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Poorly Differentiated Thyroid Carcinoma Patients with Detectable Thyroglobulin Levels after Initial Treatment Show an Increase in Mortality and Disease Recurrence

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Keywords
Poorly differentiated thyroid carcinoma · Thyroglobulin level · Survival rate · Disease recurrence

Abstract
Purpose: The role of thyroglobulin (Tg) in predicting death and recurrence risk in patients with poorly differentiated thyroid carcinoma (PDTC) is not well established. We aimed to analyze Tg levels following total thyroidectomy and adjuvant radioiodine treatment (RAI) in PDTC patients and correlate Tg levels with survival and recurrence. ***Methods:*** A retrospective analysis was conducted on 101 patients with PDTC who were treated between 1986 and 2010. Among them, 38 had no distant metastases at presentation, were managed by total thyroidectomy and adjuvant RAI, and had negative anti-Tg antibodies. An unstimulated Tg level <1 ng/mL was used as a cut-off point for undetectable Tg levels. Association of patient and tumor characteristics with Tg levels was examined by χ^2 test. Overall survival, disease-specific survival (DSS), and recurrence-free survival (RFS), stratified by Tg levels, were calculated by the Kaplan-Meier method and compared by the log-rank test. ***Results:*** Compared to patients with undetectable Tg, cases with detectable Tg had a lower probability of achieving free surgical margins (21.7 vs. 46.7%; $p = 0.04$), higher node status (73.3 vs. 21.8%; $p = 0.005$), decreased 5-year DSS (65 vs. 100%; $p = 0.009$), and worse 5-year RFS (32 vs. 84%, $p = 0.010$), with a significant number of patients having a recurrence in the first year (50 vs. 12.5%; $p = 0.021$). Patients with detectable Tg levels also showed worse locoregional (55.6 vs. 90.9%; $p = 0.014$) and distant control (5-year distant control of 46.9 vs. 91%; $p = 0.017$). ***Conclusions:*** Our results suggest that detectable Tg levels after surgery and RAI in a subset of PDTC patients appear to predict a higher rate of death and recurrence.

Introduction

Poorly differentiated thyroid carcinoma (PDTC) is a rare type of thyroid cancer accounting for <6% of all thyroid malignancies [1]. Nevertheless, it is the second cause of death from follicular cell-derived thyroid cancer after anaplastic carcinoma [2]. Death is usually secondary to metastatic disease [3]. The tumors show significant clinical, biological, and pathological heterogeneity, with char-

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acteristics in between differentiated thyroid carcinoma (DTC) and anaplastic carcinoma [4, 5]. Despite being less differentiated than DTCs, these tumors partially retain the ability to produce colloid and thyroglobulin (Tg) [6–8]. The prognostic role of Tg in PDTC was unknown due to the very limited number of available studies until the work of Ibrahimpasic et al. [9], who showed that patients with detectable Tg levels had higher a rate of disease recurrence than those with undetectable Tg but found no effect on mortality. The objective of this study was to correlate Tg values in PDTC patients following total thyroidectomy and adjuvant radioiodine treatment (RAI) with patient characteristics, tumor aggressiveness, disease recurrence, and mortality.

Study Design

We performed a retrospective study at the Portuguese Institute of Oncology Francisco Gentil, Lisbon Centre (IPOLFG), the largest referral center for thyroid cancer in Portugal, with the aim of evaluating the predictive role of Tg levels on recurrence and survival following total thyroidectomy and adjuvant RAI in PDTC patients. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board of our institution. Informed consent for management of clinical data was obtained from all individual patients included in the study.

Patients

A total of 101 PDTC patients were diagnosed and treated at IPOLFG between January 1986 and December 2010. Thirty-eight patients fulfilled the following inclusion criteria: no distant metastases at presentation (M0), treatment by total thyroidectomy and RAI, and available Tg levels with negative anti-Tg antibodies measured between 3 and 9 months after adjuvant RAI. No adjuvant radiotherapy or systemic therapy was used in these cases.

Protocol

Medical records were reviewed for patient and tumor characteristics, including the year of diagnosis, gender, age at diagnosis, tumor pathology, TNM staging, time of follow-up, time of first recurrence, and the duration of survival from the date of diagnosis. Recurrence was defined as a new diagnosis of locoregional or distant tumor by tissue biopsy or imaging at least 6 months after initial therapy. Data regarding disease-specific mortality were reviewed based on the hospital records or death certificates. Tumor size was defined as the maximal diameter of the surgical specimen, or, if this was not available, that from the previous imaging studies. The criteria in the AJCCC Cancer Staging Manual (ed 7) were used for staging [10]. Neck dissection was performed in selected patients for suspected lymph node disease at the time of surgery. The Turin proposal criteria were used to define the PDTC diagnosis as previously described [11]. An unstimulated Tg level <1 ng/mL after surgery and RAI was used as a cut-off point for undetectable Tg levels. This cut-off point was chosen to encompass the known functional sensitivities of the different assays used in our institution over time, i.e., SELco Tg Medipan Diagnostica (a functional sensitivity of 0.5–1 ng/mL) and Immulite 2000-Thyroglobulin DCP/Siemens (a functional sensitivity of 0.9 ng/mL).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows v21.0 (IBM Corp., Armonk, NY, USA). The χ^2 test was used to compare the differences in patient and tumor characteristics between those with detectable and undetectable Tg levels.

Five-year overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) were calculated by the Kaplan-Meier method and compared by log-rank test between those with a detectable and undetectable Tg value. Statistical significance was defined as $p < 0.05$.

Results

RAI and Histological Phenotype in Patients with Detectable and Undetectable Tg

The study included 38 cases from 1986 to 2011 (patient 25 in June 1997, median in January 2002, and patient 75 in October 2008).

After total thyroidectomy and RAI, 15 patients had detectable (Tg >1 ng/mL) and 23 had undetectable (Tg ≤1 ng/mL) Tg levels. Patients received a median cumulative activity of 8.362 GBq (range 1.85–20.757 GBq). Patients with detectable Tg and undetectable Tg levels received a median cumulative activity of RAI of 8.362 GBq and 6.771 GBq, respectively (p = ns). Only 1 patient (with a pT1 tumor with R0 resection and detectable Tg after initial treatment) received an activity <3.7 GBq.

The pathological subtypes in the 15 patients with detectable Tg were insular (n = 6), solid (n = 1), trabecular

(n = 1), and mixed phenotype (n = 7). In the 23 patients with undetectable Tg, these were insular (n = 10), solid (n = 3), trabecular (n = 3), and mixed phenotype (n = 7).

Characteristics of PDTC Cases Stratified by Tg Group

Patients with undetectable and detectable Tg levels showed no significant age or gender differences (Table 1). Around two-thirds of all cases were older than 45 years and the female-to-male ratio was also similar in both groups (Table 1).

Pathological tumor characteristics in the 2 groups were only statistically different for surgical margins and nodal status; patients with detectable Tg had a lower probability of achieving R0 margins (21.7 vs. 46.7%; p = 0.04) and a higher node status (73.3 vs. 21.8%; p = 0.005). Nevertheless, these patients showed a trend towards more advanced local disease with a higher pT4 status (61 vs. 37.9%; p = 0.083) and more frequent extrathyroid extension (80 vs. 52.2%; p = 0.082). No statistical significant differences between the 2 groups were found regarding the size of primary tumor, vascular invasion, or histological subtype.

Outcome of PDTC Patients Stratified by Tg Group

In our cohort of 38 PDTC patients, 14 died (37%), with 9 deaths (64%) being specifically related to the disease (Table 1). The number of disease-related deaths was significantly higher in the group with detectable Tg (50 vs. 8.3%; p = 0.004). In the first year of follow-up, deaths were observed in 13% of the patients in the group with detectable Tg levels (2 cases) compared with no deaths in the group with undetectable Tg (the first death occurred after 8.7 years of follow-up).

There were 14 cases of recurrence (36%): 7 locoregional and 7 metastatic. Patients with detectable Tg levels had a significant increase in recurrent disease (71.4 vs. 16.7%; p = 0.001). Both locoregional and distant recurrence were significantly increased in the group with detectable Tg levels (42.9 vs. 8.3%; p = 0.012 and 35.7 vs. 8.3%; p = 0.036, respectively). In the first year of follow-up, recurrence was observed in 50% of the group with detectable Tg levels and in 12.5% of the group with undetectable Tg levels (7 vs. 2 cases; p = 0.021). These 2 patients with early recurrence despite negative Tg levels both had a status of pT4, with the largest tumor diameters of 52 and 60 mm with tracheal invasion in one case and positive N1a status in the other.

After a median follow-up of 7.35 years (range 0.71–22.7 years), a trend towards a lower 5-year OS was observed in patients with detectable Tg (65 vs. 91.3%; 6.9

Table 1. Characteristics stratified by Tg group

	Tg undetectable (n = 23)	Tg detectable (n = 15)	p value[a]
Age			
<45 years	33.3 (8)	33.3 (5)	0.633
>45 years	65.2 (15)	66.7 (10)	
Sex			
Female	60.9 (14)	66.7 (10)	0.792
Male	39.1 (9)	33.3 (5)	
Tumor diameter			
≤4 cm	50 (12)	40 (6)	0.742
>4 cm	47.8 (11)	60 (9)	
pT stage			
1–3	62.1 (14)	38.9 (6)	0.083
4	37.9 (9)	61.1 (9)	
Extra thyroid extension			
Negative	47.8 (11)	20 (3)	0.082
Positive	52.2 (12)	80 (12)	
Surgical margins			
Negative	65.2 (15)	33.3 (5)	0.04
Positive	21.7 (5)	46.7 (7)	
Unknown	13 (3)	20 (3)	
Polymorphic histology			
Negative	88.9 (16)	81.8 (9)	0.642
Positive	11.1 (2)	18.2 (2)	
Vascular invasion			
Negative	21.8 (5)	13.4 (2)	0.804
Positive	78.2 (18)	86.6 (13)	
Polymorphic histology			
Negative	69.6 (16)	53.3 (8)	0.642
Positive	30.4 (7)	46.7 (7)	
pN stage			
0	78.2 (18)	26.7 (4)	0.005
1	21.8 (5)	73.3 (11)	
Overall deaths			
Yes	25 (6)	57.1 (8)	0.048
No	75 (18)	42.9 (6)	
Disease-related deaths			
Yes	8.3 (2)	50 (7)	0.004
No	91.7 (22)	50 (7)	
Overall recurrence			
Yes	16.7 (4)	71.4 (10)[b]	0.001
No	83.3 (20)	28.6 (4)	
Local recurrence			
Yes	8.3 (2)	42.9 (6)	0.012
No	91.7 (22)	57.1 (8)	
Distant recurrence			
Yes	8.3 (2)	35.7 (5)	0.036
No	91.7 (22)	64.3 (9)	

Values are expressed as % (n). Tg, thyroglobulin.

[a] By means of the χ^2 test.

[b] A patient in the detectable Tg group was found (at the same visit) to have both nodal and distant metastasis. As such, the sum of total recurrence is smaller than the sum of local and distant recurrence.

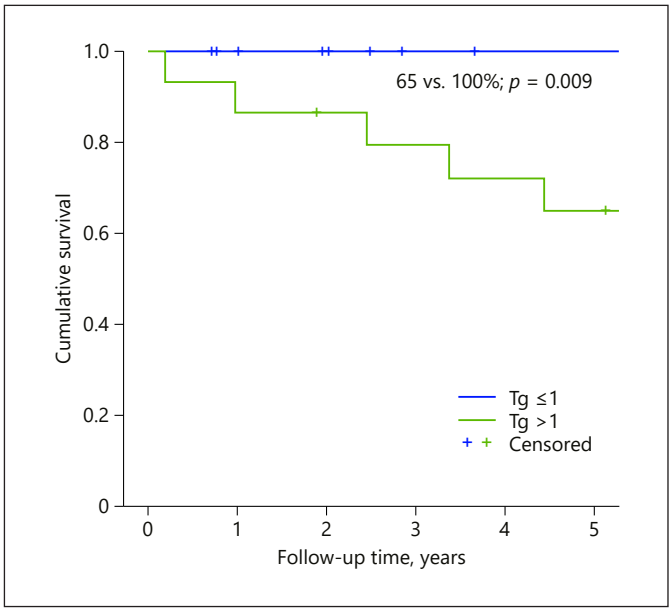

Fig. 1. Five-year disease-specific survival (DSS), stratified by Tg level.

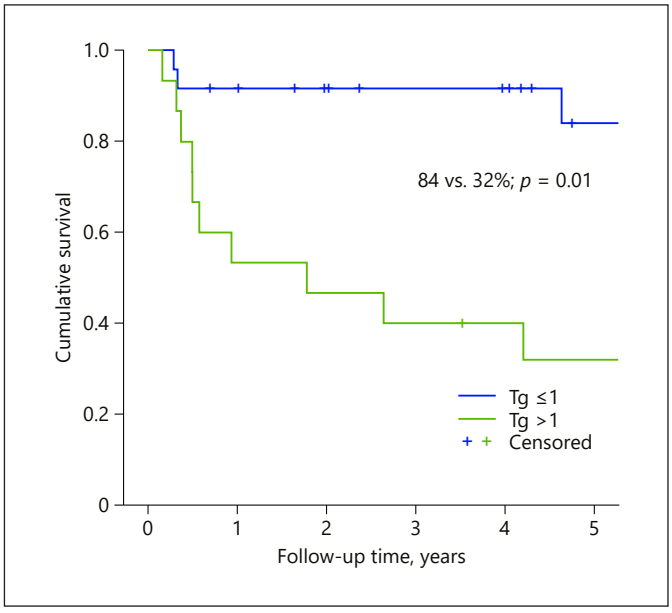

Fig. 2. Five-year recurrence-free survival (RFS), stratified by Tg level.

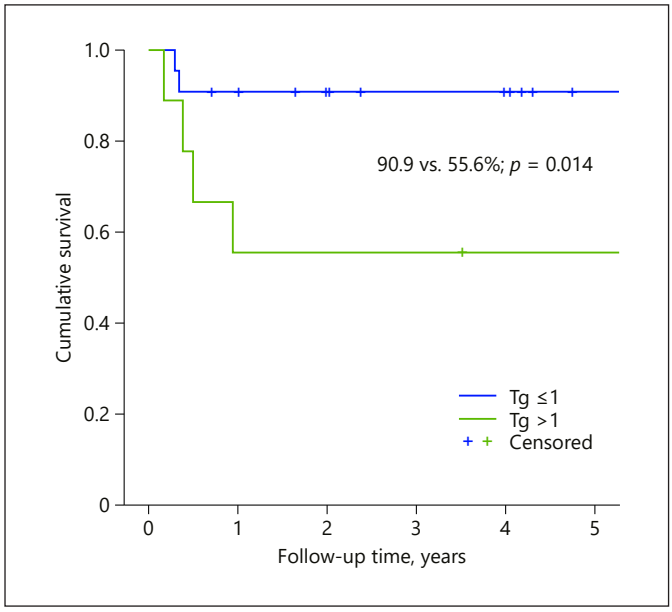

Fig. 3. Five-year regional recurrence-free survival (RFS), stratified by Tg level.

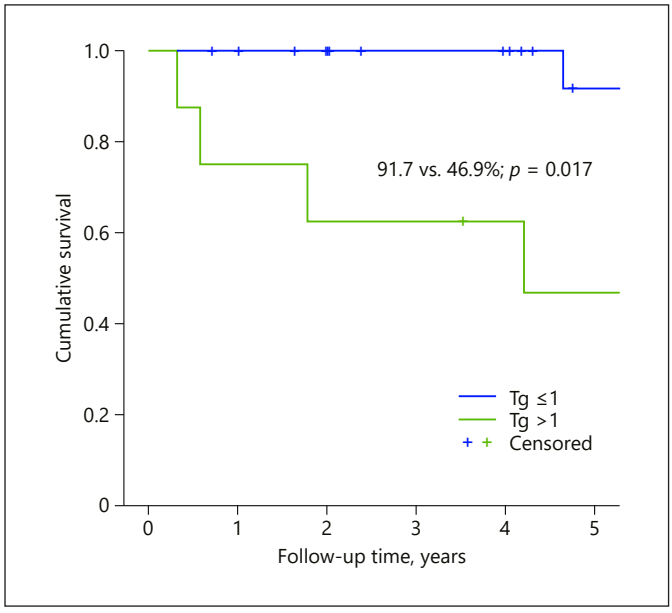

Fig. 4. Five-year distant recurrence-free survival (RFS), stratified by Tg level.

years vs. median not reached; $p = 0.096$). As shown in Figure 1, patients with detectable Tg had a significant decrease in 5-year DSS (65 vs. 100%; median 11.2 years vs. median not reached; $p = 0.009$; Fig. 1), a significant decrease in 5-year RFS (32 vs. 84%; median 1.7 years vs. median not reached; $p = 0.01$; Fig. 2), a significant decrease in 5-year regional control (55.6 vs. 90.9%; median 8.5 years vs. median not reached; $p = 0.014$; Fig. 3), as well as a decrease in 5-year distant control (46.9 vs. 91%; median 4.2 years vs. median not reached; $p = 0.017$; Fig. 4).

Discussion

PDTC is a rare and heterogenous type of thyroid cancer. Approximately 20 years have passed between its first description in 1983 [12], and 2004, when it was incorporated in the WHO Classification of Thyroid Tumors [6]. Nevertheless, the diagnostic criteria still generate controversy and the WHO classification has been difficult to implement in routine clinical practice [7]. In 2006, the Turin Consensus Group proposed a more practical diagnostic algorithm of PDTC [11]. The prognostic role of serum Tg levels obtained after initial treatment of DTC is well established [13]. On the other hand, until the study by Ibrahimpasic et al. [9], the prognostic value of Tg levels in PDTC was unclear. These authors specifically studied the role of Tg as a possible prognostic factor in 31 PDTC cases, showing that patients with detectable Tg levels after surgery and RAI had an increased margin for positive disease and higher/earlier recurrence rates. The PDTC cases were classified based on the Memorial Sloan Kettering Cancer Center (MSKCC) criteria, which differs from the Turin proposal as it only requires necrosis or a high mitotic index, regardless of growth pattern and nuclear features [14]. Despite these differences, Gnemmi et al. [15] showed that these 2 sets of criteria similarly predict an intermediate prognosis for PDTC cases (between DTC and anaplastic thyroid carcinoma).

Our study supports and expands the prognostic role of serum Tg obtained after initial treatment (surgery + RAI) in PDTC. We confirm that Tg levels can predict morbidity [9] and, in addition, we show for the first time that mortality can also be predicted by serum Tg in these patients. In fact, in our cohort, the group with detectable Tg after surgery and RAI had a significantly worse 5-year DSS than patients with undetectable Tg (65 vs. 100%, median 11.2 years vs. median not reached; $p = 0.009$). In the former group, 2 deaths were observed in the first year of follow-up while no death occurred in the first 8.7 years in the latter group. A more aggressive disease course compared to that described by Ibrahimpasic et al. [9] (a 5-year DSS in the detectable Tg group of 65 vs. 95.8% in the undetectable Tg group), associated with a larger sample size, and longer follow-up time, may explain why specific survival was only significantly correlated with serum Tg levels in our study.

We also found a reduced 5-year RFS in the group with detectable Tg (32 vs. 84%; median 1.7 years vs. median not reached; $p = 0.010$). Both locoregional and distant control were also significantly worse with detectable Tg (locoregional RFS of 55.6 vs. 90.9%; median 8.5 years vs. median not reached, $p = 0.014$; distant RFS of 46.9 vs. 91%; median 4.2 years vs. median not reached, $p = 0.017$). The group with detectable Tg had 70% of its recurrences (7 cases) in the first year of follow-up. On the other hand, the group with undetectable Tg levels had 4 recurrences, 2 (50%) in first year. The patients with detectable Tg levels also had a significant increase in positive surgical margins after surgery (46.6 vs. 21.7%, $p = 0.004$); for the first time, we have also shown a significant increase in positive nodal disease in the neck in this group (73.3 vs. 21.8%, $p = 0.005$). Other pathological characteristics such as a pT4 status (61.1 vs. 37.9%, $p = 0.083$) and extrathyroidal extension (80.0 vs. 52.2%, $p = 0.082$) only showed a trend towards higher prevalence in the group with detectable Tg levels.

Our study has some limitations. The retrospective study design associated with a clinical heterogeneous disease and a small sample size (38 patients) can limit the applicability of the study conclusions. Nevertheless, despite being a small sample, it comes from a single center with a large series of PDTC cases (101 patients, unpublished data) and is, so far, the largest series evaluating the role of Tg in PDTC patients; it also had the longest follow-up time. Furthermore, the results broadly agree with a recent paper published by Ibrahimpasic et al. [9].

In summary, we conclude that Tg levels in PDTC M0 patients after treatment with surgery and adjuvant RAI have a prognostic value similar to patients with DTC. Those with detectable Tg levels have more aggressive disease, and higher rates of persistent microscopic disease after surgery with higher rates of nodal and metastatic recurrence lead to a reduced OS. Therefore, serum Tg levels may be a useful marker for early recurrence and death in PDTC. However, although nonsuppressed Tg levels seem to predict a poorer outcome, suppressed Tg levels may fail to reveal early recurrence. We emphasize the need for larger multi-institutional studies to confirm the role of detectable Tg levels in the morbidity and mortality of PDTC patients.

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Disclosure Statement

The authors declare they have no conflict of interest.

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