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Differentiated Thyroid Cancer Clinical Trends in Quito, Ecuador

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Abstract

Introduction: Thyroid cancer is the fifth 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: The study was a retrospective case series performed in three consecutive periods from 1990 to 2019 at a tertiary level hospital, Quito Ecuador, where the clinical records of 875 patients who had been diagnosed and surgically treated for differentiated thyroid cancer were retrospectively 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 DM, more ultrasound, CT and cytology exams, smaller primary tumors, more stage I patients, and more histological variant description, were found.

Conclusion: Thyroid cancer has not only steadily increased its incidence in recent years, but the clinical presentation, diagnostic and therapeutic approaches have significantly changed over the last three decades.

Keywords: Differentiated; Thyroid; Cancer; Clinical; Trends

Abbreviations

DTC: Differentiated Thyroid Cancer; DM: Distant Metastases; SPMT: Second Primary Malignant Tumors; CT: Computed Tomography; MRI: Nuclear Magnetic Imaging; FDG-PET: Fluorodeoxyglucose Positron Emission Tomography; FNA: Fine Needle Aspiration; AJCC: American Joint Committee on Cancer; SEER: Surveillance Epidemiology and End Results; NICER: National Institute for Cancer Epidemiology and Registration

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 [1]. 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, the incidence is 6.6 and 35.0 for both sexes [2]. 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 [1] and 0.3 and 1.8, respectively, in Ecuador [2]. Clinical presentation and evaluation changes, including new staging, have occurred during the last years. In the present study, we have analyzed the evolution of these facts in a selected population of Quito, Ecuador, South America.

Methods and Materials

We retrospectively reviewed the medical records and imaging studies of 957 thyroid cancer patients who were consecutively admitted and surgically treated at a tertiary level public hospital in Quito Ecuador in the years 1999-2019. Patients were classified into three consecutive periods: 1990-1999, 2000-2009, and 2010-2019. Demographic variables, clinical, imaging, and pathological findings were retrieved from the hospital database and evaluated, searching for trends between periods. Most patients underwent subtotal or total thyroidectomy. We performed the statistical analysis using RStudio software, version 1.3.959. Categorical variables were expressed as percentages and assessed using $\chi 2$ test. Quantitative variables were represented by their means and standard deviations, after checking for normality assumption and evaluated by Analysis Of Variance (ANOVA). P values, two-tailed, less than 0.05 were considered statistically significant.

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.

Seventeen parameters and their trends trough three decades were analyzed. Eighty-three percent of patients were women, and sex distribution remained the same throughout the three periods of time. Mean age increased significantly from 43 to 50 years between the first and the other two decades (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 a university level of education, and regarding racial

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

	Total (%) 875	1990-1999 176	2000-2009 288	2011-2019 411	p
Sex					
Female	735 (84)	142 (81)	248 (86)	345 (84)	0,4298
Male	140 (16)	34 (19)	40 (14)	66 (16)	
Age					
Mean	47,7	42,9	49,8	47,9	0,00001*
Race**					
Mestizo	797 (92)	142 (81)	261 (91)	394 (97)	<0.0000001
Other	70 (8)	34 (19)	25 (9)	13 (3)	
Education level***					
None	10 (1)	4 (2)	5 (2)	1 (0,3)	0,0000440
Primary/Middle	378 (49)	77 (57)	134 (56)	167 (43)	
University	377 (49)	53 (40)	100 (42)	224 (57)	
Diagnosis					
Initial	810 (92)	152 (86)	268 (93)	390 (95)	0,001377
Persistence	5 (1)	0	2 (1)	3 (1)	
Recurrence	60 (7)	24 (14)	18 (6)	18 (4)	
Symptoms duration (months)					
Mean	14	23	14	9	<0.0001
Palpable tumor****					
Yes	625 (72,3)	161 (91,5)	238 (83,8)	226 (55,9)	<0,0000001
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)	0,000000948
Contralateral	14 (1,6)	3 (1,7)	5 (1,7)	6 (1,5)	0,9662
Initial distant metastases	18 (2,1)	6 (3,5)	10 (3,5)	2 (0,5)	0,008693
Second primary tumor	28 (3,2)	6 (3,4)	7 (2,4)	15 (3,6)	0,6559

*p between 1990-1999 and 2000-2019
**Available data in 867 patients
***Available data in 764 patients
****Available data in 864 patients

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 2: Complementary evaluation.

	Total (%) 875	1990-1999 176	2000-2009 288	2011-2019 411	p
Thyroid scan					
Performed	117 (13,4)	97 (55,1)	18(6,2)	2(0,1)	<0,0000001
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)	<0,0000001
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)	<0,0000001
MRI	6 (0,7)				
FDG-PET	1 (0,1)				
Citología por PAAF					
Realizada	770 (88)	162 (92)	258 (89,6)	390 (94,9)	0,02983
I	26 (3,4)				
II	45 (5,8)				
III	25 (3,2)				
IV	79 (10,3)				
V	148 (19,2)				
VI	447 (58,1)				

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) 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 [3], so previous reports were homologated to this system. Interestingly, 9% of patients with DTC had Bethesda I or II, and indeterminate cytology 13.5%.

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.

Table 3: Clinical stage evolution.

Stage	Total (%) 875	1990-1999 176	2000-2009 288	2011-2019 411	p
I	765 (87,4)	145 (82,3)	244 (84,7)	377 (91,7)	0,001510
II	58 (6,6)	18 (10,2)	21 (7,3)	18 (4,4)	0,02541
III	38 (4,3)	7 (4)	15 (5,2)	16 (3,9)	0,6787
IVA	5 (0,6)	2 (1,1)	3 (1)	-	0,1056
IVB	9 (1)	4 (2,3)	5 (1,7)	-	0,005517

Table 4: Distribution of T category according to the 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.

	Total (%) 875	1990-1999 176	2000-2009 288	2011-2019 411	p
≤ 5cm	760	123 (70.0)	250 (86.8)	387 (94.2)	<0,0000001
> 5cm	115	53 (30.0)	38 (13.2)	24 (5.8)	

Table 6: Histological variant report evolution.

	Total (%) 875	1990-1999 176	2000-2009 288	2011-2019 411	p
Described	503 (57,5)	36 (20,5)	183 (63,5)	284 (69,1)	<0,0000001
Not described	140 (42,5)	140 (79,5)	105 (36,5)	127 (30,9)	

For staging, we used the 8th edition of the American Joint Committee on Cancer (AJCC) Staging System [4]. 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).

Discussion

Thyroid cancer incidence has had a substantial increase in the last decades throughout the world [1]. 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 [5]. 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 [6,7]. 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) [8].

In Ecuador, the National Tumor Registry (NTR), between 1985 and 2013, reported an Annual Percentage Change (APC) of 8.5 in women (significant) and 3.6 in men between 1985 and 2013 [9]. These figures are among the highest in Latin America, after Argentina: 17.9 and -2.0 in Argentina, 8.5 and 4.7 in Costa Rica, 6.2 and 5.5 in Brazil and 6.2 and -1.4 in Chile, for females and males, respectively [10].

On a population basis, in Ecuador, differences of ratios between men and women increased from 1:2 initially to 1:5% [9,11]. 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% [12].

The mean age was 47.7 in our study, similar to the North American series [12,13]. Our population of patients younger than 55 years was 68%, somewhat higher than in Japan, 60% [14]. However, in the last two decades, patients were significantly older than in the first decade. Racial distribution, in our series as in the whole country, has a minor variation over the three decades. The educational level of our patients, however, improved: 57% had university level in the last decade.

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% [15].

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 [6], 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 or MRI. CT was increasingly used and was indicated, particularly in large tumors. FDG-PET is not recommended for newly detected thyroid nodules or thyroidal illness [6]. 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 [11]. However, Gan [16], 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 down staging 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 [12], 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 [8].

In our series, 208 (23.8%) patients had microcarcinomas. In the United States, these group of tumors have been estimated to be 30% [12,17].

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 [12]. 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 [18-20] and microcarcinomas in 25% of cases [18].

Our 95% of papillary carcinomas percentage among DTC patients, was similar to the 94% reported by NTR in Quito, an Andean city of three million inhabitants [2], slightly higher than the 88% of PTC among patients with differentiated thyroid carcinoma in the United States [12].

Conclusion

Thyroid cancer has not only steadily increased its incidence in recent years, but the clinical presentation, diagnostic and therapeutic approaches have importantly 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.

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