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A Prospective, Multicenter Study Examining the Relationship between Thyroid Cancer Treatment Outcomes and the Presence of Autoimmune Thyroiditis

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ABSTRACT

Background There is some controversy on the potential relationship between autoimmune processes and clinicopathological features as well as prognosis of differentiated thyroid cancer (DTC), and the evidence is limited by its largely retrospective nature. We examined the relationship between the presence of autoimmune thyroiditis and 1-year thyroid cancer treatment outcomes in a large, multi-center study, using prospectively collected data.

Methods We included data from consecutive DTC patients enrolled in the Italian Thyroid Cancer observatory (ITCO) database (NCT04031339). We divided the groups according to the presence (AT) or absence (noAT) of associated autoimmune thyroiditis. We used propensity score matching to compare the clinical features and outcomes between the 2 groups at 1-year follow-up.

Results We included data from 4233 DTC patients, including 3172 (75%) females. The American Thyroid Association (ATA) risk levels were as follows: 51% (2160/4233) low risk, 41.3% (1750/4233) intermediate risk, and 7.6% (323/4233) high risk. There were 1552 patients (36.7%) who had autoimmune thyroiditis. Before propensity score matching, AT patients were significantly younger, and had a smaller and bilateral tumor ($p<0.0001$). Patients with AT more frequently fell into the low and intermediate risk categories, while ATA high risk was more frequent among noAT patients ($p=0.004$). After propensity score matching, patients with AT more frequently showed evidence of disease (structural/biochemical incomplete response) versus excellent/indeterminate response, compared to patients without AT (7.3% versus 4.5%, $p=0.001$), with an OR of 1.86 (95% CI: 1.3-2.6, $p=0.0001$). However, when considering only structural persistence as the outcome, no statistically significant differences were observed between patients with or without AT (3.4% versus 2.7%, $p=0.35$). The elevated risk associated with ATA intermediate and high risk at diagnosis remained consistently statistically significant.

Conclusions In this large prospective series, biochemical persistence was more frequent, at one-year follow-up, in AT patients. However, there was no significant association between the presence of AT and structural persistence of disease. These findings may be explained by the presence of a residual thyroid tissue.

INTRODUCTION

The relationship between differentiated thyroid cancer (DTC) and thyroiditis detected in extratumoral thyroid tissue is well known (1-2). Despite being two extremely frequent diseases, their association cannot be considered fortuitous, though the underlying pathogenetic mechanisms, possibly common or interacting, are not known. Chronic autoimmune thyroiditis (AT) accompanies frequently papillary thyroid carcinoma (PTC), but it is also often found in patients with follicular carcinomas (FTC) (3). Abundant but controversial data, almost exclusively based on retrospective series, exist on the possible increased risk of developing thyroid cancer (TC) in patients with AT (4-6). Similarly, data are not definitive when considering the possible impact of the autoimmune process on TC, clinicopathological features, and prognosis. Two large meta analyses, including data largely from retrospective series, reported that patients with coexistent AT had less aggressive characteristics at presentation and better outcomes of PTC than patients without AT (2,7). However, some authors insist on a null or negative influence of the autoimmune process on cancer course (8-10). A recent study using mouse model showed that AT developing at the same time of DTC influences its course minimally, while a pre-existing thyroiditis markedly decreases both incidence and severity, indicating a critical role of the immune system on TC pathogenesis (11). Although highly valuable for insights provided to this topic, this model cannot fully recapitulate human disease, since both the carcinogenetic process and the murine iodine-induced thyroiditis are different from the corresponding human diseases. The discrepancies observed among different studies, related to the positive or negative impact of AT on DTC outcome, could be due to several factors, including the time relationship between the autoimmune and the neoplastic process, the low sample volumes, the diagnostic biases, the different outcome definitions, the genetic and environmental backgrounds and the retrospective design of the studies.

In order to obtain more reliable insights into this controversial topic, we compared the clinical features and outcomes of patients with chronic AT to those without AT in a large prospectively collected Italian database of DTC patients. We aimed to evaluate possible differences between the two groups in terms of response to initial treatment, evaluated at one-year follow up visit.

METHODS

In 2013, a web-based database was founded and named Italian Thyroid Cancer Observatory (ITCO). Starting from the Thyroid Cancer Center of Sapienza University of Rome (the coordinating center), the network expanded and now includes 51 Italian Centers. Data are prospectively collected, and to date more than 10000 patients with histologically confirmed diagnoses of differentiated, medullary, poorly differentiated, and anaplastic TC are included (see Supplemental Methods-a) (NCT04031339).

We have already reported the baseline data of the first enrolled patients (12), a validation of the baseline risk estimates on the first 2000 patients reaching 1-year follow-up evaluation (13) and an assessment of the role of extrathyroidal extension (14).

All ITCO database records were reviewed and consecutive cases that satisfied the following criteria were considered for the analysis: 1) histological diagnosis of TC (with exclusion of medullary thyroid cancer, NIFTP, WDT-UMP); 2) available information on the presence of thyroiditis based on TPO-Ab and/or Tg-Ab levels higher than the upper normal limits, and at least one of the following: a) anamnestic data consistent with AT; b) characteristic ultrasound features (i.e., non-homogeneous pattern with diffuse reduction of echogenicity) before surgery; c) histological description of a diffuse inflammatory infiltrate (15); 3) availability of all information on the initial treatment and histological data of the tumor required for ATA recurrence risk assessment (16); 4) availability of the results for the 1-year follow-up visit, including all data needed to classify the estimated treatment response; 5) complete data of the features used to compare the group; 6) clinical centers that are in the top three quartile in terms of case frequency (only high-volume were included to guarantee a more precise and reliable information).

According to the above-reported inclusion criteria, 4233 patients were included, out of the 10078 recorded at data lock (November 2021) (**Figure 1**).

Data on the initial treatment were recorded for each case. Treatment of the primary tumor was classified as thyroid lobectomy or total thyroidectomy. The latter category also included patients who had a completion thyroidectomy following thyroid lobectomy. For all patients who had a total thyroidectomy, we recorded if they received radioiodine treatment (RAI).

The estimated risk of persistent disease was determined by the study team in accordance with the 2009 ATA guidelines (17) and relevant 2015 updates (16) based on data available

immediately after the initial treatment. If the surgical treatment consisted of lobectomy followed by completion thyroidectomy, the histopathology data collected during both surgical procedures were considered. Response to initial therapy was evaluated based on the clinical evaluation carried out at the 1-year follow-up visit (6 to 18 months after the initial treatment). These data included imaging findings (cervical ultrasound in all patients and 131-I whole-body scan in selected individuals) and basal or stimulated serum thyroglobulin (Tg) and anti-Tg antibody (TgAb) levels. Additional imaging studies were performed per the clinicians' discretion. According to 2015 ATA guidelines, an excellent response was defined as no clinical, biochemical, or structural evidence of disease after initial therapy (no evidence of disease); biochemical incomplete response was defined as abnormal Tg, i.e. suppressed Tg ≥1 ng/ml or stimulated Tg ≥10 ng/ml, with negative imaging. However, because data from only one time point was evaluated, we were unable to evaluate TgAb levels trend: all cases classified as biochemical incomplete responses had measurable Tg levels.

Structural incomplete response was defined as persistent or newly identified loco-regional or distant metastasis; and indeterminate response was defined as nonspecific biochemical/structural findings that could not be confidently classified as either benign or malignant (16). Indeterminate responses included cases with Tg <1 but detectable and/or positive Tg Ab. Considering that indeterminate responses at 1-year follow-up often represent cases with an indolent tumor behavior that eventually achieve a final excellent response (18), we grouped patients as follows: a) those with excellent and indeterminate response versus those with biochemical and structural persistence, and b) those with excellent, indeterminate, and biochemical response versus those with structural persistence. The results were defined as specified in the ATA guidelines for patients who had undergone thyroidectomy followed by RAI (16), and as advocated by the European Society for Medical Oncology (19) for those whose initial treatment consisted of surgery alone (thyroidectomy or lobectomy).

The prospective study was approved by the Coordinating Center Ethics Committee (Sapienza University of Rome, ref. 3366). The study was performed in accordance with the ethical standards of the Institutional Research Committee and with the Declaration of Helsinki as revised in 2013.

Statistical analysis

For exploratory purposes, the distribution of continuous variables was summarized using median with interquartile ranges (IQR). Nominal variables were described in terms of frequency counts and corresponding percentages. The chi-squared test was used to evaluate significant associations in contingency tables. Welch's t-test was used to assess the association between continuous variables in different groups. The response to treatment, initially, was analyzed as a categorical variable with four levels (structural incomplete, biochemical incomplete, indeterminate, and excellent). We analyzed treatment response as a binary variable as either an excellent/indeterminate or structural/biochemical incomplete response, too. Finally, a binary response variable composed by excellent/ indeterminate/biochemical incomplete versus structural incomplete was analyzed (see Supplemental Methods-b).

To analyze the effect of thyroiditis on treatment response, the patients may not be comparable in terms of other features as sex, age, treatment, tumor size, extra extension, lymph node metastasis, histology, tumoral foci, vascular invasion, and administered activity of radioiodine. The propensity score was defined using these characteristics and the predicted value was used to create propensity-score matched groups (see Supplemental Methods-c). The p-value was defined as statistically significant when <0.05.

RESULTS

Patients

The clinicopathological characteristics of the 4233 patients included are reported in **Table 1**. Female patients were predominant (3172/4233, 75%) and the median age at diagnosis was of 49 years (IQR 39-59). The majority of patients (4072/4233, 96.2%) underwent total thyroidectomy, associated with central and/or lateral neck dissection in 1582/4233 (37.4%) cases. RAI treatment was performed in 2560/4233 (60.5%) patients. In terms of histology, papillary thyroid cancer (PTC) was most prevalent (3960/4233, 93.5%) and the median tumor size was 12 mm (IQR 7-20 mm). The tumor was unifocal in 2498/4233 (59%) patients and multifocal in 1675/4233 (39.6%); among these, multifocality was bilateral in 1134/1629 (69.6%) patients. Extrathyroidal extension was present in 1298/4233 (30.6%) cases, being microscopic in 1170/1298 (90.1%). Lymph node metastases were documented in 976/4233

patients (23.1%), whereas distant metastases at diagnosis were present in 109/4233 patients (2.6%). Vascular invasion was reported in 704/4233 (16.6%) cases. According to the ATA risk stratification system, 2160/4233 (51%), 1750/4233 (41.3%) and 323/4233 (7.6%) patients were classified at a low, intermediate, and high risk of recurrence, respectively. Finally, associated thyroiditis was reported in 1552/4233 patients (36.7%) of the entire cohort.

Association of thyroiditis with clinical and pathological variables

The clinical and pathological characteristics of TC patients divided according to the presence/absence of associated AT (AT/noAT) are reported in **Table 2**. AT patients were significantly younger (p<0.0001) and were more frequently female (1296/1552 (83.5%) versus 1876/2681 (70%), p<0.0001). The use of RAI was more frequent among noAT patients (1651/2681 (61.6%) versus 909/1552 (58.6%) patients with thyroiditis, p=0.01), although no differences were noted in the RAI activity administered (p=0.45). NoAT cases were treated more frequently with lobectomy (112/2681 (4.2%) versus 49/1552 (3.2%), p=0.01), while AT cases performed more often a neck dissection (654/1552 (42.1%) *v*ersus 928/2681 (34.6%), p<0.0001). Patients with AT showed more frequently had a papillary histotype (1479/1552 (95.3%) versus 2481/2681 (92.5%), p=0.0005), a smaller tumor (11 mm versus 12 mm, p<0.0001) and a bilateral tumor (472/1534 (30.8%) versus 662/2639 (25.1%), p=0.0009). No differences were found in the rates of extrathyroidal extension, vascular invasion, lymph node and distant metastatic dissemination. Finally, according to the ATA risk stratification system, patients with AT had more frequently a low (803/1552 (51.7%) versus 1357/2681 (50.6%)) and intermediate (658/1552 (42.4%) versus 1092/2681 (40.7%)) risk of recurrence, while ATA high risk was more frequent among noAT patients (91/1552 (5.9%) versus 232/2681 (8.6%), p=0.004).

The effect of thyroiditis on initial treatment response

At the 1-year follow-up visit, we observed an excellent response in 3368/4233 patients (79.6% of the entire cohort), while 141/4233 (3.3%) patients had a structural incomplete response. Patients with AT had more frequently a biochemical incomplete (62/1552 (4%) versus 48/2681 (1.8%)) and an indeterminate response (484/1552 (31.2%) versus 130/2681 (4.8%)) (**Table 3**).

Among the 141 patients with structural persistence of disease, 117 (82.9%) had a local involvement, 43 (30.5%) had distant metastases, and 19 had local and distant persistent disease (i.e. 98 cases, 69.5%, had only local disease).

After propensity score matching (**Table 4**), patients with AT more frequently had evidence of disease (structural or biochemical incomplete response) versus excellent and indeterminate response, compared to patients without AT (114/1552 (7.3%) versus 66/1552 (4.3%), p<0.0001), with an OR of 1.97 (95% CI: 1.4-2.7, p<0.0001). This risk was lower than that predicted by the ATA intermediate risk (OR 2.54, 95% CI: 1.76-3.7) and ATA high risk at diagnosis (OR 10.8, 95% CI: 6.7-17.5, p<0.0001) (**Table 5a**). However, on considering only structural persistence as the outcome, no statistically significant differences were observed between patients with or without AT (52/1552 (3.4%) versus 42/1552 (2.7%), p=0.35, with an OR of 1.3 (95% CI: 0.8-1.97, p=0.26). The risk predicted by ATA intermediate and high risk at diagnosis remained statistically significant (OR respectively of 3 [95% CI 1.77-5] and 14.2 [95% CI 7.6-26.6], p<0.0001) (**Table 5b**). Consistently, biochemical incomplete responses were more frequent in AT cases (62/1490 (4.5%) versus 24/1528 (1.5%), p<0.0001) with an OR of 2.64 (95% CI 1.6-4.4, p<0.0001).

DISCUSSION

In this study we presented the clinical features and outcomes of more than 4000 prospectively collected DTC patients, with or without associated chronic AT. AT cases had a significantly lower ATA risk and no differences were found at presentation in terms of extrathyroidal extension, vascular invasion and loco-regional or distant metastases, compared to noAT patients. Additionally, AT cases were diagnosed at a significantly younger age and had smaller tumors, likely due to the early detection of the tumor facilitated by the coexisting thyroid disease. This finding is in line with a case-control study that showed earlier stage diagnosis of papillary thyroid cancers in patients with known thyroid autoimmunity (20).

After thorough matching to minimize selection bias, we observed no significant differences in structural persistence at the one-year follow-up after initial treatment between DTC patients with and without AT. However, patients with AT more frequently exhibited evidence of disease when considering both structural and biochemical persistence together

(7.3% versus 4.3%, p=0.001). Consistently, biochemical persistence was more frequent in AT than in noAT cases (4 versus 1.5% after matching) likely due to the persistence of residual thyroid tissue. The higher occurrence of Tg-producing thyroid tissue in AT cases could be due to the greater difficulty in achieving a complete surgical thyroid removal and a complete nodal resection in patients with coexisting autoimmune thyroiditis, as such surgical cases may be subject to less mobility of the gland and a more fibrosis. The presence of thyroid autoimmunity is thus reported as one of the predictors of a challenging thyroidectomy (21,22).

Although discordant data have been always reported on this topic, a recent meta-analysis, including 47,237 patients from 65 articles, including 12,909 AT patients and 34,328 noAT cases, showed that DTC patients with AT may have favorable clinicopathological characteristics, lower recurrence rate and better 20-year survival rate (7). Nevertheless, Authors claimed for more prospective studies to reliably elucidate this relationship. Indeed, although appropriate statistical analyses, residual confounding variables influencing the results could not be ruled out, and most of the included studies were retrospective without available clinical details. In this context, the strengths of the present study need to be mentioned. The present large series is consecutive, longitudinal, and prospective. Moreover, the present patients' cohort has been collected starting from 2013, whereas the series included in the above-mentioned meta-analysis embrace a very long time-span during which different guidelines suggestions were followed and different outcome classifications applied. In particular, among the 16/65 papers on this topic, which report data on the outcome, only 6 specify the percentage of patients treated by RAI, corresponding to the majority of patients in most studies. Finally, this is the only study analyzing data after propensity score matching, applied with the aim to minimize the bias due to confounding variables such as treatment, administered activity of radioiodine, follow-up protocols or other intervention and to increase the reliability of the results obtained.

This study is subject to some limitations. The definition of AT, based exclusively on biochemical data and/or, ultrasonographic, and/or histological findings, may be considered a drawback of the study. Nevertheless, the histological classification of associated AT is extremely variable among sites and sometimes not even reported by the pathologist. A reliable assessment of the presence of associated AT will definitely need the histological

revision of cases by one or two pathologists. This will require the exchange of samples, thus leading to the reduction of the cases included. A future study including a central evaluation of specimens has been already planned. Secondly, the follow-up period was only one year. Nevertheless, it is well accepted that the risk classification performed at 1 year after initial treatment is highly predictive of the final response to treatment (23-25). Future analyses on the same series will evaluate the outcome at 5 years after initial treatment. Furthermore, indeterminate responses were likely overestimated in AT cases, due to the persistence of TgAb. These cases were included among excellent responses, based on data reporting that the vast majority of patients with an initial indeterminate response spontaneously achieve an excellent response (18), and relying on the "dilution" effect of such a large series. A longer follow-up period will provide valuable information on the percentage of cases initially classified as indeterminate or biochemically incomplete that may be reclassified as excellent responses. Finally, an inter-institutional variability in the accuracy of case descriptions, in the histological classification and in the clinical/biochemical/ultrasonographic evaluation can be envisaged due to the multicenter nature of this cohort, although we previously demonstrated that these differences did not impair the prediction of the outcomes (13).

In conclusion, our large prospective series of DTC patients demonstrated an excellent response in over 90% of cases in both groups at the one-year follow-up after initial treatment. Importantly, the presence of chronic AT did not have a significant impact on structural disease persistence, but it was associated with a higher frequency of biochemical persistence. Future studies will focus on evaluating the same patient cohort with a longer follow-up period to provide a more comprehensive assessment of treatment outcomes and the potential long-term effects of thyroiditis.

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Author Disclosure Statement

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Table 1. Clinical and pathological characteristics of the study cohort (n= 4233)

Age, *years*	Median IQR	49 39-59
Sex, *n (%)*	F	3172 (75)
Treatment, *n (%)*	TT+RAI treatment TT LT	2560 (60.5) 1512 (35.7) 161 (3.8)
Neck dissection, *n (%)*	Not performed CC LC CC + LC	2651 (62.5) 1099 (26) 90 (2.1) 393 (9.3)
Histology, *n (%)*	PTC FTC Other	3960 (93.5) 246 (5.8) 27 (0.6)
Tumor size, *mm*	Median IQR	12 7-20
Tumor foci, *n (%)*	Not specified Unilateral Multifocal (laterality not specified) Multifocal-unilateral Multifocal-bilateral	60 (1.4) 2498 (59) 46 (1.1) 495 (11.7) 1134 (26.8)
Extrathyroidal extension, *n (%)*	None Microscopic Macroscopic (T4a) Macroscopic (T4b)	2935 (69.3) 1170 (27.6) 122 (2.9 6 (0.1)
Lymph node metastases, *n (%)*	NX N0 N1a N1b	1071 (25.3) 2186 (51.6) 567 (13.4) 409 (9.7)

Vascular invasion, *n (%)*	No	3241 (76.6)
	Yes	704 (16.6)
	Not specified	288 (6.8)
Distant metastases, *n (%)*	Yes	109 (2.6)
ATA risk, *n (%)*	Low	2160 (51)
	Intermediate	1750 (41.3)
	High	323 (7.6)
Thyroiditis, *n (%)*	Yes	1552 (36.7)

Legend: F: female; IQR: interquartile range; TT, total thyroidectomy; RAI: radioactive iodine; LT: lobectomy; CC: central compartment; LC: laterocervical compartment; PTC: papillary thyroid cancer; FTC: follicular thyroid cancer; ATA: American Thyroid Association. The estimated risk of persistent disease followed the 2009 ATA guidelines (17) and relevant 2015 updates (16) according to available data after the initial treatment

Table 2. Clinical and pathological characteristics of thyroid cancer patients according to the presence/absence of associated chronic autoimmune thyroiditis, before propensity score matching.

		Patients AT	**Patients noAT**	p
n (%)		1552 (36.7)	2681 (63.3)	
Sex, *n (%)*	F	1296 (83.5)	1876 (70)	<0.0001
Age, months	Median IQR	48 38-58	49 40-60	<0.0001
Treatment, *n (%)*	TT+RAI treatment TT LT	909 (58.6) 594 (38.2) 49 (3.2)	1651 (61.6) 918 (34.2) 112 (4.2)	0.01
Neck dissection, *n (%)*	Not performed CC LC CC + LC	898 (57.9) 472 (30.4) 31 (2) 151 (9.7)	1753 (65.4) 627 (23.4) 59 (2.2) 242 (9)	<0.0001
Radioiodine activity administered, mCi	Median IQR	47.8 0-100	50 0-100	0.45
Histology, *n (%)*	PTC FTC Other	1479 (95.3) 62 (4) 11 (0.7)	2481 (92.5) 184 (6.9) 16 (0.6)	0.0005
Tumor size, *mm*	Median IQR	11 7-17	12 7-21	<0.0001
Tumor foci, *n (%) (n=4173)*	Unilateral Multifocality (laterality not specified) Multifocal-unilateral Multifocal-bilateral	874 (57) 12 (0.8) 176 (11.5) 472 (30.8)	1624 (61.5) 34 (1.3) 319 (12.1) 662 (25.1)	0.0009
Extrathyroidal extension,	None Microscopic	1076 (69.3) 436 (28.1)	1859 (69.3) 734 (27.4)	0.61

n (%)	Macroscopic (T4a) Macroscopic (T4b)	38 (2.5) 2 (0.1)	84 (3.1) 4 (0.2)	
Lymph node metastases, *n (%)*	NX N0 N1a N1b	367 (23.6) 819 (52.8) 215 (13.9) 151 (9.7)	704 (26.3) 1367 (51) 352 (13.1) 258 (9.6)	0.3
Vascular invasion, *n (%)* *(n=3945)*	Yes	243 (17.1)	461 (18.3)	0.37
Distant metastases, *n (%)*	Yes	33 (2.1)	76 (2.8)	0.19
ATA risk, *n (%)*	Low Intermediate High	803 (51.7) 658 (42.4) 91 (5.9)	1357 (50.6) 1092 (40.7) 232 (8.6)	0.004

Legend: AT: autoimmune thyroiditis; noAT: no autoimmune thyroiditis; F: female; IQR: interquartile range; TT, total thyroidectomy; RAI: radioactive iodine; LT: lobectomy; CC: central compartment; LC: laterocervical compartment; PTC: papillary thyroid cancer; FTC: follicular thyroid cancer; ATA: American Thyroid Association. Please note that, when the data was not available in the whole cohort, the number of cases included is reported into brackets in the first column.

Table 3. Treatment response at 1-year evaluation according to the presence/absence of associated chronic autoimmune thyroiditis (AT/noAT) (n=4233)

Treatment response	All, *n* (%)	Patients AT, *n* (%)	Patients noAT, *n* (%)	p
Excellent	3368 (79.6)	954 (61.5)	2414 (90)	<0.0001
Indeterminate	614 (14.5)	484 (31.2)	130 (4.8)	
Biochemical incomplete	110 (2.6)	62 (4)	48 (1.8)	
Structural incomplete	141 (3.3)	52 (3.4)	89 (3.3)	

Table 4. Clinical and pathological characteristics of thyroid cancer patients according to the presence/absence of associated chronic autoimmune thyroiditis, after propensity score matching.

		Patients AT	**Patients noAT**	p
n (%)		1552 (50)	1552 (50)	
Sex, *n (%)*	F	1296 (83.5)	1311 (84.5)	0.49
Age, months	Median IQR	48 38-58	48 39-58	0.71
Treatment, *n (%)*	TT+RAI treatment TT LT	909 (58.6) 594 (38.3) 49 (3.2)	892 (58.6) 604 (38.3) 56 (3.2)	0.7
Neck dissection, *n (%)*	Not performed CC LC CC + LC	898 (57.9) 472 (30.4) 31 (2) 151 (9.7)	931 (60) 447 (28.8) 26 (1.7) 148 (9.5)	0.63
Radioiodine activity administered, mCi	Median IQR	33 0-100	33 0-100	0.64
Histology, *n (%)*	PTC FTC Other	1479 (95.3) 62 (4) 11 (0.7)	1481 (95.4) 61 (3.9) 10 (0.6)	0.97
Tumor size, *mm*	Median IQR	11 7-17	11 7-18	0.66
Tumor foci, *n (%) (n=3071)*	Unilateral Multifocality (laterality not specified) Multifocal-unilateral Multifocal-bilateral	874 (57) 12 (0.8) 176 (11.5) 472 (30.8)	891 (58) 10 (0.7) 179 (11.6) 457 (29.7)	0.92
Extrathyroidal extension,	None Microscopic	1076 (69.3) 436 (28.1)	1076 (69.3) 464 (28)	0.93

n (%)	Macroscopic (T4a) Macroscopic (T4b)	38 (2.5) 2 (0.1)	41 (2.6) 1 (0.1)	
Lymph node metastases, *n (%)*	NX N0 N1a N1b	367 (23.6) 819 (52.8) 215 (13.9) 151 (9.7)	357 (23) 827 (53.3) 147 (9.5) 258 (9.6)	0.95
Vascular invasion, *n (%)* *(n=2852)*	Yes	243 (17.1)	249 (17.4)	0.9
Distant metastases, *n (%)*	Yes	33 (2.1)	34 (2.2)	1
ATA risk, *n (%)*	Low Intermediate High	803 (51.7) 658 (42.4) 91 (5.9)	797 (51.4) 654 (42.1) 101 (6.5)	0.75

Legend: AT: autoimmune thyroiditis; noAT: no autoimmune thyroiditis; F: female; IQR: interquartile range; TT, total thyroidectomy; RAI: radioactive iodine; LT: lobectomy; CC: central compartment; LC: laterocervical compartment; PTC: papillary thyroid cancer; FTC: follicular thyroid cancer; ATA: American Thyroid Association. Please note that, when the data was not available in the whole cohort, the number of cases included is reported into brackets in the first column.

Table 5a. Evidence of disease (SIR+BIR) after having matched patients 1:1 (top), and odds ratio for SIR+BIR vs excellent response+IR at 1-year follow-up (bottom)

Treatment response	All, *n* (%)	Patients AT, *n* (%)	Patients noAT, *n* (%)	p
Excellent + IR	2924 (94.2)	1438 (92.7)	1486 (95.7)	<0.0001
Evidence of disease (SIR + BIR)	180 (5.8)	114 (7.3)	66 (4.3)	
All		1552	1552	

	Coefficient ± SE	OR [95% CI]	p
Thyroiditis	0.68 ± 0.17	1.97 [1.4-2.7]	<0.0001
ATA Intermediate risk	0.93 ± 0.19	2.54 [1.76-3.7]	<0.0001
ATA high risk	2.38 ± 0.25	10.8 [6.7-17.5]	<0.0001

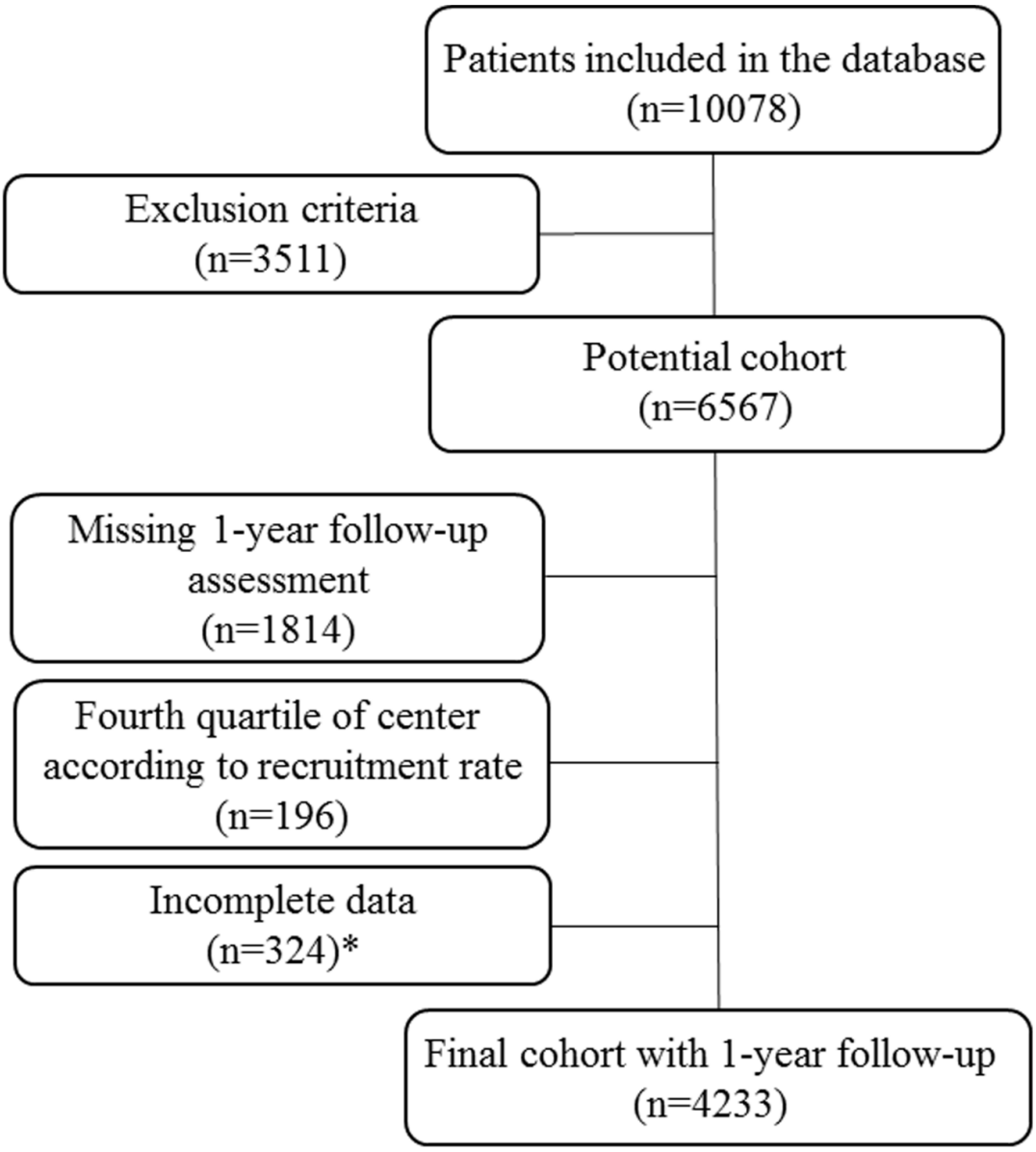
Legend: AT: autoimmune thyroiditis; IR: indeterminate response; SIR: structural incomplete response; BIR: biochemical incomplete response

Table 5b. Evidence of structural disease (SIR) after having matched patients 1:1 (top), and odds ratio for SIR vs excellent response+IR+BIR at 1-year follow-up (bottom)

Treatment response	All, *n* (%)	Patients AT, *n* (%)	Patients noAT, *n* (%)	p
Excellent + IR + BIR	3010 (97)	1500 (96.6)	1510 (97.3)	0.35
Evidence of structural disease (SIR)	94 (3)	52 (3.4)	42 (2.7)	
All		1552	1552	

	Coefficient ± SE	OR [95% CI]	p
Thyroiditis	0.25 ± 0.22	1.3 [0.8-1.97]	0.26
ATA Intermediate risk	1.09 ± 0.26	3.0 [1.77-5]	<0.0001
ATA high risk	2.6 ± 0.32	14.2 [7.6-26.6]	<0.0001

Legend: AT: autoimmune thyroiditis; IR: indeterminate response; SIR: structural incomplete response; BIR: biochemical incomplete response



Legend to Figure 1. Participants' flow chart. * there were no statistical differences in terms of sex, age, race, or ATA risk (P= 0.6, 0.5, 0.22, 0.14, respectively) between the final cohort and this group of 324 patients who were excluded due to the lack of specific information that we deemed important for our analysis.