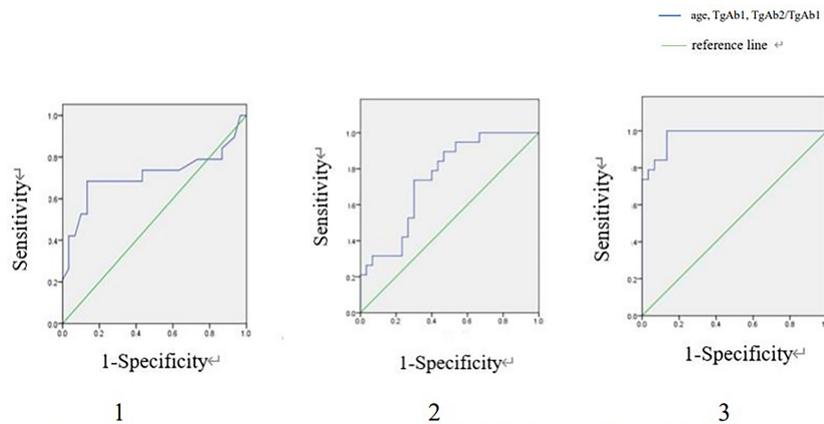


FIGURE 3 | ROC curves of age, TgAb1 and TgAb2/TgAb1 for detecting RAIR in TgAb positive group. ROC, Receiver operating characteristic; RAIR, radioactiveiodine refractory. 1. ROC curve of age for detecting RAIR in TgAb positive group. Area under the ROC curve (AUC) 0.712 (95% CI:0.539-0.885), cut-off value 55, sensitivity 0.684, specificity 0.867. 2. ROC curve of TgAb1 for detecting RAIR in TgAb positive group. AUC 0.747 (95% CI:0.612-0.883), cut-off value:297, sensitivity: 0.737, specificity 0.700. 3. ROC curve of TgAb2/TgAb1 for detecting RAIR in TgAb positive group. AUC 0.974 (95% CI:0.000-1.000), cut-off value 0.536, sensitivity 0.947, specificity 0.867.

TABLE 4 | Logistic regression analyses of factors in the TgAb negative group.

RAIR/non-RAIR	Multivariate			
	P	OR		95%CI
Age(>40.0/≤40.0)	0.025	6.285	1.256	31.446
Extra-thyroid extension (+/-)	0.014	8.299	1.521	45.269
AJCC T Stage(T4/≤T3)	0.057	6.939	0.948	50.680
Sti-Tg2/Sti-Tg1(>0.570/≤0.570)	<0.001	53.337	8.630	329.660
Sup-Tg2/Sup-Tg1 (>0.810/≤0.810)	0.003	11.404	2.270	57.288
BRAF (+/-)	0.010	7.292	1.603	33.167

consensus. There are still conflicts regarding the association between TgAb and DTC outcomes (19–23). Some previous studies suggested that a rising trend of TgAb itself could indicate cancer recurrence or persistence (19–22). However, in another study (23), TgAb was not found to predict disease status in DTC patients. In order to avoid the above inconsistency, this study divided patients into TgAb-negative group and TgAb-positive group for further separate analysis.

Regarding the influencing factors, it is known that age is an independent prognostic factor for the efficacy of RIT (24–26). It could be due to the fact that elderly patients have longer disease duration, lower radiation sensitivity, poor uptake of ¹³¹I and weaker immune system. Therefore, close follow-up monitoring and/or other management strategies should be carried out for these elderly patients to avoid unnecessary or excessive RIT.

Regarding BRAFV600E mutation in DTC, literature indicates conflicting results. Some viewpoints suggest that BRAFV600E mutation is associated with DTC recurrence and poor prognosis (27–30). The BRAFV600E mutation negatively regulates iodine metabolism genes (NIS, TSHR, Tg, TPO, etc) *via* the abnormal activation of the mitogen-activated protein kinase (MAPK) pathway (31, 32). The opposite viewpoint exists showing

BRAFV600E has limited predictive value for DTC prognosis, but, TERT and BRAF double mutations as a biomarker for predicting a worse outcome (33, 34). Our study demonstrated that the positive BRAF gene mutation was a predictor of RAIR-DTC.

In our research, we also focused on whether extrathyroid invasion could lead to RAIR-DTC. Ha's study suggested that aggressive histopathologic subtypes were significantly associated with the recurrent or metastatic lesions in RAI-negative DTC (35). Robertson et al. (36) conducted a multivariate analysis of 231 patients with thyroid cancer and found that lymphadenopathy was the only important risk factor for recurrence ($p < 0.001$), and the presence of extrathyroid invasion ($p = 0.013$) led to high mortality. Aboelnaga (37) found that the survival rate of PTC was significantly affected by age, extrathyroid invasion and extensive distant metastasis. Our study also showed that the presence of extrathyroid invasion could be used as a predictive factor for the diagnosis of RAIR-DTC.

Li et al. (38) evaluated the clinical features of patients with RAIR-DTC, which indicated that tumor size, BMI, gender and TNM staging were statistically nonsignificant trend, however,

smoking, tumor type (follicular thyroid cancer), extrathyroid extension, lymph node metastasis number (≥ 4), lymph node metastasis rate ($\geq 53\%$), and pN stage (N1) were positively correlated with the prevalence of RAIR-DTC. Our study made some amendments based on the above literature and increased the predictive value of changes in TG and TgAb for RAIR-DTC, and showed negative predictive value for lymph node metastasis size. In the TgAb negative group, those who were over 40 years old, with obvious extraglandular invasion, BRAF gene mutation, Sti-Tg decreased less than 43% and Sup-Tg decreased less than 19% would develop into RAIR-DTC. Even if these patients continue RIT, they would not benefit from it, treatment and follow-up strategy should be adjusted. However, we found no statistically significant differences in gender, primary tumor size, multifocality, AJCC N stage, AJCC M stage, lung metastasis size and lymph node metastasis size. In the TgAb-positive group, the results found that both TgAb levels and trends between RAIR and non-RAIR-DTC were quite different. The persistently high TgAb level may indicate high aggressiveness of the tumor, which was a manifestation of poor prognosis. If the TgAb level did not decrease significantly after the second RIT, the patient would not benefit from the therapy.

This study had limitations. Firstly, the design of retrospective studies has shortcomings and should be verified by future prospective studies. Secondly, the number of TgAb positive cases was small, and it was difficult to conduct multivariate analysis. Thirdly, there may be interactions between positive results obtained by univariate analysis.

CONCLUSION

In summary, this study showed for TgAb-negative DTC patients, age over 40, extraglandular invasion, mutated BRAF gene, Sti-Tg decreased less than 43%, and Sup-Tg decreased less than 19%

after the first two courses of RIT were independent predictors for RAIR-DTC. For TgAb-positive DTC patients, age over 55, extraglandular invasion, mutated BRAF gene, distant metastasis before the first RIT, level 14.8 times higher than the upper limit, TgAb dropped less than 46.4% after the first two courses of RIT were influencing factors.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of Tianjin Medical University General Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JC and RW contributed to the conception and design of the study. JC, RZ assisted with data acquisition. JC, RZ, and RW conducted the statistical analyses and drafted the manuscript. JT, ZM, QJ and GZ critically revised the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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