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Article

Differentiated Thyroid Cancer Clinical Trends in Quito, Ecuador

Tendencias clínicas del cáncer diferenciado de tiroides en Quito, Ecuador

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ABSTRACT

Introduction. Thyroid cancer is currently the first most common cancer in women in Ecuador. This study aimed to assess the changes in clinical presentation and diagnosis of differentiated thyroid cancer at a third level hospital in Quito, Ecuador.

Methods and Materials. This is a retrospective case series performed in three consecutive periods from 1990 to 2019 at a tertiary level hospital, in Quito, Ecuador. The clinical records of 875 patients who had been diagnosed and surgically treated for differentiated thyroid cancer were reviewed. Demographic, clinical, imaging, and pathological data were collected and analyzed.

Results. Significant trends toward older age, higher educational level, less palpable primary tumors, less palpable neck nodes, less distant metastases, more ultrasound, tomography and cytology exams, smaller primary tumors, more stage I patients, and more histological variant description, were found.

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Conclusion. The thyroid cancer incidence in Ecuador has not only steadily increased but also the clinical presentation, diagnostic and therapeutic approaches have significantly changed over the last three decades.

Keywords: clinical trends; Thyroid cancer; clinical epidemiology.

1. Introduction

Thyroid cancer is one of the most common malignant neoplasms in many countries around the world as well as in Ecuador. It is the most common endocrine malignancy. A steady increasing incidence has been observed in developed as well as developing countries (IARC, 2020). In the United States, in 2018, the incidence in men and women was 6.6 and 22.3 per 100.000 inhabitants, respectively. In Ecuador, current incidence is 8.2 and 40.9 for both sexes (Cueva P *et al.*, 2019). This incidence in Ecuadorian women is the fifth highest in the world. On the other hand, mortality in men and women has remained low: 0.35 and 0.47 per 100.000 inhabitants in the United States (IARC, 2020) and 1.1 and 2.7, respectively, in Ecuador (Cueva P *et al.*, 2019). In two studies about thyroid cancer burden in in Central and South America (Sierra MS *et al.*, 2016; Da Mota BAK *et al.*, 2017), Ecuador had the highest age-standardized incidence rates in females and males and the highest age-standardized mortality rates per 100,000 person-years, in 2003–2007. While the medical literature about thyroid cancer incidence and mortality trends is profuse, we have not found any study about other demographic and clinical trends, particularly in Latin America. Most clinicians must have observed these changes in their thyroid cancer patients in the last decades. The aim of the present study was to analyze statistically the evolution of these facts in a selected population of Quito, Ecuador, South America.

2. Material and methods

We retrospectively reviewed the HCAM hospital database (MIS-AS400) to retrieve the medical records and imaging studies of 957 individuals with thyroid cancer consecutively admitted and surgically treated at a tertiary level public hospital in Quito Ecuador, from 1990 through 2019. Study population was stratified in three consecutive periods (990-1999; 2000-2009; and 2010-2019).

Our analysis included demographic variables like: age at diagnosis, sex (male or female), race (Mestizo, white, indian and black), since racial disparities are recognized in many different types of cancer, though, most of Ecuadorian population is considered mestizo, a mixed ancestry with a white European and an indigenous background. The level of education was also included to know whether educated people looked for medical attention in earlier thyroid cancer stages.

Thyroid cancer was classified according to the tumor extent (T), regional lymph nodes (N), distant metastasis (M) and tumor stages codes (I, II, III, IV), based on the 8th edition of the American Joint Committee on Cancer (AJCC) Staging (Amin MB *et al.*, 2017). Clinical, pathological and imaging findings were also retrieved from the hospital database not only to describe them but also to look for trends between periods. As a whole, seventeen parameters and their trends trough three decades were analyzed.

Statistical analysis

Patients' demographics, cancer and treatment-related characteristics were compared using chi-square or Fisher's exact test. Categorical variables were presented as percentages and quantitative

variables were represented by their means and standard deviations. A bivariate analysis was performed. After checking for normality assumption, the analysis of variance (ANOVA) was applied. Statistical significance was set at p-value <0.05. All analysis was performed using RStudio software 1.3.959 version.

3. Results

Out of 957 patients, 875 had a pathological diagnosis of differentiated thyroid cancer (DTC): 836 (96%) were papillary, and 36 (4%) follicular. Eighty-two patients were excluded: 71 who had a different pathological diagnosis and 11 with DTC located in the thyroglossal tract or ectopic sites.

Eighty-three percent of patients were women, and sex distribution remained the same throughout the three studied periods. Mean age increased significantly from 43 to 50 years between the former and the latter decade (Table 1). However, in the whole study population, 68% of patients were younger than 55 years of age. Regarding the level of education, there was a significant increase in patients with College education and regarding racial distribution, we observed a considerable rise in mestizo patients (table 1). Ninety-two percent of patients were seen for a thyroid primary tumor, 7% for a locoregional recurrence, and 1% for persistent tumor. Data from these referred patients was incomplete in some of them. Patients seen with recurrence decreased significantly from 14% in the first decade to 4% in the last. The duration of symptoms also considerably reduced during the three periods of time (Table 1).

On physical examination, a palpable lesion was observed in 72% of patients in the first decade and only in 56% in the last. Clinical homolateral neck lymph nodes decreased significantly over the three decades, but contralateral nodes remained stable (Table 1).

The frequency of initial distant metastases (DM) decreased significantly during these periods, from 2.1% to 0.5%. Among 18 patients with DM, 11 had bone and 8 lung metastases. The second primary malignant tumors (SPMT) remained stable. Among 28 (3.2%) SPMT, they occurred previously in 16 cases, simultaneously in 5 and later in 7. Most frequent locations were breast in 6 patients, cervix uteri in 5, and lymphomas in 4.

Table 1.
Demographic and clinical data of patients during the three decades.

Variables	Patients	1990-1999	2000-2009	2011-2019	p
	n (%)	**n** (%)	**n** (%)	**n** (%)	
	875	176	288	411	
Sex					
Female	735 (84)	142 (81)	248 (86)	345 (84)	0.43
Male	140 (16)	34 (19)	40 (14)	66 (16)	
Age					
Mean (SD)	47.7(14.2)	42.9 (15.6)	49.8 (14.7)	47.9 (13.1)	<0.001*
Race†					
Mestizo	797 (92)	142 (81)	261 (91)	394 (97)	<0.001*
Other	70 (8)	34 (19)	25 (9)	13 (3)	
Education level‡					
None	10 (1)	4 (2)	5 (2)	1 (0,3)	<0.001*

Variables	Patients	1990-1999	2000-2009	2011-2019	p
	n (%)	**n (%)**	**n (%)**	**n (%)**	
Primary/ Middle	378 (49)	77 (57)	134 (56)	167 (43)	
College	377 (49)	53 (40)	100 (42)	224 (57)	
Diagnosis					
Initial	810 (92)	152 (86)	268 (93)	390 (95)	<0.001*
Persistence	5 (1)	0	2 (1)	3 (1)	
Recurrence	60 (7)	24 (14)	18 (6)	18 (4)	
Symptoms duration (months)					
Mean (SD)	14 (24.5)	23 (33.0)	14 (25.3)	9 (17.3)	<0.001*
Palpable tumor§					
Yes	625 (72.3)	161 (91.5)	238 (83.8)	226 (55.9)	<0.001*
No	239 (27.7)	15 (8.5)	46 (16.2)	178 (44.1)	
Palpable neck nodes					
Homolateral	119 (13.6)	43 (24.4)	42 (14.6)	34 (8.3)	<0.001*
Contralateral	14 (1.6)	3 (1.7)	5 (1.7)	6 (1.5)	0.97
Initial distant metastases	18 (2.1)	6 (3.5)	10 (3.5)	2 (0.5)	0.01
Second primary tumor	28 (3.2)	6 (3.4)	7 (2.4)	15 (3.6)	0.66

* p between periods
† Available data in 867 patients
‡ Available data in 764 patients
§ Available data in 864 patients

We analyzed complementary exams available on clinical records. Thyroid scans were used until the first decade of this study, and it is not used anymore. Ultrasound has a paramount importance currently and was performed in almost all the patients in the last decade. Computed tomography (CT scan) was used more frequently through the three periods of time, but nuclear magnetic imaging (MRI) only occasionally and fluorodeoxyglucose positron emission tomography (FDG-PET) exceptionally (Table 2). AngioCT on initial evaluation was used in only two patients.

We found a fine needle aspiration (FNA) biopsy report in 88% of cases, more frequently in the last period (Table 3). The Bethesda system for thyroid cytology was published during the second period of this study (Cibas ES *et al.*, 2009), so previous reports were homologated to this system. Interestingly, 9% of patients with DTC had Bethesda I or II, and indeterminate cytology 13.5%.

Table 2.
Complementary evaluation.

Variables	Patients	1990-1999	2000-2009	2011-2019	p
	n(%)	n(%)	n(%)	n(%)	
N	875	176	288	411	
Thyroid scan					
Performed	117 (13.4)	97 (55.1)	18(6.2)	2(0.1)	<0.001
Low uptake	104 (89)				
Normal uptake	7 (6)				
High uptake	1 (1)				
Extrathyroid	4 (4)				
Ultrasound					
Performed	697 (80)	109 (62)	223 (77.4)	365 (88.8)	<0.001
Solid	390 (74)				
Mixed	127 (24)				
Líquid	9 (2)				
Not described	171				
CT	314 (39.5)	16 (9.1)	112 (38.9)	186 (45.3)	<0.001
MRI	6 (0.7)				
FDG-PET	1 (0.1)				
FNA cytology	770 (88)	162 (92)	258 (89.6)	390 (94.9)	0.03
I	26 (3.4)				
II	45 (5.8)				
III	25 (3.2)				
IV	79 (10.3)				
V	148 (19.2)				
VI	447 (58.1)				

A previous biopsy was performed in the neck in 2 patients and the thorax in one patient. A core biopsy was performed elsewhere by another surgeon. A tracheal biopsy through endoscopy was done in another patient for invasive thyroid cancer to the trachea. Finally, an initial later neck lymph node surgical biopsy was performed in 9 cases.

The number of patients with stage I increased significantly from 82% in the first decade to 92% in the last, while those with stages II and IVB decreased significantly (Table 3). Among 18 patients with DM, 9 were included in stage II (younger than 55 years) and 9 in stage IVB (older than 55 years). The distribution of the T category according to stage appears in table 4. Interestingly, among 765 patients with stage I, 129 (17%) had T3a to T4b tumors (>4cm). Among those 18 patients with DM, 5 had T1a to T2, <4cm. Microcarcinomas, T1, <1cm, were found in 210 (24%) patients. Tumors of ≤ 5cm increased significantly through the three periods of time (Table 5). Histological variants were progressively and more frequently described along the three decades (Table 6).

Table 3.
Clinical stage evolution.

Stage	Total (%)	1990-1999	2000-2009	2011-2019	p
N	875	176	288	411	
I	765 (87.4)	145 (82.3)	244 (84.7)	377 (91.7)	0.002
II	58 (6.6)	18 (10.2)	21 (7.3)	18 (4.4)	0.025
III	38 (4.3)	7 (4)	15 (5.2)	16 (3.9)	0.678
IVA	5 (0.6)	2 (1.1)	3 (1)	-	0.106
IVB	9 (1)	4 (2.3)	5 (1.7)	-	0.005

Table 4.
Distribution of T category according to the stage.

Stage	I	II	III	IVA	IVB
0	1				
1a	208	2			
1b	212	3			1
2	215	6			1
3a	70	35			3
3b	17	9			
4a	39	3	38	5	4
4b	3				
Total	765	58	38	5	9

Table 5.
Tumor size evolution.

	n (%)	1990-1999	2000-2009	2011-2019	p
N	875	176	288	411	
≤ 5cm	760 (86.8)	123 (70.0)	250 (86.8)	387 (94.2)	<0.001
> 5cm	115 (13.2)	53 (30.0)	38 (13.2)	24 (5.8)	

Table 6.
Histological variant report evolution.

N	Total (%)	1990-1999	2000-2009	2011-2019	p
	875	176	288	411	
Described	503 (57.5)	36 (20.5)	183 (63.5)	284 (69.1)	<0.001
Not described	140 (42.5)	140 (79.5)	105 (36.5)	127 (30.9)	

4. Discussion

Thyroid cancer incidence has had a substantial increase in the last decades throughout the world. (IARC, 2020). In the United States, it has tripled in 30 years. From 1988 to 1998, it had an annual

percentage increase of 3.0%; it accelerated to 6.7% from 2010 to 2012 and stabilized at 1.75% since 2010. It has been recognized that it is an epidemic of diagnosis more than an epidemic of the disease (Morris LGT *et al.*, 2016). Refinement of indications for biopsy of thyroid nodule included in the 2015 American Thyroid Association guidelines may lead to a decline in reported incidence in the United States, resembling such a reversal in South Korea (Haugen BR *et al.*, 2016; Powers AE *et al.*, 2019). In Switzerland, between 1998 and 2012, the age-standardized rate of papillary carcinoma increased by 10% per year in women and 8% in men, according to data from The National Institute for Cancer Epidemiology and Registration (NICER) (Jegerlehner S *et al*, 2017).

In Ecuador, the National Tumor Registry (NTR), between 1985 and 2013, reported an incidence annual percentage change (APC) of 8.5 in women (significant) and 3.6 in men between 1985 and 2013 (Corral-Cordero F *et al.*, 2018).

On a population basis, in Ecuador, differences of ratios between men and women increased from 1:2 initially to 1:5% (Corral-Cordero F *et al*, 2018; Salazar-Vega J *et al.*, 2019). In our study, the mean ratio of 1:5.2 has not changed significantly over the three decades. Additionally, an 84% frequency in women was similar to the percentage reported by the NTR and slightly higher to the United States´ data, 75% (Corral-Cordero F *et al.*, 2018).

The mean age was 47.7 in our study, similar to the North American series (Lim H *et al.*, 2017; Nixon IJ *et al.*, 2016). Our population of patients younger than 55 years was 68%, somewhat higher than in Japan, 60%, (Ito Y *et al.*, 2018). However, in the last two decades, patients were significantly older than in the first decade. Racial distribution, in our series was similar to the whole country. It had a minor variation over the three decades. The educational level of our patients, however, improved: 57% had university level in the last decade. This change could explain the increase of non-palpable lesions and of smaller tumors throughout the time.

The percentage of patients who attended our service for the first time with locoregional recurrences decreased significantly throughout time. This could be explained by the fact that patients had fewer recurrences, and this, probably due to better management in other medical facilities.

On the other hand, thyroid cancer diagnosis and management have also undergone substantial changes worldwide. A similar fact has happened in Latin America and Ecuador, particularly. These changes also occurred among our patients, covered by the Ecuadorian Social Institute and who attended one of the largest third-level hospitals in this country. The number of patients has increased steadily throughout the last three decades.

Clinically, more patients have nonpalpable thyroid tumors, nonpalpable lateral neck nodes, minor duration of symptoms, and distant metastasis at the first visit. On the contrary, the second primary tumors did not change significantly in their numbers throughout the three decades.

The frequency of metastases at the initial evaluation, 2.1%, was similar to other series. Second primaries, 3.2%, were, on the contrary, less common than in Murray's report, 13.9% (Murray S *et al.*, 2013).

A thyroid scan in search of a cold nodule was obtained in most patients until the first decade of our study. It is not used anymore with the exception of patients with thyroid nodules >1cm and in whom the serum thyrotropin (TSH) is subnormal, to document whether the nodule is hyperfunctioning, is functioning or nonfunctioning. According to the 2015 Guidelines of the American Thyroid Association (Haugen BR *et al.*, 2016), a cytologic evaluation is not necessary for hyperfunctioning nodules since they rarely harbor malignancy (recommendation 2). We have had only one case of PTC in a patient with a hyperfunctioning nodule

Thyroid sonography was increasingly used during the study period, almost 90% in the last decade. Some patients did not have a preoperative ultrasound because their first surgery was performed elsewhere with a CT scan or MRI. CT scan was increasingly used and was indicated, particularly in large tumors. FDG-PET is not recommended for newly detected thyroid nodules or thyroidal illness (Haugen BR *et al.*, 2016). Only one of our patients, this study was prescribed by another physician who evaluated her previously; the report was negative for distant metastases.

Two facts were remarkable concerning the clinical stage. Firstly, Eighty-five percent of our patients were stage I while in the United States 67% of patients were classified at this stage, according to data obtained from the Surveillance, Epidemiology, and End Results-9 (SEER-9) cancer registry program about trends in thyroid cancer incidence, between 1974 and 2013 (113). However, Gan (Gan T *et al.*, 2019), using the SEER-based Kentucky Cancer Registry from 2004 to 2012, reported a change from 80% in the 7th edition to 94% in the 8th edition of the AJCC Sating System for stage I patients, due to downstaging with the new staging system. In the last decade, we had 92% of stage I patients that are similar to the Gan's report. Secondly, stage I increased, and stages II and IVB decreased, both significantly, throughout the three decades in our study. In Lim´s report (Lim H *et al.*, 2017), all stages had a significant annual percentage change. In Switzerland, an absolute increase in the incidence of early stages of thyroid cancer was sharp, especially in women. However, no statistically significant improvement was observed for advanced stages in women, while only a small absolute increase was observed in men (Jegerlehner S *et al.*, 2017).

In our series, 208 (23.8%) patients had microcarcinomas. In the United States, these group of tumors have been estimated to be 30% (Lim H *et al.*, 2017; Al-Qurayshi Z *et al.*, 2020),

An analysis of Surveillance, Epidemiology, and End Results (SEER) cancer registry data from 1980-2005 revealed substantial increases in the incidence of advanced-stage PTCs and PTCs greater than 5 cm in diameter. Because advanced-stage PTC is less amenable to treatment than localized PTC, the increasing mortality rates were considered to be a direct consequence of the trends in advanced-stage PTC (Lim H *et al.*, 2017). In our series, on the contrary, large tumors decreased significantly trough the three decades. Patients with initial distant metastases may have small thyroid primary tumors. Among our 18 PTC with DM, 5 (28%) had intrathyroidal tumors <4cm and one a microcarcinoma. The mean size of the primary thyroid tumor has been described between 3.3 and 4cm (Benbassat CA *et al.*, 2006; ven Velsen EFS *et al.*, 2020; Lin JD *et al.*, 2018) and microcarcinomas in 25% of cases (Benbassat CA *et al.*, 2006).

Our 95% of papillary carcinomas percentage among DTC patients, was similar to the 94% reported by the NTR in Quito, an Andean city of three million inhabitants (Cueva P *et al*, 2019), slightly higher than the 88% of PTC among patients with differentiated thyroid carcinoma in the United States (Lim *et al.*, 2017).

5. Conclusion

Thyroid cancer incidence in Ecuador has not only steadily increased but also the clinical presentation, diagnostic and therapeutic approaches have also changed. In the current study, performed in a third level Latin American hospital, we have found significant trends toward older age, higher educational level, less palpable primary tumors, less palpable neck nodes, less DM, more ultrasound, CT and cytology exams, smaller primary tumors, more stage I patients, and more histological variant description. These findings could be explained by the higher educactional level of our population and an increased access to diagnostic exams.

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RESUMEN

Introducción. El cáncer de tiroides es actualmente el cáncer más frecuente en la mujer en Ecuador. El presente estudio ha tenido como objetivo evaluar los cambios en la presentación clínica y el diagnóstico del cáncer diferenciado de tiroides en un hospital de tercer nivel de Quito, Ecuador.

Material y Métodos. El presente es un estudio retrospectivo de casos realizado en tres períodos consecutivos desde 1990 a 2019 en un hospital del tercer nivel en Quito, Ecuador. Los expedientes clínicos de 875 pacientes tratados quirúrgicamente por un cáncer diferenciado de tiroides fueron revisados. Los datos demográficos, clínicos, de imagen y patología fueron extraídos y analizados.

Resultados. Se encontraron tendencias significativas hacia una edad más avanzada, nivel educativo más alto, menos tumores palpables, menos adenopatías regionales palpables, menos metástasis a distancia, más exámenes de ultrasonido y tomografía, más estudios de citología, más tumores pequeños y pacientes con estadío I y más descripciones de las variantes histológicas.

Conclusiones. El cáncer de tiroides no sólo que ha aumentado continuamente en su frecuencia en los años recientes, sino que la presentación clínica, el manejo diagnóstico y terapéutico ha cambiado significativamente en las tres últimas décadas.

Palabras clave: tendencias clínicas; cáncer de tiroides; epidemiología clínica.