J Pediatr Endocr Met 2011;24(9-10):743–748 © 2011 by Walter de Gruyter • Berlin • Boston. DOI 10.1515/JPEM.2011.241

Differentiated thyroid carcinoma: presentation and follow-up in children and adolescents

Patricia Papendieck[1,*], Laura Gruñeiro-Papendieck[1], Marcela Venara[1], Oscar Acha[2], Silvana Maglio[3], Ignacio Bergadá[1] and Ana Chiesa[1]

[1] Endocrinology Division, Centro de Investigaciones Endocrinológicas (CEDIE), Ricardo Gutiérrez Children's Hospital, Buenos Aires, Argentina
[2] Surgery Department, Ricardo Gutiérrez Children's Hospital, Buenos Aires, Argentina
[3] Pathology Department, Ricardo Gutiérrez Children's Hospital, Buenos Aires, Argentina

Abstract

To review our Pediatric Endocrinology Division's experience with differentiated thyroid carcinoma (DTC) we analyzed retrospectively the records of patients with DTC that had been seen between June 1988 and June 2008.

Results: Forty-five patients (median age 13.7 years, 36 female) were diagnosed (papillary: 40, follicular: 5) with DTC presenting as a solitary nodule (n: 25), thyroid nodule with cervical adenopathy (n: 9) and multinodular goiter (n: 11). All underwent total thyroidectomy with resection of suspicious cervical lymph nodes (CLN). DTC was multicentric in 59% and revealed extrathyroidal extension in 44%. Initially, 44% had CLN metastases and 24% distant metastases. All patients underwent thyroid remnant ablation with ^{131}I and suppressive treatment. Median follow-up was 5.1 years with a disease-free survival rate at 5 years of follow-up of 75%. Eleven percent presented recurrences.

Conclusion: Pediatric DTC has an aggressive behavior at presentation. Higher preoperative TSH levels were significantly associated with a more advanced disease at diagnosis. CLT was present concomitantly in a quarter of the patients and further studies are needed to establish differences in these patients' outcome. Diagnostic approach, total thyroidectomy, ^{131}I treatment and thyrotropin suppression allowed a good progression-free survival rate.

Keywords: adolescence; childhood; differentiated thyroid carcinoma; follicular carcinoma; follow-up papillary carcinoma; radioactive iodine; thyroidectomy; thyrotropin stimulating hormone.

*Corresponding author. Patricia Papendieck MD, Gallo 1360 1425 Buenos Aries, Argentina
Phone: +541149635931, Fax: +0541149635930,
E-mail: patopapen@yahoo.com.ar
Received April 1, 2011; accepted July 29, 2011; previously published online September 20, 2011

Introduction

Differentiated thyroid carcinoma (DTC) is an uncommon pediatric malignancy, accounting for 1% of pediatric cancers in prepubertal children. The incidence of DTC rises to 7% in adolescents aged 15–19 years old. Nevertheless DTC is the most frequent endocrine cancer in childhood, with an increasing overall incidence in recent decades (1–7).

Papillary DTC is the most common subtype, being mostly sporadic with only 5% of cases inherited or familiarly associated to known germline mutations as Familial Colonic Polyposis, Cowden Disease and Werner Syndrome (8).

Previous neck and head radiation exposure, previous neoplasia and autoimmune thyroid disease are known risk factors.

Childhood onset DTC has a more aggressive presentation at initial evaluation, but no overall increase in mortality, compared to adults (3).

Up to now, the best treatment option for DTC has been total thyroidectomy followed by postoperative administration of radioactive iodine, based on the capacity of follicular thyroid cells to trap iodide (1–5).

Evidence-based guidelines for the management of thyroid cancer published by the American Thyroid Association refer primarily to adult populations and include limited references to children (9). The purpose of this report is to present the clinical diagnostic features, treatment and outcome of a large cohort of pediatric patients with DTC followed up at a pediatric endocrine tertiary care center during the last 20 years.

Materials and methods

We analyzed retrospectively the clinical charts and pathological reports of patients with a diagnosis of DTC treated at the Division of Endocrinology of our Institution between June 1988 and June 2008. Cases of medullary DTC were excluded.

Demographic and clinical data registered at diagnosis include gender, age, pubertal stage, predisposing risk factors, clinical findings, thyroid function – performed by measurement of serum thyrotropin stimulating hormone (TSH) (normal values: 0.5–5 mUI/L), total thyroxine (T4) (nv: 77–206 nmol/L), free thyroxine (fT4) (nv: 10–26 pmol/L) by EQLIA (Roche), thyroglobulin (TG) by IFMA Delfia (Perkin-Elmer) and antithyroidal antibodies against thyroperoxidase (TPOAb) and antithyroidal antibodies against thyroglobulin (TGAb) by Immulite DPC (Los Angeles, CA, USA). Diagnostic procedures as ultrasound (US), thyroid ^{99m}Tc scan and fine needle aspiration biopsy (FNAB) were also registered.

FNAB interpretation was performed by a cytopathologist with experience in thyroid cytology. Cytological results were categorized in four types: 1) malignant (positive for papillary thyroid carcinoma), 2) indeterminate (follicular or Hürthle cell neoplasia suspicious for malignancy), 3) benign (chronic lymphocytic thyroiditis, subacute thyroiditis, colloid cyst, normal follicular thyroid cells) and

4) non-diagnostic or inadequate for diagnosis (insufficient or hemorrhagic sample) (10).

All patients underwent total thyroidectomy with cervical lymphadenectomy when enlarged lymph nodes were present, and postoperative ^{131}I therapy was administered for thyroid remnant ablation, followed by thyrotropin-suppressive doses of L-thyroxine (LT4).

Postoperative complications as hematoma, vocal cord paralysis secondary to the lesion of the recurrent laryngeal nerve and hypocalcemia due to hypoparathyroidism were registered.

Anatomopathologycal data on removed tumor included histologic type, size, presence of microscopic neoplastic foci in the thyroid parenchyma outside the main nodule (multicentricity), vascular and/or capsular infiltration, invasion of perithyroidal tissues, cervical lymph node (CLN) metastases, and chronic lymphocytic thyroiditis (CLT) coexistence.

Four to 6 weeks after surgery all the patients received an ablative ^{131}I dose fixed according to the extent of the disease (100 mCi for tumors limited to the thyroid gland, 150 mCi for tumors invading the thyroid capsule, surrounding tissues and/or with CLN metastases, and 200 mCi for distant metastases) and adjusted to body surface area (3).

Follow-up consisted in periodic detailed clinical examinations, measurement of TSH to check adequate suppression and serum TG every 3–6 months. LT4 treatment was withdrawn every 6 months for the first 2 years and then annually to perform diagnostic whole body scan (WBS) with ^{131}I (2–5mCi) and serum TG levels.

In assessing the outcome, the state of no evidence of disease (NED) was defined as neither clinical nor imaging evidence of disease (no uptake on WBS and, when available, US) nor undetectable serum TG (baseline and stimulated) in the absence of TGAb. Recurrence was considered when an elevated stimulated TG or a positive ^{131}I uptake was found in a patient known to be NED for at least 6 months.

The extent of disease at initial treatment was determined by US, chest radiography and/or chest tomography without contrast, pathological report and WBS after ^{131}I ablative dose.

Number of doses of ^{131}I needed to achieve NED state, ^{131}I complications, recurrences and follow-up were recorded.

Diagnosis of coexisting CLT was based on anatomopathological findings. The patients with coexisting CLT were analyzed separately and compared to the group of patients without CLT.

The retrospective study was approved by the Ethical Committee of Ricardo Gutierrez Children's Hospital, Buenos Aires.

Statistical methods

Demographic variables were analyzed with simple descriptive statistics.

The disease-free survival rate at 3 and 5 years of follow-up was evaluated with the Kaplan-Meier survival curve.

Differences between patient groups with and without CLT were tested with χ^2-test. Median preoperative TSH level in patients with and without CLN metastases were compared with Mann-Whitney non-parametric Test. Differences were considered statistically significant with a probability of occurrence <0.05 (Infostat).

Results

Forty-five patients with DTC were diagnosed throughout the study period. Demographics and clinical characteristics at diagnosis are shown in Table 1 and Figure 1.

Of the 45 patients younger than 20 years with DTC, 80% were girls and 84.4% were pubertal. Figure 1 shows gender and age distribution of DTC patients at presentation. DTC was more prevalent between 10 and 18 years, but present in both genders since the age of 8 years. Only one girl presented with DTC at 6.2 years of age. A female predominance was found at all ages: 5:1 for 5–9 years, 3:1 for 10–14 years and 5.3:1 for patients >15 years.

Risk factors found were autoimmune thyroid disease in 12, previous neck radiation therapy in one patient due to a non-Hodgkin's lymphoma of the cavum (neck radiation dose 30 Gy) and previous non-thyroid neoplasia in four (two acute lymphoblastic leukemia, one non-Hodgkin's lymphoma and one rhabdomyosarcoma). One patient with papillary DTC had a family history of papillary DTC affecting her mother. No patient had a family history of genetic syndromes predisposing for DTC.

DTC presented as a solitary thyroid nodule in 55.5% of the patients, 20% had a thyroid nodule with enlarged CLN and 24.5% MNG.

Thyroid function evaluated at diagnosis in 35 patients showed normal thyroid function in 88.6% of the patients, hypothyroidism and subclinical hyperthyroidism (suppressed TSH with normal peripheral thyroid hormones) in 5.7%. Median TSH levels were 2.21 mUI/L (range 0.01–10.7). The median preoperative TSH level was 1.70 mUI/L (range 0.01–6.52) in patients without CLN vs. 2.78 mUI/L (range 0.45–10.70) in patients with CLN metastases ($p<0.05$).

Most of the patients were preoperatively evaluated by ^{99m}Tc thyroid scan and 39 underwent conventional cervical US performed by different operators at different centers. All nodules were cold on thyroid scan. Nodule characteristics on US were described as solid in 32 patients (82%), solitary in 27 (69.2%), heterogeneous in 11 (28.2%), multiple in 10 (25.6%), hypoechogenic in nine (23%), solid-cystic (predominantly solid) in five (12.8%), with irregular margins in five (12.8%), with pathological CLN in five (12.8%), with

Table 1 Demographic and clinical characteristics of 45 patients with DTC at diagnosis.

	n	%
Gender ♀/♂	36/9	
Age (years, median-range)	13.7 (6.2–19.6)	
Pubertal	38/45	84.4
Previous history		
Autoimmune thyroid disease	12	26.6
Neck radiotherapy	1	
Other neoplasia	4	
Presentation		
Solitary nodule	25	55.5
Nodule+cervical lymph nodes	9	20
Multinodular goiter	11	24.5
TSH (mU/L, median) (n:35)	2.21	
Normal thyroid function	31	
Hypothyroidism	2	
Subclinical hyperthyroidism	2	

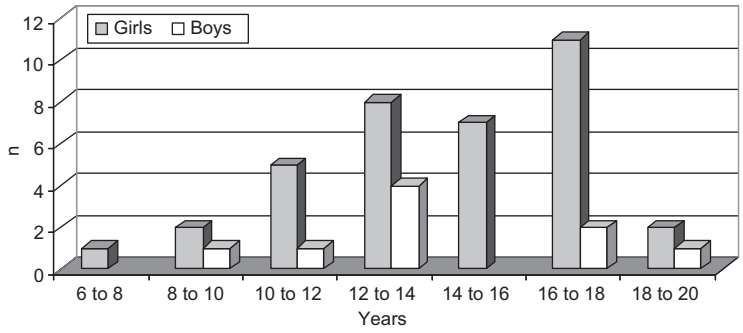

Figure 1 Gender and age distribution of DTC patients at presentation.

intranodular microcalcifications in three (7.7%) and as diffuse goiter in two (5.1%).

Thirty-nine patients underwent preoperative FNAB and in 37 enough material was obtained for diagnosis. Cytologic results were positive for malignancy in 15, indeterminate in 14 (11 follicular neoplasia and three suspicious) and negative or benign in eight (false negatives).

All patients underwent total thyroidectomy with resection of suspicious CLN.

Complications due to surgical treatment occurred in 17 patients: two transient unilateral vocal cord paralysis, seven transient hypoparathyroidism and seven definitive hypoparathyroidism requiring long-term replacement with calcium and calcitriol. In the last 5 years only one patient of 14 presented definitive hypoparathyroidism.

Pathological features of the histologic specimens of thyroidectomy are shown in Table 2. Anatomopathological study after surgery revealed 89% papillary thyroid carcinoma. Tumor size was >2 cm in 64.4% of patients. One patient with CLT who was followed up in our Institution presented with a thyroid nodule smaller than 1 cm. DTC extended within the thyroid gland in 60% and to extrathyroidal surrounding adipose or muscle tissue in 44% of patients.

Metastases in CLN were found at diagnosis in 44.4% of patients, in distant lymph nodes (mediastinal) in 11.1%, and in lungs in 13.3%.

Histological analysis revealed CLT in 12 patients (Table 3).

The absolute radioiodine dose ranged from 100 mCi to 650 mCi and the median number of radioiodine doses received to achieve NED state was 2.3 (range 1–6).

^{131}I treatment was generally well tolerated. Short-term adverse effects (nausea and vomiting, neck pain and temporary loss of taste) were not documented, whereas one patient presented chronic sialadenitis and xerostomia. Myelosuppression was not observed.

Median follow-up was 5 years (range 0.16–13.10 years).

Five patients, four pubertal, presented recurrences of DTC. In all, histologic type was papillary with a median time elapsed since initial treatment (thyroidectomy) of 3.3 years (range 3–5). In three patients the recurrence occurred in CLN, one in mediastinum and one in lungs.

None of the patients died. Statistical analysis performed with Kaplan-Meier survival curve showed a probability for a disease-free survival rate of 80% at 3 years and 75% at 5 years of follow-up.

Table 2 Pathological features of DTC in 45 patients.

Histologic type	Whole group	Papillary	Follicular
n	45	40 (89%)	5
Tumoral size (cm)			
<1	1	1	–
1–1.9	13	13	–
2–3.9	17	15	2
>4	12	9	3
Not registered	2	2	–
Multicentricity	27 (60%)	26	1
Extrathyroidal invasion	20 (44.4%)	15	5
CLN metastases	20 (44.4%)	19	1
Distant metastases	11		
Mediastinum	5 (11.1%)	4	1
Lungs	6 (13.3%)	6	–
CLT	12 (26.6%)	12	–

Table 3 Characteristics of DTC associated to CLT.

CLT	Present	Absent	p-Value
n	12	33	
Age, years	14.8	13.7	
Range	(8–19.6)	(6.2–19)	
Thyroid function			
Normal	9	32	
Hypothyroidism	2	–	
Subclinical hyperthyroidism	1	1	
TPOAb/TGAb	11	–	
Histologyc type			
Papillary	12	28	
Follicular	–	5	
Multicentricity	8	17	
CLN metastases	7 (58.3%)	13 (39.3%)	NS
Distant metastases	1 (8.3%)	10 (33.3%)	NS
NED at 3 years follow-up	87.5% (n:7)	69.5% (n:23)	NS
Recurrences	1	4	NS

Differences between patient groups with and without CLT tested with χ^2-test showed no significant differences between groups.

Discussion

DTC constitutes 3%–5% of all pediatric cancers and the third most frequent solid cancer in childhood. It accounts for 1% of cancers in prepubertal children with increasing incidence in adolescents (1–7, 11–16).

According to the Surveillance, Epidemiology and End Results (SEER) database (16), there is a predominance of boys among children below 6 years of age and a predominance of girls in older patients. The mean age of our studied group was 13.7 years with an overall female:male ratio of 4:1. We found a female predominance at all ages.

Children with prior history of head and neck radiation, leukemia or lymphoma or iodine deficiency are at increased risk for DTC (17, 18). Thyroid cancer is the most common second malignancy in children with a history of Hodgkin and non-Hodgkin's lymphomas, and the third most frequent malignancy in leukemia survivors. Children treated for cancer before age 10 years have the highest risk for thyroid cancer. In addition, the incidence of DTC increases linearly with radiation doses up to 30 Gy and declines at higher doses, probably due to the cytotoxic effects of high doses of radiation (17). Four of our patients had DTC as second malignancy (11 years after rhabdomyosarcoma, 7 years after acute lymphoblastic leukemia in two patients and 10 years after being treated for a non-Hodgkin's lymphoma of the cavum with 30 Gy neck radiation therapy).

All our patients presented with a thyroid nodule at diagnosis. Recent prevalence estimations suggest that 20% of thyroid nodules in children are malignant, as compared with 5% in adults (19, 20).

Thyroid function was normal in 88% of our patients, with a median TSH level of 2.21 mUI/L. Consistent with other authors' findings we found hypothyroidism in 5.7%, and subclinical hyperthyroidism in 5.7% (1). These last observations underscore the need to continue with the evaluation of a persistent thyroid nodule in spite of the finding of thyroid dysfunction in order to rule out malignancy. In agreement with other authors we found that higher preoperative TSH levels were significantly associated with a more advanced disease at diagnosis, according to the pathogenic role of chronic TSH stimulation (21, 22).

Most thyroid nodules (benign and malignant) express less NIS (sodium iodide symporter) than normal surrounding tissues, resulting in less ^{99m}Tc uptake and showing a decreased uptake on thyroid scan. Nevertheless, if TSH is suppressed, a radionuclide scan may identify a hyperfunctioning nodule. All our patients had "cold" nodules in ^{99m}Tc scan, even those with subclinical hyperthyroidism.

US is useful in confirming the presence of a nodule, and it can determine if it is solitary or multiple, and define echostructure, limits and characteristics of the surrounding thyroid gland and neck. Various sonographic characteristics of a thyroid nodule have been associated with a higher likelihood of malignancy. These include solid predominance, nodule hypoechogenicity, absent translucent halo, intranodular microcalcifications, irregular infiltrative margins, increased intranodular vascularity and the presence of pathological CLN. However, US characteristics alone cannot reliably distinguish between benign and malignant lesions (23–27). Due to the fact that our study was retrospective and the patients were studied in different diagnostic centers with different operators, it was difficult to compare the reported results.

FNAB is considered a valuable tool to evaluate if a thyroid nodule is malignant, orient diagnosis and guide treatment. However, FNAB cannot determine if a follicular lesion is malignant or not, because this distinction is based on vascular and/or capsular infiltration. Data for children are limited, but the sensitivity and specificity of FNAB report similar results as for adults (12, 28–30). FNAB was performed before surgery in 39 patients and it was useful in predicting diagnosis in 74.3% of them. Unsatisfactory sampling was low in spite of the lack of US guidance and cytopathologist assistance during the procedure. This may be attributed to nodule size at diagnosis. The 29 patients with positive (malignant) or indeterminate FNAB results underwent surgery. In eight patients with negative FNAB results, surgery was decided based on tumor size, nodule persistence and/or growth, and risk factors. This 20.5% of false negative results may be high in comparison with other authors (29).

Removal of all thyroid tissue (total thyroidectomy) is a crucial element in the initial management due to the high probability of multicentricity of DTC in children; it reduces the mass of thyroid tissue and facilitates postoperative treatment with radioactive iodine and permits accurate long-term surveillance for disease recurrence with the measurement of serum thyroglobulin (2, 8, 11, 13, 14). All the patients in our cohort underwent total thyroidectomy. The extent of CLN dissection is controversial as postoperative morbidity increases with more aggressive CLN resection. Resection criteria for CLN removal in our studied group was enlargement of CLN.

When performed by an experienced head and neck surgeon total thyroidectomy minimizes the risk of postsurgical complications and the need for re-intervention in the case of persistence of neck disease. Thyroidectomy was performed by different surgery teams over the study period and the global incidence of hypoparathyroidism all through the study was 15.6%. Although this incidence may be high, it is in agreement with some investigators (30–35). In the last 5 years it decreased to 7%, probably due to greater surgeon experience.

As referred in the current literature, the most frequent histological type of DTC in our children was papillary carcinoma, being multifocal in 60% and with extracapsular invasion in 44.4% (1–3, 36). The small number of patients with follicular carcinomas prevents any statistical comparison between the two different types.

Previous studies have suggested that pediatric DTC has a more aggressive behavior at diagnosis than in adults (1–4, 13, 33, 35, 36); however, prognosis seems more favorable.

At diagnosis CLN involvement is present in 40%–80% of patients and in 10%–20% distant metastases are documented (1, 2, 30, 31, 33, 34, 36). Our data support these suggestions of a more extensive disease at diagnosis.

Postoperative radioiodine completes the initial treatment of DTC. Primary goals of this therapy are remnant ablation and adjuvant therapy to destroy suspected disease and decrease recurrences. ^{131}I administration increases the sensitivity of subsequent WBS and allows the utilization of serum TG as a marker of recurrence or persistence of disease (11, 37, 38). However, there is no agreement in the activity of ^{131}I that should be administered in children. Following previous guidelines (39), our patients received fixed doses of ^{131}I.

In accordance with Lazar et al. (3) we detected recurrences in five patients (80% pubertal) with papillary DTC with a median time since thyroidectomy of 3.3 years. Disease-free survival rate at 5 years of follow-up was 75%, similar to that reported by other authors (1–5, 35).

Also, we were unable to address the issue of disease characteristics in prepuberty because of the small group of prepubertal patients.

Since the first report of Dailay et al. in 1955, the association of CLT and DTC, mostly papillary, has been documented in variable proportions (1%–30% of cases) due to ethnic, geographic, gender differences and probably mostly due to differences in histologic interpretation of CLT (40–42). The observation of a better prognosis of DTC in the presence of CLT led to the hypothesis of CLT as a protective immune reaction to control cancer cell proliferation (40, 41), but the detection of thyroid neoplasms at diagnosis of CLT does not support this protective role (19). The prevalence of CLT in our series (26.6%) is similar to other series (31). Nevertheless, probably due to the small group of patients, no statistical differences were found between patients with and without CLT.

Conclusions

Our data show that pediatric DTC has an aggressive behavior at presentation, with CLN metastases in 44% and distant metastases in 24% of cases.

Higher preoperative TSH levels were significantly associated with a more advanced disease at diagnosis highlighting its important pathogenic role.

CLT was present concomitantly in a quarter of the patients and further studies are needed to establish a difference in these patients' outcome.

Total thyroidectomy, thyroid remnant ablation with ^{131}I and suppressive treatment with L-T4 allowed a good progression-free survival rate.

Clinical decision-making by the same team of endocrinologists having uniform criteria in a large cohort of patients below 20 years of age with DTC who were treated and followed up at a single institution has allowed us to gather data on this disease evolution in childhood and adolescence. Nevertheless, to promote knowledge about the behavior of DTC in childhood and adolescence larger multicentric long-term prospective studies are needed.

Disclosure statement

This study was not funded. The authors declare that no competing financial interests exist.

References

1. Halac I, Zimmerman D. Thyroid nodules and cancers in children. Endocrinol Metab Clin N Am 2005;34:725–44.
2. Dinauer C, Breuer C, Rivkees S. Differentiated thyroid cancer in children: diagnosis and management. Curr Opin Oncol 2008;20:59–65.
3. Lazar L, Lebenthal Y, Steinmetz A, Yackobovitch-Gavan M, Phillip M. Differentiated thyroid carcinoma in pediatric patients: comparison of presentation and course between pre-pubertal children and adolescents. J Pediatr 2009;154:708–14.
4. Miller RW, Young JL, Novakovic B. Childhood cancer. Cancer 1995;75:395–405.
5. Leboulleux S, Baudin E, Hartl DW, Travagli JP, Schlumberger M. Follicular cell-derived thyroid cancer in children. Horm Res 2005;63:145–51.
6. Steliarova-Foucher E, Stiller CA, Pukkala E, Lacour B, Plesko I, et al. Thyroid cancer incidence and survival among European children and adolescents (1978–1997): report from the automated Childhood Cancer Information System project. Eur J Cancer 2006;42:2150–69.
7. Ries LA, Melbert D, Krapcho M, Mariotto A, Miller BA, et al. editors. SEER Cancer Statistics Review, 1975–2004. Bethesda: National Cancer Institute, 2007. Based on Nov 2006 SEER Data submission.
8. Vriens MR, Suh I, Moses W, Kebebew E. Clinical features and genetic predisposition to hereditary nonmedullary thyroid cancer. Thyroid 2009;19:1343–9.
9. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, et al. Revised American Thyroid Association Guidelines Taskforce Management Guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–214.
10. Sclabas GM, Staerkel GA, Shapiro SE, Fornage BD, Sherman SI, et al. Fine-needle aspiration of the thyroid and correlation with histopathology in a contemporary series of 240 patients. Am J Surg 2003;186:702–9.
11. Dinauer C, Francis GL. Thyroid cancer in children. Endocrinol Metab Clin N Am 2007;36:779–806.
12. Josefson J, Zimmerman D. Thyroid nodules and cancers in children. Pediatr Endocrinol Rev 2008;6:14–23.
13. Rachimiel M, Charron M, Gupta A, Hamilton J, Wherret D, et al. Evidence-based review of treatment and follow-up of patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 2006;9:1377–93.
14. Hung W, Sarlis N. Current controversies in the management of pediatric patients with well-differentiated nonmedullary thyroid cancer: a review. Thyroid 2002;12:683–701.
15. Gingalewski C, Newman KD. Seminars: controversies in the management of pediatric thyroid malignancy. J Surgical Oncol 2006;94:748–52.
16. Benvenga S. Update on thyroid cancer. Horm Metab Res 2008;40:323–8.
17. Rutter M, Rose S. Long term sequelae of childhood cancer. Curr Opin Pediatr 2007;19:480–7.
18. Davies SM. Subsequent malignant neoplasms in survivors of childhood cancer: Childhood Cancer Survival Study (CCSS) studies. Pediatr Blood Cancer 2007;48:727–30.

19. Niedziela M. Pathogenesis, diagnosis and management of thyroid nodules in children. Endocr Rel Cancer 2006;13:427–53.
20. Gharib H. Fine-needle aspiration biopsy of thyroid nodules: advantages, limitations, and effect. Mayo Clin Proc 1994;69:44–9.
21. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, et al. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab 2006;91:4295–301.
22. Haymart MR, Repplinger DJ, Leverson GE, Elson DF, Sippel RS, et al. Higher TSH level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. J Clin Endocrinol Metab 2008;93:809–14.
23. Brkljacic B, Cuk V, Tomic-Brzac H, Bence-Zigman Z, Delic-Brkljacic D, et al. Ultrasonic evaluation of benign and malignant nodules in echographically multinodular thyroids. J Clin Ultrasound 1994;22:71–6.
24. Chan B, Desser T, McDougall IR, Weigel RJ, Jeffrey RB Jr. Common and uncommon sonographic features of papillary thyroid carcinoma. J Ultrasound Med 2003;22:1083–90.
25. Kim E, Park C, Chung WY, Oh KK, Kim DI, et al. New sonographic criteria for recommending fine-needle aspiration biopsy of non palpable solid nodules of the thyroid. Am J Rhinol 2002;178:687–91.
26. Katz JF, Kane RA, Reyes J, Clarke MP, Hill TC. Thyroid nodules: sonographic-pathologic correlation. Radiology 1984;151:741–5.
27. Frates M, Benson C, Charbonneau J, Cibas ES, Clark OH, et al. Management of thyroid nodules detected at ultrasound: Society of Radiologists in US consensus conference statement. Radiol 2005;237:794–800.
28. Gruñeiro-Papendieck L, Cohen M, Navari C, Diez B, Bergadá C. Punción aspiración con aguja fina de tiroides en pediatría. Rev Hosp. Niños B Aires 1993;35:4–8.
29. Layfield LJ, Cibas ES, Gharib H, Mandel SJ. Thyroid aspiration cytology: current status. CA Cancer J Clin 2009;59:99–110.
30. Schlumberger M, De Vathaire F, Travagli JP, Vassal G, Lemerle J, et al. Differentiated thyroid carcinoma in childhood: long term follow-up of 72 patients. J Clin Endocrinol Metab 1987;65: 1088–94.
31. O'Gorman CS, Hamilton J, Rachmiel M, Gupta A, Ngan BY, et al. Thyroid cancer in childhood: a retrospective review of childhood course. Thyroid 2010;20:375–80.
32. Vaisman F, Alves Bulzico D, Hosannah C, Noronha Pessoa C, Neves Bordallo MA, et al. Prognostic factors of a good response to initial therapy in children and adolescents with differentiated thyroid cancer. Clinics 2011;66:281–6.
33. Silva F, Laguna R, Nieves-Rivera F. Pediatric thyroid cancer with extensive disease in a hispanic population: outcome and long term survival. J Pediatr Endocrinol Metab 2010;23:59–64.
34. Negre Busó M, Simó Perdigó M, Roca Bielsa I, Aguadé Bruix S, de Toledo JS, et al. Differentiated thyroid carcinoma in children: study of 80 cases. Med Clin (Barc) 2009;133:339–43.
35. La Quaglia M, Black T, Holcomb G III, Sklar C, Azizkhan RG, et al. Differentiated thyroid cancer: clinical characteristics, treatment and outcome in patients under 21 years of age who present with distant metastases: a report from the surgical Discipline Committee of the Children's Cancer Group. J Pediatr Surg 2000;35:955–9.
36. Dottorini ME, Vignati A, Mazzucchelli L, Lomuscio G, Colombo L. Differentiated thyroid carcinoma in children and adolescents: a 37 year experience. J Nucl Med 1997;38:669–75.
37. Handkiewicz-Junak D, Wloch J, Roskosz J, Krajewska J, Kropinska A, et al. Total thyroidectomy and adjuvant radioiodine treatment independently decrease locoregional recurrence risk in childhood and adolescent differentiated thyroid cancer. J Nucl Med 2007;48:879–88.
38. Kumagai A, Reiners C, Drozd V, Yamashita S. Childhood thyroid cancers and radioactive iodine. Endocr J 2007;54:839–47.
39. Meier DA, Brill DR, Becker DV, Clarke SE, Silberstein EB, et al. Society of Nuclear Medicine. Procedure guideline for therapy of thyroid disease with ^{131}I. J Nucl Med 2002;43:856–61.
40. Matsubayashi S, Kawai K, Matsumoto Y. The correlation between papillary thyroid carcinoma and lymphocytic infiltration in the thyroid gland. J Clin Endocrinol Metab 1999;84:3421–4.
41. Loh K, Greenspan FS, Dong F, Miller TR, Yeo PP. Influence of lymphocytic thyroiditis on the prognostic outcome of patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 1999;84:458–63.
42. Corrias A, Cassio A, Weber G, Mussa A, Wasniewska M, et al. Thyroid nodules and cancer in children and adolescents affected by autoimmune thyroiditis. Arch Pediatr Adolesc Med 2008;162:526–31.