

REVIEW ARTICLE

Surgery of the Thyroid in Children: Current Trends in Practice

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ABSTRACT

Thyroid surgery in the pediatric population is performed for a variety of benign and malignant conditions, including thyroid nodules, hyperthyroidism, goiter, and thyroid cancer. Thyroid nodules, though uncommon in children, are more likely to be malignant than in adults and require careful evaluation with history, imaging, thyroid function tests and often ultrasound-guided biopsy to determine which nodules will require further interventions. The treatment of thyroid malignancy is primarily surgical, though the extent of surgery is an area of active debate. Moreover, thyroid surgery in children may have a higher rate of complications, and a number proposals have been suggested to mitigate these risks. The guidelines developed by the 2015 American Thyroid Association Guidelines Task Force on Pediatric Thyroid Cancer are a helpful tool in directing the medical and surgical management of these complex patients, and provide a method for stratification of patient risk for recurrent disease. Children with thyroid disease are recommended to be cared for using a multidisciplinary approach and by providers and facilities experienced in management of pediatric patients. Surgery should be performed by surgeons experienced in pediatric cervical procedures. The objective of this review is to describe the range of thyroid disease affecting pediatric patients, examine current diagnostic algorithms, and discuss common treatment approaches, including the role for both surgery and adjunctive therapies.

Keywords: Carcinoma, Follicular, Grave's, Guidelines, Medullary, Nodule, Papillary, Pediatric, Thyroid.

How to cite this article: Windsor AM, Kiell EP, Berg EE, Kazahaya K. Surgery of the Thyroid in Children: Current Trends in Practice. *Int J Head Neck Surg* 2016;7(2):57-63.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Thyroid surgery is performed for a range of benign and malignant indications in children, including nodules, hyperthyroidism, goiter, and thyroid cancer (Table 1). Thyroid disorders are relatively uncommon in children compared with adults and therefore recommendations have often been guided by the adult experience. Nonetheless, these diseases may present differently, follow a unique clinical course, and have different molecular, pathologic, and genetic features in the pediatric population. The establishment of the 2015 American Thyroid Association (ATA) Guidelines Task Force on Pediatric Thyroid Cancer recognized these unique features and was an important step in developing standards for the treatment of thyroid nodules and malignancy in children. This review will discuss the spectrum of thyroid pathologies and their management in children, with an emphasis on current trends and consensus guidelines.

MANAGEMENT OF THE PEDIATRIC THYROID NODULE

Thyroid nodules are relatively rare in children, with reported incidences ranging from 1 to 2%. The incidence of malignant nodules in children is not certain, but appears to be much higher at approximately 25% compared to 5% in adults. Nodules are the most common indication for thyroid surgery.¹⁻⁴ The diagnostic algorithm is therefore geared toward identifying those nodules which are at highest risk of being malignant and require surgical excision.

The initial workup of the pediatric thyroid nodule is similar to that recommended in adults.^{2,5} Careful clinical history should be obtained, with special attention to symptoms of hyper- or hypothyroidism, local compressive symptoms, history of autoimmune thyroiditis, prior exposure to ionizing radiation, family history of thyroid cancer, and the presence of genetic syndromes associated

Table 1: Indications for pediatric thyroid surgery

Goiter with compressive symptoms or cosmetic concern
Hyperthyroidism
MEN-2 syndrome
Thyroid malignancy
Thyroid nodule of indeterminate cytology
MEN: Multiple endocrine neoplasia

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Table 2: Risk factors for malignancy in pediatric patients with thyroid nodules

Patient characteristics	Family history of thyroid cancer Exposure to ionizing radiation Presence of hereditary syndrome associated with thyroid neoplasm
Physical exam findings	Firm, fixed neck mass Cervical lymphadenopathy
Ultrasound findings	Hypoechoic nodule Undefined borders Microcalcifications Increased vascularity Subcapsular location Solitary nodule Associated lymphadenopathy

with thyroid neoplasms. Physical exam should identify any firm, fixed masses or cervical lymphadenopathy. Initial diagnostic testing should include thyroid and cervical ultrasound and thyroid function tests. Ultrasound characteristics which raise suspicion for malignancy and should prompt further investigation include nodule hypoechoic, undefined borders, microcalcifications, increased vascularity, subcapsular location, solitary nodules, and associated lymphadenopathy (Table 2).¹

As in adults, the presence of hyperthyroidism should prompt nuclear thyroid scintigraphy to determine if there is a hyperfunctioning nodule. A hyperfunctioning nodule rarely contains malignant cells, and in children the recommended definitive therapy is thyroid lobectomy with isthmusectomy.¹ In the presence of hypothyroidism or euthyroidism, ultrasound-guided fine-needle aspiration (FNA) biopsy should be considered.^{1,5} In adults, FNA is recommended for nodules at least 1 cm in diameter, increasing in size and having suspicious features on serial ultrasound, or in patients at high risk for malignancy (e.g., prior radiation exposure).² The 2015 ATA pediatric guidelines note that nodule size is less predictive of malignancy in children, particularly since the overall thyroid volume may be smaller. The guidelines recommend that clinical characteristics and ultrasound features of the nodule should prompt ultrasound-guided FNA rather than size alone.⁵ Treatment of thyroid nodules in children is guided by FNA. Cytology is stratified into six risk groups according to the Bethesda System for Reporting Thyroid Cytopathology.⁶ This classification scheme has been shown to be a sensitive means of differentiating malignant from benign nodules in children.^{7,8} Benign lesions can be observed clinically, though surgery may be considered in certain scenarios. If the patient has compressive symptoms, cosmetic concerns, increasing size of nodule, or development of other concerning sonographic features, surgery could be considered.⁵ Cytopathology that is definitively positive for malignancy necessitates surgical excision, usually by total thyroidectomy.

Management of nodules with indeterminate cytology (atypia or follicular lesion of undetermined significance or suspicious for follicular or Hürthle cell neoplasm) is more complex. The risk of malignancy in these groups has been reported to be higher in children (28–58%, respectively) compared with in adults (5–15% and 15–30% respectively).^{5,7,9} The presence of cytologic atypia in these specimens has been shown to correlate with a higher risk of malignancy in children, pointing to a potential role for pathologic subclassification among the existing Bethesda system categories which could further refine management.⁹ Risk-scoring schemes using ultrasound characteristics in combination with Bethesda system classification have been proposed as a way of further stratifying those nodules which fall into indeterminate cytology groups.¹⁰ Although repeat FNA is often considered in adults with indeterminate FNA results, the ATA pediatric guidelines recommend proceeding directly to thyroid lobectomy plus isthmusectomy given their increased rate of malignancy.⁵

Molecular mutation analysis of cytology specimens with indeterminate pathology may also identify which nodules are at higher risk of malignancy and require more aggressive management.^{7,11} A number of genetic rearrangements and mutations have been associated with thyroid malignancy (BRAF, RAS, RET/PTC, PAX8/PPAR γ). Identification of these markers may increase the positive predictive value of FNA.^{1,7,11} Therefore, a patient with an indeterminate nodule that is high risk by genetic analysis may undergo initial total thyroidectomy rather than staged surgical intervention with thyroid lobectomy followed by completion thyroidectomy if surgical pathology demonstrates malignancy. Preliminary studies in children have suggested that use of molecular testing can reduce the need for a second stage surgery in certain patients and thereby decrease the risk of surgical complications and cost of care.^{7,11} Furthermore, certain mutations have been linked to a greater risk of lymph node metastasis and therefore identification of these markers might prompt more aggressive surgical management, including lymph node dissection.^{7,11} Nonetheless, given the paucity of data validating molecular testing in children, the ATA pediatric guidelines caution against its routine use in guiding clinical decision-making.⁵ Moreover, negative molecular testing does not rule out malignancy as not all papillary thyroid cancers (PTCs) have a detectable mutation. In this situation, management of the nodule should proceed according to the guidelines outlined above.^{7,11}

In summary, ultrasound, thyroid function testing, and ultrasound-guided FNA, taken in the proper clinical context, provide an effective means of risk-stratifying pediatric thyroid nodules to direct management. Increasingly, new tools for assessing malignant potential—cytologic subclassification, molecular markers, detailed

risk-scoring systems using a combination of ultrasound and pathologic findings—are being investigated and may ultimately help refine our diagnostic and treatment algorithms.

PAPILLARY THYROID CANCER

Pediatric PTC is an aggressive disease that frequently presents with regional lymph node (52%) or distant (6%) metastasis. Prognosis is very good with 10-year survival of up to 98%.¹² Surgical resection is the treatment of choice, though some debate exists as to the extent of resection needed, indications for neck dissection, and use of postoperative radioiodine ablation. Regardless of approach, patients with PTC should undergo neck ultrasound and, if needed, computed tomography (CT) or magnetic resonance imaging, to identify central or lateral neck lymph node metastasis, or extrathyroidal extension and to guide operative planning.⁵

Current guidelines and historical practice patterns favor an aggressive approach aimed at eradicating all disease upfront; thus ATA pediatric guidelines favor total thyroidectomy over subtotal thyroidectomy or thyroid lobectomy.⁵ A number of studies have linked total thyroidectomy to lower recurrence rates compared with partial thyroidectomy.¹³⁻¹⁵ Over a third of PTCs have been reported to be multifocal; therefore, total thyroidectomy is advocated as a way of removing any additional foci of disease.¹⁶ Finally, total thyroidectomy allows for postoperative ablation of residual disease with radioactive iodine (RAI) and monitoring for recurrence using serum thyroglobulin (Tg) levels.^{5,12,16}

Total thyroidectomy has been linked to a higher rate of surgical complications compared with thyroid lobectomy. Complications are more likely in younger patients, leading some authors to advocate a conservative approach that reserves total thyroidectomy for select tumors only.^{12,16-19} Contrary to the ATA guidelines, there are several recent studies showing no difference in cancer recurrence or in overall survival based on the extent of surgery—total thyroidectomy *vs* thyroid lobectomy.^{12,16,18} An analysis of pediatric and adolescent patients treated for PTC from 1979 to 2012 at one institution concluded that thyroid lobectomy is a valid alternative to total thyroidectomy for the treatment of patients with PTC without clinical evidence of lymph node metastasis or extrathyroidal invasion.¹⁹ As an adjunct to this approach, thyroid-stimulating hormone (TSH)-suppressive therapy has been effective in managing subclinical disease and preventing relapse, enabling less aggressive surgery that does not necessitate removal of all microscopic disease.¹⁸ These studies underscore the importance of preoperative staging by imaging to guide which patients may be candidates for less aggressive management. However, thus far, no randomized

controlled trials exist comparing partial thyroidectomy to total thyroidectomy, and existing evidence is subject to the limitations of retrospective studies.

Management of lymph nodes is another subject of debate. Compartment-based lymph node dissection at the time of thyroidectomy has generally been recommended for clinically positive nodes and in cases of extrathyroidal tumor extension.^{5,14} This approach has been shown to lower the risk of locoregional recurrence compared with one which excises affected lymph nodes only or in which the neck lymph nodes are not addressed.¹⁴ Prophylactic ipsilateral central lymph node dissection has been favored by some; however, consensus guidelines recognize the need to balance eradication of subclinical disease with potential risks of surgery, and suggest that prophylactic central neck dissection be considered based on tumor characteristics and surgeon experience.⁵ Lateral neck dissection is reserved for cases of biopsy-proven lateral neck metastasis and is not routinely performed prophylactically given the additional morbidity of this procedure.^{5,19}

Postoperative RAI treatment is routinely advocated given the locally advanced stage at presentation of many pediatric PTCs and its association with decreased risk of locoregional recurrence in some retrospective studies.¹²⁻¹⁵ Moreover, it may facilitate monitoring of tumor recurrence using serum Tg levels.¹² However, one large, single-center cohort study did not show any effect of the addition of radioiodine therapy to surgery for PTC on locoregional recurrence or distant metastasis. Additionally, it noted that side effects of treatment are significant, including nausea, vomiting, sialadenitis, xerostomia, bone marrow suppression, gonadal injury, and higher risk of lifetime secondary malignancies.²⁰ Alternatively, radioiodine treatments may be reserved for patients with more advanced cancers, including those with extensive lymph node or distant metastasis.¹⁷ At the Children's Hospital of Philadelphia Thyroid Center, we take an individualized approach to the use of RAI. In a child with low risk of persistent postsurgical disease, either regional or distant metastasis, RAI is typically not administered. For those at higher risk of persistent disease, patients are evaluated with TSH-stimulated Tg and diagnostic whole body scan to assess if RAI would be beneficial. Radioactive iodine is administered if there is lab and/or radiological (¹²³I-whole body scan with or without single-photon emission computed tomography/CT) evidence of persistent disease. After this initial postsurgical time frame, all patients are placed on TSH-suppressive therapy and serial Tg levels are followed every 3 months. The timing and administration of additional RAI is based on previous response to therapy and/or if there is evidence of increasing Tg or anti-Tg levels or progressive anatomic disease that is not amenable to surgery.

FOLLICULAR THYROID CANCER

Follicular thyroid cancer (FTC) is the second most common pediatric thyroid malignancy.²¹ Many studies examining thyroid cancer in children group FTC with PTC. However, these tumors can behave differently, with a lower likelihood of lymph node metastasis and greater likelihood of hematologic spread.²¹ Long-term survival rates are similar to those of PTC.^{22,23} Few studies address the optimal management of FTC in children. Clinical guidelines recommend total thyroidectomy and postoperative RAI therapy for more advanced tumors, including those with evidence of vascular invasion, distant metastasis, and size > 4 cm.⁵ Less advanced tumors may be candidates for thyroid lobectomy without additional treatment.

HEREDITARY THYROID CANCER SYNDROMES

Most PTCs and FTCs are sporadic; however, approximately 5% of these tumors occur in a familial pattern.²⁴ They can present in association with familial cancer syndromes characterized by tumors in other parts of the body, such as PTEN (phosphatase and tensin homolog) hamartoma syndrome, familial adenomatous polyposis, Carney complex, Gardner, Peutz-Jegher and Werner syndromes. A familial form of PTC exists independently of associated cancer syndromes. Familial forms of PTC are associated with earlier age of onset, multifocal and bilateral tumors, the presence of benign thyroid nodules, greater likelihood of nodal metastasis, and worse prognosis.²⁴ No genetic testing for familial PTC is currently available, so family history and the presence of the above characteristics should raise suspicion. Given the more aggressive course of these tumors, some authors recommend treatment with total thyroidectomy with prophylactic central neck dissection and lateral neck dissection for clinically positive nodes, followed by postoperative RAI and thyroid hormone suppression.²⁵

Medullary thyroid carcinoma (MTC), which arises from the calcitonin-producing parafollicular cells of the thyroid gland, occurs in both sporadic and familial forms and represents less than 5% of pediatric thyroid cancer.²⁶ The majority of pediatric MTCs are related to multiple endocrine neoplasia (MEN) type 2a or 2b syndromes or familial MTC, and hereditary cancer syndromes caused by mutations in the *RET* proto-oncogene.²⁶ Medullary thyroid carcinomas are often multifocal and bilateral in nature, and, once spread outside of the thyroid, are usually incurable.^{26,27} Treatment is primarily surgical, aimed at removing all thyroid tissue prior to metastasis of any disease beyond the thyroid. Since MTC ultimately develops in 90 to 100% of patients with MEN 2 syndromes,

and most children with these syndromes are diagnosed prior to the onset of clinical disease, prophylactic thyroidectomy is an accepted approach.^{26,27} Recent debates focus on the optimal timing of surgery. Traditionally, serum calcitonin levels and stimulated calcitonin testing were used to guide timing of surgery. The development of genetic testing and an understanding of the varying clinical phenotypes of different *RET* mutations have led to the incorporation of genetic data in management algorithms. The 2009 ATA guidelines for management of medullary thyroid cancer reflect the central role for genetic testing and advocate an individualized approach to the timing of thyroidectomy based on the risk associated with the patient's *RET* genotype and specific family history of aggressive disease.²⁷ Patients with the highest risk mutations are recommended to undergo prophylactic thyroidectomy within the first year of life, while those with lower-risk mutations may delay surgery with close monitoring for clinical evidence of disease with neck ultrasound and serum calcitonin levels.²⁷

HYPERTHYROIDISM AND GRAVES' DISEASE

Hyperthyroidism in children is usually caused by Graves' disease, though thyrotoxicosis can also be a result of autonomous functioning nodules, congenital activating mutations of TSH receptor gene, subacute thyroiditis, chronic lymphocytic thyroiditis, and pituitary tumors.²⁸ Thyroid surgery can play a role in the management of Graves' disease and toxic adenoma.

The optimal management of pediatric Graves' disease is controversial. Many patients are initially treated with antithyroid drugs. Definitive therapy is considered in patients who fail to achieve remission, are unable to comply with medication regimen, or experience drug toxicity. Definitive therapy can be achieved by surgery (total or near-total thyroidectomy) or by RAI therapy.²⁸⁻³⁰ No evidence-based recommendations favoring one treatment strategy exist, and decision-making between these two options must balance the potential adverse effects of RAI with the risk of surgical complications.³¹ The presence of suspicious nodules, pregnancy, large goiter, compressive symptoms, and age less than 5 years have been suggested as factors to favor surgery over RAI.³⁰

Thyroid surgery in the presence of Graves' disease presents unique challenges as the gland can be highly vascular and prone to leakage of thyroid hormone into the circulation during surgery, risking life-threatening thyrotoxicosis.³² Thus, these patients must be carefully medically managed preoperatively to ensure a euthyroid state. Moreover, they may be preoperatively treated with inorganic iodide (Lugol solution) to decrease thyroid vascularity and blood loss.³²

SURGICAL TECHNIQUE AND COMPLICATIONS

The most common complications after thyroid surgery in children are hypocalcemia (0–32%) and recurrent laryngeal nerve injury (0–40%).³³ Higher complication rates have been linked to total thyroidectomy compared with partial resection, surgery performed for malignancy, and younger age.^{3,18} Several surgical techniques have been suggested to reduce the morbidity associated with these complications.

Parathyroid autotransplantation during total thyroidectomy is widely used in adults if the parathyroid glands become devascularized. This technique can reduce the rate of long-term hypoparathyroidism.^{34,35} One large review of the surgical management of papillary thyroid carcinoma found that the lowest rates of hypoparathyroidism were reported by authors who most commonly used parathyroid autotransplantation.³³ Serial postoperative calcium measurements and postoperative parathyroid hormone level measurements may also identify patients at greatest risk of hypocalcemia-related complications and determine which ones may need calcium and calcitriol supplementation; alternatively, calcium and calcitriol supplementation can be given empirically.^{36,37} The expertise of a pediatric endocrinologist is helpful in medical management of hypoparathyroidism.

Recurrent laryngeal nerve monitoring is widely used in adults as a way of helping the surgeon localize the nerve prior to visualization, particularly in challenging cases such as repeat operations or advanced malignancy. However, its use has not been clearly linked to a reduced rate of postoperative laryngeal nerve palsy.³⁸ Feasibility of intraoperative nerve monitoring has been demonstrated in children; however, commercially available endotracheal tubes used for nerve monitoring may be too large for use in very young children.^{39,40} Alternatives, such as placement of surface electrodes on smaller endotracheal tubes or use of endolaryngeal hookwire electrodes, have been described.⁴⁰

Surgeon volume and experience in pediatric thyroid surgery have been increasingly recognized as a factor reducing complication rates, reducing length of hospital stay, and overall cost of care.⁴¹ Given the relative rarity of thyroid disease in children, the importance of caring for these patients in specialized centers experienced in the care of pediatric patients cannot be underestimated.^{5,41} Moreover, given the complexity of their care and evolving debates over diagnostic and management algorithms in pediatric thyroid disease, these patients are best managed via a multidisciplinary approach, including pediatricians, endocrinologists, surgeons, nuclear medicine specialists, oncologists, radiologists, and pathologists.^{5,41}

CONCLUSION

Pediatric thyroid disease encompasses a diverse range of pathologies. Though much of our existing understanding is based on studies conducted in adults, pediatric thyroid disorders are distinct clinical entities and guidelines should be tailored to this population. Few prospective studies addressing these disorders in children exist, and their progress is made more difficult by the relative rarity of these diseases. The development of the 2015 ATA guidelines for pediatric thyroid cancer represents an important initial step in the effort in developing a consensus to guide those caring for children with thyroid malignancy. Certain trends have become evident. First is the development of increasingly refined risk-adjusted algorithms for the care of malignant disease. As more information becomes available about the clinical, pathologic, molecular, and genetic features of pediatric thyroid cancer, care may become more individualized. Care will be tailored to maximally eradicate an individual's disease while minimizing the adverse effects of overtreatment. Secondly, the rarity of thyroid disease in children has led to an increasing emphasis on treatment in centers with extensive experience in caring for these patients. In particular, there has been greater recognition of the importance of treatment by a high-volume surgeon in improving outcomes. A team approach, with multiple specialists collaborating in the complex decision-making surrounding care of pediatric patient with thyroid disease, is essential.

REFERENCES

1. Corrias A, Mussa A. Thyroid nodules in pediatrics: which ones can be left alone, which ones must be investigated, when and how. *J Clin Res Pediatr Endocrinol* 2013 Mar;5 (Suppl 1):57-69.
2. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016 Jan;26(1):1-133.
3. Scholz S, Smith JR, Chaignaud B, Shamberger RC, Huang SA. Thyroid surgery at Children's Hospital Boston: a 35-year single-institution experience. *J Pediatr Surg* 2011 Mar;46(3):437-442.
4. Buryk MA, Simons JP, Picarsic J, Monaco SE, Ozolek JA, Joyce J, Gurtunca N, Nikiforov YE, Feldman Witchel S. Can malignant thyroid nodules be distinguished from benign thyroid nodules in children and adolescents by clinical characteristics? A review of 89 pediatric patients with thyroid nodules. *Thyroid* 2015 Apr;25(4):392-400.
5. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, Dinauer CA, Hamilton J, Hay ID, Luster M, et al. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2015 Jul;25(7):716-759.
6. Cibas ES, Ali SZ, NCI Thyroid FNA State of the Science Conference. The Bethesda system for reporting thyroid cytopathology. *Am J Clin Pathol* 2009 Nov;132(5):658-665.

7. Monaco SE, Pantanowitz L, Khalbuss WE, Benkovich VA, Ozolek J, Nikiforova MN, Simons JP, Nikiforov YE. Cytomorphological and molecular genetic findings in pediatric thyroid fine-needle aspiration. *Cancer Cytopathol* 2012 Oct;25(5):342-350.
8. Stevens C, Lee JKP, Sadatsafavi M, Blair GK. Pediatric thyroid fine-needle aspiration cytology: a meta-analysis. *J Pediatr Surg* 2009 Nov;44(11):2184-2191.
9. Smith M, Pantanowitz L, Khalbuss WE, Benkovich VA, Monaco SE. Indeterminate pediatric thyroid fine needle aspirations: a study of 68 cases. *Acta Cytol* 2013;57(4):341-348.
10. Arva NC, Deitch SG. Reclassification of cytologically atypical thyroid nodules based on radiologic features in pediatric patients. *J Pediatr Endocrinol Metab* 2015 Jul;28(7-8):753-760.
11. Buryk MA, Monaco SE, Witchel SF, Mehta DK, Gurtunca N, Nikiforov YE, Simons JP. Preoperative cytology with molecular analysis to help guide surgery for pediatric thyroid nodules. *Int J Pediatr Otorhinolaryngol* 2013 Oct;77(10):1697-1700.
12. Jin X, Masterson L, Patel A, Hook L, Nicholson J, Jefferies S, Gaze M, Nassif R, Eller R, Hulse T, et al. Conservative or radical surgery for pediatric papillary thyroid carcinoma: a systematic review of the literature. *Int J Pediatr Otorhinolaryngol* 2015 Oct;79(10):1620-1624.
13. Jarzab B, Handkiewicz-Junak D, Włoch J, Kalembe B, Roskosz J, Kukulska A, Puch Z. Multivariate analysis of prognostic factors for differentiated thyroid carcinoma in children. *Eur J Nucl Med* 2000 Jul;27(7):833-841.
14. Handkiewicz-Junak D, Włoch J, Roskosz J, Krajewska J, Kropinska A, Pomorski L, Kukulska A, Prokurat A, Wygoda Z, Jarzab B. Total thyroidectomy and adjuvant radioiodine treatment independently decrease locoregional recurrence risk in childhood and adolescent differentiated thyroid cancer. *J Nucl Med* 2007 Jun;48(6):879-888.
15. Mihailovic J, Nikoletic K, Srbovan D. Recurrent disease in juvenile differentiated thyroid carcinoma: prognostic factors, treatments, and outcomes. *J Nucl Med* 2014 May;55(5):710-717.
16. Nice T, Pasara S, Goldfarb M, Doski J, Goldin A, Gow KW, Nuchtern JG, Vasudevan SA, Langer M, Beierle EA. Pediatric papillary thyroid cancer > 1 cm: is total thyroidectomy necessary? *J Pediatr Surg* 2015 Jun;50(6):1009-1013.
17. Enomoto Y, Enomoto K, Uchino S, Shibuya H, Watanabe S, Noguchi S. Clinical features, treatment, and long-term outcome of papillary thyroid cancer in children and adolescents without radiation exposure. *World J Surg* 2012 Jun;36(6):1241-1246.
18. Massimino M, Collini P, Leite SF, Spreafico F, Zucchini N, Ferrari A, Mattavelli F, Seregni E, Castellani MR, Cantù G, et al. Conservative surgical approach for thyroid and lymph-node involvement in papillary thyroid carcinoma of childhood and adolescence. *Pediatr Blood Cancer* 2006 Mar;46(3):307-313.
19. Sugino K, Nagahama M, Kitagawa W, Shibuya H, Ohkuwa K, Uruno T, Suzuki A, Akaishi J, Masaki C, Matsuzu K, et al. Papillary thyroid carcinoma in children and adolescents: long-term follow-up and clinical characteristics. *World J Surg* 2015 Sep;39(9):2259-2265.
20. Hay ID, Gonzalez-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 Jun;34(6):1192-1202.
21. Enomoto K, Enomoto Y, Uchino S, Yamashita H, Noguchi S. Follicular thyroid cancer in children and adolescents: clinicopathologic features, long-term survival, and risk factors for recurrence. *Endocr J* 2013;60(5):629-635.
22. Golpanian S, Tashiro J, Sola JE, Allen C, Lew JI, Hogan AR, Neville HL, Perez EA. Surgically treated pediatric nonpapillary thyroid carcinoma. *Eur J Pediatr Surg* 2015 Dec 18 [Epub ahead of print].
23. Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE. Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. *J Surg Res* 2009 Sep;156(1):167-172.
24. Nosé V. Familial non-medullary thyroid carcinoma: an update. *Endocr Pathol* 2008 Winter;19(4):226-240.
25. Sippel RS, Caron NR, Clark OH. An evidence-based approach to familial nonmedullary thyroid cancer: screening, clinical management, and follow-up. *World J Surg* 2007 May;31(5):924-933.
26. Waguespack SG, Rich TA, Perrier ND, Jimenez C, Cote GJ. Management of medullary thyroid carcinoma and MEN2 syndromes in childhood. *Nat Rev Endocrinol* 2011 Oct;7(10):596-607.
27. Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, Moley JF, Pacini F, Ringel MD, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid* 2009 Jun;19(6):565-612.
28. Léger J, Carel JC. Hyperthyroidism in childhood: causes, when and how to treat. *J Clin Res Pediatr Endocrinol* 2013 Mar;5 (Suppl 1):50-56.
29. Rivkees SA, Dinauer C. An optimal treatment for pediatric Graves' disease is radioiodine. *J Clin Endocrinol Metab* 2007 Mar;92(3):797-800.
30. Lee JA, Grumbach MM, Clark OH. The optimal treatment for pediatric Graves' disease is surgery. *J Clin Endocrinol Metab* 2007 Mar;92(3):801-803.
31. Stålberg P, Svensson A, Hessman O, Akerström G, Hellman P. Surgical treatment of Graves' disease: evidence-based approach. *World J Surg* 2008 Jul;32(7):1269-1277.
32. Erbil Y, Ozluk Y, Giriş M, Salmalıoğlu A, Issever H, Barbaros U, Kapran Y, Ozarmağan S, Tezelman S. Effect of lugol solution on thyroid gland blood flow and microvessel density in the patients with Graves' disease. *J Clin Endocrinol Metab* 2007 Jun;92(6):2182-2189.
33. Thompson GB, Hay ID. Current strategies for surgical management and adjuvant treatment of childhood papillary thyroid carcinoma. *World J Surg* 2004 Dec;28(12):1187-1198.
34. Testini M, Rosato L, Avenia N, Basile F, Portincasa P, Piccinni G, Lissidini G, Biondi A, Gurrado A, Nacchiero M. The impact of single parathyroid gland autotransplantation during thyroid surgery on postoperative hypoparathyroidism: a multicenter study. *Transplant Proc* 2007 Jan;39(1):225-230.
35. Walker RP, Paloyan E, Kelley TF, Gopalsami C, Jarosz H. Parathyroid autotransplantation in patients undergoing a total thyroidectomy: a review of 261 patients. *Otolaryngol Head Neck Surg* 1994 Sep;111(3 Pt 1):258-264.
36. Khan MI, Waguespack SG, Hu MI. Medical management of postsurgical hypoparathyroidism. *Endocr Pract* 2011 Mar;17 (Suppl 1):18-25.

37. Roh J-L, Park CI. Routine oral calcium and vitamin D supplements for prevention of hypocalcemia after total thyroidectomy. *Am J Surg* 2006 Nov;192(5):675-678.
38. Pisanu A, Porceddu G, Podda M, Cois A, Uccheddu A. Systematic review with meta-analysis of studies comparing intraoperative neuromonitoring of recurrent laryngeal nerves versus visualization alone during thyroidectomy. *J Surg Res* 2014 May1;188(1):152-161.
39. White WM, Randolph GW, Hartnick CJ, Cunningham MJ. Recurrent laryngeal nerve monitoring during thyroidectomy and related cervical procedures in the pediatric population. *Arch Otolaryngol Head Neck Surg* 2009 Jan;135(1):88-94.
40. Cheng J, Kazahaya K. Endolaryngeal hookwire electrodes for intraoperative recurrent laryngeal nerve monitoring during pediatric thyroid surgery. *Otolaryngol Head Neck Surg* 2013 Apr;148(4):572-575.
41. Tuggle CT, Roman SA, Wang TS, Boudourakis L, Thomas DC, Udelsman R, Ann Sosa J. Pediatric endocrine surgery: who is operating on our children? *Surgery* 2008 Dec;144(6):869-877, discussion 877.