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ORIGINAL ARTICLE

Thyroid cancer in Greece. A tertiary center experience

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Summary

Purpose: *To present the frequency and distribution of histological subtypes of primary thyroid carcinoma cases diagnosed at our Department.*

Methods: *We retrospectively analyzed the records of all patients with primary thyroid carcinoma admitted to our Department from January 01, 2002 until December 31, 2008.*

Results: *Of 1,607 patients with primary thyroid carcinoma 1510 (94%) suffered from differentiated thyroid carcinoma (DTC), 71 (4%) from medullary thyroid carcinoma (MTC), 10 (< 1%) from anaplastic thyroid carcinoma (ATC), 9 (<1%) from primary thyroid non Hodgkin's lymphoma, 1 (< 1%) from primary thyroid Hodgkin's lymphoma, 1 (< 1%) from squamous cell carcinoma of the thyroid, and 6 patients (< 1%) suffered from carcinoma of ectopic thyroid tissue (1 malignant struma ovarii, 2 carcinoma in thyroglossal duct remnants, and 3 patients presented with thyroid tissue carcinoma in cervical lymph nodes).*

Conclusion: *Differentiated thyroid carcinoma is by far the most common primary malignancy of the thyroid gland. Papillary thyroid carcinomas constitute the vast majority of these neoplasms. Larger studies are necessary to better understand and evaluate the clinical characteristics, behavior and prevalence of thyroid cancer in our country.*

Key words: Greece, histological subtypes, prevalence, thyroid carcinoma

Introduction

Thyroid carcinomas are rare malignancies, but they are the most common neoplasms of endocrine origin [1]. The vast majority of primary thyroid malignancies derive from follicular and parafollicular thyroid cells. The main types of primary thyroid malignant neoplasms are papillary (PTC), follicular (FTC), ATC and MTC. PTC, FTC and ATC arise from follicular cells and medullary thyroid cancer from parafollicular c-cells [2]. Less frequent tumors are lymphomas, probably arising from lymphoid tissue that migrates to thyroid gland, sarcomas and hemangioendotheliomas [2].

The aim of this retrospective study was to analyze the frequency and distribution of histological subtypes of primary thyroid carcinoma cases diagnosed at our Department.

Methods

We retrospectively analyzed the medical records of all patients with primary thyroid carcinoma admitted to our Department from January 1st, 2002 to December 31st, 2008. We studied the distribution of different histological subtypes of this malignancy and also their distribution according to sex. Patients with metastatic lesions to the thyroid gland were excluded.

Results

Between 01.01.2002 and 31.12.2008, 1,607 patients with history of primary thyroid carcinoma were admitted to our Department. The majority (1510 patients, 94%), suffered from DTC, 71 (4%) from MTC, 10 (<

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1%) from ATC, 9 (<1%) from primary thyroid non Hodgkin's lymphoma, 1 (< 1%) from primary thyroid Hodgkin's lymphoma, 1 (< 1%) from squamous cell carcinoma of the thyroid, and finally 6 patients (< 1%) suffered from carcinoma of ectopic thyroid tissue (Figures 1-3).

Differentiated thyroid carcinoma

The vast majority (91%) of patients with DTC suffered from PTC (1,365 patients), whilst 8% of them presented with FTC (124 patients). In 21 patients (1.4%) we observed coexistence of FTC and PTC.

In patients with PTC there was a clear female predominance (1,122 women, 82%). Only 243 (18%) patients with PTC were men.

Eighty-three (67%) patients had FTC, 30 (24%) Hurthle cell carcinoma and 4 (3%) insular thyroid carcinoma. In 6 (5%) patients we detected coexistence of Hurthle cell carcinoma and PTC, while 1 patient presented with insular and PTC. In patients with FTC we also observed clear female predominance (102 women, 82%). In patients with coexistence of FTC and PTC, 15 (71%) were women and 6 (29%) men.

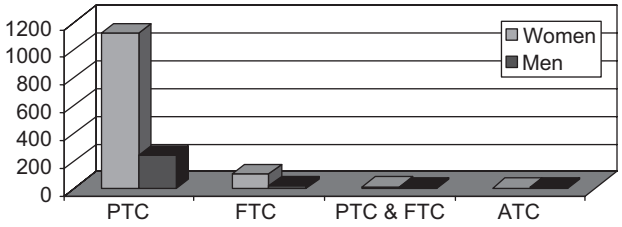

Figure 1. Epithelial thyroid carcinomas in our study group (n=1,520). PTC = 1365, FTC = 124, FTC & PTC = 21, ATC = 10. PTC: papillary thyroid carcinoma, FTC: follicular thyroid carcinoma, PTC & FTC = coexistence of papillary and follicular thyroid carcinoma, ATC: anaplastic thyroid carcinoma.

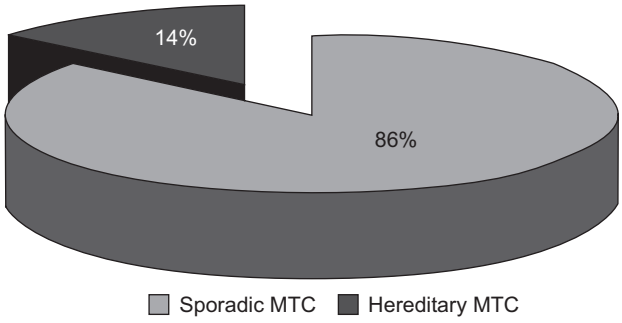

Figure 2. Distribution of sporadic (n = 61) and hereditary (n = 10) medullary thyroid carcinoma (MTC, n = 71).

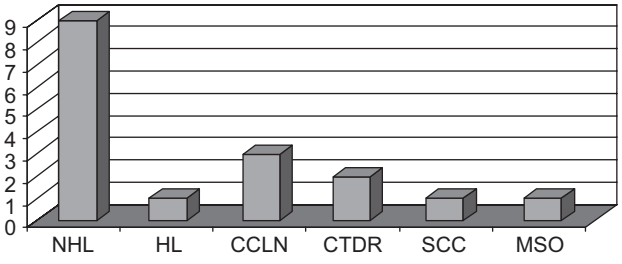

Figure 3. Rare primary thyroid carcinomas and carcinomas in ectopic thyroid tissue (n = 17). NHL: n = 9, HL: n = 1, CCLN: n = 3, CTDR: n = 2, SCC: n = 1, MSO: n = 1. NHL: non Hodgkin's lymphoma, HL: Hodgkin's lymphoma, CCLN: carcinoma in cervical lymph nodes, CTDR: carcinoma in thyroglossal duct remnants, SCC: squamous cell carcinoma, MSO: malignant struma ovarii.

Anaplastic thyroid carcinoma

ATC was the only type of epithelial thyroid carcinomas in which we observed approximately equal distribution between men and women. From 10 patients with ATC 6 were men and 4 women.

Medullary thyroid carcinoma

Seventy-one patients suffered from MTC. Sporadic MTC was detected in 61 (86%) patients while in 10 (14%) patients the neoplasm was hereditary. In 15 patients MTC coexisted with PTC and in one patient we observed coexistence with FTC. In the MTC group of patients, similar to DTC, the majority (52 patients, 73%) were women, men representing only 27% of patients (19 patients).

Primary thyroid lymphoma

Most of the thyroid lymphomas were non Hodgkin's. Eight patients had diffuse large B-cell lymphomas, 1 patient suffered from Burkitt's lymphoma and 1 from primary Hodgkin's lymphoma. In one patient with diffuse large B-cell lymphoma, coexistence with PTC was observed.

Other histologies

One female patient presented with squamous cell carcinoma of the thyroid.

Carcinoma in ectopic thyroid tissue

In 6 patients carcinoma in ectopic thyroid tissue was detected. One patient suffered from malignant struma ovarii, 2 from carcinoma in thyroglossal duct cyst, and 3 patients presented with thyroid tissue carcinoma in cervical lymph nodes.

Discussion

Primary thyroid carcinomas are rare [1]. Epithelial primary thyroid carcinomas resemble to Roman deity Janus with his two different faces. On one side, DTC, an indolent malignancy, and on the other side, ATC, one of the most aggressive and lethal carcinomas in humans [2,3].

DTC are slow-progressing neoplasms, 10-year overall relative survival being 93% for PTC and 85% for FTC [4]. In two large series in the USA the majority of primary thyroid carcinomas were DTC (92%) [4,5]. The findings from our series are similar, DTC representing 94% of primary thyroid cancers.

In our series we observed a striking predominance of PTC and female sex in the group of DTC patients. We also observed a lower prevalence of FTC than previously reported in large series of DTC in Greece [6,7]. As has been already reported in the past, prevalence of FTC has decreased in Greece over the last years, probably because of PTC increasing prevalence and adequate iodine supplementation [6,7].

Distant metastases due to DTC seldom occur, but their presence significantly reduces survival [2,8]. Approximately 1-8% of PTC and 8-33% of FTC have distant metastases at diagnosis [9]. The most frequent metastatic site are the lungs, followed by bones and less frequent by other soft tissue sites [10]. Patients with bone metastases have poorer prognosis than those with lung metastases, probably due to different response to radioiodine treatment and different clinical course [9,10]. Nevertheless, time of metastases diagnosis (simultaneously with primary tumor diagnosis or later in the course of the disease) does not seem to affect prognosis in PTC patients with lung metastases [9]. Brain metastases are rare, potentially lethal and frequently in the context of widespread metastatic disease [11].

Primary role in DTC treatment has surgery, TSH suppression therapy with levothyroxine and therapeutic doses of radioiodine administered in selected patients. Metastatic disease, especially in neoplasms that are not radioiodine-avid, is difficult to treat and still represents a therapeutic challenge [12].

ATC usually affects elderly patients but in the literature there are reports of young adults suffering from ATC [2,13,14]. Undifferentiated thyroid carcinoma is responsible for 14-39% of thyroid carcinoma-related deaths, but accounts for < 2% of all thyroid carcinomas [15-17]. The prognosis of patients suffering from ATC is very poor and the overall specific mortality rate is 68% at 6 months and 80.7% at 12 months [15]. Distant metastases are present in 46% of patients at diagnosis and in 68% of patients during the course of the disease [17]. Multimodality treatment (combination of surgery, hyperfractionated radiotherapy and chemotherapy) seems to offer better local control and moderately prolongs survival but still the prognosis is very poor as the majority of patients present with advanced, inoperable disease [15-17]. It is reported that complete surgical removal of the tumor is possible in approximately one-third of the patients [17]. Although locoregional control is achieved in several patients, death due to distant metastases and survival have not changed over the last 50 years. However, recent advances in the understanding of ATC nature and new therapeutic modalities give new hopes to improve the outcome of ATC and prolong survival [18].

C-cell-derived MTC is not a common malignancy, accounting for 3.2-10% of thyroid carcinomas [2,4,5,19]. MTC is more aggressive than DTC, 10-year overall relative survival being 65-75% [2,4,19]. The majority of MTC are sporadic but 20-30% are hereditary due to mutations of the RET proto-oncogene and can present either as familial MTC or as part of MEN 2 syndrome [2,19,20]. However, about 5% of apparently sporadic MTC are hereditary, presenting germline mutations of the RET proto-oncogene [19]. In our group of MTC patients we observed a lower prevalence of hereditary carcinomas (14%) than previously reported in the literature. This is probably due to the fact that familial MTC cases are directed to another tertiary center. Metastatic dissemination to cervical lymph nodes is frequent and half of distant metastases are present at diagnosis [19]. Common metastatic sites are the liver, lungs, bones and, less common, brain and skin [19]. Metastases often are diffuse and multiple with multiorgan involvement [19]. Fortunately, long survival is observed even in patients with distant metastases and no systemic treatment, probably due to the neoplasm's biology and slow progression [19]. The main treatment of MTC is surgical removal of the tumor as this treatment modality seems to favorably affect the course of the disease [19]. Effective treatment for systemic metastatic disease is still lacking [19].

Primary thyroid lymphomas represent a rare heterogeneous nosological entity [21]. It is postulated that they arise from lymphoid tissue which migrates to the thyroid, probably in the context of an autoimmune disease, as thyroid has no native lymphoid tissue [2]. Most of them are non Hodgkin's lymphomas, primary Hodgkin's thyroid lymphomas being extremely rare. Non Hodgkin's thyroid lymphomas belong to the large family of extranodal lymphomas. They account for < 5% of thyroid malignancies, < 2.5% of lymphomas in general, and up to 7% of extranodal lymphomas [22]. Their vast majority are diffuse large B-cell lymphomas (50-80%), followed by extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue type (20-

30%), Burkitt's lymphomas, small lymphocytic lymphomas, anaplastic large cell lymphomas and peripheral T-cell lymphomas [22]. Our group of lymphoma patients contained 2 rare types of neoplasms: a man with Burkitt's thyroid lymphoma and a woman with primary Hodgkin's thyroid lymphoma.

Thyroid Burkitt's lymphomas are nonendemic or sporadic lymphomas [23]. High proliferative rate of these neoplasms makes them very sensitive to chemotherapy but also very aggressive and their prompt diagnosis and treatment are essential [23]. Nevertheless, despite new treatment strategies, the prognosis of stage IV Burkitt's lymphoma remains poor [23].

Rarely Hodgkin's lymphomas may present first at an extranodal site such as the gastrointestinal tract, nasopharynx, central nervous system, kidney and other sites [24]. Differential diagnosis between primary thyroid Hodgkin's lymphoma and secondary involvement of the gland is usually difficult [24]. Thus frequently fine needle aspiration is not sufficient and core biopsy or even thyroidectomy is necessary to establish the correct diagnosis [24]. Patients with Hodgkin's thyroid lymphoma tend to be younger, and despite the fact that systemic Hodgkin's lymphoma has an equal male to female ratio, thyroid Hodgkin's lymphoma presents net female predominance [24].

Another very rare primary thyroid carcinoma is squamous cell carcinoma of the thyroid. The majority of squamous cell lesions are metastases to the thyroid gland from the adjacent structures (larynx, trachea, esophagus) whilst primary lesions are rare [25]. For this reason elaborate search for primary malignancies is obligatory when a squamous cell lesion is detected in the thyroid [25]. Primary squamous cell carcinomas of the thyroid usually affect patients between the fifth and sixth decades of life. They are highly malignant and have worse prognosis than secondary squamous cell carcinomas as the mean survival from diagnosis is < 6 months in the majority of patients. Fine needle aspiration is often not sufficient and confirmation of diagnosis must be made after surgery [25].

In our group of patients, besides primary thyroid malignancies, we also included patients with carcinomas in ectopic thyroid tissue: a female patient suffering from malignant struma ovarii, 2 females suffering from carcinomas in thyroglossal duct remnants and finally 3 females with carcinomas in cervical lymph nodes without primary lesion, despite the assiduous search.

Struma ovarii is an ovarian teratoma containing at least 50% thyroid tissue [26]. Malignant struma ovarii is malignant transformation of ovarian thyroid tissue and must not be confused with metastasis to the ovary from a thyroid carcinoma, although these secondary lesions are uncommon [26]. First-line treatment for malignant struma ovarii is surgery (but there is no consensus on the extend of surgery or the postoperative treatment) and near-total thyroidectomy [26].

Despite that thyroglossal duct remnants are common**,** development of tumors in them is rare [27]. It is postulated that carcinomas in thyroglossal duct remnants can be either metastases from thyroid carcinomas or *de novo* neoplasms. Nevertheless, it is a fact that about half of the patients with carcinomas in thyroglossal duct cysts don't have thyroid lesions [27]. Papillary carcinomas are the most frequent followed, interestingly, by squamous cell and follicular carcinomas. Hurthle cell, insular and anaplastic carcinomas have also been reported. Generally, the prognosis is good but in the literature there are reports of recurrences and even deaths due to carcinomas of the thyroglossal duct remnants [27,28]. Because the neoplasm is rare there is not enough evidence for its optimal management [27]. Currently, the guidelines for the management of thyroid carcinoma are used [27].

Epithelial inclusions in cervical lymph nodes may occasionally be benign and do not necessarily mean metastatic disease [29]. Previous reports describe patients with carcinoma of thyroid tissue in cervical lymph nodes without evidence of thyroid lesion [29,30]. In our group of patients we found 3 female patients with thyroid malignant lesions in cervical lymph nodes but, despite the meticulous search, we did not detect a thyroid carcinoma. Although the vast majority of malignant thyroid tissue in cervical lymph nodes is due to metastatic invasion of previously undetected thyroid microcarcinomas, it is assumed that sometimes carcinomas may develop, arising from heterotopic thyroid tissue [29,30].

In conclusion, despite the fact that –to our knowledge– this is the largest series of primary thyroid carcinoma ever reported in Greece, however more larger multicentric studies are necessary to better understand the nature, clinical behavior and prevalence of thyroid cancer in our country.

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