ORIGINAL ARTICLE

Evaluation of Factors Associated with Recurrent Differentiated Thyroid Cancer in Patients Who Underwent Total Thyroidectomy and Radioiodine Therapy with Biochemical Incomplete Responses

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Objective: The objectives of the present study were 1) to evaluate the factors that predict the recurrence of thyroid cancer in patients with biochemical incomplete responses (BIR) and differentiated thyroid cancer (DTC) patients who were treated with total thyroidectomy and radioiodine-131, 2) to determine the distribution and location of recurrences, and 3) to assess the serial serum thyroglobulin (Tg) and thyroglobulin antibodies (TgAb) to determine the diagnostic accuracy for disease recurrence.

Materials and Methods: The authors retrospectively reviewed 203 BIR patients treated between January 2004 and December 2014. Data were recorded on case report forms, including age at the time of first radioiodine-131 treatment, gender, diagnosis, surgical history, Tg and TgAb levels, pathological examination results, and radiology findings from radioiodine-131 whole-body scanning, computed tomography (CT), neck ultrasound, and F-18 FDG PET/CT scans. The 203 patients were classified into two groups, recurrence patients with 54 patients (26.6%), and non-recurrence patients with 149 patients (73.4%).

Results: The number and percentage of local recurrences or metastatic lesions were cervical lymph node metastasis in 26 patients (48.1%), local recurrence in 18 patients (33.3%), lung metastasis in 11 patients (20.4%), and bone metastasis in one patient (1.9%). Two patients had lesions in both the surgical site and cervical lymph nodes. Statistically significant clinical characteristics between the two groups included age, the American Thyroid Association (ATA) 2015 risk of recurrence, and lymph node metastasis. Optimal thresholds for recurrence were identified as a Tg velocity greater than 0.6 ng/mL/year, a Tg doubling time of less than 3.5 years, and a TgAb velocity greater than 0 IU/mL/year.

Conclusion: Risk factors for local recurrences or metastatic lesions in BIR patients include older age, lymph node metastasis, ATA high risk stratification, Tg velocity at 0.6 ng/mL/year or greater, Tg doubling time in less than 3.5 years, and TgAb velocity greater than 0 IU/mL/year. Close follow-up with CT neck and chest is recommended to detect cervical lymph node metastasis, local recurrences, and lung metastasis.

Keywords: Biochemical incomplete response; Tg velocity; Tg double time; TgAb velocity; Recurrence differentiated thyroid cancer

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Thyroid cancer is the most common type of endocrine cancer. In Thailand, the incidence of the disease was 1.17% in 2017, ranking sixth among all cancer types in the country[1]. Biochemical incomplete response (BIR) is defined as persistently abnormal, suppressed, or stimulated thyroglobulin (Tg) values or rising anti-Tg antibodies (TgAb), without any structural evidence of disease. BIR is observed in 15% to 20% of patients with differentiated thyroid cancer (DTC)[2].

The risk of developing structural disease in BIR patients has been reported to range from 8% to 17% over 5 to 10 years of follow-up, with 56% to 68% of these patients showing no evidence of disease at their final follow-up[2-4]. Currently, there is no standard guideline for the treatment and follow-up of BIR patients. Identifying factors that predict thyroid cancer recurrence in BIR patients may help in assessing the risk of disease progression, thereby influencing follow-up investigations, and optimizing treatment strategies.

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Objective

The objectives of the present study were 1) to evaluate factors that predict the recurrence of thyroid cancer in BIR DTC patients treated with total thyroidectomy and radioiodine-131, 2) to determine the distribution and location of recurrences, and 3) to assess serial serum Tg and TgAb levels to determine the diagnostic accuracy for disease recurrence.

Materials and Methods

Patients

The authors retrospectively reviewed 5,005 patients diagnosed with malignant neoplasm of the thyroid gland from the files with ICD-10-CM diagnosis code C73. Of these, 1,877 patients were excluded because they had Tg levels of less than 1 ng/mL and TgAb of less than 40 IU/mL. After screening the remaining 3,128 patients according to inclusion and exclusion criteria, 203 patients with BIRs were identified for the study.

Inclusion criteria

- Patients aged 15 years and older with DTC
- Received total or near-total thyroidectomy and at least one treatment with radioiodine-131
- Classified as BIR based on dynamic risk stratification (DRS), with stimulated Tg greater than 10 ng/mL or unstimulated Tg greater than 1 ng/mL after radioiodine ablation
- Underwent laboratory testing and radioiodine-131 total body scan (TBS)

Exclusion criteria

- History of other types of cancer
- Diagnosed with radioiodine-refractory thyroid cancer prior to BIR
- No recurrence of disease, and a follow-up period of less than one year after BIR diagnosis
- No pathology confirmation before radioiodine-131 treatment

Data collected on case record forms included age at the time of first radioiodine-131 treatment, gender, diagnosis, surgical history, Tg and TgAb levels, pathology results, and radiology findings from radioiodine-131 TBS, computed tomography (CT), neck ultrasound, and F-18 FDG PET/CT scans.

Biochemical assays

The authors used the following first- and second-generation assays for measuring Tg and TgAb:

Elecsys® Tg (1st generation), performed pre-2014 (Elecsys® TG I, Roche Diagnostics, Mannheim, Germany), with a measuring range of 0.1 to 500 ng/mL.

Elecsys® Tg (2nd generation), used since 2014 (Elecsys® TG II, Roche Diagnostics, Mannheim, Germany), with a measuring range of 0.04 to 500 ng/mL.

TgAb, measured using the Elecsys® anti-TG assay (Roche Diagnostics, Mannheim, Germany), with a measuring range of 10 to 4,000 IU/mL.

Definition of Tg velocity, Tg doubling time, TgAb velocity, and TgAb doubling time

To determine velocity (slope) or doubling time using simple linear regression, the authors collected Tg levels from the time of BIR diagnosis to either disease recurrence or the last follow-up visit, with thyroid-stimulating hormone (TSH) levels of less than 30 IU/mL during this period. Tg velocity was defined as the slope of the equation, expressed in ng/mL/year.

Tg doubling time was calculated by dividing the suppressed Tg by the slope, with the unit expressed in years. TgAb velocity and TgAb doubling time were determined using the same method as for Tg velocity and Tg doubling time.

The optimal cutoff values for Tg velocity, Tg doubling time, and TgAb velocity for clinical purposes were established through receiver operating characteristic (ROC) curve analyses.

Diagnosis of disease recurrence

Recurrence in the thyroid or cervical lymph nodes was diagnosed through pathological examination of tissue specimens obtained via fine needle aspiration, biopsy, or surgery.

Pulmonary recurrence was determined by one of the following methods:

1. Detection of radioiodine-131 uptake on a TBS.
2. Identification of multiple pulmonary nodules on CT imaging.
3. Presence of one or more pulmonary nodules, combined with:
   - o Solid or part-solid nodules, or
   - o An increase in nodule size on follow-up studies

Bone recurrence was diagnosed based on:

1. Radioiodine-131 uptake observed on a TBS, or
2. Presence of an obvious osteolytic lesion on CT or single-photon emission computed tomography (SPECT/CT) imaging.

Statistical analysis

Descriptive statistics were presented as number and percentage for categorical variables, and as mean ± standard deviation or median (interquartile range, IQR) for continuous variables. Comparisons between the two groups were made using Pearson's chi-squared test or Fisher's exact test where appropriate. Calculation of Tg velocity, Tg doubling time, TgAb velocity, and TgAb doubling time in the recurrence and non-recurrence groups using ROC curve analysis and optimal cut-off velocity and doubling time using highest area under the ROC curve (AUC) value.

All analyses were performed using R software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) with the "tidyverse 1.3.0" and "epicalc 3.5.1.7" packages. A p-value of less than 0.05 was considered statistically significant.

Ethical approval

Prior to the commencement of the present research, the study protocol was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Siriraj Hospital, under Research Project Certification No. 379/2020.

Results

The clinical characteristics of the patients are presented in Table 1. A comparison of the clinical characteristics between the recurrence and non-recurrence patient groups, along with their statistically significant differences, is shown in Table 2. Based on this analysis, the 203 patients were classified into two groups, recurrence patients with 54 patients (26.6%), and non-recurrence patients with 149 patients (73.4%).

Statistically significant differences between the two groups were observed in age, the American Thyroid Association (ATA) 2015 risk of recurrence, and cervical lymph node metastasis before radioiodine treatment. Older age, cervical lymph node metastasis prior to radioactive iodine treatment, and a high-risk classification based on the ATA 2015 guidelines were associated with a higher recurrence rate in BIR thyroid cancer patients.

The number and percentage of recurrences, stratified by metastasis characteristics, are detailed in Table 3. Notably, two patients had lesions in both the surgical site and the cervical lymph nodes, and no distant metastasis was found in organs such as the brain, liver, or kidneys.

For recurrence patients, the median duration of follow-up was 3.4 years, with an IQR of 2.3 to 4.9 years. In non-recurrence patients, the median duration was 5.7 years with an IQR of 4.1 to 7.9 years.

Table 1. Clinical characteristic of the patients (n=203)

Clinical characteristic	Results
Age (years); median (IQR)	43.8 (32.8, 56.5)
Female; n (%)	164 (80.8)
Thyroid tumor type (n=200); n (%)	
Papillary carcinoma	189 (93.1)
Follicular carcinoma	6 (3.0)
Mix papillary and follicular carcinoma	5 (2.5)
Number of RAI therapy sessions; median (IQR)	2 (2, 3)
Cumulative RAI dose (mCi); median (IQR)	300 (300, 450)
TNM staging (AJCC 8th edition) (n=187); n (%)	
Age <55 years	
• I	145 (98.6)
• II	2 (1.4)
Age ≥55 years	
• I	9 (22.5)
• II	30 (75.0)
• III	1 (2.5)
• IV	-
Lymph node metastasis (n=203); n (%)	
N0	107 (52.7)
N1a	85 (41.9)
N1b	11 (5.4)
ATA 2009 risk of recurrence (n=189); n (%)	
Low risk	12 (6.4)
Intermediate risk	149 (78.8)
High risk	28 (14.8)

IQR=interquartile range; RAI=radioactive iodine; AJCC=American Joint Committee on Cancer; ATA=American Thyroid Association

Medians for Tg velocity, Tg doubling time, TgAb velocity, and TgAb doubling time in the recurrence and non-recurrence groups are presented in Table 4. Cut-off values for Tg velocity, Tg doubling time, and TgAb velocity were determined using ROC curve analyses, as shown in Table 5-7, respectively. However, the differences in TgAb doubling times between the recurrence and non-recurrence groups were not statistically significant, so cut-off values for TgAb doubling time were not calculated.

Diagnostic properties of Tg velocity based on factors associated with disease recurrence are presented in Table 5. The optimal Tg velocity cut-off was greater than 0.6 ng/mL/year, yielding the highest AUC value of 62.36, with a sensitivity of 30.77%, specificity of 93.96%, and accuracy of 77.61%.

The diagnostic properties of Tg doubling time are presented in Table 6. An optimal cut-off of less than 3.5 years provided the highest AUC value of 70.96,

Table 2. Comparison of the clinical characteristics of the recurrence and non-recurrence patient groups, and their statistic significant differences

Clinical characteristic	Recurrence patient (n=54)	Non-recurrence patient (n=149)	p-value
Age (years); median (IQR)	47.6 (35.5, 61.5)	41.6 (30.6, 54.4)	0.025
Female; n (%)	41 (75.9)	123 (82.6)	0.391
Number of RAI therapy sessions; median (IQR)	2 (2, 3)	2 (2, 3)	0.169
Cumulative RAI dose (mCi); median (IQR)	300 (300, 450)	300 (60, 450)	0.448
Papillary thyroid cancer; n (%)	50 (92.6)	141 (94.6)	0.836
ATA 2009 risk of recurrence; n (%)			0.036
Low	2 (3.9)	10 (7.3)	
Intermediate	36 (70.6)	113 (81.9)	
High	13 (25.5)	15 (10.9)	
ATA 2009 risk of recurrence; n (%)			0.023
Non-high	38 (74.5)	123 (89.1)	
High	13 (25.5)	15 (10.9)	
Lymph node metastasis; n (%)			0.004
N0	19 (35.2)	88 (59.1)	
N1	35 (64.8)	61 (40.9)	
Microscopic invasion; n (%)	19 (35.2)	34 (22.8)	0.111
Macroscopic invasion; n (%)	4 (7.4)	7 (4.7)	0.488
Vascular invasion; n (%)	15 (27.8)	46 (30.9)	0.376
Metastasis on 1st post therapeutic TBS; n (%)			
Lymph node metastasis	44 (29.9)	20 (37.7)	0.397
Lung metastasis	2 (1.4)	0 (0.0)	1.000
Bone metastasis	0 (0.0)	0 (0.0)	-
Post-operative TSH-stimulated Tg (ng/mL); n	42	124	
Median (IQR)	20.0 (6.3, 113.4)	29.0 (9.9, 103.8)	0.567

IQR=interquartile range; RAI=radioactive iodine; ATA=American Thyroid Association; TBS=total body scan; TSH=thyroid-stimulating hormone; Tg=thyroglobulin

Analysis of the data resulted in the 203 patients being classified into two groups: recurrence patients (n=54, 26.6%), and non-recurrence patients (n=149, 73.4%). The clinical characteristics of the 2 groups which had a statistically significant were age, ATA 2009 risk of recurrence, and lymph node metastasis.

Table 3. Number and percentage of recurrences by metastasis characteristic

Location of recurrence	n (%)
Cervical lymph node metastasis	26 (48.1)
Local recurrence	18 (33.3)
Lung metastasis	11 (20.4)
Bone metastasis	1 (1.9)

Two patients had lesions at both the surgical site and the lymph nodes in the neck. There was no spread of the disease to distant organs, such as the brain, liver, or kidneys.

For the recurrence BIR patients, the median duration was 3.4 years, and the interquartile range was 2.3 to 4.9 years. As to the non-recurrence BIR patients, the median duration was 5.7 years and the interquartile range was 4.1 to 7.9 years.

with a sensitivity of 70%, specificity of 71.93%, and accuracy of 71.26%.

The diagnostic properties of TgAb velocity are shown in Table 7. An optimal TgAb velocity greater than 0 IU/mL/year yielded the highest AUC of 60.23% and a specificity of 81.25% but its sensitivity was only 39.22%.

The highest AUC value of Tg velocity, Tg doubling, and TgAb velocity, 60% to 70%, is not an accurate diagnosis to predict the recurrence or non-recurrence of the disease.

Discussion

There is limited information on the factors associated with disease recurrence in BIR thyroid cancer patients. The present study found that older age, a high ATA 2015 risk of recurrence, and cervical lymph node metastasis prior to radioiodine treatment were statistically significant factors. These information will aid in the follow-up of BIR patients who are older, have a high risk of recurrence, or have a history of cervical lymph node metastasis. These patients will require more intensive investigations and close monitoring to identify any signs of recurrence or metastatic lesions.

Table 4. Medians of the Tg velocities, Tg doubling times, TgAb velocities, and TgAb doubling times of the recurrence and non-recurrence patient groups

Data (unit)	Recurrence (n=54)	Non-recurrence (n=149)	p-value
Tg velocity (ng/mL/year); median (IQR)	(n=33) 0.240 (–0.168 to 2.537)	(n=106) –0.042 (–0.217 to 0.107)	0.002
Tg doubling time (year); median (IQR)	(n=33) 0.72 (0.37 to 4.41)	(n=106) 6.86 (2.47 to 21.57)	<0.001
TgAb velocity (IU/mL/year); median (IQR)	(n=9) 116.60 (77.42 to 340.29)	(n=18) 17.14 (–7.77 to 186.57)	0.041
TgAb doubling time (year); median (IQR)	(n=9) 1.76 (0.52 to 2.61)	(n=18) 4.90 (2.00 to 7.25)	0.120

Tg=thyroglobulin; TgAb=thyroglobulin antibodies; IQR=interquartile range

The cut-off values of Tg velocity, Tg doubling time, and TgAb velocity for clinical purposes were determined by ROC analyses. However, given that the differences in the TgAb doubling times of the recurrence and non-recurrence groups were not statistically significant. TgAb doubling time cut-off values were not calculated.

Table 5. Analytic of the diagnostic properties of Tg velocity levels analyze, based on the factors associated with disease recurrence

Tg velocity	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	Accuracy (%)
≥ –0.4	86.54	12.08	25.57	72.00	50.69	31.34
≥0	57.69	61.74	34.48	80.70	59.72	60.70
≥0.4	34.62	89.93	54.55	79.76	62.27	75.62
≥0.6	30.77	93.96	64.00	79.55	62.36	77.61
≥0.8	26.92	95.30	66.67	78.89	61.11	77.61
≥1.0	26.92	95.30	66.67	78.89	61.11	77.61
≥1.5	26.92	96.64	73.68	79.12	61.78	78.61
≥2.0	25.00	98.66	86.67	79.03	61.83	79.60

Tg=thyroglobulin; PPV=positive predictive value; NPV=negative predictive value; AUC=area under the receiver operating characteristic curve

The optimum values were found when the Tg velocity was greater than 0.6 ng/mL/year. This cut-off velocity had the highest AUC value (0.624), a sensitivity of 30.77%, a specificity of 93.96%, and an accuracy of 77.61%.

Table 6. Analysis of the diagnostic properties of the Tg doubling time levels, based on the factors associated with disease recurrence

Tg doubling time	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	Accuracy (%)
<0.5	30.00	92.98	69.23	71.62	61.49	71.26
<1	50.00	87.72	68.18	76.92	68.86	74.71
<1.5	53.33	84.21	64.00	77.42	68.77	73.56
<2	60.00	78.95	60.00	78.95	69.47	72.41
<2.5	60.00	75.44	56.25	78.18	67.72	70.11
<3.0	63.33	73.68	55.88	79.25	68.51	70.11
<3.5	70.00	71.93	56.76	82.00	70.96	71.26
<4.0	70.00	71.93	56.76	82.00	70.96	71.26
<4.5	73.33	61.40	50.00	81.4	67.37	65.52

Tg=thyroglobulin; PPV=positive predictive value; NPV=negative predictive value; AUC=area under the receiver operating characteristic curve

The optimum Tg doubling time was less than 3.5 years. With a sensitivity of 70%, a specificity of 71.93% and an accuracy of 71.26%, this cut-off yielded the greatest AUC of 0.710.

In the present study, most of the detected lesions were cervical lymph node metastases, local recurrences, and lung metastases. Therefore, CT imaging of the neck and chest would be useful in detecting recurrent lesions in BIR patients.

At the Twenty-Second European Congress of Endocrinology[5], it was proposed that the progression of BIR to structural disease could be predicted by factors such as older age, extrathyroidal extension, higher ATA risk, or advanced stage according to the Eighth edition of the tumor-node-metastasis (TNM) system. However, postoperative Tg was not identified as a predictor for BIR patients.

Two major tools are recommended for risk assessment of DTC patients prior to radioactive iodine treatment, 1) the TNM staging system, and 2) the modified ATA risk stratification system. Before radioactive iodine treatment, patients are classified as low, intermediate, or high risk of recurrence according to the Eighth Edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM staging system and the ATA

Table 7. Analysis of the diagnostic properties of the TgAb velocity levels, based on the factors associated with disease recurrence

TgAb velocity	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	Accuracy (%)
≥ –10	92.16	7.64	26.11	73.33	50.10	29.74
≥ 0	39.22	81.25	42.55	79.05	60.23	70.26
≥ 10	17.65	88.89	36.00	75.29	53.27	70.26
≥ 20	15.69	93.06	44.44	75.71	54.37	72.82
≥ 40	15.69	94.44	50.00	75.98	55.07	73.85
≥ 60	15.69	95.14	53.33	76.11	55.41	74.36
≥ 80	11.76	95.83	50.00	75.41	53.80	73.85
≥100	9.80	95.83	45.45	75.00	52.82	73.33

TgAb=thyroglobulin antibodies; PPV=positive predictive value; NPV=negative predictive value; AUC=area under the receiver operating characteristic curve
The optimum TgAb velocity was greater than 0 IU/mL/year. This value gave the highest AUC (0.602) and a specificity of 81.25%, however its sensitivity was only 39.22%.

risk stratification. After radioactive iodine treatment, DRS is used to evaluate the treatment response during the first year of follow-up. The DRS system categorizes responses into four groups as 1) excellent, 2) indeterminate, 3) BIR, and 4) structural incomplete response.

In the current investigation, lymph node metastasis and ATA risk stratification were significant predictors of cancer recurrence in BIR patients. However, TNM staging was not found to be a significant factor.

Since Tg is produced by both benign and DTC cells, it serves as an effective tumor marker for DTC patients, particularly after total or near-total thyroidectomy and I-131 thyroid ablation. Monitoring serum Tg levels is a valuable approach for detecting recurrent or metastatic disease in DTC patients[6].

In the present study, postoperative stimulated Tg levels measured just before radioactive iodine treatment were not valuable for predicting cancer recurrence in BIR patients. In DTC patients with positive TgAb following radioactive iodine treatment, serum Tg was measured using an immunometric assay, which is likely to be interfered with by TgAb, potentially leading to an underestimation of serum Tg levels.

In the study by Kim et al.[7], the cut-off values for Tg measured just before radioactive iodine treatment (Tg-RAI), Tg-on thyroxine, and Tg-off thyroxine for predicting recurrence were 11.8, 1.4, and 3.3 ng/mL, respectively. The corresponding sensitivity was 85.4%, 82.2%, and 93.3%, and the specificities were 89.2%, 92.4%, and 88.0%. Additionally, the positive predictive values (PPVs) were 71.9%, 77.1%, and 77.0%, while the negative predictive values (NPVs) were 95.0%, 94.4%, and 97.8%, respectively.

For distant metastases, the Tg cut-off values were 27.4, 2.5, and 7.9 ng/mL. At these cut-off points, the sensitivity were 86.7%, 87.5%, and 92.3%, with specificities of 86.2%, 90.8%, and 80.2%. The PPVs were 34.2%, 46.7%, and 25.0%, while the NPVs were 98.7%, 98.8%, and 99.3%.

In Szujo et al. study[8], one-year non-stimulated Tg had excellent prognostic value, with an AUC of 0.933, for structural disease, using a 0.85 ng/mL cut-off value, the diagnostic accuracy was 88.1%.

The determination of Tg velocity, Tg doubling time, TgAb velocity, and TgAb doubling time are simple and clinically applicable, and their uses avoid the adverse effects and patient inconvenience associated with obtaining endogenous TSH stimulation.

There has been limited research on the use of Tg velocity, Tg doubling time, TgAb velocity, and TgAb doubling time to predict recurrence in BIR patient's post-thyroidectomy and post-radioactive iodine ablation for papillary thyroid cancer (PTC). In the present study, a Tg velocity greater than 0.6 ng/mL/year produced the highest AUC value of 62.36, with a sensitivity of 30.77%, a specificity of 93.96%, and an accuracy of 77.61%. In comparison, a Tg doubling time of less than 3.5 years yielded the highest AUC value of 70.96, with a sensitivity of 70%, a specificity of 71.93%, and an accuracy of 71.26%. A TgAb velocity greater than 0 ng/mL/year produced the highest AUC value of 60.23, with a sensitivity of 39.22%, a specificity of 81.25%, and an accuracy of 70.26%.

The present study found low accuracies for Tg velocity, Tg doubling time, and TgAb velocity in detecting recurrence among BIR patient's post-thyroidectomy and post-radioactive iodine ablation for PTC. This may have been due to the small number of recurrence or metastasis cases within the BIR group, which was 33 cases for Tg velocity and Tg doubling time, and nine cases for TgAb velocity, with

some data lost for Tg and TgAb.

Based on the authors' findings, a Tg doubling time of less than 3.5 years in BIR patients is the most reliable predictor of structural disease development. The authors recommend that these patients undergo further investigation, including CT, F-18 FDG PET/CT, or therapeutic whole-body scanning with radioiodine-131.

A previous study reported on Tg velocity and Tg doubling time, but only in DTC patients. Miyauchi et al.[9] were the first to suggest that Tg doubling time could predict locoregional recurrence, distant metastases, and disease-specific survival. They proposed four categories of Tg doubling time, based on arbitrary cut-offs as 1) falling Tg values, 2) less than one year, indicating a rapidly growing disease, 3) one to three years, indicating a slowly growing disease, and 4) greater than three years, suggesting a stable disease.

Wong et al.[10] retrospectively studied the increase in suppressed Tg levels to predict disease recurrence in PTC patients with Tg values exceeding 0.2 ng/mL who had been treated with radioactive iodine. The likelihood of disease recurrence was calculated using logistic regression. Suitable conditions for predicting disease recurrence included a Tg velocity greater than or equal to 0.3 ng/mL/year, with a sensitivity of 83.3% and a specificity of 94.4%. Although a Tg velocity exceeding 0.6 ng/mL/year predicted recurrence with a higher sensitivity of 92.3%, the specificity remained unchanged at 94.4%. Patients with a low Tg velocity, less than 0.3 ng/mL/year, were found to have better recurrence-free and overall survival.

Iwasaki et al.[11] found that the difference in the Tg doubling times between the stable disease group and the progressive disease group was not statistically significant. While Tg doubling time was useful for detecting recurrence and distant metastases, it was not a suitable indicator of disease progression in cases with positive distant metastases.

Limitation

Firstly, the mean follow-up time of 5.7 years for non-recurrent BIR patients may not be long enough to detect recurrence or metastatic lesions, given the natural history of thyroid cancer. Previous studies support this, including Alzahrani et al.[12], whose retrospective cohort study evaluated the survival of 105 DTC patients with elevated Tg levels and negative radioactive iodine-131 whole-body imaging. Over a median period of 5.9 years, 58% of the patients showed improvement, while 11% still had the disease. Other studies[3,13] have reported that 8% to 17% of BIR patients experienced relapses within five to ten years.

Furthermore, only a small number of BIR patients underwent 18F-FDG PET/CT testing. The 18F-FDG PET/CT plays a significant role in detecting recurrence and metastatic disease. Giovanella et al.[14] found that 18F-FDG PET/CT could detect pathological lesions in BIR patients with Tg levels around 5.5 ng/mL or a Tg doubling time of over one year.

Lastly, the present retrospective review analyzed electronic medical records dating back as far as 2004. Inevitably, some data points were missing. Specifically, post-operative Tg levels were unavailable for 64 cases (31.5%), and post-operative TgAb levels had not been recorded for 176 cases (86.7%), which may have impacted the present study calculations of Tg velocities, Tg doubling times, TgAb velocities, and TgAb doubling times in the recurrence and non-recurrence groups.

Conclusion

The present study identified significant factors for recurrence or metastatic disease in BIR response DTC patients, including older age, lymph node metastasis, high-risk ATA stratification, a Tg velocity of 0.6 ng/mL/year or more, a Tg doubling time of less than 3.5 years, and a TgAb velocity of more than 0 ng/mL/year. However, the highest AUC value of Tg velocity, Tg doubling, and TgAb velocity of 60% to 70% does not accurately predict recurrence or non-recurrence. The most common types of recurrence were cervical lymph node metastases, local recurrences, and lung metastases. Close follow-up with CT neck and chest is recommended to detect cervical lymph node metastasis, local recurrences, and lung metastases.

What is already known about this topic?

There are no standard guidelines for the treatment and follow-up of BIR patients. Identifying factors that predict thyroid cancer recurrence, as well as the incidence and location of local recurrences or metastatic lesions in BIR patients, may help assess the risk of disease progression. This, in turn, could influence follow-up investigations and optimize treatment strategies.

What does this study add?

Risk factors for local recurrences or metastatic lesions in BIR patients include older age, lymph node

metastasis, high ATA risk stratification, Tg velocity of 0.6 ng/mL/year or greater, Tg doubling time of less than 3.5 years, and TgAb velocity greater than 0 IU/mL/year. Close follow-up with neck and chest CT is recommended to detect cervical lymph node metastasis, local recurrences, and lung metastases.

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Conflicts of interest

The authors declare no conflict of interest.

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