

# May preablative thyroglobulin level be a prognostic indicator for papillary thyroid cancer?

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## Abstract

**Aim:** To investigate the effect of preablative thyroglobulin (Tg) levels without L-thyroxine (T4) suppression (Tg-off) on prognosis together with other risk factors in a large, long-term followed-up papillary thyroid cancer patient group.

**Materials and methods:** A total of 212 PTC patients were included to the study. All the patients underwent total or near-total thyroidectomy. Serum thyroid stimulating hormone (TSH) and Tg-off levels were obtained before radioiodine ablation. After radioiodine treatment, patients were followed-up by serum Tg measurements (under and off T4 suppression), I-131 whole body scintigraphy (wbs), neck ultrasonography (USG) and neck or thorax computerized tomography (CT). Mean follow-up time was 6.2 years (range: 3-17 years). In addition to well-known risk factors such as age, sex, tumor size, capsule invasion, vascular invasion, lymph node metastasis, serum preablative Tg-off levels of the patients were also noted. For statistical analysis, a single variable called 'risk status' representing the combination of three risk factors (capsule invasion, vascular invasion and lymph node metastasis) was defined.

**Results:** Recurrence was detected in 14 of 212 (6.6%) patients. In the univariate analysis, among the disease-related variables, tumor size ( $p=0.002$ ), capsule invasion ( $p=0.001$ ), lymph node metastasis ( $p=0.015$ ) and risk status ( $p=0.000$ ) were significantly associated with recurrence. However, vascular invasion ( $p=0.176$ ) and preablative Tg-off ( $p=0.514$ ) were not associated with recurrence. In the multivariate analysis, tumor size ( $p=0.013$ ) and risk status ( $p=0.002$ ) was associated with recurrence but preablative Tg-off was not significantly associated. However, if the relation between preablative Tg-off and recurrence was studied in two different groups (low risk and high risk), it was found that in the low risk group there was no significant relation between the recurrence rates and increasing preablative Tg-off levels ( $\chi^2=0.241$ ,  $p=0.623$ ), but in the high risk group, although it was not statistically significant, there was a trend to raise in the recurrence rates with the increasing preablative Tg-off levels ( $\chi^2=3.482$ ,  $p=0.062$ ).

**Conclusion:** In this retrospective study where a large long-term followed-up papillary thyroid cancer patient group was included, it is founded that preablative Tg-off value is not a statistically important prognostic risk factor when compared to the other risk factors.

## Introduction

Well differentiated papillary carcinoma accounts for approximately 90% of thyroid cancers [1]. Well differentiated thyroid cancer (DTC) has a quite well prognosis with 85-93% 10 year survival rates [2]. Therapy of DTC is surgery and then radioactive iodine treatment. The aim of the radioiodine therapy is the ablation of the possible residual thyroid tissue after surgery and detection of metastatic foci. After surgery and radioiodine ablation, serum thyroglobulin (Tg) levels is an important marker in the follow-up of the disease. The high specificity of Tg depends on the fact that the only source of Tg in the human body is the thyroid parenchymal cells. The presence of Tg after total thyroidectomy and radioiodine ablation is an indicator for persistent disease or recurrence. Especially, progressive increase in the Tg levels is an early and real marker for recurrent disease [3]. It has been reported that the Tg levels measured 6 or 12 months later than the radioiodine ablation without L-thyroxine (T4) suppression (Tg-off) is an important parameter for detection of disease progression risk [4-6].

Moreover, in the literature, there are many studies investigating the role of preablative Tg levels in the clinical management of DTC. Some investigators reported that preablative Tg levels could be a predictor for progressive or metastatic disease in the long term follow-up period and could be regarded as another criterion together with lymph node invasion for choosing high risk patients [7-10]. Despite this, preablative

Tg level is not as frequently used as postablative Tg level in the clinical practice.

The results of the Surveillance, Epidemiology and End Results programme of the National Cancer Institute [11] and National Cancer Database [2] showed that risk factors affecting prognosis in DTC are age, sex, tumor size, histopathological type and grade, local invasion, multicentricity and distant metastasis. Based on these prognostic indicators, many scoring or grading systems have been created within the last 20 years. In the recent guidelines published by the American Thyroid Association (ATA) [12], European Thyroid Association (ETA) [13] and British Thyroid Association (BTA) [14], patients are divided into risk groups for the possibility of recurrence based primarily on age, tumor size, presence of nodal invasion and metastasis. However, preablative Tg levels were not taken into consideration and its effect on

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prognosis was not mentioned in any of these guidelines.

The aim of this study was to investigate the effect of preablative Tg-off levels on prognosis together with other risk factors in a large, long-term followed-up papillary thyroid cancer (PTC) patient group.

## Material and method

### Patients

Between 1993 and 2009 years, 508 PTC patients who underwent radioiodine ablation in our clinic were reviewed. Two hundred and ninety-six patients who had high levels of antithyroglobulin antibody, distant metastasis or macroscopic residual thyroid tissue at the beginning of the treatment and who could not be followed-up regularly were excluded. In the remaining 212 PTC patients (177 F, 35 M; mean age:  $49.8 \pm 12.9$ y) were included in the study. In addition to well-known risk factors such as age, sex, tumor size, capsule invasion, vascular invasion, lymph node metastasis, serum Tg-off levels of all the patients were also identified. Furthermore, results of performed diagnostic tools; ultrasonography (USG), neck or thorax computerized tomography (CT), I-131 whole body scintigraphy (wbs), serum Tg measurements (under and off T4 suppression) were evaluated. Additional surgical procedures (lymph node dissection) and radioiodine treatments (doses and numbers) were also taken into consideration. We classified the patients into two groups; high risk who have at least one of these histopathological criteria (capsule invasion, vascular invasion, lymph node metastasis) and low risk who have none of them.

All patients had undergone radioiodine ablation following total or near-total thyroidectomy. Diagnostic scintigraphy was not performed before ablative doses in order to prevent the stunning effect. Serum TSH and Tg-off measurements were obtained on the same day before the radioiodine therapy. I-131 was applied if the TSH level was higher than 30 IU/mL. The doses of radioiodine was determined according to fixed dose protocol, 1850-3700 MBq for low risk group and 4625-5550 MBq for high risk group. T4 suppression treatment was started after 48 hours of radioiodine ablation treatment.

At the 3<sup>rd</sup> month of ablation therapy, serum TSH and Tg levels were checked under T4 suppression. At the 6<sup>th</sup> month of therapy, I-131 wbs with 185MBq radioiodine was performed with measurement of serum TSH and Tg levels at the T4 off state. The next steps of the follow-up procedure were specified individually, depending on the risk factors of the patients by the measurement of Tg levels, I-131 wbs, neck USG, neck or thorax CT.

Serum Tg levels were measured by using a commercial immunoradiometric assay (IMMULITE Systems, EURO/DPC Ltd; Normal range was 1.6-59.9 ng/ml) until 2005. After 2005, serum Tg measurements were done with immunoassay method. (Beckman Access Systems Thyroglobulin assay, BECKMAN COULTER Ltd; Normal range was 1.15-35 ng/ml).

### Statistical analysis

Continuous data are presented as the mean±standard deviation (SD), median, and ranges, and categorical data are expressed as the frequency and proportions. The analyses were performed in two steps. First, the independent variables were entered into the logistic model one by one. Then, to determine the independent risk indicators of having recurrence, we performed a multiple logistic regression following the Hierarchical Backward Elimination Approach. All variables with p values less than 0.25 in univariate analysis were included in multivariate analysis. The analyses were performed using the SPSS software, version

11.5.0 (SPSS Inc., Chicago, Illinois, USA).

## Results

In all our patients with papillary thyroid cancer, mean tumor size was calculated as  $14.4 \pm 5.9$  mm (range 5-45mm). However, 158/212 (74.5%) patients had a tumor size  $\leq 10$  mm. Capsular invasion, vascular invasion and lymph node metastasis have been seen in 41/212 (19.3%), 4/212 (1.9%) and 19/212 (9%) patients, respectively. In the detailed evaluation of the patients according to risk status, 159 of the 212 (75%) patients were in the low risk and the rest of the patients were in the high-risk groups. Radioiodine treatment was applied as a mean  $3570 \pm 447.7$  MBq in the low risk group and a mean  $4713 \pm 773$  MBq in the high-risk group. Mean follow-up time was 6.2 years (range: 3-17 years). Mean preablative Tg-off level was found 7.57 ng/ml (range: 0.01-602 ng/ml). Preablative Tg-off levels were measured 1-2 months later than the operation. When the patients were classified according to their preablative Tg-off levels as Tg<5 ng/ml, Tg: 5-10 ng/ml and Tg>10 ng/ml, 86/212 (40.6%), 32/212 (15.1%) and 94/212 (44.3%) patients were found in each group respectively. The characteristics of the 212 patients are shown in Table 1.

During the follow-up period, recurrence was detected in 14 of 212 (6.6%) patients. Lymph node metastasis in 10 patients, recurrence in the thyroid bed in 3 patients and lung metastases in one patient were determined. 4/14 patients who had recurrence was in the low risk group (preablative Tg-off values <5 ng/ml in two, 5-10 ng/ml in one and >10 ng/ml in one), 10/14 patients was in the high risk group (preablative Tg-off values <5 ng/ml in one, 5-10 ng/ml in one and >10 ng/ml in eight). When the separate univariate logistic models were used to

**Table 1.** Characteristics of patients.

	Statistics (n=212)
Age, Mean±SD (Range)	49.8 ± 12.9 (13-84)
<45 years	60 (28.3)
≥ 45 years	152 (71.7)
Sex, n (%)	
Female	177 (83.5)
Male	35 (16.5)
Tumor Size, Mean±SD (Range)	14.4 ± 5.9 (5-45)
Tumor Size, n (%)	
≤10 mm	158 (74.5)
>10 mm	54 (25.5)
Capsule Invasion, n (%)	
No	171(80.7)
Yes	41 (19.3)
Vascular Invasion, n (%)	
No	208 (98.1)
Yes	4 (1.9)
Lymph Node Metastasis, n (%)	
No	193 (91)
Yes	19 (9)
Risk Status*, n (%)	
Low	159(75)
High	53 (25)
Preablative Tg, Median (Range)	7.57 (0.01-602)
Preablative Tg levels, n (%)	
<5 ng/ml	86 (40.6)
5-10 ng/ml	32 (15.1)
>10 ng/ml	94 (44.3)

\*Patients who have at least one of these histopathological criteria (capsule invasion, vascular invasion, lymph node metastasis) were classified as high risk patients.

analyze the independent variables one by one, there were statistically significant associations among recurrence, the outcome variable, and several independent variables. Table 2 gives the odds ratios (OR) and corresponding 95% confidence intervals (CI) for each demographic (age, sex) and disease-related variables. In current study according to Table 2, there was no difference between sex and age groups. Among the disease-related variables, tumor size, capsule invasion, lymph node metastasis and risk status were significantly associated with recurrence. However, vascular invasion and preablative Tg-off levels were not associated with recurrence.

In this study, patients who have at least one of these histopathological criteria were classified as high-risk patients: capsular invasion, vascular invasion and lymph node metastasis. For this reason, there is a statistical relationship between these three risk factors and variable defined as "risk status". Because the dependent variables cannot be included to multivariate logistic regression analysis, the risk status representing both three variables was used for the multivariate analysis. Tumor size and preablative Tg-off, the variables which had p values <0.25 in the univariate analysis were also added to the multivariate analysis.

In the multivariate logistic regression model presented in Table 3, the effects of the risk factors were estimated simultaneously and the effect associated with each factor was therefore adjusted depending

on the influence of the other variables in the model. Multivariate logistic regression analysis was slightly different from the results of univariate analyses. In the final model, tumor size remained significantly associated with the recurrence. Patients who have >10 mm tumor was more likely to have recurrence than patients with ≤10 mm tumor size (OR=4.5, p=0.013). Not surprisingly, risk status was the most significant indicator associated with recurrence. Patients having high risk had a significantly higher risk of recurrence compared with patients having low risk (OR=7.1, p=0.002) (Table 3). Pre-ablative Tg-off was not significantly associated with recurrence.

In the regression analysis, preablative Tg-off levels were not to be related with recurrence. However, if the relation between preablative Tg-off levels and recurrence was studied in two different groups (low risk and high risk), it was found that in the low risk group there was no significant relation between the recurrence rates and increasing Tg-off levels ( $\chi^2=0.241$ , p=0,623), but in the high risk group, although it was not statistically significant, there was a trend to raise in the recurrence rates with the increasing Tg-off levels ( $\chi^2=3.482$ , p=0,062) (Table 4).

### Discussion

Age, sex, tumor size, histological type and grade, local invasion, multicentricity and metastases have been defined as well-known prognostic risk factors of DTCs [2,11]. In this study, tumor size, capsule invasion, lymph node metastasis and risk status have been found to be risk factors to affect disease prognosis.

Age at diagnosis has been described as a strong prognostic factor [2,11,15-17]. It has been reported that recurrence and death rates linearly increase after the age of forty-five [18]. Therefore it has been thought that, age-related risk increase might be related to the fact that these patients generally have aggressive histological tumor variants at presentation with locally aggressive behavior and a high incidence of distant metastasis. However, this explanation seems insufficient to explain why children have very good long-term prognosis despite having extensive disease, high incidence of lymph node metastasis and recurrent disease [19-21]. Since age appears not to be an independent risk factor, some authors suggested that age should be considered together with multiple age-related factors such as nutrition, immune

**Table 2.** Univariate Logistic Regression Analyses for individual risk factors of recurrence.

Risk Factors	Recurrence		Univariate analysis	
	Yes n (%)	No n (%)	OR (95% CI)	p
<b>Age (years)</b>				
<45	4 (6.7)	56 (93.3)	1(Ref)	
≥45	10 (6.6)	142 (93.4)	0.9(0.3-3.3)	0.982
<b>Sex</b>				
Female	11 (6.2)	166 (93.8)	1(Ref)	
Male	3 (8.6)	32 (91.4)	1.4(0.4-5.4)	0.610
<b>Tumor Size (mm)</b>				
≤10	5 (3.2)	153 (96.8)	1(Ref)	
>10	9 (16.7)	45 (83.3)	6.1(1.9-19.2)	0.002
<b>Capsule Invasion</b>				
No	6 (3.5)	165 (96.5)	1(Ref)	
Yes	8 (19.5)	33 (80.5)	6.7(2.1-20.5)	0.001
<b>Vascular Invasion</b>				
No	13 (6.3)	195 (93.8)	1(Ref)	
Yes	1 (25)	3 (75)	5(0.5-51.5)	0.176
<b>Lymph Node Metastasis</b>				
No	10 (5.2)	183 (94.8)	1(Ref)	
Yes	4 (21.1)	15 (78.9)	4.8(1.4-17.4)	0.015
<b>Risk Status</b>				
Low	4 (2.5)	155 (97.5)	1(Ref)	
High	10 (18.9)	43 (81.1)	9 (2.7-30.2)	0.000
<b>Preablative Tg levels</b>				
<5 nq/ml	3 (3.5)	83 (96.5)	1(Ref)	
5-10 nq/ml	2 (6.3)	30 (93.8)	1.8 (0.3-11.6)	0.514
>10 nq/ml	9 (9.6)	85 (90.4)	2.9 (0.8-11.2)	0.116

OR; Odds Ratio, CI; Confidence Interval

**Table 3.** Multivariate Logistic Regression Analyses for risk factors of recurrence.

Risk Factors	Multiple analysis	
	OR (95% CI)	p
<b>Tumor Size (mm)</b>		
≤10	1(Ref)	
>10	4.5(1.4-14.9)	0.013
<b>Risk Status</b>		
Low	1(Ref)	
High	7.1 (2.1-24.5)	0.002

OR; Odds Ratio, CI; Confidence Interval

**Table 4.** Preablative Tg and recurrence relation in the risk status groups.

Risk Status	Preablative Tg, nq/ml	Recurrence		$\chi^2$	p
		Yes n (%)	No n (%)		
Low	<5	2 (2.9)	68 (97.1)	0.241	0,623
	5-10	1 (4.3)	22 (95.7)		
	>10	1 (1.5)	65 (98.5)		
High	<5	1 (6.3)	15 (93.8)	3.482	0,062
	5-10	1 (11.1)	8 (88.9)		
	>10	8 (28.6)	20 (71.4)		

status, DNA repair ability, effect of genetic mutations. On the other hand, no difference has been seen in the survival rates of the patients at same age and same stage of the disease [11]. In our study, we did not find a relationship between the age of the patients and the disease prognosis. This situation might be explained by low recurrence rate of our study which might be as a result the patients with extensive disease at the presentation were not included in the study.

Sex is one of the other prognostic factors of DTC [2,11,17,22]. No relationship between sex and prognosis was found in our study. Similarly, some authors have failed to show that sex is an independent prognostic factor [19,20]. In conclusion, sex has not been accepted as a strong risk factor [11,15].

The other described risk factor in predicting disease prognosis is tumor histology [1,2,11,16,22-23]. As known, papillary thyroid carcinoma is the most common histological subtype that generally has good outcomes [24]. However, follicular thyroid carcinoma has been described with poor prognosis [25-27]. Because only papillary thyroid carcinoma subtype was included in our study, we investigated prognostic risk factors of just this histologic subtype not follicular type. It is known that histological variant is the one of the important risk factors for papillary thyroid carcinomas [18]. But, since the patients had undergone thyroidectomy in different hospitals and pathologic examinations had performed by different pathologists, we could not reach enough detailed information about pathological results. For this reason it was not possible to compare the prognosis of different histopathological subtypes of papillary thyroid cancer.

Tumor size is another well-known prognostic factor and also it has been reported that a tumor size larger than 4 cm and extra-thyroidal invasion are poor prognostic factors [1,2,11,16,22,24]. Disease prognosis gets worse while tumor size becomes larger in both the papillary and follicular thyroid carcinomas. In our study, in both the univariate and multivariate analyses, we found a statistically significant correlation between tumor size and recurrence incidence. Although recurrence rate of patients with tumor size less than 1 cm is low, interestingly 5 out of 14 (35%) patients with recurrent disease had microcarcinoma.

It is believed that there is no prognostic importance of regional lymph node metastasis in papillary thyroid cancer patients. However, recent studies have showed that presence of lymph node metastasis is related to high recurrence rate and in older patients associated with increased disease related death risk [28-30]. Similarly, we found a statistically significant relationship between presence of lymph node metastases at the presentation and recurrence rate.

Extracapsular invasion at the presentation is a real prognostic parameter for both papillary and follicular thyroid carcinomas [2,11,17]. Although presence of extracapsular invasion is common in papillary thyroid carcinomas, especially in poor prognostic histological subtypes, vascular invasion is not very common [24,31]. In our study, it has been seen that presence of extracapsular invasion is related to high recurrence rates which is compatible with current literature. Similarly, we have seen a low rate of vascular invasion which was not associated with recurrence disease in the univariate analysis. Our general treatment approach is to apply higher doses of radioiodine to patients with presence of least one of these criteria: extracapsular invasion, vascular invasion and lymph node metastasis. Additionally we interpreted the disease recurrence rates of patients by classifying them according to risk status. Not surprisingly, in multivariate analysis, we have detected that risk status is an important parameter for recurrent disease.

In our study, additional to well-known risk factors, the contribution of preablative Tg-off levels to the disease prognosis was evaluated. The importance of preablative Tg levels is controversial because of presence of remnant thyroid tissue. In a few studies, it has been reported that there might be a correlation between preablative Tg levels and presence of metastatic or recurrent disease [8,32,33]. Toubeau *et al.* showed that although not as important as postablative Tg, preablative Tg levels might be helpful to predict disease prognosis of DTC. They recommended that patients with lymph node metastases or high preablative Tg levels at the presentation should be followed-up carefully [10]. Hall *et al.* reported that high tumor stage at diagnosis) and Tg-off levels, higher than 20 ng/ml, which was measured at the postoperative 3rd month, might be a predictor for disease recurrence [32]. Similarly, Lin *et al.* showed that postoperative serum Tg levels, greater than or equal to 10 ng/ml, are a useful marker to predict prognosis in patients with papillary and follicular thyroid cancer [33]. Different from literature, in our study, any relationship between preablative Tg-off levels and recurrence rate was not found in both univariate and multivariate analyses. It might be because a small numbers of patients developed recurrent disease. In the detailed analysis of patients according to disease stage, while a correlation between preablative Tg-off levels and the recurrence rates of low risk group was not found, a correlation in high risk group was seen which was not statistically significant but very close to significance limit. Recently, it has been claimed that some of low risk stratified patients might be followed-up without applying radioiodine ablation treatment and in this case, preablative Tg levels could be helpful in selecting suitable patients [34-36]. Therefore, in our study, the disease recurrence has been seen in two patients with a preablative Tg-off level under 5 ng/ml in low risk group. For this reason, we believe that radioiodine treatment should be given even in this low risk patient group.

As a conclusion, in this retrospective study where a large long-term followed-up papillary thyroid cancer patient group was included, it is founded that preablative Tg-off value is not a statistically important prognostic risk factor when compared to the other risk factors.

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