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Thyroid cancer profile in Mures County (Romania): a 20 years study

RAMONA CĂTANĂ[1)], ADELA BOILĂ[2)], ANGELA BORDA[2,3)]

[1)]*Department of Endocrinology, Emergency County Hospital, Targu Mures*
[2)]*Department of Histology, University of Medicine and Pharmacy of Targu Mures*
[3)]*Department of Pathology, Emergency County Hospital, Targu Mures*

Abstract

The aim of the present study was to present data on frequency of thyroid cancer in Mures County (Romania) and border counties, a goiter endemic area, and to analyze its histopathological characteristics, over a 20 years period (1990–2009). *Materials and Methods*: Demographic, clinical and pathological data were obtained from database registries. Histological subtypes of thyroid cancer were classified according to the *WHO* criteria (sixth edition, 2004) in the following categories: papillary thyroid carcinoma with its histological subtypes, follicular thyroid carcinoma, poorly differentiated thyroid carcinoma, undifferentiated thyroid carcinoma, medullary carcinoma, lymphoma, metastatic tumors. *Results*: Our analyze included 524 cases of thyroid cancer of the 3460 surgical thyroid specimens resected between 1990–2009: 410 (78.2%) cases of papillary carcinoma, 19 (3.6%) cases of follicular carcinoma, 24 (4.6%) cases of poorly differentiated carcinoma, 33 (6.3%) cases of undifferentiated carcinoma, 22 (4.1%) medullary carcinomas, eight (1.6%) lymphomas, and eight (1.6%) metastatic tumors. Papillary thyroid carcinoma is the most common histological form (78%) and an increasing incidence of this form was observed. A statistical significant increase in the incidence of the follicular variant of papillary carcinoma was noticed between 2000–2009, compared to 1990–2000. An increased incidence of small tumors was also found (6.66%, 1990–1999 *vs.* 23.5%, 2000–2009). The undifferentiated thyroid cancer had a marked decreasing trend (20%, 1990–1999 *vs.* 3.45%, 2000–2009). *Conclusions*: Our study demonstrates an increasing trend in the incidence of thyroid cancer in the last 20 years. This increase is mainly due to the small papillary cancers, by contrast to the undifferentiated thyroid cancers that have a decreasing trend. A better understanding and description of the morphological criteria could explained the increasing incidence of the follicular variant of papillary carcinoma.

Keywords: thyroid cancer, papillary carcinoma, incidence, microcarcinoma.

Introduction

Although thyroid cancer is a relatively rare neoplasm worldwide, accounting for approximately 1–5% of all cancers in women and less than 2% in men, during the past several decades, an increasing incidence of thyroid cancer has been reported in European countries [1–3], USA [4] and Canada [5]. Thyroid cancer is two to three times more common among women, and in this gender group it is now the fastest growing cancer type and the 6th most common [1, 4, 6].

The growing incidence of thyroid cancer is almost entirely due to papillary thyroid carcinoma. Papillary thyroid carcinoma and its variants represent by far, the most common thyroid malignancy, accounting for more than 80% of all cases [2, 7, 8]. Part of the increasing incidence of thyroid cancer is due to the use of more efficient diagnostic tools. The ultrasonography and fine-needle aspiration biopsy are widely used in the current practice leading to an increased detection of small subclinical tumors. The more frequent discovery of thyroid cancer microscopical foci in the surgical specimens is due in part to a more careful examination of the whole surgical specimens. Other important aspects responsible for the rising incidence of the papillary thyroid carcinoma are the improvements in defining the pathological diagnostic criteria for this type of thyroid cancer [9].

The aim of our 20 years retrospective study (1990–2009) was to describe recent trends in the incidence rates of thyroid cancer in Mures County (Romania) and border areas, an iodine deficient goiter endemic area, and to analyze its histopathological characteristics.

Materials and Methods

The design of the study was a retrospective review of thyroid carcinomas from January 1990 to December 2009, in Mures County (Romania) and in border counties. All patients diagnosed with thyroid cancer after a total or partial thyroidectomy were included. We excluded only a few cases that underwent completion of the previous partial thyroidectomy in patients already diagnosed with thyroid cancer at the final histo-pathological examination.

Patient demographics (age, gender) and clinico-pathological features (tumor type, the presence of lymph node metastases and the presence of extra-thyroidal extension) were obtained from database registries of the Department of Pathology (for the years 1995 to 2009) and Department of Surgery (for the years 1990 to 1994), Emergency County Hospital, Targu Mures.

To classify thyroid cancer in its different histological subtypes the *WHO* (6th edition, 2004) criteria were used. According to this classification, the following categories were established: papillary thyroid carcinoma (PTC) with its histological subtypes*:* the conventional variant CVPTC (Figure 1), the follicular variant FVPTC (Figure 2), the oncocytic variant, the tall cell variant (Figure 3), the diffuse sclerosing variant (Figure 4), follicular carcinoma (FTC), poorly differentiated carcinoma (PDTC) (Figure 5), undifferentiated or anaplastic carcinoma (ATC), medullary carcinomas (Figure 6), lymphomas, and metastatic tumors. PTC with areas of PDTC was included in the PDTC category, since the presence of these areas carries out a worse prognostic. Thyroid microcarcinomas (MC) (Figure 7) are designated by the *WHO* as thyroid tumors of 1 cm or less and incidentally discovered.

Incidence trends for each of these categories were examined.

Descriptive statistical analyses were done. Statistic analyses were performed using Epi-Info 2010 and Excel 2007 programs. The statistical evaluation included the *chi*-square test with a level of significance $p<0.05$ and confidence intervals at 95%.

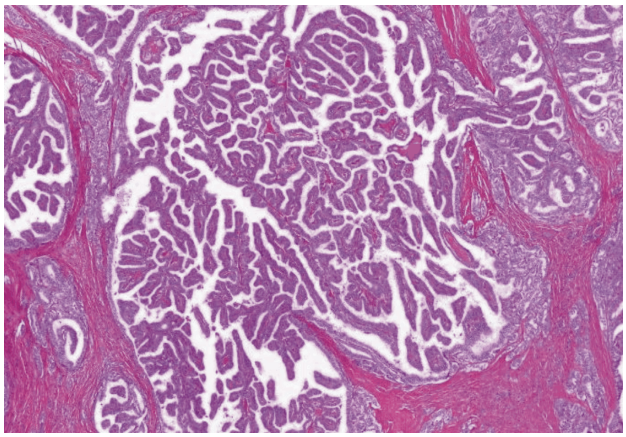

Figure 1 – ***Conventional variant of papillary carcinoma (HE stain, ob. 4×).***

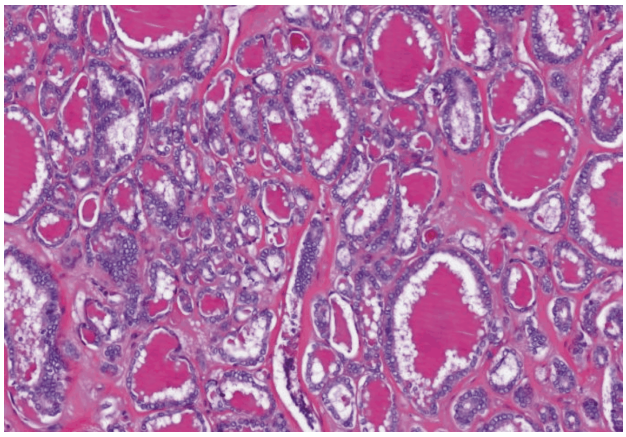

Figure 2 – ***Follicular variant of papillary carcinoma (HE stain, ob. 10×).***

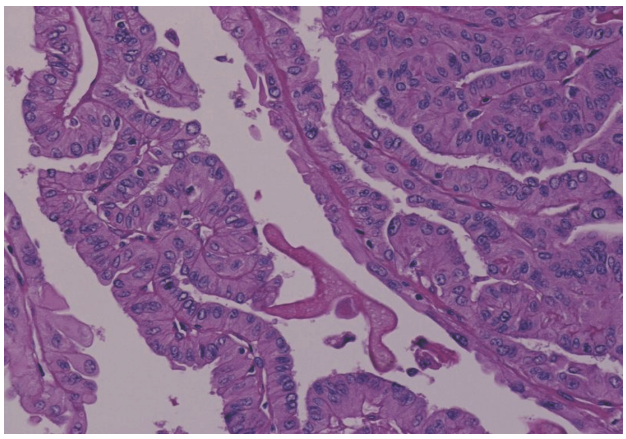

Figure 3 – ***Tall cell variant of papillary carcinoma (HE stain, ob. 20×).***

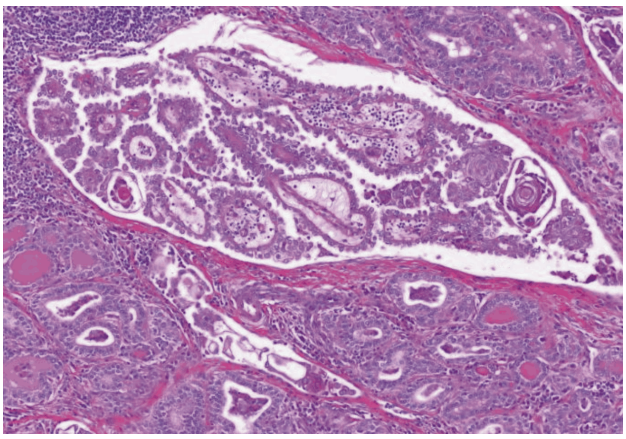

Figure 4 – ***Diffuse sclerosing variant of papillary carcinoma (HE stain, ob. 10×).***

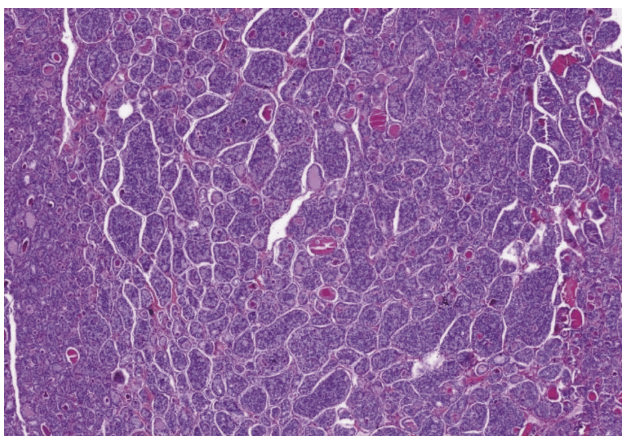

Figure 5 – ***Poorly differentiated thyroid carcinoma (HE stain, ob. 4×).***

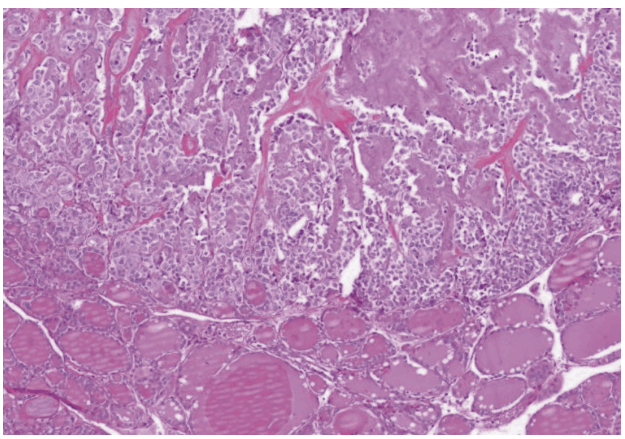

Figure 6 – ***Medullary carcinoma of the thyroid (HE stain, ob. 4×).***

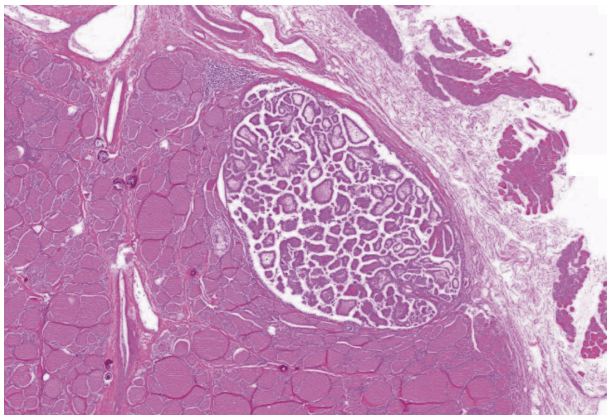

Figure 7 – ***Microcarcinoma located near the thyroid capsule. Many psammoma bodies spread in the adjacent parenchyma (HE stain, ob. 4×).***

Results

Over the 20 years period (1990–2009) a total of 3460 cases of thyroid pathology were examined in the Department of Pathology of the Emergency County Hospital of Targu Mures, and from these, 524 cases were thyroid cancers.

The 524 carcinomas of the thyroid gland involved 456 women (87.02%) and 68 men (12.98%); men/women ratio of 1:6.7. The mean age at diagnosis was 48.91 years for women and 49.75 years for men (range 15–83 years). Incidence rates by age groups in men and women for all types of thyroid cancers are shown in Figure 8. A maximal incidence was observed in the age group of 50–59 year for women, while in men the incidence remains constant for the four, five, six decades.

The highest mean age at diagnosis is recorded in ATC category, around 68 years for women and 67 years for men and the lowest mean age in the PTC category: 47.73 years for men and 47.02 years for women (Figure 9). Women predominance is obvious in all thyroid cancer forms (7.3/1 PTC; 8.5/1 FTC; 5/1 PDTC; 15.5/1 ATC; 3.4/1 MTC; 3/1 lymphomas), except the metastatic tumors category where we noticed an equal ratio gender.

The every year proportion of thyroid cancers reported to the thyroid pathology cases is shown in Figure 10. Between 1990–1999, the proportion was somehow constant around 10%. From 2000, the frequency of thyroid cancer noticed an increasing trend, and in 2009, it reached almost 25% of all thyroid resected specimens.

The most common histological form is PTC, which represents 78% of all thyroid cancer variants (Figure 11).

Comparing the incidence of the histological variants of thyroid cancer between 1990–1999 and 2000–2009, a particular dynamics is seen (Table 1).

We observed that the ATC was well represented in the first 10 years (20%), but its incidence noticed a statistically significant decrease compared to the well-differentiated forms after 2000 (3.46%, p=0.00002). Lymphomas and metastatic tumors were rare and sporadic cases. PDTC and medullary carcinomas had a low incidence.

A significant increase in the incidence of PTC was observed between 2000–2009, compared to 1990–2000 (61.1% *vs.* 81.8%). The PTC/FTC ratio increased from 7.8:1 (1990–1999) to 29.5:1 (2000–2009).

The distribution of PTC variants was also analyzed (Table 2) and the most common form was the CVPTC (57.8%) followed by the FVPTC (32.9%).

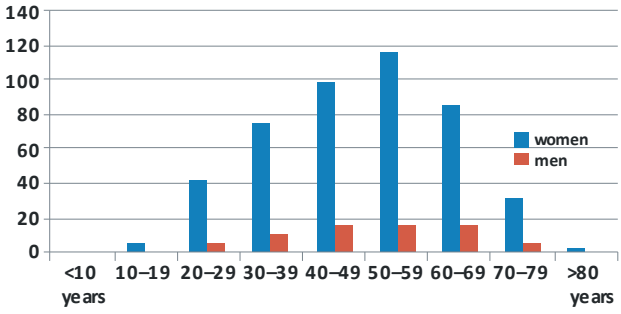

Figure 8 – ***Incidence rates of thyroid cancer by age groups in men and women***

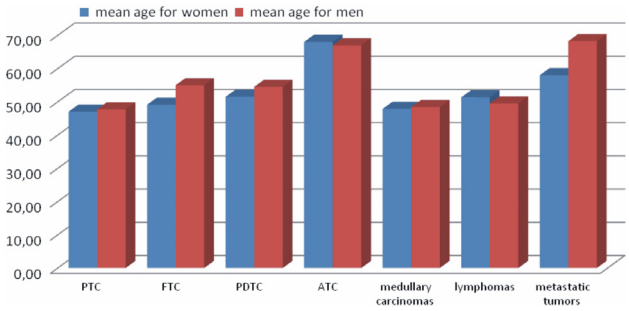

Figure 9 – ***The mean age at diagnosis for the histological forms of thyroid cancer.***

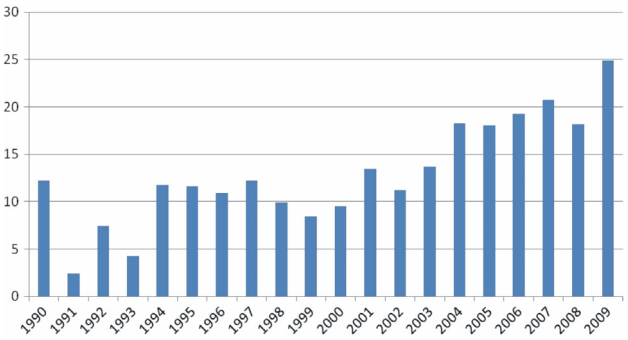

Figure 10 – ***The proportion [%] of the malignant thyroid tumors reported to the thyroid surgical specimens (1990–2009).***

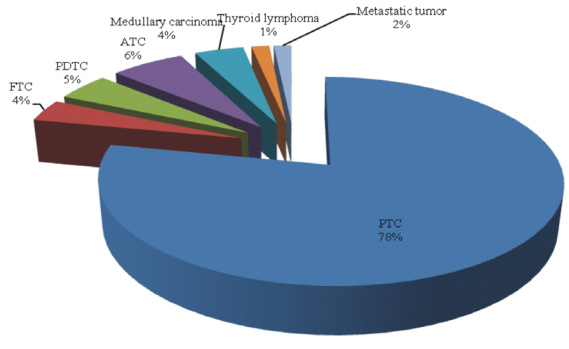

Figure 11 – ***The distribution of histopathological types of thyroid cancer diagnosed between 1990–2009.***

Table 1 – *Histopathological characteristics of the thyroid cancer*

Histopathological types	No. of cases Total	No. of cases 1990–1999	No. of cases 2000–2009
Thyroid cancers	524	90	434
Papillary carcinoma	410	55 (61.11%)	355 (81.79%)
Follicular carcinoma	19	7 (7.77%)	12 (2.76%)
Poorly differentiated carcinoma	24	4 (4.45%)	20 (4.60%)
Undifferentiated carcinoma	33	18 (20%)	15 (3.46%)
Medullary carcinoma	22	4 (4.45%)	18 (4.15%)
Thyroid lymphoma	8	0 (0%)	8 (1.85%)
Metastatic tumor	8	2 (2.22%)	6 (1.39%)

Table 2 – *Histopathological characteristics of the 410 cases of papillary thyroid carcinoma diagnosed between 1990–2009*

	No. of cases Total	No. of cases 1990–1999	No. of cases 2000–2009
Papillary carcinoma	410	55	355
Conventional	237 (57.8%)	49 (89.09%)	188 (52.96%)
Follicular variant	135 (32.9%)	5 (9.09%)	130 (36.62%)
Other variants (oncocytic, tall cell, solid, diffuse sclerosing)	38 (9.3%)	1 (1.82%)	37 (10.42%)

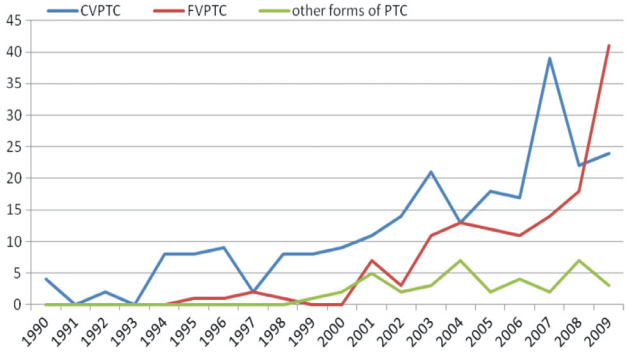

Figure 12 – *Number of cases per year of classical, follicular and other variants of papillary carcinoma.*

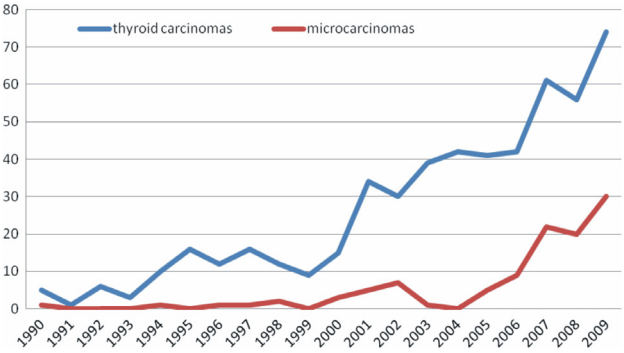

Figure 13 – *The distribution of the microcarcinomas compared to the malignant tumors over the 20 years.*

Discussion

In our study we found that over the 20 years the incidence of thyroid cancer in Mures County and border areas, had an increasing trend, after 2000. This increase was mainly due to PTC (61.1%, 1990–1999 *vs.* 81.8%, 2000–2009), which represented the large majority of thyroid carcinomas (78%). Similar results were reported worldwide [1–5, 10–12]. Only few authors [13] concluded that the rise in thyroid cancer incidence is now abating and this result could reflect standardization in diagnostic procedures. The differences regarding the populations considered by the studies could be partially responsible for these differences.

There has been much speculation about why the incidence of differentiated thyroid carcinoma is rising. Some researchers have suggested that potential risk factors including radiation exposure [14, 15], iodine deficiency [16], head and neck radiation therapy [17, 18] are more common nowadays. It has been also suggested that certain female hormonal and reproductive factors may play a role [19–21] in the development of this malignancy and this could explain the net female predominance of thyroid carcinoma. The increasing use of more advanced techniques for the diagnosis of cancer in general and especially of its subclinical forms has significantly contributed to the detection of more tumors in the last 10 years [22, 23].

The other histological variants of PTC had a low incidence (a total of 9.3%). PTC variants had an interesting evolution: FVTC had a very low incidence before the 2000 (9.09%), but its frequency increased significantly (36.62%, $p<0.001$) in the second half of the study period, as it is demonstrated in Figure 12.

Other forms had also a slight increase trend in the last ten years of the study (1.82%, 1990–1999 *vs.* 10.43%, 2000–2009).

MC represented 20.6% of all tumors (108 cases), 96.3% of them being papillary form. We noticed an important increase in the incidence of MC from 1990–1999 (6/90, 6.66%) to 2000–2009 (102/434, 23.5%, $p=0.00004$) (Figure 13).

Our results show that the incidence of micro-carcinomas (tumors <1 cm) increased significantly, especially in the last 10 years, parallel to the general increasing incidence of PTC. We think that a significant contribution to the detection of these subclinical tumors, had the widely use of the ultrasound and fine-needle aspiration in current clinical practice. We also consider that the significant changes in pathological practice are not less important. Sampling techniques have undergone major changes, with a more careful examination of the whole surgical specimen and a larger number of samples per case. We noticed that if in 1990 only two samples/thyroid lobes were included, in 2009 the number increased to eight. It is obvious that in this way the chance to detect a microcancer has considerably increased. Similar results were found by Grodski S *et al.* when they reviewed 2260 retrosternal goiters undergoing surgery, and reported that the incidence of well-differentiated thyroid carcinomas in the specimens doubled over four decades. In the same time, the number of blocks sampled per thyroid increased from 2.5 to 9.1, leading the authors to attribute the excess cancers to improved detection by pathologists [24].

Since, from database registries the precise tumor size was not available for tumors larger than 1 cm, we were unable to assess the incidence trend of the larger tumors, but some literature data also indicate an

increasing incidence for larger tumors (>4 cm and >6 cm) between 1973–2006 [1, 12] and this argues against advanced diagnostic techniques or increased attention to small nodules as the only explanation for the observed increasing trend of thyroid cancer.

It is also important to emphasize that the histopathological classification system and a more precise definition of the diagnostic criteria for thyroid cancer have evolved over time. Since 1998, in the *WHO* classification it was recognized that nuclear features are more important than architectural patterns in classifying thyroid papillary cancer. It has been described the FVCPT with follicular architecture and nuclear features of PTC that might be partially or totally encapsulated. As a result, many cancers previously classified as follicular carcinomas are now categorized as FVPTC. These changes in the classification had an obvious impact on the distribution of PTC cases with follicular pattern, in that the FVPTC rarely diagnosed before 2000, noticed a significant increasing rate between 2000–2009, and in 2009, this form overcame the CVPTC, which had been the most common variant of PTC until then. An increasing rate of FVPTC (by 173%) was also reported by Albores-Saavedra J *et al.* in a 30 years study (1973–2003) [25].

A better understanding and description of the morphological criteria could explained the increasing trend of other rare variants of PTC (the oncocytic form, the tall cell form, the solid form and the diffuse sclerosing form) after 2000.

The changes in the *WHO* classification might also have partially influenced the decrease of the incidence of the FTC, and consequently increased the PTC/FTC ratio from 7.8:1 (1990–1999) to 29.5:1 (2000–2009). Another hypothesis responsible for this ratio change could be the iodine prophylaxis measures, introduced at the beginning of 2000's. It has been noticed that when iodine prophylaxis occurs in iodine deficient regions, the proportion of PTC often increases [26, 27], while FTC form decreases.

The decrease incidence of ATC cases was significant (20%, 1990–1999 *vs.* 3.46%, 2000–2009) and one explanation for this finding could be the ability to detect and to treat cancer in an earlier stage of evolution, which may reduce the possibility to undergo dedifferentiation [25]. Some studies from Italy showed a reduction of ATC from 4% to 1% between 1969 and 1973, while other studies from India and Sri Lanka showed a decline from 8% to 4% between 1989 and 1993 [28–31]. Although well-differentiated thyroid cancer has increased in Japan, the incidence of ATC has remained stable [32, 33]. The incidence of ATC did not change significantly in a study from Scotland [34]. One explanation for the decreasing incidence of ATC in these several locations could be that a more accurate clinical diagnosis. Another reason for the ATC reducing incidence might be the iodine prophylaxis, knowing that ATC is more common in areas with endemic goiter, and thus with improvements in iodine supplementation, the incidence of this tumor would be expected to decline [35].

In our study, we did not observe important changes in the incidence rates of PDTC or medullary carcinoma that remain rare forms of thyroid cancer.

Regarding the mean age at diagnosis and the net prevalence of the female gender, our results are not surprising, the findings complying with the data from literature [2, 4]. It is interesting to note that the average age at diagnosis increases with decreasing degree of differentiation of carcinoma, (PTC – 47 years, FTC – 52 years, PDTC – 53 years, ATC – 6.5 years) suggesting that old age does not favor increasing incidence of thyroid cancer, but is a poor prognostic factor.

Conclusions

Our study demonstrates the increasing incidence rates of thyroid cancer in the last years. This growing incidence was entirely due to PTC, especially to the increased detection of small papillary cancers. Differences in the incidence trends of the histological variants of PTC have also been observed, especially the increasing incidence of the FVTC. The aggressive forms of thyroid cancer like ATC have become a rare pathological diagnosis in the last years.

Although advances in imaging and diagnostic techniques improve the detection of thyroid tumors, we believe that it is unlikely that only these entirely explain the real increasing incidence of thyroid cancer.

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Corresponding author

Ramona Cătană, MD, Department of Endocrinology, Emergency County Hospital, Târgu Mureş, 38 Gheorghe Marinescu Street, 540139 Târgu Mureş, Romania; Phone +40740–079 954, e-mail: catana.ramona@yahoo.com

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