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Thyroid autoimmunity, thyroglobulin autoantibodies and thyroid cancer prognosis

Running title**: Thyroid autoimmunity and thyroid cancer**

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Abstract

Relevance of thyroid autoimmunity to prognosis of papillary thyroid carcinoma is still unsettled. We decided to investigate the impact of thyroid autoimmunity on prognosis of papillary thyroid carcinoma and the handling of TgAbs. We evaluated the clinical course of a large group of patients according to the presence (PTC-LT) or absence (PTC) of lymphocytic thyroiditis at histology.

We studied 194 consecutive patients with a diagnosis of PTC and treated with total thyroidectomy plus ^{131}I ablation between 2007 and 2009. Median follow-up (with 25th-75th percentiles) was 84·0 (56·4-118·0) months. The remission criteria were: basal Tg <0·2 ng/mL (or stimulated Tg <1), TgAbs <8 IU/mL (otherwise "decreasing TgAb trend", a decline of ≥20% in sequential TgAb measurements) and unremarkable imaging.

PTC-LT and PTC patients had comparable treatment.TgAbs were detectable in 72·5% of PTC-LT and 16·5% of PTC patients. Time to remission was longer in the detectable than in the undetectable TgAb cohort (28·5 vs· 7·5 months [median]; HR 0·54, CI 0·35-0·83, p=0·005). When comparing PTC-LT to PTC patients the difference was maintained in the detectable TgAb (29·3 vs 13·0 months; HR 0·38, CI 0·18-0·80; p=0·01), but not in the undetectable TgAb cohort (7·7 vs 7·3 months; HR 0·90, CI 0·55-1·47; p=0·68). Using the decreasing TgAb trend, the influence of detectable TgAbs on time to remission was abolished.

Thyroid autoimmunity does not influence the prognosis of papillary thyroid carcinoma. A decreasing TgAb trend seems an appropriate criterion to establish the remission of papillary thyroid carcinoma.

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Introduction

The incidence of thyroid carcinoma has been reported to be 13.2 per 100,000 person-years in 2018 in the USA (Olson *et al.* 2019). In papillary thyroid carcinoma and other less frequent histotype of differentiated thyroid carcinoma of follicular origin (DTC) the finding of undetectable thyroglobulin (Tg) after thyroidectomy and thyroid remnant ablation indicates the absence of thyroid tissue (Mazzaferri *et al.* 2003). However, Tg autoantibodies (TgAbs), reported in 7.5-25% of DTC patients (Pacini *et al.* 1988, Kumar *et al* 1994, Spencer *et al.* 1998*,* Latrofa *et al.* 2012 (a)), hamper the reliability of Tg results (Baloch *et al.* 2003). In patients with TgAbs, Tg is lower than expected when measured by immunometric assays (IMAs) because TgAbs interfere with Tg detection (Spencer *et al.* 2005, Spencer *et al.* 2011) and enhances its clearance (Latrofa *et al.* 2011, Latrofa *et al.* 2012(a), Netzel *et al. 2015,* Latrofa *et al.* 2018). After the demonstration that complete ablation of thyroid tissue through total thyroidectomy plus ^{131}I treatment resulted in their disappearance, TgAbs were proposed as the surrogate marker for Tg in DTC (Chiovato *et al.* 2003, Spencer & Fatemi 2013, Haugen *et al.* 2016, Carvalho *et al.* 2017). Changes in TgAb levels over time are relevant to the follow-up of DTC. Stable or rising TgAb levels have long being associated with persistent or progressive disease (Pacini *et al.* 1988, Rubell *et al.* 1992, Chung *et al.* 2002, Kim *et al.* 2008, Reverter *et al.* 2020). On the other hand, the question whether TgAbs should turn out undetectable in order to establish DTC remission, is still unclear. The latest guidelines of the American Thyroid Association (ATA) on management of papillary thyroid carcinoma require the absence of TgAbs to define a patient as cured (Haugen *et al.* 2016). However, the observations that after total thyroid ablation TgAbs required a long time (3.0 years) to disappear (Chiovato *et al.* 2003) and that a significant reduction in TgAb levels after thyroidectomy correlated with a low risk of persistence or recurrence of DTC prompted scholars to suggest decreasing TgAb levels over time as a favorable prognostic sign (Kim *et al.* 2008, Rosario *et al.* 2016*,* Ernaga-Lorea *et al.* 2018, Sun *et al.* 2020). However, other Authors recommended caution in using TgAbs as a prognostic marker of DTC (Chung *et al.* 2002).

Besides thyroperoxidase autoantibodies (TPOAbs), coexistent hypothyroidism and a hypoechoic pattern at thyroid ultrasound, serum TgAbs have long been acknowledged as a feature of thyroid autoimmunity (Latrofa *et al.* 2008*,* Latrofa *et al.* 2010). All these features correlate with lymphocytic thyroiditis at histology (Marcocci *et al.* 1991, Latrofa *et al.* 2010, Guan *et al.* 2019). Because of the effect of TgAbs on Tg

measurement and their dual role as a marker of thyroid autoimmunity and a surrogate of Tg, the issue of the influence of thyroid autoimmunity on the course of DTC proves quite a conundrum. Indeed, the prognostic value of lymphocytic thyroiditis on DTC is controversial, being reported as favorable by some but not all Authors (Loh *et al. 1999, Kebebew et al.* 2001*,* Carvalho *et al.* 2017, Myshunina *et al.* 2018). In addition, positive TgAbs were correlated to a worse prognosis of DTC outcome in some studies (Chung *et al.* 2002, Durante *et al.* 2014, Trimboli *et al.* 2017*),* but did not influence the course of DTC in others (McLeod *et al. 2014,* Bueno *et al.* 2020).

In this study we aimed at establishing the influence of thyroid autoimmunity on the prognosis of papillary thyroid carcinoma. In addition, we sought to define the handling of TgAbs in these patients, i.e., the consequence of considering as a remission criterion the decreasing TgAb trend instead of undetectable TgAb levels.

Materials and methods

Study group

The cohort included 194 consecutive, unselected patients who had been treated with total thyroidectomy (and lymphadenectomy when metastatic lymph nodes were identified) because of a papillary thyroid carcinoma. Data were assessed retrospectively from chart review. Patients were enrolled at the Endocrinology Unit of University Hospital of Pisa, Italy, from October 2007 to September 2008 at the time of thyroid remnant ablation with ^{131}I (activity: 30-150 mCi) administered after L-thyroxine withdrawal, 3 to 6 months after total thyroidectomy. They were divided into two groups, according to the presence (PTC-LT) or absence (PTC) of lymphocytic thyroiditis at histology (see below). Subsequent treatment consisted of L-thyroxine at TSH-suppressive or replacement dose, ^{131}I for functioning metastatic lesions, surgery for metastatic lymph nodes and tyrosine kinase inhibitor therapy for nonfunctioning metastatic lesions. Median follow-up (with interquartile range) was 84.0 (56.4-118.0) months, with a range of 12 to 132 months. All patients signed an informed consensus for collection and treatment of their data. The Institutional Review Board of the Department of Endocrinology approved the study.

Histological classification

Data were assessed retrospectively from histological review. Clinico-pathological features were evaluated including variants according to WHO 2004 Classification (DeLellis *et al.* 2004). Lymphocytic thyroiditis

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was diagnosed by evaluating lymphocytic density with an anti-CD45 monoclonal antibody (Roche-Ventana Medical Systems, Inc., Tucson, AZ) at 40X magnification, in a complete section. An associated lymphocytic thyroiditis was diagnosed when more than 10 lymphocytes per field were detected in the extra-tumoral tissue, with the possible association of oxyphilic follicular cells or lymphoid follicles (Latrofa *et al.* 2012(a)).

Laboratory tests, neck ultrasound and whole body scan

Tg was measured by an IMA (Access Thyroglobulin assay; Beckman Coulter, Inc., Fullerton CA) (functional sensitivity 0.1 ng/ml) and TgAbs were assessed by AIA-Pack 2000 (Tosoh Corporation, Tokyo, Japan) (analytic, functional and positive cut-offs: 6, 8 and 30 IU/mL, respectively). The interfering cutoff of this assay, i.e. the threshold for interference with Tg measurement, is 9.3 IU/mL (Latrofa *et al.* 2016). Its inter-assay imprecision is <20% through the entire curve. TPOAbs were checked by AIA-Pack 2000 (Tosoh Corporation, Tokyo, Japan) (analytic and positive cut-offs: 3 and 10 IU/mL, respectively). Neck ultrasound was performed by Technos (Esaote Biomedica, Genova, Italy), with a 7.5-MHz linear transducer. After the administration of ^{131}I activity, whole body scan (WBS) was obtained by a dual-head large field-of-view camera (Philips Axis, Picker International, Inc, Highland Heights, Ohio) with a 6/8-inch-thick crystal equipped with high-energy high-resolution collimators (HEHR).

Follow up

At the time of enrollment, all patients had Tg, TgAbs and TPOAbs measured and underwent neck ultrasound and WBS. Laboratory tests and neck ultrasound were next performed every 6-12 months. Central and bilateral neck lymph node compartments and the superior mediastinum were evaluated at ultrasound. Suspected lymphadenopathies or local recurrences were evaluated by ultrasound-guided fine needle aspiration for cytological examination and measurement of Tg in the washing liquid. Suspected distant metastasis were investigated by WBS, Computed Tomography and ^{18}F-Fluorodeoxyglucose Positron Emission Tomography.

Remission of papillary thyroid carcinoma was established on the following criteria: basal (on levothyroxine) Tg <0.2 ng/mL or recombinant human TSH-stimulated Tg <1 ng/mL, no evidence of structural thyroid disease and TgAbs <8 IU/mL. PTC was considered as persistent when basal Tg was ≥ 0.2 ng/mL or when recombinant human TSH-stimulated Tg was ≥1 ng/mL, or in presence of structural disease or when TgAbs were ≥8 IU/mL. We then chose a novel criterion for TgAbs, i.e. the “decreasing TgAb trend”. Since the

inter-assay imprecision of the assay we employed was <20%, a decrease in TgAb level was established for a reduction of ≥ 20%. The decreasing TgAb trend started with the earliest of consecutive time points, all reporting a decrease in TgAb level compared to the previous one. We considered the patients in remission from the first time-point of the decreasing TgAb trend.

Statistical analysis

Statistical data analysis was performed using SPSS 21 (IBM Corp., Armonk, NY). Major demographic, clinical and histological features are reported as median value with interquartile range (IQR) for continuous variables or as count and percentage for categorical variables. The Chi-squared test or the Fisher exact test were used to evaluate the associations between lymphocytic thyroiditis at histology and remnant thyroid volume, 24-h thyroid uptake, histological variants, staging, ATA risk level, total ^{131}I administered, additional surgical treatment and positive TgAbs and TPOAbs, as appropriate. The Kaplan-Meier 'time-to-event' method was used to generate curves of persistence of the disease according to the presence or absence of lymphocytic thyroiditis at histology, detectable or undetectable TgAbs and positive or negative TPOAbs at the time of ablation. Multivariate analyses using Cox proportional hazards model were conducted to assess the independent effects of clinical variables on time to remission. The assumption of proportional hazards was tested for each variable by examining the partial residual plots. Sensitivity analyses were conducted separately for detectable or undetectable TgAb groups and considering the two different criteria for TgAbs (i.e., TgAbs <8/IUmL and decreasing TgAb trend).

Results

Demographic characteristics, histological variants and post-thyroidectomy status of PTC-LT and PTC patients

Table 1 shows the number, age and gender of patients with papillary thyroid carcinoma divided in two groups, according to the presence (PTC-LT patients) or absence (PTC patients) of lymphocytic thyroiditis at histology. The female to male ratio was higher in the PTC-LT (6.6:1) than in the PTC group (2.3:1). Remnant thyroid volume, 24-h thyroid uptake, histological variants, TNM staging, ATA risk, total ^{131}I activity administered and additional treatments are also reported. One patient of the PTC group died from thyroid cancer.

TgAbs and TPOAbs in PTC-LT and PTC patients

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Detectable TgAbs and positive TPOAbs after thyroidectomy were more common and TgAb and TPOAb levels resulted higher in PTC-LT than in PTC patients (Supplementary Table 1). Compared to positive TPOAbs, detectable TgAbs proved to be more sensitive but less specific for lymphocytic thyroiditis.

Detectable TgAbs, positive TPOAbs, lymphocytic thyroiditis and time to remission of papillary thyroid carcinoma

At univariate analysis performed according to undetectable TgAb as remission criterion, post-surgical detectable TgAbs and positive TPOAbs and lymphocytic thyroiditis at histology were all associated with a longer time to remission: 28.5 vs. 7.5 months (median) (0.42; 0.30-0.59) (HR and CI) ($p<0.001$) for detectable vs undetectable TgAbs, 28.0 vs 8.0 months (0.60; 0.42-0.86) ($p=0.005$) for positive vs negative TPOAbs and 19.5 vs. 7.5 months (0.48; 0.34-0.65) ($p<0.001$) for PTC-LT vs PTC. At multivariate analysis only detectable TgAbs were associated with a longer time to remission (Table 2).

Time to remission of PTC-LT and PTC in the detectable and undetectable TgAb cohorts

To evaluate the influence of lymphocytic thyroiditis on the clinical course of papillary thyroid carcinoma, regardless of post-surgery TgAb status, we then split our cohort into two groups, one with detectable and the other with undetectable TgAbs. The time to remission was longer in PTC-LT compared to PTC patients in the detectable TgAb cohort: 29.3 vs 13.0 months (0.38; 0.18-0.80) ($p= 0.01$) (Figure 1A), but not in the undetectable TgAb cohort: 7.7 vs 7.3 months (0.90; 0.55-1.47) ($p=0.68$) (Figure 1B).

Decreasing TgAb trend and time to remission of papillary thyroid carcinoma

When the decreasing TgAb trend took place of TgAbs <8/IUmL as remission criterion, at univariate analysis detectable TgAbs and lymphocytic thyroiditis were associated with a longer time to remission: 15.75 vs. 7.5 months (median) (0.67; 0.49-0.92) (HR and CI) ($p=0.01$) for detectable vs undetectable TgAbs, and 12.0 vs. 7.5 months (0.71; 0.52-0.98) ($p=0.04$) for PTC-LT vs. PTC. No difference was observed in time to remission comparing positive and negative TPOAb patients: 8.33 vs 8.25 months (0.98; 0.68-1.41) ($p=0.92$). At multivariate analysis neither positive TPOAbs nor detectable TgAbs were associated with a longer time to remission (Table 3 and Figure 2).

According to TgAbs <8/IUmL as remission criterion, 27 PTC-LT and 17 PTC patients were not cured at the end of follow up (Supplementary Table 2). Patients considered not cured because of detectable TgAbs were almost all in the PTC-LT group. When the decreasing TgAb trend took place of TgAbs <8/IUmL as

remission criterion, the number of PTC-LT patients considered not cured because of their TgAb status (stable or rising TgAb levels) was much lower.

Seven patients of PTC-LT group and no patient of the PTC group experienced a rise in TgAb levels during their follow up. Six of them showed afterwards a reduction in TgAb levels whereas one showed a recurrent structural disease. No patient showing the decreasing TgAb trend experienced a later recurrence.

Discussion

TgAbs are a marker of autoimmune thyroid diseases (Latrofa *et al.* 2008, Latrofa *et al.* 2010), but may be also detected, usually at low levels, in DTC and other non-autoimmune thyroid diseases (Pacini *et al.* 1988, Kumar *et al* 1994, Spencer *et al.* 1998,) as well as in few subjects with no thyroid disease (Latrofa *et al.* 2012(a)). In papillary thyroid carcinoma, TgAbs are frequently due to an associated lymphocytic thyroiditis but might be also induced by the stimulation of the immune surveillance elicited by the tumor (Latrofa *et al.* 2008). In the follow up of DTC the measurement of Tg, the marker of DTC, goes with that of TgAbs, because TgAbs interfere with Tg measurement and are a surrogate marker for persistent thyroid tissue (Spencer *et al.* 2011).

The impact of concomitant thyroid autoimmunity on the course of DTC is debated. Some studies reported a favorable effect (28, 38-42 Kashima *et al.* 1998, Matsubayashi *et al.* 1999, Pilli *et al.* 2019, Xu *et al. 2021*), whereas others observed a minor or no effect on survival or recurrence risk (Loh *et al.* 1999, Carvalho *et al.* 2017, Guan *et al.* 2019,). Some studies related positive TgAbs after near-total or total thyroidectomy to higher rates of persistent and recurrent DTC (Chung *et al.* 2002, *Kebebew et al.* 2001, Myshunina *et al.* 2018). At variance, a nationwide US multicenter registry study reported no correlation between positive TgAbs and disease-free and overall survival of DTC (Durante *et al.* 2014) and another ruled out the influence of the TgAb status on the response to therapy (Trimboli *et al.* 2017). The additional observation that, among DTC patients with positive TgAbs, those with a TgAb pattern typical of thyroid autoimmunity had a less favorable prognosis supported the negative influence of thyroid autoimmunity on the course of DTC (Lupoli *et al.* 2015). On the other hand, a recent study suggested that positive TPOAbs are associated with a lower risk of DTC recurrence (Song *et al.* 2019). It is worth noting that in many of these studies the characterization of lymphocytic thyroiditis and its correlation with TgAbs were inadequate or even lacking.

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We sought clarifying the apparently inextricable issue of the influence of thyroid autoimmunity on the prognosis of papillary thyroid carcinoma and the related question of the management of DTC patients harboring TgAbs after thyroidectomy. To this purpose we evaluated a large group of DTC patients treated with total thyroidectomy and thyroid remnant ablation and followed for a long period thereafter. Lymphocytic thyroiditis was carefully characterized and correlated with TgAbs and TPOAbs. The levels of Tg, TgAbs and TPOAbs as well as the results of imaging were available in all patients throughout the follow up. According to the latest guideline from the ATA, nowadays many patients included in the study would have been advised a less aggressive treatment (Haugen *et al.* 2016). However, by means of total thyroid ablation we achieved undetectable values of both Tg and TgAbs, findings that, besides negative imaging, enabled us to accurately establish when patients could be defined as cured.

In agreement with previous studies, females predominated in the whole study population and mainly in the PTC-LT cohort (Marcocci *et al.* 1991, Matubayashi *et al.* 1995, Guan *et al.* 2019). The prevalence of the variants of papillary thyroid carcinoma was similar to that reported by epidemiological studies (McLeod *et al.* 2014), and their distribution was similar in PTC-LT and PTC patients. By correlating lymphocytic thyroiditis with TgAbs and TPOAbs, we observed that detectable TgAbs were more sensitive, but less specific, for lymphocytic thyroiditis than positive TPOAbs. These results are at odds with previous reports showing that TPOAbs more that TgAbs (measured by less sensitive methods) correlate with lymphocytic infiltration (Yoshida *et al.* 1978*,* Matubayashi *et al.* 1995).

While at univariate analysis detectable TgAbs, positive TPOAbs and lymphocytic thyroiditis were all associated with a longer time to remission, at multivariate analysis only detectable TgAbs impacted on it. Taken at face value, these results seemed to point to a negative effect of thyroid autoimmunity on the outcome of papillary thyroid carcinoma. However, we questioned whether the longer time to remission observed in patients harboring TgAbs was merely due to the need to accomplish the remission criterion of undetectable TgAbs, which was attained *ab initio* by TgAb negative patients. Indeed, we observed that lymphocytic thyroiditis significantly prolonged the time to remission of the TgAb positive but not of the TgAb negative cohort. This finding rules out the influence of thyroid autoimmunity on the course of papillary thyroid carcinoma in our cohort. A recent paper reported that patients with papillary thyroid carcinoma had less structural recurrence and mortality when it was associated with HT (Xu et al. 2021).

Accordingly to what suggested in previous studies (Kim *et al.* 2008, Rosario *et al.* 2016*,* Ernaga-Lorea *et al.* 2018, Sun *et al.* 2020), then we introduced a less stringent TgAb criterion (the decreasing TgAb trend) and evaluated its impacts on the time to remission in the TgAb positive cohort. We set the percentage decrease in TgAb levels according to the coefficient of variation of our TgAb assay. The decreasing TgAb trend started with the earliest of consecutive time points, each with a ≥20% reduction (a value higher than the inter-assay coefficient of variation) in TgAb level compared to the previous one. According to this criterion, time to remission of the TgAb positive cohort was similar to that of the TgAb negative cohort and the number of PTC-LT patients considered not cured because of their TgAb status significantly decreased. Therefore the requirement of undetectable TgAbs improperly delays the time to remission of papillary thyroid carcinoma. In addition, no patient showing a decreasing TgAb trend experienced a later recurrence. Our results, in addition to previous reports, supports the concept that a decrease in TgAb levels over time, although probably not sufficient to define DTC patients as cured, is appropriate to establish that they are in remission. It is worth highlighting that in our cohort TgAbs were measured by the same assay throughout the entire follow up, as required when serial TgAb results are compared, because of the well-know discrepancy in the results obtained by commercial TgAb assays (Spencer *et al.* 2005*,* Latrofa *et al.* 2012(b)). The results of the present study can be extended to DTC patients treated with total thyroidectomy and not ablated with ^{131}I because, as ablated patients, they experience a decrease in and then the eventual disappearance of TgAbs (Matrone *et al.* 2018).

In conclusion, our data demonstrate that thyroid autoimmunity *per se* does not influence the prognosis of papillary thyroid carcinoma. A decreasing TgAb trend seems an appropriate criterion to establish the remission of papillary thyroid carcinoma.

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Figures legend

Figure 1. Persistence of papillary thyroid carcinoma after thyroidectomy in patients with (PTC-LT) or without (PTC) lymphocytic thyroiditis at histology in two cohorts of patients: with detectable (A) or undetectable TgAbs (B) after thyroidectomy. Remission criteria: basal Tg <0.2 ng/mL (or recombinant human TSH-stimulated Tg <1 ng/mL), no evidence of structural thyroid disease and TgAbs <8 IU/mL.

Figure 2. Persistence of papillary thyroid carcinoma in patients with detectable or undetectable TgAb after thyroidectomy. Remission criteria: basal Tg <0.2 ng/mL (or recombinant human TSH-stimulated Tg <1 ng/mL), no evidence of structural thyroid disease and decreasing TgAb trend

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Table 1: Characteristics of patients with papillary thyroid carcinoma divided according to the presence (PTC-LT patients) or absence (PTC patients) of lymphocytic thyroiditis at histology.

	PTC-LT patients (n. 91)	**PTC patients (n. 103)**
Age at diagnosis	43.0 (33.0-50.0)	46.0 (37.0-55.0)
Sex[a]		
F	79 (86.8%)	72 (69.9%)
M	12 (13.2%)	31 (30.1%)
Remnant thyroid volume (mL)	0.1 (0-4.8)	0.1 (0-14.1)
Thyroid uptake at 24-h (%)	4.3 (1.6-9.0)	4.7 (2.3-9.9)
Histological variant:		
Follicular	30 (33.0%)	44 (42.7%)
Classic	48 (52.7%)	49 (47.6%)
Tall cells	8 (8.8%)	8 (7.8%)
Solid	5 (5.5%)	2 (1.9%)
Staging		
T		
1	38 (41.7%)	54 (52.4%)
2	19 (20.9%)	10 (9.7%)
3	34 (37.4%)	37 (35.9%)
4	0 (0.0%)	2 (2.0%)
N		
0	81 (89.0%)	88 (85.4%)
1	10 (11.0%)	15 (14.6%)
M		
0	90 (98.9%)	100 (97.1%)
1	1 (1.1%)	3 (2.9%)
ATA Risk		
Low	50 (54.9%)	62 (60.2%)
Intermediate	39 (42.9%)	35 (34.0%)
High	2 (2.2%)	6 (5.8%)
Total ^{131}I administered (mCi)	30 (30-426)	30 (30-680)
Additional surgical treatment	7 (7.7%)	12 (11.9%)
Tyrosine kinase inhibitor therapy	1 (1.1%)	1 (1.0%)

Data are expressed as median with 25th-75th percentiles for age at diagnosis, remnant thyroid volume, thyroid uptake at 24-h and total ^{131}I administered or number with percent for sex, histological variants, staging, American Thyroid Association (ATA) risk, additional surgical treatment, tyrosine kinase inhibitor therapy.

[a] p=0.005.

Table 2. Effect of detectable thyroglobulin autoantibodies (TgAbs) and positive thyroperoxidase autoantibodies (TPOAbs) after total thyroidectomy and lymphocytic thyroiditis at histology on time to remission of papillary thyroid cancer considering TgAbs <8 IU/mL as remission criterion

HR= hazard ratio, CI=confidence interval

	HR	**CI**	**p**
Detectable TgAbs after total thyroidectomy	0.54	0.35 – 0.83	0.005
Positive TPOAbs after total thyroidectomy	0.95	0.59 – 1.54	0.85
Lymphocytic thyroiditis at histology	0.74	0.48 – 1.13	0.16

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Table 3. Effect of detectable thyroglobulin autoantibodies (TgAbs) and positive thyroperoxidase autoantibodies (TPOAbs) after total thyroidectomy and lymphocytic thyroiditis at histology on time to remission of papillary thyroid cancer considering TgAb trend as remission criterion

HR= hazard ratio, CI=confidence interval

	HR	**CI**	**p**
Detectable TgAbs after total thyroidectomy	0.68	0.46 – 1.02	0.07
Positive TPOAbs after total thyroidectomy	1.39	0.89 – 2.17	0.14
Lymphocytic thyroiditis at histology	0.78	0.52 – 1.17	0.23

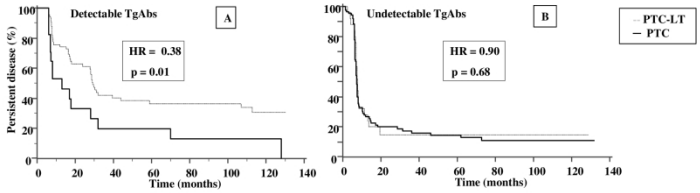

Figure 1

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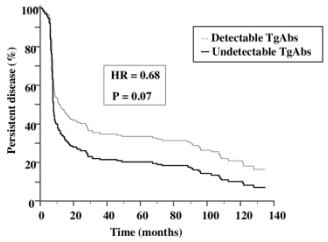

Figure 2

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Supplementary Table 1: Detectable and undetectable thyroglobulin autoantibodies (TgAbs), positive and negative thyroperoxidase autoantibodies (TPOAbs) in patients with papillary thyroid carcinoma and associated (PTC-LT patients) or absent (PTC patients) lymphocytic thyroiditis at histology. TgAb and TPOAb levels are also reported.

	PTC-LT patients (n. 91)	**PTC patients (n. 103)**
TgAbs		
Detectable	66 (72.5%)	17 (16.5%)
Undetectable[a]	25 (27.5%)	86 (83.5%)
Levels (IU/mL)[a]	27.5 (0-2000)	0.0 (0-2000)
TPOAbs		
Positive	42 (46.2%)	3 (2.9%)
Negative[a]	49 (53.8%)	100 (97.1%)
Levels (IU/mL)[a]	6.3 (0-1000)	0.0 (0-19)

Undetectable TgAb: <8 IU/mL; detectable TgAb: ≥8 IU/mL.

Negative TPOAb: <10 IU/mL; positive TPOAb: ≥10 IU/mL.

Percent of positive for detectable and undetectabale TgAbs and TPOAbs, median and range for TgAb and TPOAb levels are reported. [a]$p<0.001$

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Supplementary Table 2. Persistent papillary thyroid carcinoma at the end of follow up in patients with (PTC-LT patients) or without (PTC patients) lymphocytic thyroiditis at histology. Remission criteria: basal Tg <0.2 ng/mL (or recombinant human TSH-stimulated Tg <1 ng/mL), no evidence of structural disease and TgAbs <8 IU/mL or decreasing TgAb trend.

	Remission criterion: TgAbs <8 IU/mL			**Remission criterion: decreasing TgAb trend**	
	PTC-LT patients (n. 91)	**PTC patients (n. 103)**		**PTC-LT patients (n. 91)**	**PTC patients (n. 103)**
Structural thyroid disease or detectable Tg	9	16	**Structural thyroid disease or detectable Tg**	9	16
Detectable TgAbs	18	1	**Stable or rising TgAbs**	9	1
Total	27	17	**Total**	18	17