

Surgical Management in Patients with Thyroid Carcinoma and Concurrent Hyperthyroidism: 10-Year Surgical Experience of a Single Center

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1. Abstract

Cuncurrent Thyroid Cancer (CT) and hyperthyroidism is rare though increasly being reported. The association is extremely variable as indicated in the medical literature currently available. Several factors have been proposed to explain the variability of results: geographic areas, neck irradiation, type of surgery in patient with hyperthyroidism, radioactive iodine. During the period between 2012 and 2022 a total of 398 patient underwent thyroid surgery, 232 patient underwent surgery for hyperthyroidism. In 23 patients were found cuncurrent thyroid cancer and hyperthyroidism. Patient with multinodular toxic goiter had associated malignances in 8,6% (12/138), while patient with uninodular toxic goiter had an incidence of 6.1% (4/65) ; Patients with toxic adenoma had an incidence of CT of 11.8% (2/17) . Only one Patient with Graves disease (1/12 cases) had thyroid cancer. With the combined of ultrasound examinations, scintiscans, and FNAB, were able to diagnose the presence of cancer in 19 of 23 cases. Many authors have reported a high frequency of aggressive subtypes of thyroid carcinoma in hyperthyroidism, being larger, more often multicentric, locally invasive or metastatic. An aggressive approach, including total thyroidectomy with prophylactic central lymph node dissection, seems justified in these cases, following current trend in thyroid surgery. The incidence, as well as the prognosis of thyroid cancer associated with hyperthyroidism is a matter of debate, from

our personal experience every suspicious nodule associated with hyperthyroidism should be evaluated carefully.

2. Introduction

For several years now, a correlation has been acknowledged between hyperthyroidism and thyroid cancer (CT), with various controversies regarding its incidence, pathogenesis, and therapeutic strategy. In the past, hyperthyroidism was considered as a protective factor for the development of thyroid cancer, but, as early as the 1950s, authors such as Sokol et al. and Leiter et al., described a number of cases of CT in patients with a hyperfunctioning thyroid disease [1,2]. Since the 1990s, several authors have suggested that, not only is thyroid cancer often associated with hyperthyroidism, in particular Graves' disease, but it also has an aggressive behavior [3,4]. TSH appears to play a key role in this scenario, being the most important factor that stimulates the growth of normal thyroid tissue and, as it was reported, neoplastic thyroid tissue, containing functional TSH receptors. Filetti and Mazzaferri observed that thyroid-stimulating antibodies, similar to TSH and present in Graves' disease, can promote tumor growth by activating TSH receptors [3-5]. The aim of this retrospective study is to evaluate the pathological characteristics and clinical behavior of thyroid cancer arising in hyperthyroid patients and whether there are any relevant differences comparing them to euthyroid patients. Our study will address the latest developments regarding the association between

hyperthyroidism and thyroid carcinoma, reporting both personal data and those that appear in medical literature.

3. Patients and Methods

From January 2012 to December 2022, 398 patients underwent surgery for thyroid disease. Among them 232 patients were also suffering from hyperthyroidism. All patients included in the study lent themselves to preoperative physical examination, serum thyroid hormone testing - including TSH, Tg and anti-Tg antibodies - and neck ultrasound. In case of suspicious nodules, Fine Needle Aspiration Cytology (FNAC) was performed. To assess the mobility of the vocal cords, all patients routinely underwent preoperative fibrolaryngoscopy, while thyroid scintigraphy was regularly performed in hyperthyroid ones. All patients were preoperatively treated with β -blockers and/or antithyroid drugs. 92 (39.7%) subtotal thyroidectomies, 95 total thyroidectomies (40.9%), 45 lobectomies (19.4%) were performed. The surgical procedure consisted of a total extracapsular thyroidectomy; the recurrent laryngeal nerves were systematically exposed until their insertion into the larynx and any attempt was made to preserve the parathyroid glands. Patients with preoperative or intraoperative suspicion of lymph node metastases underwent central compartment dissection or radical lateral compartment dissection to achieve curative treatment. A subfascial drainage was routinely used.

4. Results

A neoplastic thyroid disease was found on histological examination in 23 patients undergoing thyroid surgery with concomitant hyperthyroidism; in particular: 16 were the cases of papillary carcinoma and 8 those of follicular carcinoma. Patients with toxic multinodular goiter had associated malignancy in 8.6% (12/138), while patients with uninodular toxic goiter had an incidence of 6.1% (4/65) and patients with toxic adenoma of 11.8% (2/17). Only one patient with Graves' disease (1/12 cases) had thyroid cancer (8.3%). The diameter of the tumor mass varied between 1.4 cm and 2.8 cm. The neoplasm was found in 12 cases in warm nodules, and in 4 cases in cold nodules, present in the context of the gland. The preoperative diagnosis of malignant neoplasm by FNAB was carried out in 19 out of 23 cases, in the remaining cases the definitive histological diagnosis was decisive. Total thyroidectomy with central compartment lymphadenectomy was performed in patients with preoperative diagnosis of thyroid malignancy and hyperthyroidism. Completion thyroidectomy, with central compartment completion lymphadenectomy, was performed in two patients with postoperative diagnosis of thyroid cancer who underwent hemithyroidectomy.

Patients with toxic adenoma were treated with lobectomy and in only one patient a thyroid carcinoma was found on histological diagnosis. In patients undergoing hemithyroidectomy for benign disease, even with a pathological examination positive for carcinoma, removal of the contralateral lobe was unnecessary

for small (<1cm) unique, low-risk, intrathyroidal nodules without lymph node metastases. In our series, we found only 1 case of carcinoma arising in patients with toxic adenoma.

All 23 patients underwent total thyroidectomy with central compartment lymphadenectomy. In the patient with CT, Graves' disease and intraoperative finding of metastases in the laterocervical compartment and in the patient with papillary CT and preoperative ultrasound findings of involvement of the lateral lymph nodes (Figures 1a,1b) it was also necessary to perform laterocervical lymphadenectomy. At the follow-up of 206 months, only 2 patients died from other causes, such as AMI and breast K.

Discussion and Conclusions Thyroid hormones play an important role in regular growth, development and metabolism. Over a century of research has supported an association between thyroid hormones and the pathophysiology of various types of cancer. Studies and research on animal models have shown an effect of the thyroid hormones T3 and T4 on cancer proliferation, apoptosis, invasiveness and angiogenesis in vitro. Thyroid hormones appear to mediate their effects on the cancer cell through a number of non-genomic pathways, including the activation of the $\alpha\beta 3$ integrin of the plasma membrane receptor. Furthermore, the development and progression of cancer are influenced by the dysregulation of the local bioavailability of thyroid hormones. Case-control and population-based studies provide conflicting results regarding the connection between thyroid hormones and cancer. However, a wide range of evidence suggests that subclinical and clinical hyperthyroidism increases the risk of several solid tumors, while hypothyroidism can reduce their aggression or delay their onset. Another hypothesis is that TSH and thyroid stimulating antibodies play a key role in tumor genesis and in promoting the growth and metastatic spread of thyroid cancer. Tumors with aggressive behavior are, in fact, less frequent in patients with low or suppressed serum TSH levels, but more frequent in those with chronic stimulation of the TSH receptor by thyroid-stimulating antibodies [6,7]. The data relating to the incidence of thyroid cancer in patients suffering from hyperthyroidism, as literature suggests, are extremely varied: Sokol et al. showed the presence of thyroid cancer in 0.06% of patients undergoing surgical treatment for Graves' disease and in 0.75% of the ones undertaking surgery for uninodular or multinodular goiter [2]. Blondeau et al. observed a correlation between thyroid cancer and hyperthyroidism in 0.45% of patients with GD and 3% of patients with uninodular or multinodular goiter [8]. Livadas et. al showed the same association in 5.2% of patients with GD and 21% of patients with MTG [9].

The prevalence of thyroid cancer in hyperthyroid patients widely varies in literature, ranging from 0.5 to over 20%. The reason for this difference is probably related to the selection of hyperthyroid patients suitable for surgery, to the type of surgery (total or subtotal thyroidectomy) and to the geographic variation in the incidence

of thyroid cancer. Furthermore, the incidence is higher in retrospective studies which include only patients who have undergone thyroidectomy and lower in studies including also patients with hyperthyroidism who have not undergone surgery. However, most authors report a higher incidence of thyroid cancer in hyperthyroid patients than in euthyroid ones [7]. Yeh analyzed data from 1 million patients from the Taiwan National Health Insurance database in a large population-based cohort study and reported an increased risk of head and neck cancer, in particular thyroid cancer, in patients with hyperthyroidism [10]. Belfiore described a higher incidence of thyroid cancer in patients suffering with Graves' disease than in the ones with toxic adenoma [11]. Many authors [11-13] have reported a high frequency of aggressive subtypes of thyroid carcinoma in hyperthyroid patients, diametrically larger, often multicentric, locally invasive or metastatic. In our personal experience we identified the presence of thyroid cancer in 9.9% (23/232) of hyperthyroid patients and we noticed that the only case of CT arising in Graves' disease and CT in a case of hyperfunctioning multinodular goiter had greater local aggression, for which it was necessary to perform a total thyroidectomy with lymphadenectomy of the central and laterocervical compartment homolateral to the malignant lesion. In 17 of the cases the malignancy arose on a warm nodule which tested positive for malignant cell on preoperative FNAC examination. In 6 of the cases the malignancy arose on a cold nodule in the context of a hyperfunctioning gland. An autonomous thyroid nodule presented as thyroid carcinoma requires careful evaluation and consideration. Its exact incidence is difficult to quantify; one reason is the variability surrounding warm nodules definition. When malignancy is present, it can coexist together with the hyperfunctioning tissue, within the same gland, but in different sites. The risk of malignancy in the warm nodule increases with family history, large size, rapid growth, irregular contour and lack of mobility within the surrounding tissue [14]. For this reason, apart from the functional distinction between "warm" and "cold" nodule, in presence of risk factors for thyroid cancer, fixed nodules of increased consistency, clinically pathological lymph nodes or alteration of the voice, is necessary to perform ultrasound to select nodules that deserve cytological evaluation [15,16]. In conclusion, from a surgical point of view, it should be emphasized that, being aware of the aggressive behavior of thyroid cancer in hyperthyroid patients, a more aggressive surgical approach is suggested for hyperthyroid patients (e.g. more extensive lymphadenectomies). The presence of a warm nodule not always rule out thyroid cancer. Therefore, a careful evaluation of the nodule is necessary in order not to neglect a malignant neoplasm [17]).



Figure 1a: Whole thyroid gland with lateral compartment lymph node tissue in a patient with hyperfunctioning multinodular goiter.

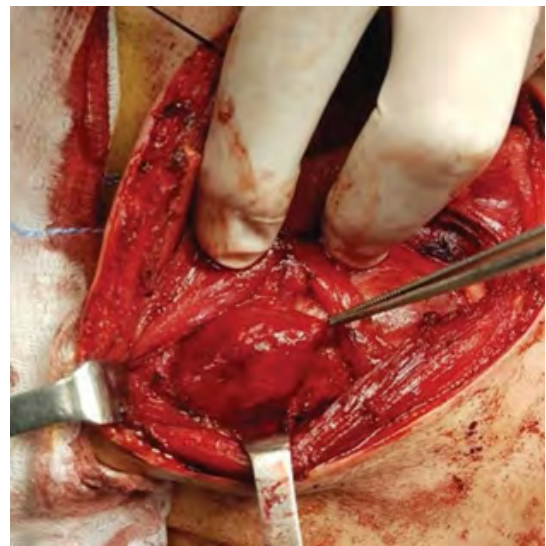


Figure 1b: Voluminous lymph node with a maximum size of 3.5 cm in the lateral compartment (intraoperative finding) in a patient with hyperfunctioning multinodular goiter

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