

## Factors associated with advanced thyroid cancer in pediatric patients in a high specialty medical unit in Northeast Mexico

Lizbeth Ariana García-Castillo, Ana Laura Bahena-García\*, Luz María Sánchez-Sánchez and Gerardo del Carmen Palacios-Saucedo

Pediatrics Department, UMAE No. 25, Centro Médico Nacional del Noreste, Monterrey, N.L., México

### Abstract

**Introduction:** Thyroid cancer represents 2% of all childhood malignances. Its incidence rises 1.1% per year. In comparison with adults, childhood thyroid cancer is detected in a more advanced stage, but with a survival rate above 95%. The objective of this study was to evaluate whether there are factors associated with advanced stages of thyroid cancer in pediatric patients.

**Results.** Nineteen patients were included, 13 (68.4%) were female and six male, all between 7-15 years, with a median of 11 years. Fifteen in advanced and four in early stage. The median age of patients in advanced stage at time of diagnosis was 10.6 years (7-15) and 13.2 (12-14) were in early stage ( $p = 0.075$ ). There was a delay of nine months to get a diagnosis in advanced stage, and 7.2 in early stage ( $p = 0.931$ ). Three of the patients with advanced stage and two with early stage were from Nuevo León (Mexico) and the rest were foreign ( $p = 0.567$ ). In the group with advanced stage, two had thyroid cancer familiar history, and none in the early stage group ( $p = 0.452$ ). Nine patients in advanced stage and three in early stage presented thyroid nodule as the first sign of illness. Six patients in advanced stage and one in early stage presented goiter ( $p = 0.590$ ). None of the studied patients had radiation history. Six patients in advanced stage and one in early stage suffered from Hashimoto's Thyroiditis ( $p = 0.590$ ). Eleven in advanced stage and one in early stage had papillary histologic variety. Four in advanced stage and three in early stage had papillary histologic variety with a follicular pattern ( $p = 0.083$ ). Eight patients presented lung metastasis at time of diagnosis ( $p = 0.061$ ). **Conclusions:** There are no factors associated with advanced stage thyroid cancer in pediatric populations. Although half of studied patients presented lung metastasis, treatment response and survival is satisfactory. (Gac Med Mex. 2015;151:674-7)

**Corresponding author:** Ana Laura Bahena García, ana.bahena3@gmail.com

**KEY WORDS:** Thyroid cancer. Associated factor. Advanced stage.

### Introduction

Thyroid cancer is relatively uncommon during childhood and adolescence. In spite of having a survival rate higher than 95%, it is often more advanced than in adults. The prevalence of most common distant

metastasis at the pulmonary level is 20-30%, it has higher numbers of regional recurrences and its treatment may lead to a higher number of complications but with less mortality and better prognosis than in adults<sup>1-4</sup>.

Among the factors described as predisposing to the development of thyroid carcinoma, the following stand out: previous exposure to radiation, chemotherapy,

#### Correspondence:

\*Ana Laura Bahena-García  
Servicio de Pediatría  
UMAE No. 25  
Centro Médico Nacional del Noreste  
Av. Lincoln y Gonzalitos, s/n  
Col. Morelos, C.P. 64180, Monterrey, N.L., México  
E-mail: ana.bahena3@gmail.com

Date of reception: 21-11-2014

Date of acceptance: 06-01-2015

autoimmune thyroid disease, originating from a geographical zone with iodine deficiency and some hereditary syndromes<sup>7</sup>.

The most common presentation form in children is as a single mass in up to 60% of cases and less frequently as multinodular goiter. In the pediatric patient, the thyroid nodule represents higher risk for thyroid carcinoma than in adults and, therefore, its detection mandates searching for thyroid cancer. The diagnostic approach includes TSH determination, thyroid ultrasound (US) and a fine needle aspiration biopsy (FNAB). Once the diagnosis is confirmed, the disease has to be staged. Distant metastases assessment depends on locoregional involvement; stages I and II are classified as early stage and stages III and IV as advanced stage<sup>4-11</sup>.

In children, total thyroidectomy is recommended as treatment option, since there is local recurrence reduction, enables treatment with radioactive iodine for the management of microscopic disease and allows for follow-up with thyroglobulin to be carried out<sup>5</sup>.

In pediatrics, no prognostic or advanced disease-associated factors have been described; in adults, patient and disease characteristics have been analyzed trying to differentiate patients at higher risk, including tumor size, gender, family history of thyroid cancer, previous cervical radiotherapy, distant metastases, histological features, diagnosis or treatment initiation delay, and it is concluded that stages III and IV, as well as the presence of metastasis or not, constitute the most important poor prognosis factors<sup>15</sup>.

## Material and methods

A retrospective, cross-sectional, analytical observational study was conducted, where clinical records of pediatric patients diagnosed with thyroid cancer being followed-up by the pediatric endocrinology outpatient unit were reviewed in order to determine if there were advanced stage thyroid cancer-associated factors.

In all patients with that diagnosis, the following was analyzed: place of origin, family history of thyroid cancer, age at diagnosis, time of diagnosis delay, taken as the time elapsed since the initial clinical manifestation to the date the diagnosis was established, sex, clinical initial manifestations, association with thyroid autoimmune diseases, prior history of exposure to radiation, tumor histology, stage of the disease and presence of pulmonary metastases at diagnosis. Patients at early stage were compared with those who were at advanced stage at diagnosis. Statistical data were analyzed using absolute and relative frequencies, as well as central tendency and dispersion measures.

For analysis, descriptive statistics and the chi-square test were used to determine the odds ratio (OR) with a 95% confidence interval (CI), and a p-value < 0.05 was considered to be a statistically significant difference.

## Results

Nineteen thyroid cancer-diagnosed pediatric patients on follow-up by the pediatric oncology outpatient clinic were included, 13 (68.4%) of the female and 6 (31.5%) of the male gender, with ages ranging from 7 to 15 years (median: 11 years). For their study, they were divided into 2 groups, taking into account the stage at diagnosis of the disease (stages III and IV were considered as advanced stages and stages I and II were regarded as early stages): 15 (78.9%) patients were at advanced stage and 4 (21%) were at early stage at diagnosis.

In the group with advanced stage, 9 (60%) patients were of the female sex versus 4 (100%) in the early stage group ( $p = 0.355$ ). In the advanced stage group, median age was 10.6 years (7-15), and in the early stage group, 13.25 years (12-14) ( $p = 0.075$ ), with median time elapsed from the onset of symptoms to the date of diagnosis of 9 months (0-30) in the advanced stage group and 7.25 months (2-13) in the early stage group ( $p = 0.931$ ).

With regard to the place of origin, most patients came from 3 States: 3 patients (20%) in the advanced stage group were from Nuevo León, as were 2 (50%) in the early stage group ( $p = 0.567$ ); 3 patients (20%) in the advanced stage group and 1 patient (25%) in the early stage group were from San Luis Potosí ( $p = 0.636$ ); and 6 patients (40%) in the advanced disease group and none in the early stage group came from Tamaulipas ( $p = 0.355$ ).

As for family history of thyroid cancer, 2 patients (13.3%) in the advanced stage group had some, but none in the advanced stage group ( $p = 0.452$ ). With regard to the form of presentation, 9 patients (60%) in the advanced stage group versus 3 (75%) in the early stage group had thyroid nodule; 6 patients (40%) in the advanced stage group versus 1 (25%) in the early stage group had advanced goiter ( $p = 0.590$ ). No patient had previous history of external radiation.

Regarding the association with autoimmune diseases, 6 patients (40%) in the advanced stage group versus 1 (25%) in the early stage group had Hashimoto's thyroiditis diagnosis ( $p = 0.590$ ). With regard to histology, 11 patients (73.3%) in the advanced stage group had papillary type versus 1 (25%) in the early stage group; 4 patients (26.6%) in the advanced stage group had the papillary variety with follicular pattern

versus 3 (75%) in the early stage group ( $p = 0.083$ ). In the advanced stage group, 8 patients (53.3%) had pulmonary metastases at diagnosis ( $p = 0.061$ ).

## Discussion

Thyroid cancer is an uncommon disease in pediatric patients: it accounts for less than 3% of all malignancies in this age group. Diana L. Diesen et al. describe that its incidence increases 1.1% annually. Thyroid carcinoma in pediatric patients is different from that in adults in clinical manifestations and results. In spite of having a survival rate higher than 95%, childhood thyroid cancer is often more advanced, with higher rates of recurrence and its treatment may lead to a higher number of complications, but with less mortality<sup>1-4</sup>.

In children younger than 10 years, incidence is 1 case per 1,000,000, and in children from 10 to 14 years of age, 1 case for each 200,000; after puberty, girls have 4 times more possibilities of having thyroid differentiated carcinoma than boys, which is related to estrogen sensitivity of the thyroid gland. In this study, median age was 11 years, a number that supports reports by other authors<sup>1,3</sup>.

Aleida Rivera et al., in a study conducted at the Centro Médico Nacional de Pediatría Siglo XXI, refer a predominance in the female sex of 1.6:1. In this case series, higher prevalence was found in the female gender, with a 2.1:1 ratio, very similar to the findings in this Mexican study and in those by other international authors.

Among the factors described by multiple authors as predisposing for the development of thyroid carcinoma, prior exposure to radiation and chemotherapy associated to successful treatment of other childhood malignancies stand out, but none of the patients in this study had this type of previous history.

An association with immune disease, especially Hashimoto's thyroiditis, has been also reported<sup>6,8,10</sup>. Two patients diagnosed at advanced stages of the disease and none of the children diagnosed at early stage had this previous history, but there was no statistical difference.

Other predisposing factors include originating from a geographical zone with iodine deficiency and some hereditary syndromes<sup>7</sup>. In the studied patients, no differences were found with regard to the place of origin. Of note, 6 of the 14 foreign patients were from Tamaulipas and all had advanced stage at diagnosis. However, a significant association with the place of origin of these patients could not be documented.

Family history has been associated with different types of thyroid cancer; nevertheless, most patients have no family history of the disease<sup>14</sup>. In this case series, previous history of thyroid cancer was documented in 2 patients at advanced stage, with no statistically significant differences being found.

Thyroid carcinoma most common form of presentation in children is as a thyroid-located single mass (in up to 60% of cases) and, less frequently, as multinodular goiter<sup>2,7</sup>. In the present study, 63% of patients were found to have thyroid nodule as initial clinical manifestation, a similar percentage to that reported in the literature, but this finding could not be documented in relation to the advanced stages of thyroid cancer. Nevertheless, the presence of a thyroid nodule in childhood mandates for the possibility of cancer to be ruled out.

The diagnostic approach includes TSH determination, thyroid US and performing a FNAB<sup>4</sup>. Once the diagnosis is confirmed, the disease has to be staged. In most cases, physical examination and ultrasound are enough to determine primary tumor extension. Assessment of distant metastases depends on locoregional involvement<sup>11</sup>. Most cases of thyroid cancer in children are of the papillary histological type (approximately 75-80% of cases<sup>6</sup>). In this case series, all children had a papillary histology biopsy report, but 7 had follicular pattern as well. Histological type was not a factor associated with thyroid cancer advanced stages in the children included in this study.

Thyroid carcinoma tends to be more aggressive in pediatric than in adult populations. From 10 to 30% cases have been described in the literature as having pulmonary metastases at diagnosis<sup>16</sup>. In the patients included in this study, the incidence of pulmonary metastases at diagnosis is higher than that reported in other studies, reaching over 50%, which may be owing to the fact that the primary care physician generally omits thyroid examination in children or is unaware that thyroid cancer is a disease that also occurs at pediatric ages and, therefore, there is a delay in the reference of the patient to a tertiary care center with the endocrinology specialist.

With regard to factors associated with advanced stage, there are no studies describing them in the pediatric population; in adults, to try to differentiate the patients at higher risk, some characteristics of the patient and the disease have been analyzed, such as tumor size, gender, family history of thyroid cancer, previous history of cervical radiotherapy, distant metastases, histological characteristics, diagnosis or treatment initiation delay, and it has been concluded that stages III and IV and the presence of metastases

**Table 1. Clinical and histopathological characteristics of 19 pediatric patients with thyroid cancer under the care of a High Specialty Medical Unit of Northeast Mexico**

	Advanced stages (n = 15)	Early stages (n = 4)	p
Sex			0.355
Male	6 (40%)	0	
Female	9 (60%)	4 (100%)	
Age (years)	10.6 (7-15)	13.2 (12-14)	0.075
Time of diagnosis delay (months)	9 (0-30)	7.2 (1-13)	0.931
Origin			
Nuevo León	3 (20%)	2 (50%)	0.567
San Luis Potosí	3 (20%)	1 (25%)	0.636
Tamaulipas	6 (40%)	0	0.355
Coahuila	2 (13.3%)	1 (25%)	0.839
Zacatecas	1 (16.6%)	0	0.465
History of thyroid cancer	2 (13.3%)	0	0.452
Presentation form			
Nodule	9 (60%)	3 (75%)	0.590
Goiter	6 (40%)	1 (25%)	
Previous history of radiation	0	0	
Autoimmune thyroiditis	6 (40%)	1 (25%)	0.590
Histological variety			
Papillary	11 (73.3%)	1 (25%)	0.083
Papillary/follicular	4 (26.6%)	3 (75%)	
Pulmonary metastases at diagnosis	8 (53.3%)	0	0.061

or not are the most important factors<sup>15</sup>. The prognosis of thyroid carcinoma is generally good for the pediatric population. Cáceres et al. describe a survival rate higher than 90%<sup>6</sup>. In this case series, almost 80% had advanced stage disease detected, and out of these, half had had pulmonary metastases at diagnosis; but, in spite of prognosis being unfavorable, survival has been good.

Thyroid cancer is not such an infrequent disease in the pediatric population; when this group of patients was analyzed, similar statistics to those described in the literature were documented. Of note, in the studied population, the presence of pulmonary metastases was the double to that previously described, which could be because the primary care physician is unaware of the magnitude of this disease and there is a delay in the reference of the patient to a tertiary care center. Fortunately, in the patients included in the study, this has so far not had an impact on survival, since all of them are still alive after surgical treatment and medical therapy with radioactive iodine, and continue on follow-up by the endocrinology outpatient clinic (Table 1).

## References

- Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE. Pediatric Thyroid Carcinoma: Incidence and outcomes en 1753 patients. *J Surg Res.* 2009;156(1):167-72.
- Park S, Jeong JS, Ryu HR, et al. Differentiated thyroid carcinoma of children and adolescent 27-year experience in the yonsei university health system. *J Korean Med Sci.* 2013;28(5):693-9.
- Rivkees SA, Mazzaferri EL, Verburg FA, et al. The treatment of differentiated thyroid cancer in children: emphasis on surgical approach and radioactive iodine therapy. *Endocr Rev.* 2011;32(6):798-826.
- Tubiana M, Schlumberger M, Rougier P, et al. Long term results and prognosis factors in patients whit differentiated thyroid carcinoma. *Cancer.* 1985;55(4):794-804.
- Sosa JA, Tuggle CT, Wang TS, et al. Clinical and economic outcomes of thyroid and parathyroid surgery in children. *J Clin Endocrinol Metab.* 2008;93(8):3058-65.
- Cáceres F, Vancells M, Cruz O, et al. [Thyroid carcinoma in pediatrics: a 30-year follow-up]. *Cir Pediatr.* 2010;23:229-35.
- Rodríguez Sánchez, Roldán Martín B, Rodríguez Arnao D. Patología tiroidea. *Pediatr Integral.* 2007;XI:581-92.
- Palmer BA, Zarroug AE, Poley RN, Kollars JP, Moir CR. Papillary thyroid carcinoma en children: Risk factors and complications of disease recurrence. *J Pediatr Surg.* 2005;40(8):1284-8.
- Hernán González D, Mosso L. Cáncer papilar de tiroides: visión actual. *Boletín de la Escuela de Medicina.* 2006;31(3).
- Goldust M, Sokouti M, Montazeri V, Fakhrijo A, Samankan S. A clinical epidemiologic study of thyroid carcinoma in patients under 25 years old in Tabriz, Iran (1995-2010). *J Pak Med Assoc.* 2012;62(11):1265-8.
- Oyarzábal M, Chueca M, Berrade S. Nódulo tiroideo en la infancia.
- Guía de práctica clínica. Diagnóstico y tratamiento del tumor maligno de tiroides.
- Holcomb III GW, Murphy P. Ashcraft's pediatric surgery. 5.ª ed. p. 1037-42.
- American Cancer Society. Cáncer de tiroides.
- Gonzalez JM, Cajas P. Factores pronósticos en cáncer diferenciado de tiroides.