Thyroid surgery in pediatric patients: causes and results

J. Ordóñez Pereira, L. Pérez Egido, M.A. García-Casillas, A. del Cañizo, M. Fanjul, M. de la Torre, I. Bada, M.D. Blanco, J. Cerdá, E. Molina, D. Peláez, J.C. de Agustín

Pediatric Surgery Department. Gregorio Marañón University General Hospital. Madrid (Spain).

ABSTRACT

Objective. Even though thyroid surgery is rare in pediatric patients, frequency has increased in the last years. The objective of this study was to analyze the causes and results of these procedures in a pediatric surgical facility.

Patients and methods. Retrospective study including all patients requiring thyroid surgery in our department from 2000 to 2019. Demographic data, diagnostic data, associated pathology, type of surgical procedure, pathological results, and intraoperative and postoperative complications were recorded.

Results. 47 patients with a mean age of 8.9 ± 3.9 years at surgery were included. The most frequent diagnosis was MEN syndrome (n = 30, 29 MEN 2A and 1 MEN 2B), followed by thyroid papillary carcinoma (n = 5), follicular adenoma (n = 5), multinodular goiter (n = 4), follicular carcinoma (n = 1), thyroglossal duct papillary carcinoma (n = 1), and Graves-Basedow syndrome (n = 1). 38 total thyroidectomies (73.7% of which were prophylactic), 3 double hemithyroidectomies, 5 hemithyroidectomies, and 5 lymphadenectomies were performed. No intraoperative complications or recurrent laryngeal nerve lesions were noted. Mean postoperative hospital stay was 1.3 ± 0.6 days. 7 patients had transitory asymptomatic hypoparathyroidism, and 1 patient had persistent symptomatic hypoparathyroidism. Pathological results of prophylactic thyroidectomies were: 18 C cell hyperplasias, 7 microcarcinomas, and 3 cases without histopathological disorders.

Conclusions. Thyroid surgery in pediatric patients is safe if performed by specialized personnel. Even though it remains rare, frequency has increased in the last years.

KEY WORDS: Thyroid gland surgery; Thyroidectomy; MEN 2; Thyroid nodule.

Corresponding author: Dr. Javier Ordóñez Pereira.
E-mail address: javier.ordonez.pereira@gmail.com

This study was presented at the 2019 National Congress of the Spanish Pediatric Surgery Society held in Vigo (Spain), and at the EUPSA European Congress held in Belgrade (Serbia) in 2019.

Date of submission: May 2020 *Date of acceptance:* September 2020

CIRUGÍA TIROIDEA EN LA EDAD PEDIÁTRICA: CAUSAS Y RESULTADOS

RESUMEN

Objetivo. La cirugía tiroidea es poco frecuente en la edad pediátrica, aunque ha aumentado su frecuencia en los últimos años. El objetivo de este estudio es analizar las causas y los resultados de estos procedimientos en un centro quirúrgico pediátrico.

Métodos. Estudio retrospectivo que incluyó a todos los pacientes que necesitaron cirugía tiroidea en nuestro servicio entre 2000-2019. Se recogieron datos demográficos, diagnóstico, patología asociada, tipo de procedimiento quirúrgico realizado, resultados anatomopatológicos y complicaciones intra y posoperatorias.

Resultados. Se incluyeron 47 pacientes con una edad media en el momento de la intervención de 8,9 ± 3,9 años. El diagnóstico más frecuente fue síndrome MEN2 (n = 30, 29 MEN2A y 1 MEN2B), seguido de carcinoma papilar de tiroides (n = 5), adenoma folicular (n = 5), bocio multinodular (n = 4), carcinoma folicular (n = 1), carcinoma papilar del conducto tirogloso (n = 1) y síndrome de Graves-Basedow (n = 1). Se realizaron 38 tiroidectomías totales (el 73,7% fueron profilácticas), tres dobles hemitiroidectomías, cinco hemitiroidectomías y en cinco casos fue necesario realizar una linfadenectomía. No se presentaron complicaciones intraoperatorias ni lesiones de nervio laríngeo recurrente. La estancia media posoperatoria fue de 1,3 ± 0,6 días. Siete pacientes presentaron hipoparatiroidismo transitorio asintomático y en un caso, persistente sintomático. Los resultados anatomopatológicos de las tiroidectomías profilácticas fueron: 18 hiperplasias de células C, 7 microcarcinomas y 3 sin alteraciones histopatológicas.

Conclusiones. La cirugía tiroidea en la edad pediátrica es segura en manos de equipos especializados. Aunque sigue siendo un procedimiento poco habitual, su frecuencia está aumentando en los últimos años.

PALABRAS CLAVE: Cirugía glándula tiroides; Tiroidectomía; MEN2; Nódulo tiroideo.

INTRODUCTION

The incidence of thyroid gland surgical pathologies, especially those of tumorous origin, has increased in the last years. Thyroid nodule incidence is currently estimated at 0.5-1.8 cases per 100,000 inhabitants. It is more frequent

in female patients and in patients close to adolescence[1,2]. Specific clinical guidelines for pediatric patients have changed management in this age range[3,4]. Indeed, thyroid nodule malignity is higher in children than in adults (22-26% *vs.* 5-10%), and tumor aggressiveness is also greater in pediatric patients, but treatment response and survival rate are better[5,6].

A frequent cause of thyroidectomy in pediatric patients is prophylaxis for thyroid medullary carcinoma (TMC) prevention in multiple endocrine neoplasia syndrome type 2 (MEN2)[7,8]. TMC represents 1-2% of all thyroid tumors, but it is the main cause of death in this syndrome[9]. The updated *American Thyroid Association (ATA 2015)* TMC guidelines[4] have changed management, highlighting the importance of identifying RET gene mutation (which determines TMC aggressiveness), measuring calcitonin, and performing total thyroidectomy (TT) as the primary prevention mechanism.

There is a certain debate regarding the differential characteristics of thyroid pathology in children as well as the surgery professionals that should be involved in these procedures. In addition, there is no consensus as to whether the approach should be different from that used in adults. The objective of this study was to analyze the causes and results of thyroid pediatric surgery performed by a pediatric surgery team in a tertiary center.

PATIENTS AND METHODS

A retrospective study including all patients under 16 years of age requiring thyroid surgery in our healthcare facility from 2000 to 2019 was carried out. Demographic data, associated pathology, personal and family history, diagnosis, type of procedure, pathological results, need for additional treatment, and intraoperative and postoperative complications were recorded. In the case of MEN syndrome patients, treatment adherence to ATA 2015 guidelines[4] was analyzed.

Thyroid pathology patients requiring surgery were managed by a cross-disciplinary team, made up of pediatric endocrinology, pediatric oncohematology, pediatric surgery, pediatric anesthesiology, pediatric radiology, genetics, and nuclear medicine specialists. Surgical indication was established according to international recommendations[3,4]. In our healthcare facility, MEN2 patients are followed up at pediatric endocrinology and pediatric oncohematology consultations. Once diagnosis has been achieved and gene mutation has been studied, they are referred to our consultation for TT without lymphadenectomy, since the latter is only carried out in case of suspected lymph node involvement at ultrasound examination or in the presence of increased serum calcitonin. In these cases, surgery is indicated within an age limit according to the relevant mutation. In MEN2B, surgery is indicated before one year of age; in high risk MEN2A mutations, before five years of age; and in moderate risk mutations, before adult age. Surgery is performed at diagnosis if the latter has been achieved above the age limit established.

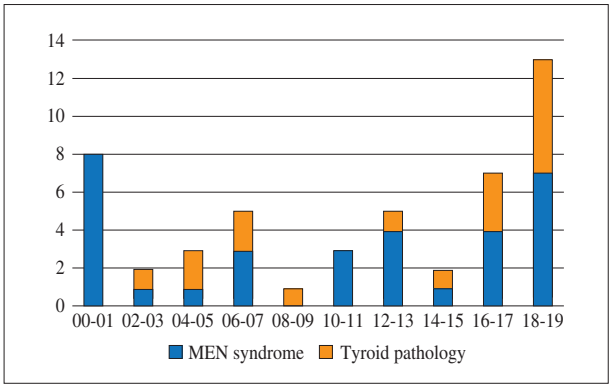

Figure 1. Annual number of procedures. MEN: multiple endocrine neoplasia.

All surgeries were carried out by the same surgical team. In the immediate postoperative period, patients were admitted at the resuscitation unit, where calcium and PTH controls were conducted. One day following surgery, they were admitted at the pediatric surgery unit, and they were discharged 24-48 hours following the procedure. Thyroid hormone replacement treatment was implemented from discharge in TT cases, with oral calcium and vitamin D supplements in case of hypoparathyroidism at postoperative controls.

RESULTS

47 patients were included, 29 (61.7%) of whom were female. They were divided into two groups according to diagnosis: 30 patients had MEN syndrome 2 (29 MEN2A and 1 MEN2B), and 17 patients had other thyroid pathologies (5 papillary carcinomas, 5 follicular adenomas, 4 multinodular goiters, 1 follicular carcinoma, 1 thyroglossal duct papillary carcinoma, and 1 Graves-Basedow syndrome). Figure 1 features patient distribution per year. Median follow-up was 29 months (range: 6-171 months).

MEN syndrome 2

Surgery in MEN2A patients was carried out with prophylactic purposes, except in two cases of late diagnosis: one 10.7-year-old boy diagnosed with MEN2B (918 mutation of RET gene's exon 16), and one 11.1-year-old girl with high risk mutation (C634T). In the first patient, TT with central and lateral lymphadenectomy was carried out. He was diagnosed with TMC as a result of the pathological study, and he required radical cervical and mediastinal lymphadenectomy. He had recurrence 5 years later in the form of hepatic and pulmonary metastases which did not respond to treatment; this was the only death recorded in

Table I. Characteristics of MEN2A and prophylactic thyroidectomy patients.

Mutation	*Risk*	*Calcitonin*	*Age*	*PR*	*Mutation*	*Risk*	*Calcitonin*	*Age*	*PR*
C618R	MOD	30.4	2.8	CCH	–	–	–	5.5	CCH
C634T	HIGH	–	3.1	CCH	C634S	HIGH	12.4	6.5	MCC
–	–	3	3.2	CCH	V804L	MOD	2	6.8	Normal
C618R	MOD	3.2	3.4	CCH	C634W	HIGH	23.4	7.3	MCC
C634S	HIGH	6.8	3.4	CCH	C634S	HIGH	19	7.5	MCC
C618W	MOD	6.7	3.9	CCH	C634S	HIGH	14	8.3	MCC
C634T	HIGH	10.5	4.3	CCH	–	–	2.8	8.7	CCH
634	HIGH	7	4.6	CCH	C634Y	HIGH	–	9.2	CCH
C611P	MOD	13.1	4.7	CCH	C634S	HIGH	34	9.5	CCH
T263stop	IND	5.5	5.1	CCH	C630T	MOD	2.1	11.1	CCH
C634S	HIGH	17.2	5.1	MCC	V804M	MOD	2	11.4	Normal
C634T	HIGH	13.6	5.1	CCH	C634W	HIGH	20.7	11.9	MCC
C634T	HIGH	–	5.3	Normal	–	–	–	12.7	MCC
C634Y	HIGH	24.4	5.3	CCH	C609Y	MOD	2	13.7	CCH

Risk: mutation-associated risk[4], which can be MOD (moderate), HIGH, or the highest; Calcitonin: calcitonin levels prior to surgery; PR: pathological results; Normal: thyroid gland with no histological disorders; CCH: C cell hyperplasia; MCC: microcarcinoma.

the study. In the second patient, TT and bilateral central and lateral lymphadenectomy were performed. She was diagnosed with TMC as a result of the pathological study. She is now free of disease after receiving iodine ablation and after 15 years of follow-up.

The characteristics of the 28 MEN2A patients requiring prophylactic surgery (TT without lymphadenectomy) are featured in table 1. Mean age at surgery was 6.8 ± 3.1 years, and pathological results were thyroid tissue without histopathological disorders (n = 3), C cell hyperplasia (n=18), and medullary microcarcinoma (n = 7). In all cases, there was family history of MEN tumors, except for one case with personal history of Hirschsprung's disease (HD) where a new mutation of exon 4 (T263Stop) was detected at the RET gene mutation screening carried out in all HD patients in our healthcare facility. Pathological result in this patient was C cell hyperplasia. Mean age of microcarcinoma patients at pathological examination was 8.5 ± 2.8 years.

In MEN2 patients, no intraoperative complication or recurrent laryngeal nerve (RLN) lesion was noted. Mean hospital stay was 1.4 ± 0.7 days. 8 postoperative hypoparathyroidism patients were recorded, all of whom recovered before 6 months, except one who had persistent hypoparathyroidism with symptomatic hypocalcemia.

Other thyroid pathologies

Of the 17 patients with other thyroid pathologies, 7 (41.2%) had malignant tumor etiology. Characteristics are described in table 2. Patients were predominantly male (57.1%), and mean age at surgery was 12.4 ± 3.3 years. Fine-needle-puncture-aspiration (FNPA) was performed in 4 patients: one with Bethesda category I pathology (final result: nodular hyperplasia), one with Bethesda category II pathology (final result: follicular adenoma), and two with Bethesda category III pathology (final diagnosis: papillary carcinoma and follicular carcinoma). No intraoperative complication or RLN lesion was noted, and only one case of transitory hypoparathyroidism was recorded. Hospital stay was 1 ± 0 days.

In the benign etiology group, 5 patients had follicular adenoma, 2 of whom had personal history: one DICER1 gene mutation (history of congenital pulmonary malformation and multicystic nephroma), and one PTEN gene mutation as part of Bannayan-Riley-Ruvalcaba syndrome. In this group, 4 hemithyroidectomies (HT) and one TT in the PTEN mutation case –given the high recurrence risk– were performed. Of the 4 multinodular goiter patients, 3 had relevant personal history: one PAX8 mutation (history of renal transplantation), one neurosensory hypoacusis patient with no identified mutation, and one history of metastatic Wilms tumor. Patients were treated with TT (n = 3, given the large thyroid size) and HT (n = 1, PAX8 mutation). Finally, one patient with Graves-Basedow syndrome refractory to medical treatment required TT. No intraoperative complication, RLN lesion or postoperative hypoparathyroidism was noted. Mean hospital stay was 1.3 ± 0.5 days.

DISCUSSION

Even though thyroid gland surgery is rare, it has become more frequent in the last years. In this review,

Table II. Clinical characteristics of tumor thyroid pathology patients (non-MEN2).

Diagnosis	*Personal history*	*Surgical procedure*	*Age*	*Pathological anatomy*	*Complementary treatment*	*Long-term evolution*	*Follow-up time*
PC	–	TT + lymphadenectomy	6.7	PC + mediastinal lymph node involvement	Radical cervical lymphadenectomy + iodine ablation	No recurrence	204
Thyroid nodule	Neuroblastoma	TT	9.8	FC. No lymph node involvement	None	No recurrence	36
PC lymph node recurrence	–	Left lateral cervical lymphadenectomy	12.0	PC in 1 out of the 7 lymph nodes analyzed	Iodine ablation	No recurrence	25
Thyroid nodule	–	Left hemithyroidectomy	14.4	PC	Right hemithyroidectomy	No recurrence	190
Thyroid nodule	–	Right hemithyroidectomy	15.4	PC without lymph node involvement	Left hemithyroidectomy + iodine ablation	No recurrence	157
Thyroid nodule	–	Left hemithyroidectomy + lymphadenectomy	16.0	PC + lymph node involvement	Right hemithyroidectomy + radical cervical lymphadenectomy. Iodine ablation	Lymph node recurrence. Extended lymphadenectomy	45
Thyroglossal cyst	–	Cystectomy (Sistrunk procedure)	12.7	PC in thyroglossal cyst	TT (pathological anatomy: normal thyroid tissue)	No recurrence	17

PC: papillary carcinoma; FC: follicular carcinoma; TT: total thyroidectomy.
Age at surgery expressed in years; follow-up time expressed in months.

we report our experience in our healthcare facility over nearly 20 years. The importance of MEN syndrome 2, the impact of age at surgery on oncological results, the need for a cross-disciplinary team for thyroid pathology management, the individual experience of the surgical personnel to prevent complications, and the importance of genetic study for diagnostic and prognostic purposes (both for MEN syndrome 2 and other genetic disorders associated with a higher predisposition to thyroid tumors) should be highlighted.

The incidence of thyroid nodules in pediatric patients has raised in the last years, with an annual increase of up to 1.1% in the last decades[1,2,10]. Considering this, as well as the greater knowledge available on genetic mutations and the spread of genetic counselling (especially in MEN2 cases), the need for thyroid surgery in children is expected to increase[11,12]. Pediatric patients with thyroid pathology have specific characteristics which differ from those found in adults, such as higher prevalence of large, multicentric tumors, with greater lymph node involvement (31.5% *vs.* 14.7%) and pulmonary metastasis (5.7% *vs.* 2.2%)[13]. In addition, thyroid nodule malignity rate is higher in adult patients (22-26% in children vs. 5-10% in adults)[5,14,15]. Our study also demonstrated higher incidence (Fig. 1), as well as higher thyroid nodule malignity rate. In spite of this, survival rate is higher in pediatric patients.

Thyroid nodule assessment by means of fine-needle-puncture-aspiration (FNPA) is carried out under the same criteria than in adults (according to Bethesda classification[16]). However, recent studies report a higher malignity rate for each category, including undiagnosed ones[17-19]. As a result of higher malignancy risk[6], some authors such as Cherella et al.[18] suggest more aggressive surgical attitudes are required (TT instead of HT). In our experience, FNPA findings should be correlated with ultrasound characteristics[19], since cytological analysis is sometimes complex and can lead to diagnostic mistakes. According to our protocol, HT should be performed in case of suspected malignant nodules, followed by TT if malignancy is confirmed. In our opinion, this reduces recurrence and tumor progression risks owing to the tendency to multifocality, without increasing morbidity and mortality.

Regarding MEN2 patients, we believe strictly complying with ATA 2015 guidelines[4] is key to prevent TMC development. In our series, all microcarcinomas were detected in patients where surgery had been carried out at an older age than recommended (except in one 5.1-year-old patient with high risk mutation), even with normal calcitonin levels. TMC was detected in two late diagnosis patients, both with high preoperative calcitonin levels. Lymphadenectomy during prophylactic thyroidectomy is not recommended, since lymph node involvement is

unlikely in patients without suspected advanced disease. Like Bussières et al.[8], we believe systematically using this technique would increase surgical risk without reducing oncological risk. Last, a balance between oncological risk, which increases with age, and surgical risk, which is higher in younger children, should be achieved.

Genetic mutations are very frequent in pediatric patients with thyroid pathology, with disorders being found in up to 47% of malignant tumors[20]. In addition, they are more prone to malignancy at a younger age[15]. In our series, mutations were detected in 33 of the 47 patients undergoing surgery (70.2%), most of them (n = 30) being RET gene mutations. One of these patients had personal history of HD. Nowadays, this gene is estimated to be altered in 50% of familial HD cases and in up to 15-20% of non-familial HD cases[21,22], whereas 2-5% of HD patients are estimated to have MEN2. Therefore, our HD patient management protocol includes RET gene study in order to be able to provide with genetic counselling and assess the need for prophylactic thyroidectomy[23].

In terms of surgical complications, no local complications (bleeding, hematoma, dehiscence, or wound infection) or RLN lesions were noted. Recent studies assess RLN intraoperative monitoring[24]; we believe this technique can be useful in more complex cases, but routine use could add morbidity, especially as a result of longer operating times. Regarding parathyroid gland (PG) lesion, 8 patients (17.0%) had postoperative hypoparathyroidism, and only 1 (2.1%) had persistent hypoparathyroidism. Complication incidence was similar to or lower than the incidence described in the literature[25,26], which associates higher complication rates with younger patients and the need for lymphadenectomy.

Over these years, we have learnt that thyroid surgery's greatest difficulty lies in the erratic route of the RLN and its relationship with the thyroid gland, as well as in PG identification. The availability of a sealing/dividing instrument has facilitated thyroid dissection while limiting the use of monopolar scalpel, which causes local heat transmission to more sensitive structures, and blunt dissection, which entails a high risk of bleeding. The RLN is often difficult to identify; therefore, dissection should always be subcapsular to the thyroid gland, while being particularly cautious at the tracheoesophageal space – where the RLN is usually located. RLN's insertion point in the trachea is usually very firm, and sometimes, thyroidectomy requires the use of a cold scalpel, especially in younger children, as a result of the disproportion between the sealing/dividing device and the size of the operating field. PG identification represents a surgical challenge in younger patients, where adenopathies are frequent and can even be mistaken for the thymus. The lower PGs are usually more difficult to identify, since they are located further from the operating field and close to thyme remnants, and they can even have an intrathyroid location, which is relatively frequent.

Consequently, we believe thyroid surgery is safe if performed by specialized pediatric surgeons supported by a cross-disciplinary team[25]. In our view, this type of surgery should always be carried out by the same surgical personnel to increase individual experience, since there are few cases and the operating field is highly complex. Decreased complications have been associated with an increase in the annual number of procedures, with some authors recommending at least 25-30 thyroidectomies every year[3,27,28]. Bussières et al.[25] argue similar results could be achieved with a lower annual number of procedures due to the nature of pediatric surgery, where low-incidence, technically demanding pathologies are frequent. Our results support this hypothesis.

This article has a retrospective design, which means it has the limitations inherent to retrospective studies. In addition, it analyzes the results from a single tertiary center, where complex patients from other healthcare facilities are referred to. Therefore, our results may show a higher proportion of malignant tumor pathologies.

CONCLUSIONS

Even though thyroid surgical pathology is rare, prevalence has increased in the last years. Pediatric patients with thyroid lesions are more prone to malignity than adult patients. Mutation analysis and genetic study have proved to be an indispensable tool, especially in TMC prevention in MEN2 syndrome. Finally, these surgeries are safe and effective if performed by specialized pediatric surgery personnel (as part of a cross-disciplinary team), with a low complication rate and good long-term results.

REFERENCES

1. Hogan AR, Zhuge Y, Pérez EA, Koniaris LG, Lew JI, Sola JE. Pediatric Thyroid Carcinoma: Incidence and Outcomes in 1753 Patients. J Surg Res [Internet]. 2009; 156(1): 167-72.
2. Papendieck P, Gruñeiro-Papendieck L, Venara M, Acha O, Cozzani H, Mateos F, et al. Differentiated thyroid cancer in children: Prevalence and predictors in a large cohort with thyroid nodules followed prospectively. J Pediatr. 2015; 167(1): 199-201.
3. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, et al. Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2015; 25(7): 716-59.
4. Wells SA, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American thyroid association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015; 25(6): 567-610.
5. Chow SM, Law SCK, Mendenhall WM, Au SK, Yau S, Mang O, et al. Differentiated Thyroid Carcinoma in Childhood and Adolescence - Clinical Course and Role of Radioiodine. Pediatr Blood Cancer. 2004; 42(2): 176-83.

6. Hay ID, González-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. World J Surg. 2010; 34(6): 1192-202.
7. Prete FP, Abdel-Aziz T, Morkane C, Brain C, Kurzawinski TR, Hindmarsh P, et al. Prophylactic thyroidectomy in children with multiple endocrine neoplasia type 2. Br J Surg. 2018; 105(10): 1319-27.
8. Bussières V, Roy S, Deladoey J, Rousseau É, St-Vil D, Piché N. Prophylactic thyroidectomies in MEN2 syndrome: Management and outcomes. J Pediatr Surg [Internet]. 2018; 53(2): 283-5.
9. Pappa T, Alevizaki M. Management of hereditary medullary thyroid carcinoma. Endocrine. 2016; 53(1): 7-17.
10. Corrias A, Mussa A, Baronio F, Arrigo T, Salerno M, Segni M, et al. Diagnostic features of thyroid nodules in pediatrics. Arch Pediatr Adolesc Med. 2010; 164(8): 714-9.
11. Margraf RL, Crockett DK, Krautscheid PMF, Seamons R, Calderon FRO, Wittwer CT, et al. Multiple endocrine neoplasia type 2 RET protooncogene database: Repository of MEN2-associated RET sequence variation and reference for genotype/phenotype correlations. Hum Mutat. 2009; 30(4): 548-56.
12. Kuhlen M, Frühwald MC, Dunstheimer DPA, Vorwerk P, Redlich A. Revisiting the genotype-phenotype correlation in children with medullary thyroid carcinoma: A report from the GPOH-MET registry. Pediatr Blood Cancer. 2020; 67(4): 1-9.
13. Al-Qurayshi Z, Hauch A, Srivastav S, Aslam R, Friedlander P, Kandil E. A national perspective of the risk, presentation, and outcomes of pediatric thyroid cancer. JAMA Otolaryngol - Head Neck Surg. 2016; 142(5): 472-8.
14. Gupta A, Ly S, Castroneves LA, Frates MC, Benson CB, Feldman HA, et al. A standardized assessment of thyroid nodules in children confirms higher cancer prevalence than in adults. J Clin Endocrinol Metab. 2013; 98(8): 3238-45.
15. Guille J, Opoku-Boateng A, Thibeault S, Chen H. Evaluation and management of the solitary thyroid nodule. Oncologist. 2015; 20: 19-27.
16. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2017; 27(11): 1341-6.
17. Norlén O, Charlton A, Sarkis LM, Henwood T, Shun A, Gill AJ, et al. Risk of malignancy for each Bethesda class in pediatric thyroid nodules. J Pediatr Surg [Internet]. 2015; 50(7): 1147-9.
18. Cherella CE, Angell TE, Richman DM, Frates MC, Benson CB, Moore FD, et al. Differences in Thyroid Nodule Cytology and Malignancy Risk between Children and Adults. Thyroid. 2019; 29(8): 1097-104.
19. Richman DM, Benson CB, Doubilet PM, Peters HE, Huang SA, Asch E, et al. Thyroid nodules in pediatric patients: Sonographic characteristics and likelihood of cancer. Radiology. 2018; 288(2): 591-9.
20. Mostoufi-Moab S, Labourier E, Sullivan L, Livolsi V, Li Y, Xiao R, et al. Molecular Testing for Oncogenic Gene Alterations in Pediatric Thyroid Lesions. Thyroid. 2018; 28(1): 60-7.
21. Asai N, Jijiwa M, Enomoto A, Kawai K, Maeda K, Ichiahara M, et al. RET receptor signaling: Dysfunction in thyroid cancer and Hirschsprung's disease. Pathol Int. 2006; 56(4): 164-72.
22. Tomuschat C, Puri P. RET gene is a major risk factor for Hirschsprung's disease: a meta-analysis. Pediatr Surg Int. 2015; 31(8): 701-10.
23. Decker RA, Peacock ML. Occurrence of MEN 2a in familial Hirschsprung's disease: A new indication for genetic testing of the RET proto-oncogene. J Pediatr Surg. 1998; 33(2): 207-14.
24. Schneider R, Machens A, Sekulla C, Lorenz K, Weber F, Dralle H. Twenty-year experience of paediatric thyroid surgery using intraoperative nerve monitoring. Br J Surg. 2018; 105(8): 996-1005.
25. Bussières V, Roy S, Deladoey J, Rousseau É, St-Vil D, Piché N. Pediatric thyroidectomy: Favorable outcomes can be achieved by a multidisciplinary team of pediatric providers. J Pediatr Surg. 2019; 54(3): 527-30.
26. Christison-Lagay E. Complications in head and neck surgery. Semin Pediatr Surg [Internet]. 2016; 25(6): 338-46.
27. Tuggle CT, Roman SA, Wang TS, Boudourakis L, Thomas DC, Udelsman R, et al. Pediatric endocrine surgery: Who is operating on our children? Surgery [Internet]. 2008; 144(6): 869-77.
28. Adam MA, Thomas S, Youngwirth L, Hyslop T, Reed SD, Scheri RP, et al. Is there a minimum number of thyroidectomies a surgeon should perform to optimize patient outcomes? Ann Surg. 2017; 265(2): 402-7.