Heliyon 10 (2024) e26092

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

The effect of positive thyroglobulin antibodies on the prognosis and treatment response in patients with papillary thyroid carcinoma

Mojgan Sanjari [a], Marzieh Ordooei [b,*,1], Ladan Amirkhosravi [a,*,1], Ahmad Naghibzadeh-Tahami [c], Sarir Nazemi [d]

[a] Endocrinology and Metabolism Research Center, Kerman University of Medical Sciences, Kerman, Iran
[b] Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
[c] Modeling in Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
[d] Department of Radiology, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran

ARTICLE INFO

Keywords:
Thyroid cancer
Papillary thyroid carcinoma
Anti-thyroglobulin antibody
Persistence and prognosis

ABSTRACT

Almost 15–30% of patients with papillary thyroid carcinoma (PTC) experience some degree of recurrence after treatment. Long-term follow-up and examination after thyroidectomy are very important in dealing with this issue. Serum thyroglobulin (Tg) level and neck ultrasound are the main part of follow-up for this purpose. The presence of thyroglobulin antibodies (TgAbs) leads to unreliable thyroglobulin (Tg) levels. The present study aims to evaluate the relationship between the simultaneous measurement of Tg and TgAb with long-term survival and response to treatment in these patients. This study was conducted by surveying available data from the medical records of 204 out of 600 patients over a 20-year period. In this research, 104 patients with positive TgAb were considered as the case group, and 100 patients with negative TgAb were selected as the control group. The relationship of TgAb titer was investigated with the staging, response to treatment (including the surgery number, number of radiotherapies, and dose of radioactive iodine), and recurrence in these patients. Also, the trend of TgAb changes was examined in the presence of high or low thyroglobulin levels during the follow-up period. Patients with high TgAb levels had more lymph node involvement, higher cumulative dose, a higher number of times received iodine, more surgical number, higher recurrence rate, and less excellent response (ER) to treatment during follow-ups. This effect of TgAb worsened in the presence of high Tg titer and remained up to 36 months. Overall, the baseline level of TgAb and its changes can be a suitable factor for predicting subsequent response to treatment and recurrence in patients with PTC. Accordingly, in cases with high TgAb and Tg levels, close follow-up should be considered up to Tg and TgAb normalization.

1. Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid cancer among children and adults, accounting for 85%–90% of

* Corresponding authors.
E-mail addresses: dr.m.ordouei@gmail.com (M. Ordooei), l.amirkhosravi@kmu.ac.ir (L. Amirkhosravi).
[1] Both corresponding authors contributed equally.

https://doi.org/10.1016/j.heliyon.2024.e26092
Received 1 July 2023; Received in revised form 7 February 2024; Accepted 7 February 2024
Available online 13 February 2024

differentiated thyroid carcinoma (DTC) [1]. Although most PTC patients have an indolent clinical course and a favorable prognosis, 15%–30% of them experience recurrence. Therefore, a lengthy surveillance period is needed, owing to the risk of recurrence after initial treatment [2]. About 1–7% of patients with PTC have distant metastasis at diagnosis [3]. Also, a scoring index has been devised to predict the risk groups of PTC patients. This index includes 4 independent variables: tumor size, tumor spread rate, tumor grade, and patient age [4].

Thyroglobulin (Tg) is the primary DTC serum marker, particularly when assessed after stimulation with recombinant thyroid hormone or during hypothyroidism [5]. Normal thyroid cancer cells or thyroid tissue are the sole bodily Tg origin, leading to its high specificity [6]. Increase or persistence in Tg concentrations after total thyroidectomy or radioiodine treatment is a valid index of disease persistence or recurrence in PTC [6,7]. A non-stimulated thyroglobulin level of less than 10 usually indicates persistent and recurrent disease in the neck. Values between 10 and 100 indicate pulmonary metastasis, and values in the range of several thousand can indicate bone metastases [8]. In this regard, neck ultrasound is the main part of this follow-up. Thyroglobulin antibodies (TgAbs) may be induced by the reaction to the release of Tg produced by thyroid cancer cells or thyroid tissue [7].

TgAb is produced in approximately 25% of patients with thyroid cancer and 10% of the general population. The presence of TgAbs, even at very low levels, may lead to unreliable Tg measurements, resulting in an incorrect diagnosis of recurrent disease or persistent [9,10]. Guidelines instruct that the estimation of Tg levels should continually go with a TgAb test in patients with DTC at intervals of 6–12 months [2]. Destruction of normal or neoplastic thyroid cells decreases the level of TgAbs. Therefore, except for a few cases, a constant or rising level of antibodies can indicate the recurrence or non-treatment of cancer [11]. However, after thyroidectomy, the level of these antibodies in the body increases due to the immune response to the intervention [11].

Various studies have shown a positive and significant relationship between the TgAbs level and the increased risk of non-response to treatment or recurrence [12–14]. Patients with an incomplete response (IR) had central compartment lymph node metastases and higher baseline TgAb in comparison to those with an excellent response (ER) [13]. The existence of TgAb is indicative of an active tumor. Sequential TgAb change is a good disease prognosis predictor and is useful for clinical decision-making. Recent studies have also shown that a reduction of antibodies level by at least 50% after treatment will significantly reduce the recurrence risk [12,15,16].

Côrtes et al. stated that among low- or intermediate-risk patients with undetectable Tg and the normal US after thyroidectomy, those with borderline TgAb are at no greater risk of tumor persistence or recurrence. In contrast, when undetectable Tg levels continue, recurrence should be suspected in the case of a TgAb elevation above the reference limit [17]. Besides, PTC patients with positive serum TgAb titer during the first year after primary treatment were more likely to have persistent/recurrent disease than those who were consistently TgAb-negative. Finally, the negativization of TgAb presented an excellent prognosis [17,18]. The presence of perioperative TgAbs is associated with aggressive histological features and thyroiditis. Detection of TgAbs perioperatively may encourage surgeons to consider more extensive initial surgery [19]. A rising trend in Tg-Ab ensures further investigation to identify recurrent diseases. Stable or declining Tg-Ab levels do not seem to reflect a risk for recurrence [20].

According to above mentioned, a high level of TgAb is related to the possibility of recurrence and persistence of disease increases. This study examined the relationship between high levels of thyroglobulin antibodies (TgAb) and the duration of needed follow-up and recurrence rate. Also, we investigated the trend of changes in serum levels of TgAbs and the evidence of recurrence in PTC patients with positive and negative TgAbs during follow-up sessions according to the simultaneous changes in serum thyroglobulin levels.

2. Material and methods

This retrospective study enrolled 600 PTC patients treated at the specialist referral clinic in Kerman (a city in the southeast region of Iran) between 2001 and 2021. The study protocol was approved by the ethics committee of the Kerman University of Medical Sciences, Kerman, Iran (Ethic code No IR. KMU.REC.1401.427). Verbal informed consent was obtained for the use of patients' information. All patients underwent total thyroidectomy at our institution or a regional hospital. Patients underwent biopsy-proven lymph node metastases, central compartment neck dissection (CCLND) in advanced primary tumors, or suspicious neck USG findings preoperatively. In this research, 130 out of 600 PTC patients had thyroglobulin antibody levels higher than the normal range of standard referral laboratory (TgAb positive). On the other hand, 470 patients had negative thyroglobulin antibody levels. TgAb $\geq$115 IU/ml was defined as TgAb positive, and TgAb $<$115 IU/ml was defined as TgAb negative.

We included patients who 1) were diagnosed with PTC (based on the pathology sample obtained from thyroid surgery) and had a minimum of one-year follow-up, 2) had a valid phone number to verify their survival status, 3) the availability of TgAb and Tg levels (reported by the standard center) at the same time after surgery and during the follow-up period, 4) the amount and number of doses of radioactive iodine received, and the definiteness of reported recurrence (recurrence was defined as any documented evidence of recurrence that was noted by sonography, isotope scan, PET scan or the development of elevated serum thyroglobulin (Tg). Histopathology reports of the surgical samples were used to define lymph node status, extrathyroidal extension, and thyroiditis, according to the current definitions [21]. Also, a thyroid ultrasound with lymph node mapping was applied [22]. Exclusion criteria were: 1) Death of a patient for a cause other than thyroid cancer, 2) The follow-up period was less than 1 year (whether due to the occurrence of diagnosis less than one year ago or non-referral despite contact), and 3) Missing or inaccessible surgical records. Finally, 104 TgAb-positive PTC patients were included in the study. The control group included PTC patients with negative TgAb, and 100 TgAb-negative patients were selected. Based on patients' record number, a PTC patient record was examined before and after positive TgAb and patients who had been followed up for at least three years, had complete data, were matched by age, gender, tumor size, Tg level, etc. based on analysis and their visit time was close to that of the positive TgAb patient were selected as the control group or negative TgAb. As presented in Table 1, basic specifications were the same and only the outcomes were different (Fig. 1).

The information of patients from their file included age, sex, tumor size, serum TgAb (reported after thyroidectomy and reported

during follow-up and treatment), serum TgAb simultaneous with thyroglobulin (Tg) serum, serum TgAb simultaneous with simultaneous TSH level (stimulated and non-stimulated), the disease stage (staging based on initial surgery and pathological findings), Classification Risk Based on Risk Stratification System (Low, Intermediate, and High), lymph node (LN) involvement, recurrence and (isotope scan, local or metastasis noted by sonography, the development of elevated serum thyroglobulin (Tg) or PET scan) and time to recurrence (as the number of months between the time of diagnosis and time of recurrence based on information in the medical records), and TNM classification and staging. Moreover, therapeutic information included the number of surgeries, radioactive iodine (cumulative dose and frequency of receiving radioactive iodine), and final response to treatment (Excellent, Biochemical incomplete, Structural incomplete, Indeterminate), all extracted from the patient's file. Tests and dates of Tg, TgAb, and TSH tests (stimulation without levothyroxine treatment and non-stimulation with levothyroxine treatment) were also extracted and recorded from the patients' files. TgAb positive and negative groups were divided into 2 subgroups based on serum thyroglobulin level simultaneously (Fig. 1). The study groups were compared in 3 steps: 1) The difference between the mentioned data was investigated between 4 groups, 2) The TgAb positive group in terms of changes of antibody level (remaining positive or becoming negative) and its relationship with Tg level and recurrences reported in 6 follow-up sessions (including 6 months, 12 months, 24 months, 36 months, 72 months, and 108 months) were investigated. 3) In TgAb positive and negative groups, the trend of antibody titer and thyroglobulin (Increasing, Declining, Stable, and Undetectable) were investigated in the follow-up sessions, and the presence of recurrence or non-recurrence at the same time.

2.1. Laboratory

TgAb levels were measured by an automated chemiluminescence assay, Immulite 2000 system, and Siemens kits (Siemens Healthcare Diagnostics Products Limited, Munich, Germany). Serum Tg quantifications were accomplished by radioimmunoassay (Tg

Table 1
Baseline characteristics of patients in positive and negative TgAb groups.

	Negative TgAb	Positive TgAb	p-value
[a] **Age**	38.55 ± 13.49	37.55 ± 12.36	0.84
[a] **Tg**	30.56 ± 8.63	64.56 ± 25.34	0.53
Follow-up (months)	52.44 ± 29.62	56.76 ± 35.24	**0.01***
[a] **Tumor size (cm)**	2.15 ± 1.25	1.86 ± 0.95	0.14
[a] **Cumulative dose of iodine**	157.73 ± 13.86	218.54 ± 17.97	**0.01***
[b] **sex**			
Female	86(48.3)	92(51.7)	0.67
Male	14(53.8)	12(46.2)	
[b] **TNM Stage**			
1	38(45.2)	46(54.8)	0.71
2	38(50.0)	38(50.0)	
3	10(50.0)	10(50.0)	
4	14(58.3)	10(41.7)	
[b] **LN**			
Yes	46(38.0)	54(65.1)	**<0.001*****
No	54 (65.1)	29 (34.9)	
[b] **Metastasis**			
Yes	6 (75.0)	2 (25.0)	0.28
No	89 (50.3)	88(49.7)	
[b] **Stage**			
1	82(48.0)	89(52.0)	0.35
2	8(44.4)	10(55.6)	
3	10(66.7)	5(33.3)	
[b] **Number of surgeries**			
1	77(52.0)	71(48.0)	**0.02***
2	20(52.6)	18(47.4)	
3	3(27.3)	8(72.7)	
4	0	7(100)	
[b] **Recurrent**			
Yes	16(32.0)	34(68.0)	**0.006****
No	84(54.5)	70(45.5)	
[b] **Risk Stratification System**			
Low	23(44.2)	29(55.8)	0.72
Intermediate	38(50.7)	37(49.3)	
High	39(50.6)	38(49.4)	
[b] **Response to treatment**			
Excellent	90(58.8)	63(41.2)	**<0.001*****
Biochemical incomplete	2(28.6)	5(71.4)	
Structural incomplete	4(21.1)	15(78.9)	
Indeterminate	4(16.0)	21(84.0)	

Data are shown as mean ± SD (a) and number(percent) (b). Mann–Whitney *U* test/Chi-square test. *P < 0.05, **P < 0.01, and ***P < 0.001. Tg: Serum Thyroglobulin, TgAb: Serum Antithyroglobulin antibody, LN: Lymph node.

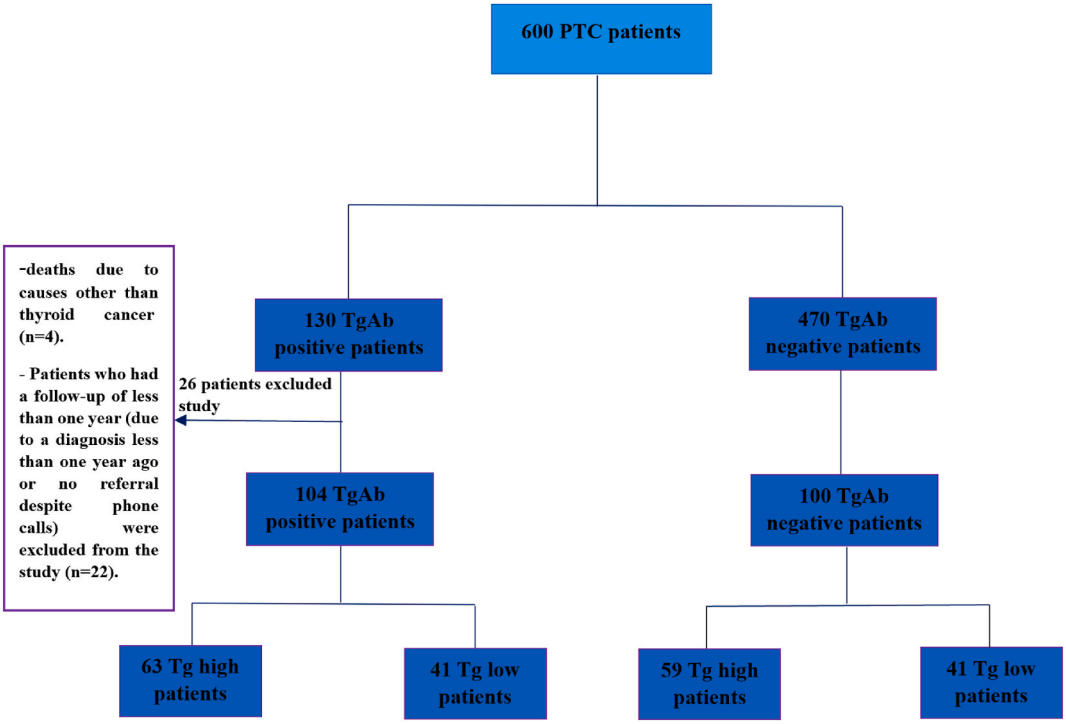

Fig. 1. Flow chart shows the recruitment of the study subjects. PTC: Papillary thyroid cancer, TgAb: Antithyroglobulin antibodies, Tg: Thyroglobulin.

IRMA; CIS-Bio International, Bagnols-sur-Cèze, France). The serum level of TSH was measured using an ELISA kit following the manufacturer's instructions.

3. Statistical analysis

Means were compared between groups using the nonparametric Mann-Whitney *U* test or the student t-test. Chi-square test or Fisher's exact test was used to identify differences in the ratio of cases. A p-value lower than 0.05 was determined to be significant. Continuous variables were expressed as mean ± standard deviation and nominal variables as the number of cases and (%). The data were analyzed using logistic regression at 95% confidence level. Variables with P-value less than 0.1 in univariate analysis were added to the final multivariate models in order to control the effect of confounding variables. The receiver operating characteristics (ROC) curve was utilized to calculate the area under the curve (AUC) and appropriate cut-off value with corresponding specificity and sensitivity for detecting recurrence by TgAb levels. The data were analyzed using the IBM SPSS Statistics V-22 (SPSS Inc., Chicago, IL, USA).

4. Results

4.1. Baseline characteristics

Of the 600 PTC patients enrolled in the study, the data from 204 patients (104 patients with positive antibodies and 100 patients with negative antibodies) were collected. The mean age of patients was 38.04 ± 12.91 years, with a range of 13–78 years. About 86.7% of patients were women. The mean Tg, tumor size, and cumulative dose of prescribed iodine were 47.9 ± 13.61 (ng/ml), 2 ± 1.11 (cm), and 188.73 ± 165.38 (UI/ml), respectively. Also, 60.9% of patients had LN involvement, 4.3% had metastases, and most were in stage one disease (79.4%). Furthermore, more than half of the patients had undergone surgery once (71.1%), and most of them were prescribed radioactive iodine once (64.7%). Finally, 24.5% of patients had a recurrence, and 74.0% of them showed excellent responses to treatment.

4.2. Comparison of variables in positive and negative TgAb groups

The two groups of positive and negative TgAb in terms of LN involvement ($P < 0.001$), the mean of follow-up time ($P = 0.01$), the number of surgeries ($P = 0.023$), the cumulative dose of iodine ($P = 0.012$), recurrence ($P = 0.006$), and response to treatment with the excellent final response ($P < 0.001$) had a significant relationship (Table 1). In terms of LN involvement, a higher percentage of

individuals in the positive TgAb group (65.1%) had LN involvement than those in the negative TgAb group (38.0%). Patients with positive TgAb (100%) underwent more surgeries than those with negative TgAb (0.0%). A higher percentage of individuals in the positive TgAb group (68.0%) experienced recurrence than the group with negative TgAb (32.0%) (Table 1). There was no significant difference between the two groups of positive and negative TgAb in terms of tumor size ($P = 0.058$), metastasis ($P = 0.17$), disease stage ($P = 0.350$), TNM ($P = 0.71$), and Risk Stratification System ($P = 0.72$) (Table 1).

4.3. Comparison of variables in TgAb (negative and positive) and Tg (low and high) subgroups

The mean difference in the cumulative dose of iodine between the four groups was significant ($P < 0.001$). Positive TgAb and high Tg group received the highest cumulative dose of iodine (265.06 ± 25.96; Table 2) compared to TgAb negative-Tg high ($P < 0.05$), TgAb negative-Tg low ($P < 0.001$) and TgAb positive -Tg low subgroups ($P < 0.01$). In terms of LN variables ($P < 0.001$), the number of surgeries ($P < 0.001$), frequency of receiving radioactive iodine ($P < 0.001$), the recurrence rate ($P = 0.008$), and the response to treatment (final class) of cancer ($P < 0.001$) showed a significant difference between the four groups. The group of positive TgAb and high Tg (40.5%) had the most involvement in LN (Table 2) compared to TgAb negative-Tg high ($P < 0.01$). Only the positive TgAb and high Tg group underwent 4 surgeries (100%). In the case of undergoing 3 surgeries, the highest proportion belonged to the positive TgAb and high Tg groups (63.6%), followed by the negative TgAb and high Tg groups (27.3%). A higher percentage of patients in the positive TgAb and high Tg (47.6%) group received iodine more than once compared to TgAb negative-Tg high ($P < 0.05$) and TgAb negative-Tg high groups ($P < 0.001$). In terms of receiving radioactive iodine, the negative TgAb and low Tg group was significant compared to negative TgAb and high Tg group ($P < 0.05$). Besides, the highest proportion of recurrence was seen in the positive TgAb

Table 2
Baseline characteristics of patients in TgAb (negative and positive) and Tg (low and high) subgroups.

	TgAb negative-Tg high	TgAb negative-Tg low	TgAb positive -Tg high	TgAb positive -Tg low	p-value
[a] **Age**	39.44 ± 1.87	37.26 ± 1.89	38.63 ± 1.62	35.90 ± 1.79	0.83
[a] **Tumor size**	2.00 ± 0.14	2.38 ± 0.22	1.98 ± 0.12	1.67 ± 0.12	0.03*
Follow-up (months)	48.2 ± 27.69	58.53 ± 31.54	61.71 ± 34.2	49.17 ± 35.77	0.07
[a] **Cumulative dose of iodine**	177.52 ± 21.97	129.23 ± 10.85	265.06 ± 25.96	147.07 ± 17.15	**<0.001*****
[b] **sex**					
Female	49(27.5)	37(20.8)	56(31.5)	36(20.2)	0.699
Male	10(38.5)	4(15.4)	7(26.9)	5(19.2)	
[b] **TNM Stage**					
1	23(27.4)	15(17.9)	25(29.8)	21(25.0)	0.741
2	21(27.6)	17(22.4)	27(35.5)	11(14.5)	
3	5(25.0)	5(25.0)	5(25.0)	5(25.0)	
4	10(41.7)	4(16.7)	6(25.0)	4(16.7)	
[b] **LN**					
Yes	31(25.6)	15(12.4)	49(40.5)	26(21.5)	**<0.001*****
No	28(33.7)	26(31.3)	14(16.9)	15(18.1)	
[b] **Metastasis**					
Yes	5(62.5)	1(12.5)	2(25.0)	0(0)	0.184
No	51(28.8)	38(21.5)	52(29.4)	36(20.3)	
[b] **Stage**					
1	46(26.9)	36(21.1)	54(31.6)	35(20.5)	0.350
2	6(33.3)	2(11.1)	5(27.8)	5(27.8)	
3	7(46.7)	3(20.0)	4(26.7)	1(6.7)	
[b] **Number of surgeries**					
One time	40(27.0)	37(25.0)	35(23.6)	36(24.3)	**<0.001*****
Two time	16(42.1)	4(10.5)	14(36.8)	4(10.5)	
Three time	3(27.3)	0(0)	7(63.6)	1(9.1)	
Four time	0(0)	0(0)	7(100)	0(0)	
[b] **Radioactive Iodine treatment**					
One time	43(72.9)	37(90.2)	33(52.4)	31(75.6)	**<0.001*****
More than one time	16(27.1)	4(9.8)	30(47.6)	10(24.4)	
[b] **Recurrent**					
Yes	13(26.0)	3(6.0)	23(46.0)	11(22.0)	**0.008****
No	46(29.9)	38(24.7)	40(26.0)	30(19.5)	
[b] **Risk Stratification System**					
Low	15(28.8)	8(15.4)	16(30.8)	13(25.0)	0.189
Intermediate	17(22.7)	21(28.0)	20(26.7)	17(22.7)	
High	27(35.1)	12(15.6)	27(35.1)	11(14.3)	
[b] **Response to treatment**					
Excellent	50(32.7)	40(26.1)	35(22.9)	28(18.3)	**<0.001*****
Biochemical incomplete	2(28.6)	0(0)	3(42.9)	2(28.6)	
Structural incomplete	4(21.1)	0(0)	6(31.6)	9(47.4)	
Indeterminate	3(12.0)	1(4.0)	19(76.0)	2(8.0)	

Data are shown as mean ± SD (a) and number(percent) (b). Kruskal-wallis test/Chi-square test. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$. Tg: Serum Thyroglobulin, TgAb: Serum Antithyroglobulin antibody, LN: Lymph node.

and high Tg group (46.0%; Table 2) compared to TgAb negative-Tg high and TgAb positive- Tg low groups ($P < 0.05$). Excellent response was seen in negative TgAb and high Tg (32.7%), negative TgAb and low Tg group (26.1%), positive TgAb and high Tg (22.9%), and positive TgAb and low Tg group (18.3%). More patients with final class 1 cancer were in the negative TgAb and low Tg group. Tumor size also showed a significant difference between groups ($P < 0.05$; Table 2). This variable was significant between negative TgAb and low Tg group and positive TgAb and low Tg group ($P < 0.05$).

4.4. Sequential changes of serum thyroglobulin antibody levels and recurrence in positive TgAb group during follow-up

After a 12-month follow-up, more than 50% of TgAb-positive patients (n = 104) were negative. Also, 48% of patients (n = 50) remained TgAb positive, of which 33 were in the high Tg subgroup and 17 were in the low Tg subgroup. Recurrence was observed in 16.3% of positive TgAb patients (n = 17), among which 15 were in the high Tg subgroup and 2 were in the low Tg subgroup (Fig. 2). After 24 months of follow-up, 80% of antibodies were negative. Meanwhile, 22.1% of patients (n = 23) were positive TgAb, of which 15 were in the high Tg subgroup and 8 were in the Tg negative subgroup. Moreover, recurrence was observed in 12.5% of patients (n = 13), among which 10 patients were TgAb positive and 3 were TgAb negative. Moreover, 12 patients were in the high Tg subgroup and 1 patient in the low Tg subgroup. In the 36-month follow-up, more than 85% of antibodies were negative. Besides, 14.4% of patients (n = 15) were TgAb positive, of which 11 were in the Tg high subgroup, and 4 were in the Tg low subgroup. Also, recurrence was observed in 4.8% of patients (n = 5), among which 3 were TgAb positive and 2 were negative TgAb, of which 4 patients were in the high Tg

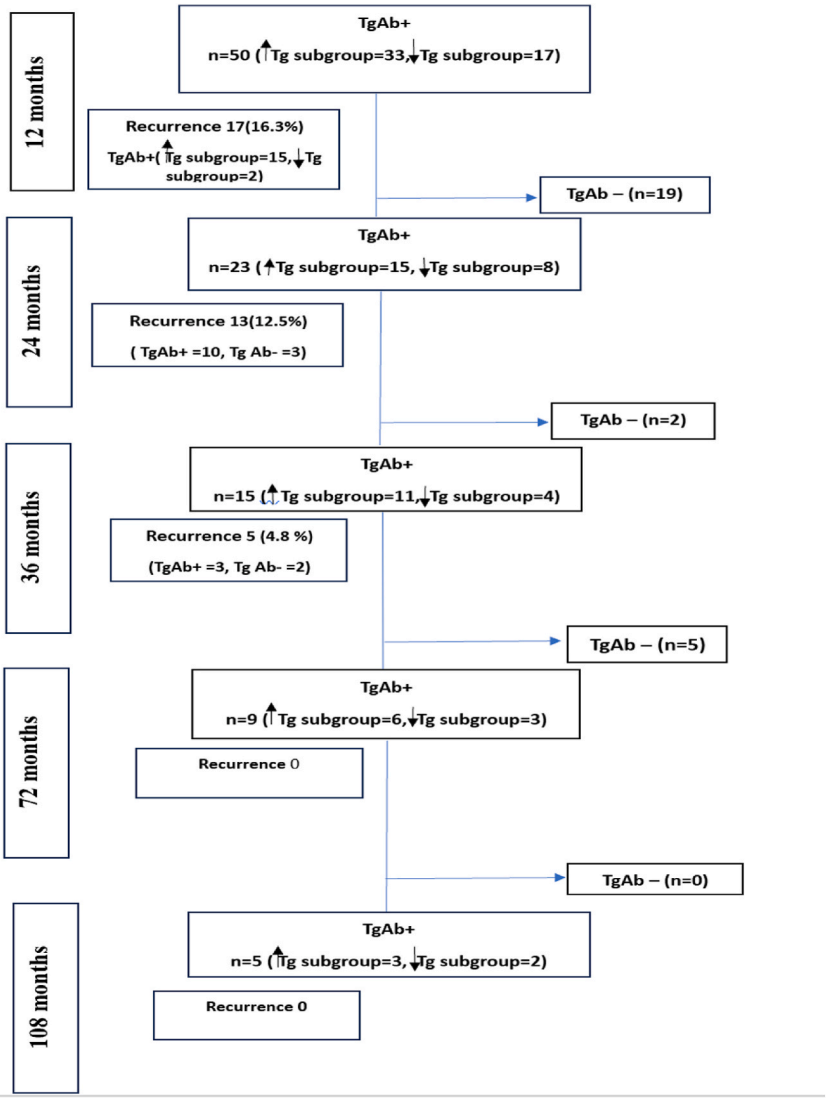

Fig. 2. The changes of serum TgAb levels and recurrence in patients with positive TgAb in Tg high and low subgroups during follow-up. TgAb: Antithyroglobulin antibodies, Tg: Thyroglobulin.

subgroup and 1 in the low Tg subgroup. In the 72-month follow-up, more than 90% of antibodies were negative and 8.6 % of patients (n = 9) were TgAb positive, of which 6 were in the high Tg subgroup and 3 were in the low Tg subgroup. Recurrence was not observed during this follow-up. Finally, after 108 months of follow-up, despite no recurrence, 5 patients remained positive TgAb, of which 3 were in the high Tg subgroup and 2 were in the low Tg subgroup. In addition, at the end of the study, 3 cases of non-response to treatment were seen, with high Tg despite the negative antibody level (Fig. 2).

4.5. TgAb and Tg trend

The TgAb trend during follow-up is shown in Fig. 2. The follow-up results of the positive TgAb group indicated that the patients with increasing TgAb were from 31% at the beginning of the study to 9.8% at 36 months and 7.4% at the end of the study. Also, during the follow-up period, the percentage of patients with a declining TgAb trend was 48% in the beginning and reached 11% in 36 months, which was the largest decrease during this period. In addition, these patients showed undetectable levels over time as at the beginning of the study, only 16% had undetectable levels, reaching 60% in 36 months and 77% at the end of the study (Fig. 3A).

The TgAb trend in the positive TgAb and high Tg groups showed that the patients with the increasing trend of antibodies were from 31.7% to 12.5% in 36 months and 5.8% at the end of the study. Also, the patients with a declining trend of antibodies were from 65.7% at the beginning of the study to 26% at 36 months and 11.7% at the end of the study. This decrease was due to the increase in the percentage of patients with undetectable antibody levels. Also, the patients with a decreasing trend of antibodies were 65.7% at the beginning of the study, 26% at 36 months, and 11.7% at the end of the study. This decrease was due to the increase in the percentage of patients with undetectable antibody levels (from 3.17% at the beginning of the study to 62% in 36 months and 82% at the end of the study). Also, this trend of change occurred mostly in 36 months (Fig. 3B).

The trend of TgAb in the positive TgAb and low Tg groups demonstrated that the increasing trend of antibodies in 31% of patients at the beginning of the study changed to 12.5% at 72 months follow-up. Also, the decreasing trend from 21.9% at the beginning of the study reached 6.25% in 72 months (the biggest decrease occurred in the first 36 months). The antibody levels of many of these patients also reached undetectable levels during the follow-up period. As a result, 36.5% of this group had undetectable levels of antibodies at the beginning of the study, while this amount reached 75% in 72 months (Fig. 3C).

The trend of Tg during follow-up is shown in Fig. 3. The results for the follow-up of the positive TgAb group indicated that the patients with increasing Tg were 23% (n = 24) at the beginning of the study, 14.2% (n = 10) in 36 months, and 3.7% (n = 1) at the end of the study. Patients with declining Tg were 53% (n = 56) at the beginning of the study, 17% (n = 12) in the 36 months, and 3.7% (n = 1) at the end of the study. The undetectable level of Tg increased from 19.23% at the beginning of the study to 54% at 36 months and 81.4% at the end of the study (Fig. 4A). In the follow-up of the negative TgAb group, the increasing trend of Tg in 27% of patients at the beginning of the study reached 49.1% of patients in 36 months. Also, the declining trend of Tg in 42% of patients at the beginning of the study reached 13% of patients in 36 months and 0% at the end of the study. All these patients showed an undetectable Tg level at the end of the follow-up period, such that it was 31% at the beginning and 100% at the end of the study (Fig. 4B).

The trend of Tg changes in positive TgAb and high Tg groups was as follows: The proportion of patients with an increasing trend of Tg was 30% at the beginning of the study to 5.8% at the end. In addition, the proportion of people with an undetectable trend of Tg level increased from 11.11% at the beginning of the study to 36% at 36 months and 70.5% at the end of the study. The biggest change

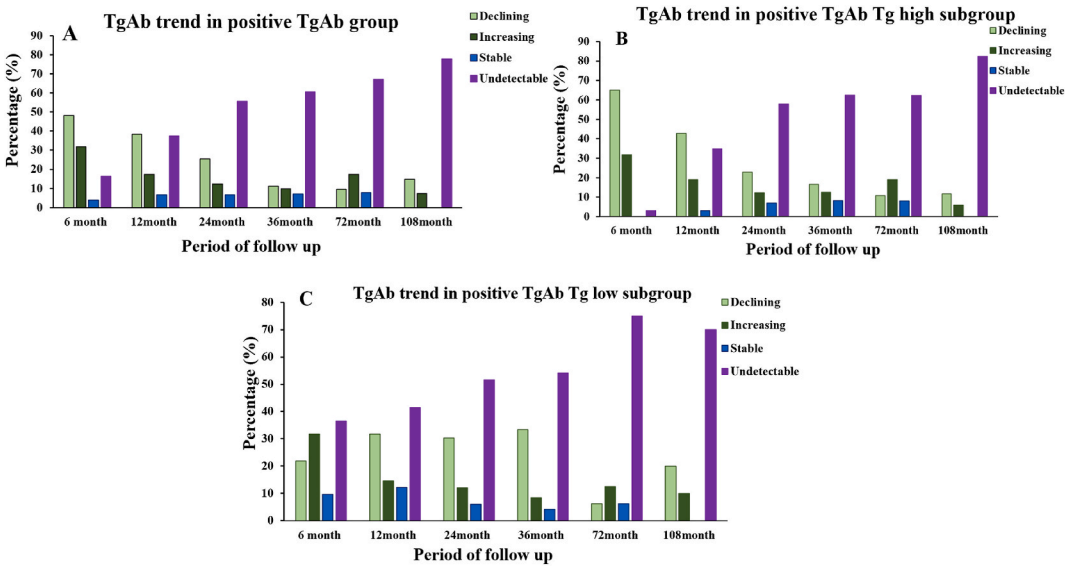

Fig. 3. TgAb trend in positive TgAb group, positive TgAb Tg high subgroup, and positive TgAb Tg low subgroup. Increasing and declining TgAb trend decreases during 36 months, but undetectable levels increase.

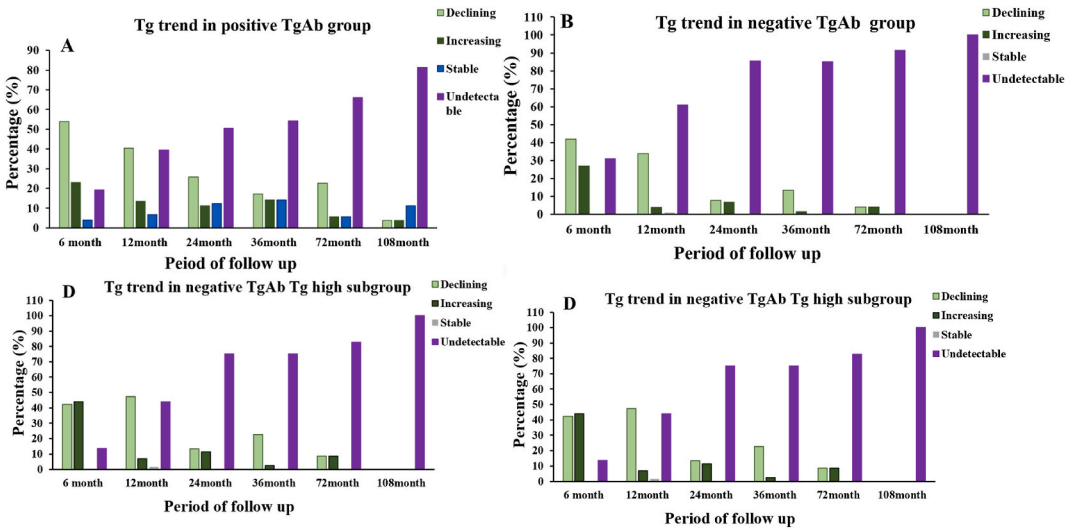

Fig. 4. Tg trend in positive TgAb group, negative TgAb group, positive TgAb Tg high subgroup, and negative TgAb Tg high subgroup. The percentage of patients who showed an undetectable trend in TG levels increased at 36 months and at the end of the study, being the highest in the first 36 months.

was in the first 36 months (Fig. 4C). The trend of Tg changes in the group of negative TgAb and high Tg. In this group, the proportion of patients with the increasing trend of Tg was from 64% at the beginning of the study to 2.5% at 36 months and 0% at the end of the study during the follow-up period. Also, the proportion of patients with decreasing trend of Tg was from 42% at the beginning of the study to 22.5% in 36 months and 0% at the end. Notably, all these patients started to have negative Tg levels such that 100% of them showed undetectable Tg levels at the end of the study (Fig. 4D).

Table 3
Univariate and multivariate analysis for predictors of recurrence in PTC patients.

Variable	Recurrent			
	yes N (%)	No N (%)	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
TgAb				
Negative	16 (32. 00)	84 (54.55)	Referent	Referent
Positive	34 (48.00)	70 (45.45)	2.55 (1.30–5.0)	3.84 (1.76–8.33)
Sex				
Women	39 (78.00)	139 (90.26)	Referent	Referent
Men	11 (22)	15 (9.74)	2.61 (1.11–6.14)	1.09 (0.86–5.85)
Age				
>55 years	46(92.00)	140 (90.91)	Referent	
<55 years	4 (8.00)	14 (9.09)	0.86 (0.27–2.77)	–
Tumor size				
>4 cm	49 (98.00)	147 (95.45)	Referent	–
<4 cm	46 (32.86)	28 (10.00)	0.42 (0.51–3.57)	
Risk Stratification System				
Low	5 (10.00)	47 (30.52)	Referent	Referent
Intermediate	16 (32)	59 (38.31)	2.54 (0.78–7.46)	2.71 (0.88–8.31)
High	29 (58.00)	48 (31.17)	5.67 (0.42–0.26)	5.62 (1.88–16.84)
Subgroup				
TgAb negative-Tg Low	3 (6.00)	38 (24.68)	Referent	Referent
TgAb negative-Tg High	13 (26.00)	46 (29.87)	3.57 (0.94–13.49)	3.08 (0. 75–12.65)
TgAb positive -Tg Low	11 (22.00)	30 (19.48)	4.64 (1.18–18.15)	6.96 (1.64–29.53)
TgAb positive -Tg High	23 (46.00)	40 (25.97)	7.28 (2.02–26.25)	8.90(2.29–34.51)
TNM stage				
1	16(32.00)	68(44.16)	Referent	
2	21(42.00)	55(35.71)	1.62 (0.77–3.4)	–
3	6 (12.00)	14 (9.09)	1.82 (0.6–5.47)	
4	4 (14.00)	17 (11.04)	1.75 (0.62–4.92)	
Stage				
1	38 (76.00)	133 (86.36)	Referent	Referent
2	3 (6.00)	15 (9.74)	0.7 (0.19–0.4)	0.52 (0.13–2.08)
3	9 (18.00)	6 (3.9)	5.25 (1.75–15.67)	5.36(1.56–18.37)

CI: confidence interval.

4.6. Assessment of factors affecting recurrence among PTC patients

Table 3 presents the factors affecting recurrence among PTC patients. As indicated, 32% and 48% of negative TgAb and positive TgAb patients experienced recurrence, respectively. Accordingly, the adjusted odds ratio (AOR) of TgAb-positive patients was 3.84 times more, indicating the recurrence risk in positive TgAb patients was 3.84 times more than that of negative TgAb patients (AOR: 3.84 CI: 1.76–8.33). The univariate analysis results indicated age was not correlated with increased recurrence risk (OR: 0.86, 95% CI: 0.27–2.77). Moreover, the univariate analysis results revealed tumor size was not correlated with increased recurrence risk (OR: 0.42, 95% CI: 0.51–3.57). The adjusted odds ratio of male patients was 1.09 times more, indicating the recurrence risk among men was 1.09 times more than that of women (AOR: 1.09, 95%CI: 0.86–5.85). Analyzing the four subgroups showed recurrence in TgAb negative Tg low group was only 6%, while it was 26% in TgAb negative Tg high group. The adjusted odds ratio analysis revealed recurrence in TgAb negative Tg high subgroup was three times more; however, this correlation was not significant (AOR: 3.08, 95%CI: 0.75–12.65). The recurrence risk in TgAb positive Tg low subgroup was approximately 7 times more than that in TgAb negative Tg low subgroup (AOR: 6.96, 95%CI:1.64–29.53). The highest recurrence risk, with the odds ratio of 8.9, was observed in TgAb negative Tg high subgroup, which was significant (AOR: 8.90, 95% CI: 2.29–34.51). The highest recurrence risk based on RSS was observed in high risks compared to low risks, so that based on the adjusted odds ratio, it was 5 times more (AOR: 5.62, 95%CI: 1.88–16.84). The univariate analysis results showed TNM stage was not correlated with increased recurrence risk. The highest recurrence risk with the odds ratio of 5.62, was observed in stage 3 patients. This odds ratio shows that the risk of recurrence in stage 3 patients was more than 5 times that of stage 1 patients (AOR: 5.36, 95% CI: 1.56–18.37) (Table 3). We depicted an ROC curve to specify a cut-off point for the high TgAb to predict the possibility of recurrence. The area under the ROC curve (AUC) was 68.95% for the positive TgAb group (Fig. 5), which was above the 50% standard reference line. Since the test precision is above the 50% cut-off point for positive TgAb, the possibility of recurrence could be reliably and adequately evaluated. From the available TgAb level cut-off values, the cut-off value, i.e., at TgAb = 409 IU/ml (Sensitivity = 61%; Specificity = 70%), was considered the best cut-off value.

5. Discussion

The follow-up examination of patients with PTC due to the interference of thyroglobulin level and the thyroglobulin antibody has been among the challenges of researchers and therapists in recent years. Accordingly, the present study attempted to determine factors for predicting the prognosis and clinical course. The results showed that patients with high TgAb levels (especially in the case of concomitant high thyroglobulin levels) had a worse prognosis and a more severe clinical course than the control group with low antibody levels. Besides, patients in the positive TgAb and high Tg group significantly experienced a higher recurrence rate during the follow-up and a lower number with class 1 cancer. Also, the 36-month follow-up showed a significant difference in the recurrence rate between positive TgAb and negative TgAb groups. The highest rate of relapse in the first 36 months in the group with high Tg can point to the diagnostic and predictive value of a high Tg level in the presence of positive antibodies. Moreover, the declining and increasing trends of thyroglobulin antibodies have decreased over 36 months while it increased to an undetectable number.

The current study included a wide age range from Youth to the elderly, most of whom were women. Like numerous previous studies, most patients with PTC were female [17,23,24].

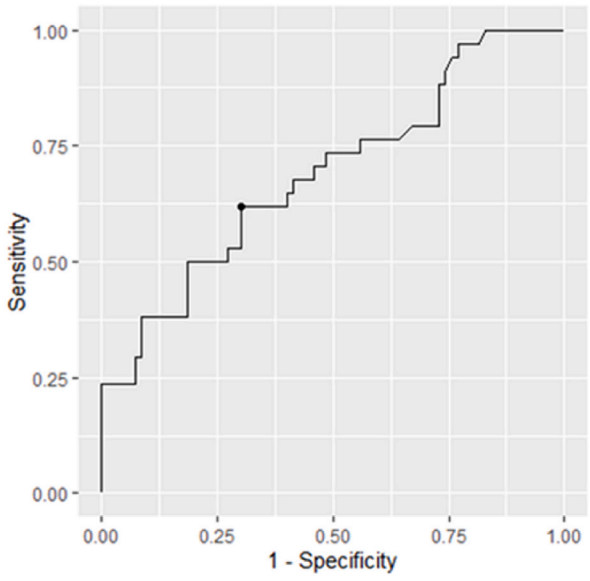

Fig. 5. ROC curve showing diagnostic accuracy of the positive TgAb level to detect recurrence during the follow-up. Area under curve (AUC): 68.9%.

The results showed that patients with positive TgAb and high-Tg groups had a higher recurrence rate during follow-up and a lower number rate in class I final cancer. This finding suggests a significant effect of antibody levels on the outcome of patients with PTC. In line with this study, Jia et al. showed a higher risk of PTC malignancy among positive TgAb patients [25]. Also, changes in TgAb levels in the first year after surgery can predict the risk of persistence/recurrence of positive TgAb patients with PTC [26]. Besides, the negative titers of TgAb at 1 year may be associated with an excellent prognosis [18].

Detecting TgAbs perioperative associates with a higher rate of extrathyroidal extension and aggressive histological features [19]. Tsushima et al. show that patients with postoperative TgAb higher than half of the preoperative values had a poorer prognosis than those whose postoperative TgAb was less than half of the preoperative values levels [16].

In another study, Turanli and Mersin reported that TgAb positivity had no predictive value for persistence or recurrence in patients with PTC [27]. The difference between this result and those of us can be attributed to the small number of patients with positive antibodies in this study. In addition, the results of the present study showed that the highest recurrence rate was in the group with high Tg (high-risk level group) and the first 36 months. In agreement with the present study, an ascending trend in TgAb justifies further investigation to detect recurrent disease. On the other hand, declining or stable TgAb levels do not seem to reflect a risk for recurrence [23].

The patients with stable or declining TgAb without a concomitant rise in Tg developed a recurrence. Four patients suffered a recurrence. Three of these patients had a rising Tg-Ab trend, with 2 having an undetectable Tg [23]. Yamada et al. showed that in a follow-up period of 35 months, 12 patients had PTC recurrence and 11 showed TgAb increase later than 1 year after surgery and postoperative Tg positivity [24]. In terms of the declining and increasing TgAb trend during follow-up, Bueno et al. reported that changes in TgAb levels over time are more instructive than an absolute TgAb value at a sole time point in predicting structural incomplete response in patients with DTC after I therapy [28]. Previous studies also showed that the recurrence rate of patients who had a high TgAb level from the beginning or experienced some degree of increase in TgAb during follow-up was significantly higher [25,29]. In this respect, a study showed that pediatric patients with declining or increasing TgAb usually have invasive clinicopathologic factors, such as high initial risk stratification and extra-thyroidal extension. This finding shows that the TgAb trend links with invasive clinicopathologic features in pediatric PTC patients [30].

Therefore, we can assume that changes in TgAb levels could be a prognostic factor in patients with PTC from another viewpoint. Based on the results of this study, the groups with positive TgAb and high Tg groups and low TgAb and high Tg groups had higher cumulative doses and number of received iodine and a greater number of surgical treatments, suggesting more resistance of these two groups to treatment. A previous study showed a significant relationship between the number of courses for ^{131}I therapy and the number of thyroid surgeries in pediatric PTC patients [30] and adult patients [13] with high TgAb and high Tg group.

One of the limitations of this study was the impossibility of a complete follow-up of some patients for 108 months. However, most antibody negativization and relapses occurred within 36 months, and some patients had not yet completed their follow-up. One of the strengths of this study was the long-term duration of the patient's follow-up, having a control group, having 4 subgroups, comparing all subgroups together, and investigating the simultaneous effect of antibody and thyroglobulin levels. Also, the trends of TgAb and Tg were evaluated during the follow-up.

In conclusion, the current study indicated that a high level of TgAb in patients with PTC predicts a more severe course and a worse prognosis and can be one of the danger signs for the recurrence of the disease. In case of the simultaneous increase in Tg and TgAb, the risk of recurrence increases, and the presence of Tg becomes prominent. In this study, most antibody and thyroglobulin negativization and recurrence cases occurred within 36 months. Hence, it is recommended to follow up on these patients with regular tests and imaging and monitor them during the first 36 months after thyroidectomy. After this period, the follow-up and examinations depend on the continuation of the treatment process in case of response or non-response to treatment, recurrence, and clinical evidence.

Data availability statement

The datasets generated during and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Ethics statement

Verbal informed consent was obtained for the use of patients' information. The study protocol was approved by the ethics committee of the Kerman University of Medical Sciences, Kerman, Iran (Ethic code No IR. KMU.REC.1401.427).

CRediT authorship contribution statement

Mojgan Sanjari: Project administration, Data curation, Conceptualization. **Marzieh Ordooei:** Methodology, Investigation, Formal analysis. **Ladan Amirkhosravi:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Ahmad Naghibzadeh-Tahami:** Formal analysis. **Sarir Nazemi:** Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2019, CA. Cancer J. Clin. 69 (2019) 7–34, https://doi.org/10.3322/caac.21551.

[2] B.R. Haugen, E.K. Alexander, K.C. Bible, G.M. Doherty, S.J. Mandel, Y.E. Nikiforov, F. Pacini, G.W. Randolph, A.M. Sawka, M. Schlumberger, K.G. Schuff, S. I. Sherman, J.A. Sosa, D.L. Steward, R.M. Tuttle, L. Wartofsky, 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 (2016) 1–133, https://doi.org/10.1089/thy.2015.0020.

[3] R.A. DeLellis, Pathology and genetics of thyroid carcinoma, J. Surg. Oncol. 94 (2006) 662–669, https://doi.org/10.1002/JSO.20700.

[4] S.L. Asa, The current histologic classification of thyroid cancer, Endocrinol. Metabol. Clin 48 (2019) 1–22, https://doi.org/10.1016/J.ECL.2018.10.001.

[5] A.J. Van Herle, G. Vassart, J.E. Dumont, Control of thyroglobulin synthesis and secretion, N. Engl. J. Med. 301 (1979) 239–249, https://doi.org/10.1056/nejm197908023010504.

[6] A. Kumar, D.H. Shah, U. Shrihari, S.R. Dandekar, U. Vijayan, S.M. Sharma, Significance of antithyroglobulin autoantibodies in differentiated thyroid carcinoma, Thyroid 4 (1994) 199–202, https://doi.org/10.1089/thy.1994.4.199.

[7] C.A. Spencer, M. Takeuchi, M. Kazarosyan, C.C. Wang, R.B. Guttler, P.A. Singer, S. Fatemi, J.S. LoPresti, J.T. Nicoloff, Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma, J. Clin. Endocrinol. Metab. 83 (1998) 1121–1127, https://doi.org/10.1210/jcem.83.4.4683.

[8] R.J. Robbins, S. Srivastava, A. Shaha, R. Ghossein, S.M. Larson, M. Fleisher, R.M. Tuttle, Factors influencing the basal and recombinant human thyrotropin-stimulated serum thyroglobulin in patients with metastatic thyroid carcinoma, J. Clin. Endocrinol. Metab. 89 (2004) 6010–6016, https://doi.org/10.1210/jc.2003-031573.

[9] C.A. Spencer, Clinical utility of thyroglobulin antibody (TgAb) measurements for patients with differentiated thyroid cancers (DTC), J. Clin. Endocrinol. Metab. 96 (2011) 3615–3627, https://doi.org/10.1210/jc.2011-1740.

[10] F.A. Verburg, M. Luster, C. Cupini, L. Chiovato, L. Duntas, R. Elisei, U. Feldt-Rasmussen, H. Rimmele, E. Seregni, J.W.A. Smit, C. Theimer, L. Giovanella, Implications of thyroglobulin antibody positivity in patients with differentiated thyroid cancer: a clinical position statement, Thyroid 23 (2013) 1211–1225, https://doi.org/10.1089/thy.2012.0606.

[11] D. Rubello, D. Casara, M.E. Girelli, M. Piccolo, B. Busnardo, Clinical meaning of circulating anti-thyroglobulin antibodies in differentiated thyroid cancer: a prospective study, J. Nucl. Med. 33 (1992) 1478–1480.

[12] G.K. Won, H.Y. Jong, B.K. Won, Y.K. Tae, Y.K. Eui, M.K. Jung, J.S. Ryu, G. Gong, J.H. Suck, K.S. Young, Change of serum antithyroglobulin antibody levels is useful for prediction of clinical recurrence in thyroglobulin-negative patients with differentiated thyroid carcinoma, J. Clin. Endocrinol. Metab. 93 (2008) 4683–4689, https://doi.org/10.1210/jc.2008-0962.

[13] M. Ora, A.H. Nazar, P. Mishra, S. Barai, A. Arya, P.K. Pradhan, S. Gambhir, Clinical outcome of patients with differentiated thyroid cancer and raised antithyroglobulin antibody levels: a retrospective study, Thyroid Res. 14 (2021) 8, https://doi.org/10.1186/s13044-021-00099-w.

[14] C. Spencer, S. Fatemi, Thyroglobulin antibody (TgAb) methods - strengths, pitfalls and clinical utility for monitoring TgAb-positive patients with differentiated thyroid cancer, Best Pract. Res. Clin. Endocrinol. Metabol. 27 (2013) 701–712, https://doi.org/10.1016/j.beem.2013.07.003.

[15] C.A. Spencer, Clinical review: clinical utility of thyroglobulin antibody (TgAb) measurements for patients with differentiated thyroid cancers (DTC), J. Clin. Endocrinol. Metab. 96 (2011) 3615–3627, https://doi.org/10.1210/jc.2011-1740.

[16] Y. Tsushima, A. Miyauchi, Y. Ito, T. Kudo, H. Masuoka, T. Yabuta, M. Fukushima, M. Kihara, T. Higashiyama, Y. Takamura, K. Kobayashi, A. Miya, T. Kikumori, T. Imai, T. Kiuchi, Prognostic significance of changes in serum thyroglobulin antibody levels of pre- and post-total thyroidectomy in thyroglobulin antibody-positive papillary thyroid carcinoma patients, Endocr. J. 60 (2013) 871–876, https://doi.org/10.1507/ENDOCRJ.EJ12-0410.

[17] M.C.S. Côrtes, P.W. Rosario, L.F.F. Oliveira, M.R. Calsolari, Clinical impact of detectable antithyroglobulin antibodies below the reference limit (borderline) in patients with papillary thyroid carcinoma with undetectable serum thyroglobulin and normal neck ultrasonography after ablation: a prospective study, Thyroid 28 (2018) 229–235, https://doi.org/10.1089/thy.2017.0350.

[18] C. Durante, S. Tognini, T. Montesano, F. Orlandi, M. Torlontano, E. Puxeddu, M. Attard, G. Costante, S. Tumino, D. Meringolo, R. Bruno, F. Trulli, M. Toteda, A. Redler, G. Ronga, S. Filetti, F. Monzani, PTC Study Group, Clinical aggressiveness and long-term outcome in patients with papillary thyroid cancer and circulating anti-thyroglobulin autoantibodies, Thyroid 24 (2014) 1139–1145, https://doi.org/10.1089/thy.2013.0698.

[19] G.B. Morand, S.D. da Silva, A.M. Mlynarek, M.J. Black, R.J. Payne, M.P. Hier, Clinicopathological relevance of antithyroglobulin antibodies in low-risk papillary thyroid cancer, Clin. Otolaryngol. 42 (2017) 1130–1134, https://doi.org/10.1111/coa.12835.

[20] P.W. Rosario, M.C. Souza Côrtes, G.F. Mourão, Follow-up of patients with thyroid cancer and antithyroglobulin antibodies: a review for clinicians, Endocr. Relat. Cancer 28 (2021) R111–R119, https://doi.org/10.1530/ERC-21-0012.

[21] R. Ghossein, Update to the College of American Pathologists reporting on thyroid carcinomas, Head Neck Pathol 3 (2009) 86–93, https://doi.org/10.1007/s12105-009-0109-2.

[22] L. Boucai, A patient with papillary microcarcinoma undergoing active surveillance, in: Thyroid Cancer, Springer International Publishing, Cham, 2021, pp. 25–33, https://doi.org/10.1007/978-3-030-61919-0_4.

[23] S.G.A. de Meer, W.M.C.M. Vorselaars, J.W. Kist, M.P.M. Stokkel, B. de Keizer, G.D. Valk, I.H.M. Borel Rinkes, M.R. Vriens, Follow-up of patients with thyroglobulin-antibodies: rising Tg-Ab trend is a risk factor for recurrence of differentiated thyroid cancer, Endocr. Res. 42 (2017) 302–310, https://doi.org/10.1080/07435800.2017.1319858.

[24] O. Yamada, A. Miyauchi, Y. Ito, A. Nakayama, T. Yabuta, H. Masuoka, M. Fukushima, T. Higashiyama, M. Kihara, K. Kobayashi, A. Miya, Changes in serum thyroglobulin antibody levels as a dynamic prognostic factor for early-phase recurrence of thyroglobulin antibody-positive papillary thyroid carcinoma after total thyroidectomy, Endocr. J. 61 (2014) 961–965, https://doi.org/10.1507/endocrj.ej14-0275.

[25] X. Jia, P. Pang, L. Wang, L. Zhao, L. Jiang, Y. Song, X. Fan, Y. Wang, S. Zhao, J. Ba, G. Yang, X. Wang, W. Gu, L. Zang, Y. Pei, J. Du, Y. Mu, Z. Lyu, Clinical analysis of preoperative anti-thyroglobulin antibody in papillary thyroid cancer between 2011 and 2015 in Beijing, China: a retrospective study, Front. Endocrinol. 11 (2020) 452, https://doi.org/10.3389/fendo.2020.00452.

[26] A. Ernaga-Lorea, M.C. Hernández-Morhain, E. Anda-Apiñániz, J.J. Pineda-Arribas, I. Migueliz-Bermejo, N. Eguílaz-Esparza, A. Irigaray-Echarri, Prognostic value of change in anti-thyroglobulin antibodies after thyroidectomy in patients with papillary thyroid carcinoma, Clin. Transl. Oncol. 20 (2018) 740–744, https://doi.org/10.1007/s12094-017-1782-3.

[27] S. Turanli, H. Mersin, Serum antithyroglobulin antibody levels are not a good predictive factor on detection of disease activity in patients with papillary thyroid carcinoma, J. Cancer Res. Therapeut. 16 (2020) 624–629, https://doi.org/10.4103/jcrt.JCRT_340_17.

[28] F. Bueno, M.G.G. Falcone, M.A. Peñaloza, E. Abelleira, F. Pitoia, Dynamics of serum antithyroglobulin antibodies in patients with differentiated thyroid cancer, Endocrine 67 (2020) 387–396, https://doi.org/10.1007/s12020-019-02112-7.

[29] M. Sanjari, Z. Kordestani, M. Safavi, M. Mashrouteh, M. FekriSoofiAbadi, A. Ghaseminejad Tafreshi, Enhanced expression of Cyclin D1 and C-myc, a prognostic factor and possible mechanism for recurrence of papillary thyroid carcinoma, Sci. Rep. 10 (2020) 5100, https://doi.org/10.1038/s41598-020-61985-1.

[30] C. Xi, G.Q. Zhang, H.J. Song, C.T. Shen, L.Y. Hou, Z.L. Qiu, Q.Y. Luo, Change in antithyroglobulin antibody levels is a good predictor of responses to therapy in antithyroglobulin antibody-positive pediatric papillary thyroid carcinoma patients, Internet J. Endocrinol. 2022 (2022), https://doi.org/10.1155/2022/7173919.