

## Research Article

## Impact of Autoimmune Thyroiditis on Surgical Decision Making in Patients with TIR3 Nodules

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### Abstract

**Background:** Since 19th century, various researchers had investigated the relationship between Autoimmune Thyroiditis (AT) and thyroid cancer (TC). They found double effect of the pathology on the gland; inflammation could be considered like a trigger in tumorigenic process, but lymphocytic infiltration of the gland determines lower local aggressiveness. Sometimes, autoimmune thyroiditis appears together with multinodular goiter that is analyzed with cytological evaluation. SIAPEC-IAP (Italian Society for Anatomic Pathology and Cytology joint with the Italian Division of the International Academy of Pathology) together with other Italian endocrine association admits five risk class of malignancy for suspected nodules, and it suggests for each one a clinical action. The appropriate behaviour to be taken in patients with thyroid nodules with TIR3A/B positive cytology is still debated. The aim of this study is to evaluate if a FNAC (fine needle aspiration cytology) positive for TIR3A/B can be considered as an independent prognostic factor of malignancy in patients with autoimmune thyroiditis and, therefore, if it is legitimate to perform an early radical intervention on the gland.

**Materials and Methods:** The study was lead in the Endocrine Surgery Department of A.O.U. Mater Domini of Catanzaro. A total of 119 patients were selected from 2015 to 2018. Inclusion criteria were: age over 18, thyroid nodules with positive cytology for TIR3A and TIR3B. Patients were divided into AT group (TIR3A/B and autoimmune thyroiditis) and NO AT group (TIR3A/B and no autoimmune thyroiditis).

**Results:** 27.7% of the population with TIR3 nodules had a thyroid cancer. 44.4% of patients had a TIR3 nodules and an autoimmune thyroiditis. The incidence of thyroid cancer was not different between AT Group and non AT Group (OR 0.63, p = 0.30).

**Discussion:** Although thyroiditis is considered a risk factor for the development of thyroid cancers, in our study we have shown that the presence of TIR3A/B nodules with a diagnosis of autoimmune thyroiditis does not have a cumulative effect in cancer risk assessment, so we are not entitling to modify surgical planning.

### Introduction

Thyroid Cancer (TC) is the most common endocrine malignancy. In Italy the incidence of malignant thyroid neoplasms is very different between males and females, so it was respectively 11.1/100.000 individuals for women and 3.6/100.000 for men. In the last decades, the incidence of TC has considerably increased, due to the best and simple access to diagnosis tools [1]. Otherwise, there isn't an increase of the mortality rate associated with TC.

Among differentiated thyroid cancer, the most common are papillary (PTC) and follicular thyroid cancer.

The Autoimmune Thyroiditis (AT) is chronic inflammatory process associated with hypothyroidism or hyperthyroidism; it originates from deregulation of the immune system with consequent damage of the thyroid gland by T cells, with consistent lymphocytic infiltration of the parenchyma [2]. Inflammation and lymphocytic infiltration in AT patients can create a favourable environment for

malignant transformation, with the production of ROS (reactive oxygen species) that induces DNA damage, so mutations that could generate PTCs. On the other hand, lymphocytic infiltration could be considered an immunological response with a cancer-inhibiting effect, which contributes to a favourable PTC outcome. The relationship between AT and TC has not yet been completely explained. Some studies observed a positive relationship between AT e TC [3]; the prevalence of PTC in patients with AT was 27.56% with an average risk ratio of 1.59 [4]; but other authors do not recognize a defined link between papillary carcinomas and chronic thyroiditis presence [5-9]. A meta-analysis conducted by Xingjian shows that patients with AT are predisposed to the development of PTC [10]. Although several hypotheses have been formulated, the exact mechanism behind this association still needs to be determined.

Often, patients with thyroid diseases have a cytological evaluation of suspected nodules. In 2014 the Italian Thyroid

Association (AIT), the Italian Association of Clinical Endocrinologists (AME), the Italian Society of Endocrinology (SIE) and the SIAPEC-IAP updated five risk class of malignancy for suspected nodules, and suggested for each one a clinical action [11]. There are no difficulties in the interpretation of benign (TIR2) or malignant/suspected malignant (TIR4-5) nodules. The therapeutic problem occurs with indeterminate lesion (TIR3) which corresponds to adenomatous hyperplasia, follicular adenoma, follicular carcinoma and follicular variant of papillary carcinoma without obvious nuclear features. Risk cancer assessment in the entire TIR3 category varies from 5-30% [12,13]. TIR3A consists of follicular hyperplasia with poor colloid and alterations that can be classified as benign; expected risk of neoplasia is 5-15%; TIR3B consists of follicular proliferations with poor colloid and Hurthle cell or suspected follicular neoplasms with a higher risk (about 20-30%) of malignancies. However, these alterations are not so clear to treat such as TIR4 (Table1). TIR3A or B are equivalent of III and IV categories of Bethesda system [14].

	<b>HYSTOLOGICAL FEATURES</b>	<b>DIAGNOSTIC CLASSES</b>	<b>RISK OF MALIGNANCIES</b>
<b>TIR3A</b>	↑↑Cellularity ↓↓Colloid	LOW RISK INDETERMINATED LESIONS	5-15%
<b>TIR3B</b>	↑↑↑Cellularity ↓↓Colloid Hurthle's cell Nuclear alteration	HIGH RISK INDETERMINATED LESIONS	10-30%

**Table 1:** Characteristics of TIR3A and B categories.

The approach, in these cases, depends on clinical, sonographic and dimensional characteristics of nodules [15]. For TIR3A nodules they suggest a conservative approach, while for TIR3B they suggest a surgical one. Often, patients with TIR3A nodules come to the surgeon with a diagnosis of multinodular goitre with compression symptoms. Although surgery is not indicated for their histological features, it must be performed due to compression symptoms. Therefore, other risk factors should be considered in the clinical decision. From the analysis carried out, the AT appears to be risk factors for the onset of thyroid carcinomas. So how should we behave towards patients with AT and a TIR3A nodule? If we consider the positive association between PTC and AT, it is indicated to discard the conservative approach for a total thyroidectomy intervention? The aim of this study is to evaluate if a FNAC positive for TIR3 (A/B) can be considered as an independent prognostic factor of malignancy in patients with autoimmune thyroiditis; we want to identify if patients with AT,

and FNAC positive for TIR3A/B, have an increased impact of thyroid cancer when compared to population with same FNAC but no AT. Therefore, we would like to validate TIR3 cytology like a risk factor and to legitimize surgeon to more radical intervention. If this hypothesis is correct, our approach could reduce the number of post-hemi thyroidectomy totalization interventions, with a reduction of unnecessarily surgically treated TIR3.

### Materials and Methods

The retrospective study was conducted in the Department of Endocrine Surgery of A.O.U. Mater Domini in Catanzaro. 119 patients (93 women and 26 men) were enrolled between 2015 and 2018. Inclusion criteria were age >18; thyroid disease for which it is necessary thyroidectomy or hemi-thyroidectomy; FNAC positive for TIR3A or TIR3B. All patients with a FNAC positive for TIR3 underwent surgery following endocrinologist opinion. Total thyroidectomies or hemi-thyroidectomy were performed.

Total thyroidectomy was performed because of multinodular bilateral disease. Histopathological examination was executed after surgery, and results were categorized as benign when nodular goitre, follicular adenomas were found or malignant when follicular carcinoma, papillary carcinoma or Hurtle cell's cancers were found. Patients with AT were identified from anamnesis, presence of high levels of thyroid antibodies or histological examination of gland. It was not possible to identify antibody levels in all clinical records. We considered 4 categories of patients (each patient had a FNAC: TIR3A/B): a) patients with AT and malignant histopathology, b) patients with AT and benign histopathology, c) patients with No AT but malignant histopathology, b) patients with No AT and benign histopathology (Table 2).

	TIR3A or TIR3B	
	Thyroid Cancer	No Thyroid Cancer
Autoimmune Thyroiditis (AT)	9	32
NO Autoimmune Thyroiditis (NO AT)	24	54

Table 2: Study groups.

### Statistics

The odds ratio (OR) for the determination of thyroid cancer in the presence of autoimmune thyroiditis, with FNAC TIR3A or TIR3B was calculated. 95% Confidence Intervals (CI) were determined using XLSTAT statistical software. Data were analysed with Fisher's exact and Chi square test. P-value  $\leq 0.05$  was considered statistically significant.

### Results

The descriptive characteristics of the 119 patients are summarized in Table 3. The mean age of the 119 patients was 51.5 [18-85]. 89 Total thyroidectomies and 30 hemi-thyroidectomies were performed. 15 thyroid totalizations were executed. 26 patients (21.8%) were males and 93(78.2%) were females. AT were diagnosed to 41 patients (34.4%); 25 patients of these were females (61%) and 16 were males (39%). 63 (52.94%) individuals had a FNAC positive for TIR3A and 56 (47.06%) for TIR3B. Thyroid cancers were found in 33 patients (27.7%). 9 Patients of 41 (22%) had autoimmune thyroiditis and thyroid cancer (AT Group). Papillary subtype was the only one found in AT Group (100%). 24 patients of 78 (30.7%) had a thyroid cancer but no autoimmune thyroiditis (No AT Group). Cancer subtypes were: 62.5% papillary cancer, 12.5% follicular cancer and 25% Hurthle cell cancer.

	N	%
<b>MEAN AGE</b>	51.5[18-85]	
<b>GENDER</b>		
• Female	93	78,2%
• Male	26	21.8%
<b>FNAC</b>		
• TIR3A	63	52,94%
• TIR3B	56	47,06
<b>AUTOIMMUNE THYROIDITIS (AT)</b>	41	34.4%
<b>THYROID CANCER (TC)</b>	33	27.7%
<b>1. AT+ TC</b>	9	22%
○ Papillary + AT	9	100%
○ Follicular + AT	0	
○ Hurtle cells+ AT	0	
<b>2. TC WITHOUT AT</b>	24	30.7%
○ Papillary	15	62.5%
○ Follicular	3	12.5%
○ Hurtle cells	6	25%
• <b>INTERVENTION</b>		
○ Total Thyroidectomy	89	74,7%
○ Hemithyroidectomy	30	25,2%
○ Thyroid Totalization	15	

Table 3: Descriptive characteristics of the study.

The amount of patients with thyroid cancer was not different between AT Group and non AT Group (OR 0.63, p = 0.30) (Table 4). We analysed TIR3A and TIR3B as a subgroup analysis. There were 12 (19%) patients with TIR3A and thyroid cancer, 5 from AT group and 7 of no AT group. The rate of thyroid cancer was not different between two groups (OR 1.05, p = 0.93). There were 21(38%) patients with TIR3B and thyroid cancer, 4 from AT Group and 17 from NO AT Group. The rate of thyroid cancer was not different between two groups. (OR 0.49, p = 0.28).

	TIR3		TIR3A		TIR3B	
	AT	NO AT	AT	NO AT	AT	NO AT
<b>THYROID CANCER</b>	22%	30%	19%	18%	27%	42%
OD	0.63		1.05		0.49	
P	0.3		0.93		0.28	

Table 4: Sub-classification of TIR3A and TIR3B; Odds Ratio and p.

## Discussion

Numerous studies have investigated the existing relationship between AT and thyroid cancer, concluding for a tight association between two entities [16,17]. Several studies combine the presence of an AT with a better prognosis in patients suffering from papillary thyroid carcinoma, probably because lymphocyte infiltration has been interpreted as an active response of the host [18-21]. Other studies recognize a lower aggressiveness of papillary carcinomas in patients with AT in terms of extra-thyroidal extension and central compartment metastasis, but a higher prevalence of multifocal lesions [22]. Furthermore, it's clear that papillary pathologic subtype is more strictly associated with AT. In addition, Zhang's study finds out a higher rate of thyroid malignancies in patients with AT (40.7%), despite an overestimation of the data [23]. Thyroid cytological aspiration allows discerning between benign or malignant nature of nodules; but when result is TIR3A or B we are in a grey area, so we can talk about probability or suspected of malignancies. Definitive diagnosis will only come from the analysis of the whole nodule or surrounding tissue. In these cases, an emithiroidectomy is indicated if the nodule is unique or a total thyroidectomy must be performed if the suspected nodules are two-sided.

It appears from the literature that only 20% of the indeterminate nodules treated are malignant. Therefore, most of the patients undergo to "unnecessary" surgery, because the nodule will prove to be benign. According to our data we do not identify different prevalence between patients with AT and No AT, with the same FNAC. The percentage of thyroid cancer in patient with TIR3 nodules was 22% in AT group and 31% in no AT group; the percentage of thyroid cancer in patient with TIR3A nodules was 20% in AT group and 21% in no AT group; the percentage of thyroid cancer in patients with TIR3B nodules was 26.6% in AT group and 42% in no AT group. From these data we can conclude that the presence of AT does not increase the risk of malignancies in patients with indeterminate cytology nodules. Female sex is greatly affected by autoimmune pathology as already highlighted in other studies (61%) [24,25]. Papillary subtype was the most representative histological type in AT patients (100%). Our study confirms previous data that reveal a relationship between papillary histological type, female sex and autoimmune thyroiditis [23]. Further evaluations can be carried out by expanding the sample. We can therefore conclude that the presence of TIR3A or B cytology cannot be considered as an additional factor of risk in AT-patients, and therefore cannot legitimate a change of the surgical decision making.

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