

## Thyroid carcinoma in multinodular goiter

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### Abstract :

**Background:** It is suggested that hyperthyroidism protects against thyroid malignancy. It was suggested that the incidence of malignancy is lower in toxic multinodular goiters than in non-toxic multinodular goiters. Recent studies show controversies.

**Material and methods:** The aim of this study is to determine the incidence and type of thyroid carcinoma in toxic and nontoxic multinodular goiter in our country (Albania), through histopathological examination of thyroidectomy specimens.

**Results:** It is a retrospective, observational study in the Service Nr1 of General Surgery in Tirana, Albania. Histology reports of patients operated for toxic MG, non-toxic MG were reviewed to identify thyroid cancer incidence. The incidence of TC in TMG was found to be 9.1%, in NMG was found to be 9.4%.

**Conclusions:** As we see the incidence of malignancy in TMG is not very low as thought and it resulted nearly the same as in NMG. Which reminds physicians to consider the possible association between hyperthyroidism and cancer. The risk of malignancy should not be underestimated and FNAC should be done for all prominent nodules to discover neoplasia.

**Keywords:** cold nodule (CN), differentiated thyroid carcinoma (DTC), Graves disease (GD), non toxic multinodular goiter (NMG), thyroid carcinoma (TC), toxic multinodular goiter (TMG).

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### I. Introduction

Hyperthyroidism is a condition characterized by the effect of excessive circulating thyroid hormones. Grave's disease (GD) is the most common form and toxic multinodular goiter (TMG) is another [1, 2]. Nontoxic multinodular goiter (NMG) is a clinicopathological entity characterized by an increased volume of thyroid gland with nodules formation.

Many authors have stated that hyperthyroidism protects against thyroid carcinoma and pretended that the incidence of malignancy is lower in patients with TMG than in those with non-toxic multinodular goiter (NMG). On the other hand, it was reported in different studies that the incidence of malignancy in TMG was not as low as previously thought [1, 2]. The prevalence of TC in patients with hyperthyroidism varies from 1.6%-21.1% [3].

Also an unresolved topic is whether NMG is significantly associated with malignancy. It has traditionally thought to be at low risk for malignancy as compared to a solitary thyroid nodule. However various studies the last 10 years, report an incidence of malignancy of 7-17% in NMG [4]. Conditions which predispose to the development of TC and especially the most common form, DTC (differentiated thyroid cancer) are: ionizing radiation, autoimmunity, high circulating thyroid –stimulating hormones (TSH levels), nodules presence and female sex. Several authors have analyzed the potential association of DTC with Grave's Disease (GD) and Hashimoto Thyroiditis [5-7] characterized the both of them by autoimmune processes. Some studies suggest that autoimmunity is a risk factor [5, 6], others that it protects against DCT [7]. The presence of thyroid stimulating immunoglobulins (TSIs) should promote increase prevalence of DTC due to the TSH-like action. Other authors emphasized that patients with thyroid nodules have a greater risk of developing DTC than with no nodules [6, 8-10].

In the present study, we compared the incidence of thyroid cancer in toxic and non-toxic multinodular goiter, in patients undergoing thyroidectomy for benign thyroid disease at our center, which is the unique Tertiary Hospital Center in Albania. The introduction of the paper should explain the nature of the problem, previous work, purpose, and the contribution of the paper. The contents of each section may be provided to understand easily about the paper.

### II. Material and methods

It is a retrospective study, carried on the Service nr 1 of General Surgery Department of "Mother Teresa" Hospital Center. For retrospective analysis, we reviewed 620 patients operated between January 2010-January 2013. Of them 545 had multinodular goiter (toxic and non-toxic). Ninety eight (98) of them were toxic

multinodular goiters, 447 were non-toxic multinodular goiters, 58 were cold solitary nodules and 17 were GD. In the TMG group (22 male, 76 female), recurrent hyperthyroidism after medical treatment, enlarging nodule, persistent drug side-effects, cytological evidence/suspicious of malignancy and symptoms of tracheal or esophageal compression were the criteria of surgery. The surgery was performed only after euthyroidism was achieved by propylthiouracil or methimazole. Hyperthyroidism was diagnosed by elevated tri-iodothyronine / thyroxine ratios and low thyroid-stimulating hormone with clinical signs and symptoms. All patients were evaluated with ultrasonography (USG) and scintigraphy. The fine needle aspiration biopsy (FNAB) was done just in a few of patients, for technical impossibility of Endocrinology and Histopathology Service in that time. Total or near total thyroidectomy was the choice of the surgery.

In the NMG group (92 male, 355 female) indications for surgery were: cosmetic or pressure effects, a dominant nodule increasing in size or showing cytological features raising the possibility of malignancy or retrosternal extension. All patients were evaluated with USG and scintigraphy. The fine needle aspiration biopsy (FNAB) was done just in a few of patients, for technical impossibility of Endocrinology and Histopathology Service. Total thyroidectomy, bilateral subtotal thyroidectomy, near total thyroidectomy, lobectomy + subtotal or near total thyroidectomy, were the procedures performed in the NMG group.

### III. Results

Demographic information for the patients is set out in Table 1. Most of the patients were females (84%) compare to males (16%). The average age was 44.56 years old. From the 620 patients 505 were in euthyroid state, 115 were in hyperthyroid state. Sixty nine (69) patients resulted with thyroid malignancy, of them 58 were females and 11 were males.

**Table 1.** Patients characteristics (620)

\*TC- thyroid carcinoma

Variables	Nr
Males, n%	101 (16%)
Females, n%	519 (84%)
Female: Male ratio	5.14:1
Age (years),mean	44.56
Euthyroid	505 (81%)
Hyperthyroid	115 (19%)
Female with TC*	58 (11.17%)
Males with TC*	11 (10.8%)
Female: Male ratio(TC)	5.27:1

In the TMG a total of 9 cases of 98 patients from the histological examination resulted thyroid carcinomas. Of them seven papillary, one medullary and one Hurthle cell carcinomas were found (Table 2). The incidence of malignancy was 9.1% in this group. The prevalence was 9.2% (7/76) in female and 9% (2/22) in male patients.

Multifocality in TMG was found in 11.11% of cases. It was detected in one (1) patient, a focus of papillary carcinoma and a focus of oncocytic carcinoma (Table 3). In fact in GD we didn't found any case of thyroid carcinoma. All carcinomas were detected in TMG. In this group were evidenced 2 cases of papillary carcinoma in concomitant presence of a lymphocytic thyroiditis and in one (1) case a follicular carcinoma was found in concomitance with lymphocytic thyroiditis.

In the NMG group histological examination revealed thyroid carcinoma in 42 of the 447 patients, with an incidence of 9.4%. The cancer prevalence was 5.4% (5/92) in male and 10.5% (37/355) in female patients. Following thyroidectomy, histology revealed papillary carcinomas (29), follicular carcinomas (4), insular (1), Hürthle cells/oncocytic (5), clear cells (1), medullary (1), and anaplastic cancer (1)(Table 2).

Multifocality was detected in three (3) patients or 7.1%. Two foci of follicular carcinoma in a 57 year-old patient, two foci of papillary carcinoma in a 32 year-old patient and the same in a 41 year-old patient.

A number of 58 cold nodules (CN) were subjected to partial thyroidectomy. Of them 18 resulted thyroid carcinomas, with a malignancy incidence of 31%. None of thyroid carcinomas were found in the GD patients.

	TMG(98)	NMG(447)	CN*(58)	GD**(9)	TA*** (8)
Papillary carcinoma	7	29	12	0	0
Follicular carcinoma	0	4	5	0	0
Medullary carcinoma	1	1	0	0	0
Insular carcinoma	0	1	0	0	0
Oncocitary/Hürthle cell carcinoma	1	5	1	0	0
Clear cells carcinoma	0	1	0	0	0
Anaplastic carcinoma	0	1	0	0	0
Total	9	42	18	0	0

**Table 2.** Distribution of TC by preoperative diagnosis CD\*- Cold nodule, GD\*\*- Grave's Disease, AT\*\*\*-Toxic

As we see, the most common type of thyroid carcinoma, resulted the papillary carcinoma with 70% of cancers. In association with the follicular type they represent more than 83% of thyroid cancers. The DTC resulted as the most common form of thyroid cancer in our study with 93% of thyroid cancer (Table 3). The other types are undifferentiated thyroid cancers.

**Table 3** Distribution of malignancies in patients

Histopathologic type	Nr (%)
Papillary	48 (70%)
Follicular	9 (13%)
Medullary	2 (2.8%)
Anaplastic	1 (1.4%)
Hürthle cells/Oncocitary	7 (10.1%)
C cells	1 (1.4%)
Insulary	1 (1.4%)
*patients with dual pathology	4 (5.8%)

#### IV. DISCUSSION

Thyroid carcinomas accounts for 1% of all malignancies and they are the most common endocrine tumors. The incidence has increased by up to five times during the past 60 years [11]. All thyroid disorders showed predominance in women. From epidemiological studies it appears that the gender factor may influence the risk of benign thyroid diseases and thyroid cancer in women. On the other hand, some studies pointed out that the incidence of thyroid cancer showed male/female parity in patients from endemic areas compared with patients from non-endemic areas [10, 13]. It also has been proposed that the availability of better and more sensitive diagnostic tools may be responsible for the increasing incidence of TC, especially in the TMG.

The overall incidence of TC in our series resulted (69/620) 11.12%. Incidence of TC resulted 9.1% in TMG and 9.4% in NMG. The incidence of TC in cold nodules were 31% meanwhile in GD we didn't found any case of TC. Male/female ratio was 2/7 (28%) in the TMG group and 5/37 (13.5%) in the NMG group in our study.

It was believed that hyperthyroidism was a protector against thyroid cancer and the risk of thyroid cancer in hyperthyroidism was reported to be as low as 1-2% [14]. While the frequency of carcinoma in TMG was reported to be less than 1% [2], some investigators found the incidence of carcinoma as high as 21% [15]. Papillary carcinoma was the most frequently reported cancer type. In the recent study, the incidence of malignancy in TMG was found to be 9.1% and most of them were papillary carcinoma. 77.8% of thyroid carcinomas in TMG resulted to be DTC.

On the other hand, the incidence of cancer in NMG was reported between 6.2-9.7% in several studies [22, 23]. NMG has traditionally thought to be at a low risk for malignancy as compared to a solitary thyroid nodule. However various studies have shown that the risk is quite high in NMG. A study by Benzarti *et al* in Tunis, found a 9.5 incidence of malignancy in MNG [16]. Wherever Sarajevo reported an 8% incidence of malignancy in his study [17]. Prades *et al* reported a high incidence of 12.2% [18]. Mofti observed higher incidence of thyroid malignancy up to 29% in a study of 158 patients [19]. According to this study the incidence of TC in NMG resulted 9.4%. In this group the most common variant of thyroid carcinoma was the papillary carcinoma present in 77% of thyroid cancer. 78.6% of thyroid cancer in this group was DTC. In our study, any significant difference in the incidence of cancer between toxic and non-toxic MG could not be detected (9.1:9.4).

In the toxic group one of nine patients and in the non-toxic group three of forty two patients had multifocality. Prior studies have shown an increased prevalence of DTC in patients diagnosed with nodular goiter and a stronger association of DTC with NMG than with TMG [20]. It is hypothesized that its lower frequency in the latter may be related to the abolition of the trophic effect of TSH on the follicular thyroid cells. In fact, hyperthyroidism is considered as a factor which protects against the development of DTC. Because of this, the guidelines for the management of DTC do not recommend routine cytological testing in hyperthyroid patients with nodular disease. This recommendation must, however, be followed with caution because some evidence has led to fine needle aspiration in hyperthyroid patients being recommended, too [21].

More information is available about the potential association of hypothyroidism and DTC. In a study of 1500 patients, the prevalence of malignancy increased from 2.8% when TSH levels were less than 0.4mU/L to 29.7% when TSH levels were higher than 5.5mU/L [8]. A subsequent study showed that patients diagnosed with DTC in more advanced stages had higher TSH levels [9].

It has also been reported that lymphocyte infiltration, which is a characteristic of thyroid autoimmune conditions, protects against the development of DTC, or is at least associated with a good prognosis of the disease [22]. However, other research has suggested that, in addition to serum TSH levels, the presence of positive anti-thyroglobulin antibodies is an independent predictor of malignancy in patients with thyroid nodules, despite the concomitant presence of thyroid autoimmune disease [6]. Analysis of these studies with conflicting results is difficult because although Hashimoto thyroiditis and GD share the potential effect associated with the modulating role of autoimmune disorder on oncogenesis, their functional presentation differs. While GD causes hyperthyroidism, patients with Hashimoto thyroiditis eventually develop thyroid hypofunction. Thus, studies showing an increased prevalence of DTC in GD stated that this finding may be related to the TSH-like action of TSI antibodies and attributed to these the ability to stimulate the proliferation of neoplastic follicular cells [23].

There are studies [23] which report a higher incidence of thyroid cancer in GD as compared to NMG. Thyroid cancer in GD varies from 0.5% to 15% [3]. In one study thyroid cancer was found in 22.2% of patients with TMG compared with 2.9% of patients with GD. In our series, we didn't found TC in GD patients. Incidental DTC was only found in a single patient with TMG in our sample, which prevented a comparison of the prevalence between GD and TMG patients. It may be assumed that multicentricity occurs as a consequence of the influence of stimulating or risk factors for the development of DTC. In our series, incidental DTC was multicentric in only one of the eight patients with TMG and in three patients of NMG. However, a higher trend to multifocality was seen in NMG, which agrees with the finding of a greater size and prevalence of DTC in these patients (Table 3).

Another result is that the prevalence of incidental DTC is lower in GD as compared to TMG and NMG. This finding may indicate: a certain predisposition to DTC in patients with nodular disease and/or that the autoimmune reaction may prove to be a factor which protects against the development of neoplastic disease.

## V. Conclusion

The incidence of malignancy in TMG is not very low as thought before and is nearly the same as in NMG. Our findings, remind physicians to consider the possible association between hyperthyroidism and cancer. The increasing incidence of cancer in toxic multinodular goiter in recent years could be attributed to better nodule detection, differences in the extent of thyroid resection and the number of histological sections examined per specimen. The surgery should not be done only to maintain euthyroidism but also to prevent the risk of cancer in TMG patients. The risk of malignancy should not be underestimated and FNAC should be done for all prominent nodules to discover neoplasia.

**Conflicts of interest:** none to declare

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