



# Demographic and Clinical Features of Thyroid Carcinomas in Republic of Macedonia (1999-2010)

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## Abstract

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**BACKGROUND:** Thyroid carcinomas (TC) are the most common endocrine malignancies. In some parts of the world, the incidence of TCs has increased over the past few decades, especially in females according to some studies.

**AIM:** We have set as the objective for our study to analyse the demographic, ultrasound features, thyroid hormonal status and frequency of thyroid carcinomas in the Republic of Macedonia according to histopathological type.

**MATERIALS AND METHODS:** Retrospective analysis of medical data from all diagnosed and treated patients with TC at the Institute of Pathophysiology and Nuclear Medicine for the period 1999-2010 was performed. Demographic characteristics: age at diagnosis, gender, histopathological type of TC and from clinical features: US findings and thyroid hormonal state at initial examination and their distribution in eight state regions were evaluated.

**RESULTS:** Total number of 204 patients with TC in the Republic of Macedonia was registered. Papillary thyroid carcinoma (PTC) was the most frequent with 131 pts (64.21%), follicular (FTC) with 13 pts (6.37%) was second thyroid malignoma, followed by medullary (MTC) with 12 pts (5.88%), anaplastic (ATC) 11 pts (5.39%) and the rarest types were Hurtle cell carcinoma and intrathyroid sarcoma with only 1 diagnosed case. Age varied widely from 7 yrs to 88 yrs age (average  $47.9 \pm 16.6$  yrs). PTC was more prevalent in younger age groups, while ATC was diagnosed in elderly patients. In all of the eight-country regions, the prevalence rate was higher for females than males (3:1) or  $15.21/10^5$  female to  $5.03/10^5$  male prevalence rate. According to US appearance mostly TC was unilateral in 42.65% and multifocal in 7.84% with dimensions from 15 to 50 mm.

**CONCLUSION:** There is an increase in incidence and prevalence rate of TCs in our country, mostly PTC, while reduction exists in the number of diagnosed cases of ATC and FTC, comparing with previous studies before iodine prophylaxis program. Different from described in the literature is female: male (4:1) ratio for ATC. According to US features, we can conclude that introduction of more detailed reporting system may improve diagnostic accuracy.

## Introduction

Thyroid carcinomas (TC) are the most common endocrine malignancies. In some parts of the world, the incidence of TC has increased over the past few decades, especially in female patients according to some studies [1-3]. Thyroid malignancies are a heterogeneous group of tumors, with papillary (PTC) and follicular thyroid carcinomas (FTC) known as follicular cell-derived or differentiated thyroid carcinomas, medullary thyroid carcinoma (MTC) originating from neuroendocrine calcitonin-producing C – cells and less common anaplastic thyroid carcinoma (ATC) with poor prognostic

outcome and very rare intrathyroid lymphomas originating from intrathyroid lymphoid tissue and sarcomas arising from intrathyroid connecting tissue [4-6].

Advances in histopathology techniques, immunohistochemical staining and molecular pathology reveal that there are further subtypes in differentiated thyroid carcinomas, PTC and FTC, with different genetic alterations, different histopathological features and different prognosis and outcome. Described subtypes of PTC are: typical variant, follicular variant of PTC, tall cell, oncocytic, columnar cell, diffuse sclerosing, solid, clear cell, cribriform morular, macrofollicular, PTC with fasciitis-like stroma,

PTC with prominent hobnail features, Warthin – like PTC, mixed papillary and medullary thyroid carcinoma and PTC with dedifferentiation to ATC [6]. FTC is divided into subtypes according to the patterns of growth related to capsular and vascular invasions into minimally invasive follicular carcinoma (MIFC) and widely invasive follicular thyroid carcinoma (WIFC), and according to the World Health Organisation (WHO) Hürthle cell, adenocarcinoma is also included as a variant of FTC [7-9]. Poorly differentiated thyroid carcinoma (PDTC) as a distinct group between differentiated thyroid carcinoma and ATC was originally described in 1983 and included in the WHO classification of thyroid tumours in 2004.

A consensus conference held in Turin in 2006 confirmed geographical differences among claimed forms of PDTC according to suggested diagnostic algorithm based on the presence of a solid/trabecular/insular pattern and high-grade features. Evaluation recognised some overlap with solid and tall cell variants of PTC and FTC with predominant solid and trabecular growth pattern [10]. Insular thyroid carcinoma (ITC) was firstly described in 1984 by Carcangiu et al., as a distinct clinicopathological entity. ITC is characterised by insulae consisted of small, uniform cells sometimes associated with small thyroglobulin-containing follicles and according to its aggressive biology and the worst prognosis is included into the PDTC group of thyroid tumours [11,12]. MTC include sporadic (not inherited), MEN 2A and MEN 2B (multiple endocrine neoplasias, genetic syndromes that involve other parts of the endocrine system), and familial (inherited, but not linked to other MEN-related endocrine tumours). Metastatic thyroid tumours (ms) are also included in thyroid malignancies, mostly resulting from contiguous infiltration from carcinoma of the larynx, oesophagus or by hematogenous dissemination from breast, lung, kidney carcinoma, metastatic deposits from melanoma, etc. [13].

Due to the deficit of state cancer register and absence of published papers about TC in the population of Republic of Macedonia we have set as the objective for our study to analyse the demographic, ultrasound features and the frequency of thyroid carcinomas in the Republic of Macedonia according to histopathological type for the period 1999-2010.

## Materials and Methods

Retrospective analysis of data of all diagnosed and treated patients with TC at the Institute of Pathophysiology and Nuclear Medicine for the period 1999 – 2010 was performed. For the analysed period our Institute was the healthcare institution that

treats most of the patients with thyroid carcinomas. From the total number of diagnosed patients with TC, their demographic characteristics were evaluated: age at diagnosis, gender, histopathological type of TC, while from the clinical features: US findings and thyroid hormonal state at initial examination.

Using the basic demographic indicators from Statistical State Office and data from census in 1994 and 2002 we assessed the yearly incidence rate per 100.000 female and male, differences in incidence rate and prevalence rate of different histopathological types between gender and their distribution in age groups, dividing the patients into four age groups (0-19, 20-40, 41-60 and >61 years). Regional distribution of histopathological types of TC in R Macedonia was analysed also. Incidence and prevalence rate of distinct types of TC were evaluated for eight geographical regions of the whole country according to data from the Republic State Statistical Office from 2009 [14].

Initial US features were analysed, and from the initial US representation were recorded dimensions of the thyroid nodules, echogenicity, the presence of calcifications, enlarged neck lymph nodes and localisation of a tumour. According to the dimensions, thyroid nodules were divided into four groups (occult tumours in the absence of the clearly defined lesion in the thyroid gland, small tumours <15 mm, 15 – 50 mm, gross tumours > 50 mm). Multifocal or multicentric TCs were also described as the distinct group according to findings from the histopathological report. Another described US feature was the echogenicity and according to this characteristic we have described anechoic, hyperechoic, hypoechoic, isoechoic and heterogeneous nodules, also the presence/absence of calcifications, localisation (isthmus, right, left lobe and bilateral) and detection of enlarged neck lymph nodes at the initial representation of the patients.

## Results

A total number of 204 patients with TC in R Macedonia was registered. The Annual incidence rate showed the slight increase of thyroid malignomas comparing with previous studies for the period 1966-1980, with the highest incidence rate in 2000 when  $1.18/10^5$  was recorded. The evaluated prevalence rate for our population increased from  $6.5/10^5$  in 1966-1980 to  $10.15/10^5$  in 1999-2010 [15]. Average disease-specific mortality for the period 1999-2010 was  $0.044/10^5$  [15]. Distribution according to the histopathological type of TC showed that papillary thyroid carcinoma (PTC), for the analysed period including all histopathological variants of PTC was the most frequent with 131 pts (64.21%). From known

histopathological variants of PTC in our population most common was typical PTC with 97 pts (47.55%) then second according to frequency was follicular variant of PTC 29 pts (14.21%), 4 cases (1.96%) PTC with osteoclast-like multinucleated giant cells PTC and PTC with nodular fasciitis-like stroma 1 case (0.49%). Follicular thyroid carcinoma (FTC) with 13 pts (6.37%) was the second thyroid malignoma according to frequency, followed by MTC with 12 pts (5.88%), anaplastic (ATC) 11 pts (5.39%) and rarest types were Hurtle cell variant of follicular carcinoma and intrathyroid sarcoma with only 1 diagnosed patient respectively for the evaluated period (Figure 1).

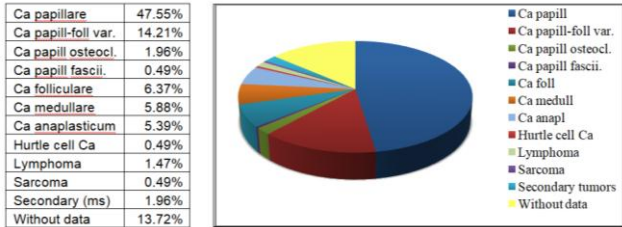


Figure 1: Annual frequency of TC by histopathological type

From the demographic features, we have analysed age of the patients at the time of diagnosis. Age of the patients varies widely from 7 yrs to 88 yrs age (average  $47.9 \pm 16.6$  yrs) (Figure 2a). Annual average age of the patients in the moment of diagnosis was calculated and according to this data youngest patients were diagnosed in 2002 with an average age of 36 years ( $\pm 16.18$ ) and oldest in 2001 with an average age of 57.9 years ( $\pm 10.87$ ) (Figure 2b).

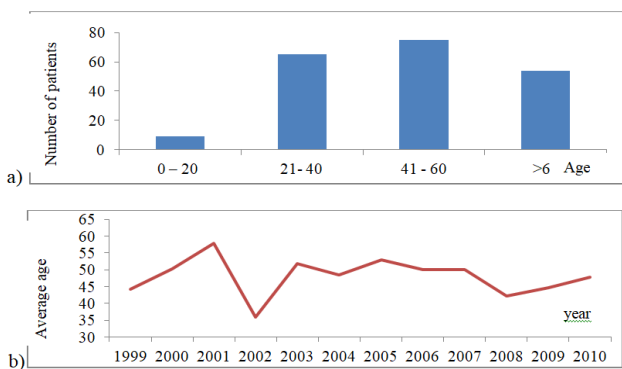


Figure 2: Distribution of TC by age groups. a) Frequency of all TC by age groups; b) Average age of the patients at the diagnosis yearly

Analysis of the distribution of histopathological types by age indicates that PTC was more prevalent in younger age groups, while ATC was diagnosed in age groups above 40 years and the highest frequency above 61 years in elderly patients. The average age for PTC was  $43 (\pm 14.7)$  yrs,  $51.8$  yrs ( $\pm 16.6$ ) for FTC,  $47.5 (\pm 18.9)$  yrs for MTC and  $67 (\pm 8.3)$  yrs for ATC (Figure 3).

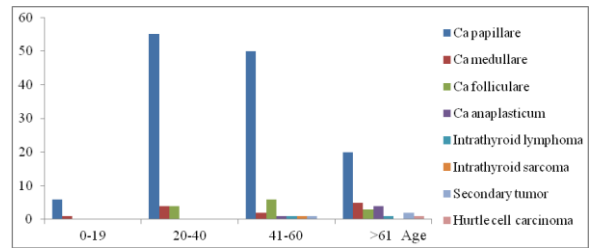


Figure 3: Distribution of different histopathological types by age groups

Age-standardized distribution of TC in both genders indicates that in females TCs were most frequently in age groups from 20-40 years and with almost similar frequency in the age group 41-60, while in male most TCs were distributed in the age group 41-60 and older age above 61 years (Figure 4).

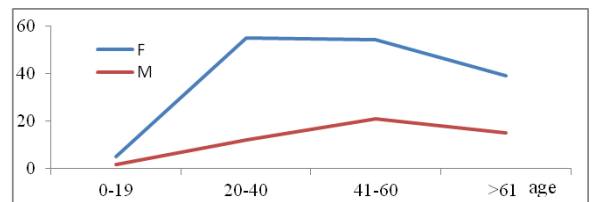


Figure 4: Distribution of TC by gender according to age groups

The incidence rate of TC related to gender was evaluated and around three times higher incidence rate was recorded in female population than a male with the exception in 1999 when slightly higher incidence rate in the male population of  $0.69/10^5$  compared to a female with an incidence rate of  $0.59/10^5$  (Figure 5). Analysis revealed three times higher prevalence rate ( $15.21/10^5$ ) of TC in female compared to ( $5.03/10^5$ ) male gender.

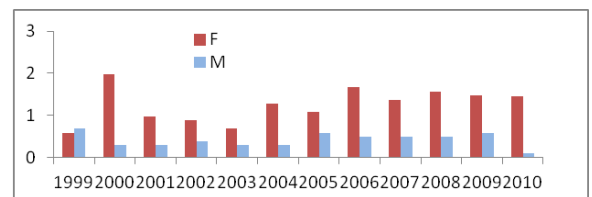


Figure 5: Annual incidence rate by gender/100.000 f/m (1999-2010)

Distribution of histopathological types by gender revealed a similar pattern in female and male population, with PTC type as most frequent in both genders and MTC second most prevalent TC in female and FTC in the male population. Anaplastic thyroid carcinoma was more frequently diagnosed in female than male in our population (Figure 6).

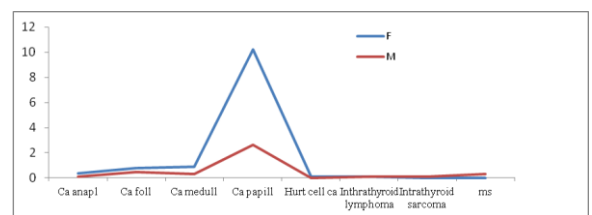


Figure 6: Distribution of different histopathological types by gender

The prevalence rate of TC by gender per 100.000 female and male individuals in eight regions of our country were analysed. In all regions, prevalence rate was higher for female population than male, especially in Vardar region where only female TC pts were diagnosed for the analysed period. The highest prevalence rate for male population was detected in East region, while for a female in Skopje region (Figure 7).

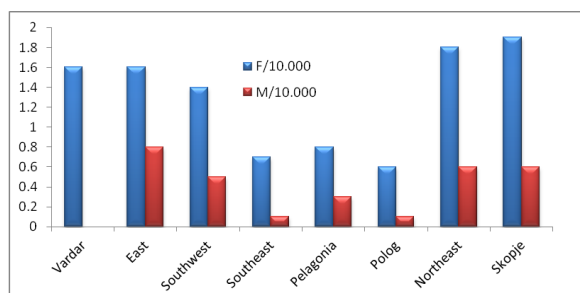


Figure 7: Prevalence rate by gender in eight regions of our country

According to ultrasound (US) appearance of TC at initial presentation, 12 cases were diagnosed as occult thyroid carcinoma because of absence of clearly defined lesion in thyroid gland, 149 pts were with detected thyroid nodules on the US, from which 93 pts were with one nodule, struma nodosa athyreotic (SNE) and 56 pts with multinodular goiter, struma multinodosa athyreotic (SMNE) and 43 pts lacking first US examination descriptions in medical files, mostly due to the fact that their first examination at our Institute was performed after the surgical treatment or TC was incidentally diagnosed after thyroidectomy of multinodular goiter. Another parameter that derived from US examination and additional pathology report features, was the largest diameter of the thyroid nodule at first examination and thereafter at intervention and appropriately according to dimensions we have divided pts in to four groups, respectively as small thyroid tumors less than 15 mm, 15 – 50 mm, large tumors > 50 mm and multifocal carcinoma. Mostly TCs were unilateral and with dimensions from 15 to 50 mm with 42.65% and the rarest were multifocal with 7.84%. According to US appearance, most nodules were described as hypoechoic (29.9%), and with similar representation heterogeneous (29.4%), hyperechoic solid nodules (5%), isoechoic (3.4 %) and rarest anechoic cystic lesions (1.5%), in 30.9% description of echogenicity of the nodule was missing. In 19% of TC presence of calcifications were described. Nodules were usually localised in thyroid lobes more frequently in the right lobe (34.8%), than left lobe (26.5%), rarely with bilateral involvement (8.3%) and lesions with thyroid isthmus involvement with only 4.4%. In 30% of patients on the initial US were detected enlarged neck lymph nodes. According to thyroid hormonal status at initial examination most of the patients were euthyroid 153/204 (75%), subclinical hypothyroidism had 11/204

(5.39%), subclinical hyperthyroidism had 8/204 (3.92%), hyperthyroid state was detected in 4/204 (1.96%) and hypothyroid only in 1/204 (0.49%) (Table 1).

Table 1: The US features at initial examination of diagnosed thyroid carcinomas 1999-2010

Nodules	Pts	(%)	Echogenicity	Pts	(%)
Occult	12	5.88%	Anechoic	3	1.471%
SNE	93	45.59%	Hyperechoic	10	4.902%
SMNE	56	27.45%	Hypoechoic	61	29.902%
Without data	43	21.08%	Isoechoic	7	3.431%
			Heterogeneous	60	29.412%
			Without data	63	30.882%
Dimensions	Pts	(%)	Localisation	pts	(%)
<15 mm	20	9.804%	Isthmic	9	4.412%
15 - 50 mm	87	42.647%	Right lobe	71	34.804%
> 50 mm	23	11.275%	Left lobe	54	26.471%
Multifocal	17	8.333%	Bilateral	17	8.333%
Without data	57	27.941%	Without data	53	25.980%
Neck lymph nodes	Pts	(%)	Calcifications	pts	(%)
Present	55	26.961%	Present	39	19.118%
Without	125	61.275%	Without	165	80.882%
Without data	24	11.765%			

## Discussion

Thyroid carcinoma comprises a spectrum of different tumours with the wide range of biological behaviour and prognosis and from highest priority is the early differential diagnosis, which leads to appropriate treatment of the patient [16]. The importance of epidemiological data is in the possibility of giving the true distribution of the disease in the population and using different scientific methods, which indicate of possible etiological influences in the pathogenesis. Many studies have analysed epidemiological trends in TC. Gathered data showed that as in other countries, in our country there was a trend of increase in the incidence and prevalence rate, compared with the published data for the period 1966-1980, from 6.5/10<sup>5</sup> to 10.15/10<sup>5</sup>, or around 1.6 times increase in prevalence rate between two analysed decades [15, 17]. This prevalence rate is lower than reported in many countries and may be due to environmental, genetic factors or due to underdiagnosis of TC [3- 5].

From all TCs in R Macedonia, PTC predominates with 64.21% representation, females affected more frequently than males in ratio 3.3:1. Cancer gender disparity in incidence, disease aggressiveness and prognosis has been observed for a variety of cancers, and according to literature, thyroid cancer has 2.9-times higher rate in women (data from USA study), but in the literature this gender disparity in TC is also specific to the histologic subtype, data indicates that more aggressive types of TC, ATC and MTC have similar rates of incidence in men and women. Meanwhile, differentiated thyroid cancer of follicular cell origin, such as FTC and PTC, are more common in women [18, 19]. We found same female/male ratio for PTC and MTC 3:1 and even

higher ratio for ATC of 4:1 and almost similar prevalence for FTC by gender. According to V. LiVolsi and other data from the literature, almost 80 – 85% of all TC are PTC, with a female: male ratio varying 2:1 to 4:1 [3, 18, 20]. A similar distribution of histopathological types of TC was described in the Ellis Fischel Cancer Center Registry Data for the period 1998-2012, with registered 57% of PTC in all TC. Furthermore, it is concluded that this frequency of PTC is recorded both in iodine deficiency and iodine sufficiency regions and it is recognised as the most indolent type of TC. Evaluations of epidemiological trends showed that papillary microcarcinomas are more frequently diagnosed. One probability is that global increase in the incidence of TC is due to improved diagnosis of papillary microcarcinomas [21].

The important fact is that papillary carcinomas are also subdivided into different subtypes, with different biological behaviour. In the current study from 204/97 pts or 47.55% were typical PTC, then the second was a follicular variant with 14.21%, 1.96% tall cell and only 0.495 or 1 patient was PTC with nodular fasciitis-like stroma type [20].

Second most common TC is FTC with 6.37% representation of all TC in our population for 1999-2010 periods. In literature, the incidence rate varies greatly from 10 to 32 %, the known environmental factor is dietary iodine intake, and it is recognised that greater frequency of FTC exists in iodine deficiency regions [22]. B. Karanfilski et al. (1990), published data about the distribution of TC for period 1966 – 1988 in our country and according to those data FTC was represented with 17.5% in all TC. We found 2.8 times reduction in the representation of FTC in all TC [17]. This observation is recorded in other studies in countries after the introduction of iodine deficiency correction programs. The territory of R Macedonia was iodine deficient region till 1956 when iodine prophylaxis program was started with the introduction of salt iodination with 10 mg KJ/1kg salt till 1999 when the second program was initiated with 20 - 30 mg KJO<sub>3</sub>/1 kg salt. In 2003 expert team by WHO, UNICEF, ICCID and National Committee conducted an evaluation and concluded in their final report that iodine deficiency in R Macedonia was corrected. Change in iodine intake in the analysed period is a possible mechanism for the lowered frequency of FTC in our population comparing to the study for previous decades [23, 24]. We assume that correction of iodine deficiency in R Macedonia is also the reason for the detected reduction in the frequency of ATC from 17.9% (second commonest) in 1966-1988 to 5.39% in 1999-2010. On the other hand increase in the number of MTC, cases were detected. This increase in MTC, as third most common TC with 5.88%, compared to 2.2% in 1966-1988 published data, may be due to advanced diagnostic facilities.

Age distribution of histopathological types showed younger age at the moment of diagnosis of

PTC, compared to ATC in our study, described in other studies as well. Thyroid cancer is the only malignancy with age as a prognostic indicator included in the staging systems. The theory of the pathogenesis of ATC describes the possibility of development of this poorly differentiated TC from undifferentiated follicular cells of PTC with the process of genetic alterations leading to loss of TSH receptor expression and loss of iodine avidity of a tumour [25].

According to US features and histopathological data, TC was usually unilateral and with dimensions from 15 to 50 mm with 42.65% representation and most rarely was multifocal with 7.84%. Mostly nodules were described as hypoechoic (29.9%) and inhomogeneous (29.4%). 30% of patients were detected with enlarged neck lymph nodes on the initial US. Many studies indicate that detection of nonpalpable thyroid nodules has increased with wider application of US and other imaging modalities [26]. The study revealed mostly thyroid tumours with dimensions from 15 to 50 mm (42.65%), while only 9,8% were smaller than 15 mm. According to literature one of a possible reasons for the increase in the incidence of TC is improved diagnosis of microcarcinomas, less than 1 cm.

From all patients only in 19.11% were described calcifications in the thyroid nodules at initial US examination. According to Hoang et al., one of the most specific US features for malignancy is the presence of calcifications with a described specificity of 85.8%–95% and positive predictive value of 41.8%–94.2% [27, 28]. Microcalcifications represents psammoma bodies and are usually described in PTC, while coarse calcifications more likely to be found in MTC. This discordance between our data and literature may be due to the absence in the detailed description of US examinations according to Thyroid imaging reporting and data system (TIRADS) criteria [29].

In conclusion, there is an increase in the incidence and prevalence rate of TCs in R Macedonia for the period 1999-2010 compared with data from the previous study (1966-1980). According to histopathological type, the most common was PTC, second FTC, and third MTC, followed by ATC and most rare were Hurtle cell adenocarcinoma and intrathyroid sarcoma with only 1 case. Comparing with the data from the previous study for period 1966-1988 in our country, there is a reduction of diagnosed ATC and FTC. We conclude that this change in the distribution of histopathological types may be due to the introduction of iodine prophylaxis and elimination of the problem of iodine deficiency in our country. All histopathological types were more common in females than males, (f/m ratio 3:1). Age-standardized distribution of TC in both genders indicates that in females TCs were more frequently diagnosed in younger age than in males. PTC was usually diagnosed in younger age (average 43 yrs), while ATC was mostly diagnosed in elderly people (average

age at diagnosis 67 yrs). Analyzed US features indicates that introduction of more detailed reporting system may improve the diagnostic accuracy. Further prospective studies with the introduction of TIRADS system on our populations are needed for evaluation of diagnostic accuracy of this method and selecting suspicious thyroid nodules for more detailed examinations.

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