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Consensus Statement

Consensus Statement by the American Association of Clinical Endocrinology (AACE) and the American Head and Neck Society Endocrine Surgery Section (AHNS) on Pediatric Benign and Malignant Thyroid Surgery

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ABSTRACT

Objectives: To provide a clinical disease state review of recent relevant literature and to generate expert consensus statements regarding the breadth of pediatric thyroid cancer diagnosis and care, with an emphasis on thyroid surgery. To generate expert statements to educate pediatric practitioners on the state-of-the-art practices and the value of surgical experience in the management of this unusual and challenging disease in children.
Methods: A literature search was conducted and statements were constructed and subjected to a modified Delphi process to measure the consensus of the expert author panel. The wording of statements, voting tabulation, and statistical analysis were overseen by a Delphi expert (J.J.S.).
Results: Twenty-five consensus statements were created and subjected to a modified Delphi analysis to measure the strength of consensus of the expert author panel. All statements reached a level of consensus, and the majority of statements reached the highest level of consensus.

Abbreviations: AACE, American Association of Clinical Endocrinology; AHNS, American Head and Neck Society; ATA, American Thyroid Association; CT, computed tomography; DSVPTC, diffuse sclerosing variant of papillary thyroid carcinoma; DTC, differentiated thyroid carcinoma; FFL, flexible fiberoptic laryngoscopy; FNA, fine-needle aspiration; IONM, intraoperative nerve monitoring; MRI, magnetic resonance imaging; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; RLN, recurrent laryngeal nerve; Tg, thyroglobulin; TSH, thyroid stimulating hormone; US, ultrasound.

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Conclusion: Pediatric thyroid cancer has many unique nuances, such as bulky cervical adenopathy on presentation, an increased incidence of diffuse sclerosing variant, and a longer potential lifespan to endure potential complications from treatment. Complications can be a burden to parents and patients alike. We suggest that optimal outcomes and decreased morbidity will come from the use of advanced imaging, diagnostic testing, and neural monitoring of patients treated at high-volume centers by high-volume surgeons.

Introduction

Children with thyroid cancer present challenges because physical examination, imaging, and diagnostic techniques are not well defined and have been largely adapted from the adult experience. Pediatric thyroid cancer has a unique natural history, and the burden of surgical complications and the risk of recurrence are endured for many more years than adults. Aggressive diffuse sclerosing variant, more common in young patients, often presents at a more advanced stage and poses significant surgical challenges.

The American Thyroid Association (ATA) has published pediatric thyroid cancer guidelines, and a revision is anticipated shortly. While helpful, they do not fully explore all facets of pediatric thyroid surgical management.[1] This consensus statement provides practical information from experts about how to optimize care for the pediatric patient. It focuses on preoperative workup, surgical planning, intraoperative decisions, and perioperative management. We address evaluation of the thyroid nodule in the pediatric patient, including bloodwork, ultrasound (US) features, when and how to perform a needle biopsy, laryngeal assessment, and when additional imaging for lymph node mapping should be performed. This manuscript will discuss specific surgical issues, including intraoperative nerve monitoring (IONM), surgical decisions, when to consider staging the surgery, and postoperative cancer surveillance. Finally, we will emphasize the **preoperative** identification of these individuals so that appropriate resources and experience can be directed to them.

This expert consensus statement is from the American Association of Clinical Endocrinology (AACE) in collaboration with the American Head and Neck Society (AHNS) Endocrine Surgery Section. We do not present this material as representing an accepted standard of care. The AHNS represents the largest U.S. society with expertise in the surgical management of the thyroid, with a focus on complex thyroid cancer management. It is our hope that this document improves the quality of medical and surgical care of the pediatric patient, reduces variation in the management of such patients, and facilitates further research for these thyroid surgical patients.

Methods

This AACE consensus statement on pediatric thyroid cancer surgery is based on the writing committee's expert opinion, a review of current scientific literature, and the application of recent guidelines developed by the American Academy of Otolaryngology-Head and Neck Surgery, AHNS, and ATA. A librarian conducted a literature search on May 31, 2019, in PubMed (2009-2019) using the following terms: *thyroid neoplasm, thyroid surgery, complications, treatment outcome, pediatric* (aged <18 years), *child, adolescent, papillary thyroid cancer, sclerosing variant, surgical/surgeon volume, nerve damage, laryngeal nerve, tracheotomy,* and *hypocalcemia*. The search resulted in 315 citations, including 69 specific complications, 34 general complications, and 34 surgical volume considerations.[2]

The librarian who conducted the literature search was a staff librarian from the University of Arkansas for Medical Sciences and not an AACE or AHNS employee. Literature was limited to the English language. Search terms were selected by the organizing authors (B.C.S and G.W.R). This consensus protocol was modeled after similar efforts performed by many of the authors of this work.[3] This was not a meta-analysis. Preferred Reporting Items for Systematic Reviews and Meta-Analyses analysis was not done. The literature search was used to inform the experts of contemporary literature on the subject. This AACE/AHNS writing committee drafted concluding statements, wrote the supporting text, and utilized a modified Delphi method to determine consensus.[4–6] Clinical statements were divided according to surgical and diagnostic topics and circulated to surgeons specifically or all authors, respectively, to vote using a 1 to 9 Likert scale to achieve consensus (Table 1). Votes based on available evidence and expert opinion of the committee decided the level of consensus among committee members regarding statements, indicated as strongly agree, agree, or no consensus. Criteria for consensus were a mean $\geq$7 (agree) with 0 to 1 outliers or a mean $\geq$7 with 2 outliers but with neither outlier value <5 (neutral). All surgical statements reached a consensus, but

Table 1
Delphi Results

Statements	Vote value[a] Mean (range)	Consensus
Diagnostic		
S1a	8.6 (7-9)	Yes
S1b	8.6 (5-9)	Yes
S3a	8.9 (8-9)	Yes
S3b	8.9 (8-9)	Yes
S3c	8.2 (3-9)	Yes
S3d	8.4 (5-9)	Yes
S3e	7.3 (3-9)	No
S3f	8.0 (3-9)	Yes
S3g	8.8 (7-9)	Yes
S4a	7.9 (5-9)	Yes
S4b	7.6 (5-9)	No
S4c	8.3 (5-9)	Yes
S6	8.9 (7-9)	Yes
S7e	8.9 (7-9)	Yes
S9	8.6 (7-9)	Yes
Surgical		
S2a	8.0 (5-9)	Yes
S2b	7.6 (5-9)	Yes
S5	8.6 (5-9)	Yes
S7a	8.2 (6-9)	Yes
S7b	8.2 (7-9)	Yes
S7c	8.7 (7-9)	Yes
S7d	9.0 (9-9)	Yes
S8	8.8 (7-9)	Yes
S10	9.0 (9-9)	Yes
S11	7.4 (5-9)	Yes

[a] Each panel member selected a vote value for each statement based upon the following scale: 1, strongly disagree; 3, disagree; 5, neither agree nor disagree; 7, agree; and 9, strongly agree. Vote values of 2, 4, 6, or 8 were allowed if the strength of opinion fell between categories.

2 diagnostic statements did not reach consensus (3e and 4b). Data analysis was performed by 2 authors (J.R. and J.J.S.) using Stata 15.0 (StataCorp LLC). The governing bodies of AACE and AHNS provided a final review of the document, iterative feedback, and ultimate approvals prior to journal submission.

The following consensus statements, as interpreted by weighted scoring (Table 1), should be used by the reader for general clinical guidance. Specific clinical circumstances may not be explicitly applicable to the statements presented in this document.

Part I: Pediatric Thyroid Surgery Fundamentals

Statement 1a: Knowledge of whether there is a history of generalized radiation exposure or exposure specifically to the neck in a pediatric patient being evaluated for thyroid cancer is essential. Committee consensus: strongly agree (average Likert score, 8.6).

Statement 1b: Knowledge of a family history of thyroid cancer in a pediatric patient being evaluated for thyroid cancer is important. Committee consensus: strongly agree (8.6).

History

Thyroid nodules are rare in children; however, the risk of malignancy is significantly higher than in adults (22%-26% vs 5%-10%).[7] According to the National Cancer Institute registry, 1.8% of all thyroid malignancies diagnosed in the United States are in patients aged <20 years. Thyroid cancer represents the second most common malignant tumor in teenage girls.[7]

Most pediatric thyroid malignancies are differentiated thyroid carcinomas (DTCs), with a great majority being papillary thyroid carcinoma (PTC) and its variants. Thyroid cancer in children usually presents as an asymptomatic thyroid mass detected by medical care providers, parents, or the patients themselves. Nonpalpable thyroid nodules are often detected on imaging performed for the evaluation of other medical conditions. Occasionally, thyroid cancer presents as cervical lymphadenopathy. Less commonly, thyroid carcinoma in children can present as pulmonary metastases, typically detected by chest imaging for other purposes. Several clinical features and risk factors are associated with thyroid nodules and cancer in the pediatric population (Box 1 and 2).[8–22]

Box 1
Concerning History and Physical Findings for Pediatric Thyroid Cancer

Patient history
- Prior thyroid disease or treatment
- Head and neck irradiation
- Bone marrow transplantation
- Other malignancies

Family history
- Thyroid cancers, specifically papillary/follicular/medullary thyroid cancer types
- Autoimmune thyroiditis or thyroid nodules
- Multiple colon polyps, colon cancer
- Pheochromocytoma/paraganglioma/MEN syndromes

Physical examination findings
- Pain at the site of the nodule
- Hoarseness
- Difficulty in swallowing and/or breathing

References: 8–16,18–21.

Box 2
General Clinical Characteristics of Familial Thyroid Tumors

- Gender incidence equal
- Family history of nodular thyroid disease or cancer and, in some cases, other endocrine or nonendocrine lesions
- Multifocal and bilateral tumors
- Precursor lesions (C-cell hyperplasia)

References: 8–10,14,16.

Statement 2a: Voice assessment and laryngeal examination are fundamental components of the preoperative physical examination. Committee consensus: between agree and strongly agree (8.0).

Statement 2b: Voice assessment and laryngeal examination are fundamental components of the postoperative physical examination. Committee consensus: between agree and strongly agree (7.6).

Physical Examination

All children presenting for thyroid cancer evaluation require a thorough physical examination. Vocal quality and respiration should be assessed for signs of vocal fold dysfunction or airway compression. This examination may involve listening, endoscopy, and/or neck US. The central neck should be palpated for laryngeal landmarks, neck contour, gland size, and nodularity. The lateral neck should be carefully examined, taking note of any enlarged lymph nodes. As children often have palpable cervical nodes, nodes identified in a child with suspected thyroid malignancy should be further evaluated by US and cytology, as indicated (see below).

Children with thyroid cancer frequently have large-volume thyroid disease that places critical anatomy at risk during surgery. All pediatric patients should undergo a preoperative laryngeal examination to establish baseline laryngeal function prior to surgery for thyroid nodules or multifocal or bilateral malignant thyroid disease (see below).[23,24] Laryngeal US may be considered as an alternative to endoscopy to evaluate vocal fold motion if the examination adequately demonstrates glottic function.[25]

Fine-needle Aspiration

Evaluation of thyroid nodules in pediatric patients is based on clinical risk factors and ultrasonographic features coupled

Table 2
Clinicopathologic Features of Medullary Thyroid Carcinoma Syndromes

Medullary thyroid carcinoma syndromes	Clinicopathologic features
MEN-2A	Medullary thyroid carcinoma, C-cell hyperplasia
Sipple syndrome	Adrenal pheochromocytoma and adrenal medullary hyperplasia
	Parathyroid hyperplasia (adenomas)
MEN-2B	Medullary thyroid carcinoma and associated C-cell hyperplasia
	Adrenal pheochromocytoma and adrenal medullary hyperplasia
	Neuromas of the oral cavity and gastrointestinal tract, musculoskeletal abnormalities (Marfanoid habitus), eye lens abnormalities

References: 11,15,18.

Table 3
Nonmedullary Thyroid Cancer as the Main Tumors of Familial Syndromes

Disorder; chromosome location	Thyroid lesion
Familial papillary thyroid carcinoma/papillary renal neoplasia; 1q21	Papillary thyroid carcinoma, adenomatoid nodules, papillary renal neoplasia
Familial nonmedullary thyroid carcinoma with oxyphilia; 19p13.2	Adenomatoid nodules, papillary thyroid carcinoma with oxyphilia
Familial nonmedullary thyroid carcinoma 1; 2q21	Papillary thyroid carcinoma, adenomatoid nodules
Familial nonmedullary thyroid carcinoma; 19p13, 9p22.33, 14q13.3	Papillary thyroid carcinoma, adenomatoid nodules
Familial multinodular goiter with papillary thyroid carcinoma; 14q, 8p23.1-p22	Papillary thyroid carcinoma, multinodular goiter with cyst formation, adenomatoid nodule, follicular adenoma

References: 12–14.

Table 4
Nonmedullary Thyroid Lesions Associated with Familial Tumor Syndromes

Disorder; chromosome location; gene	Thyroid lesion
Familial adenomatous polyposis; 5q21; *APC*	Papillary thyroid carcinoma cribriform-morular variant
PTEN hamartoma tumor syndrome; 10q22-23; *PTEN*	Papillary thyroid carcinoma, follicular thyroid carcinoma, adenomatoid nodule, lymphocytic thyroiditis
Carney complex; 17q24; *PRKA-R1a*	Adenomatoid nodule, follicular adenoma, follicular thyroid carcinoma, papillary thyroid carcinoma
MEN-1; 11q13; *MEN1*	Nodular goiter, follicular adenoma
MEN-2A; 10q11.2; *RET*	Papillary thyroid microcarcinoma
McCune-Albright syndrome; 20q13.1-13.2; *GNAS1*	Nodular goiter/follicular thyroid carcinoma, follicular adenoma
Peutz-Jeghers syndrome; 19p13.3; *LKB1*	Nodular goiter, papillary thyroid carcinoma
DICER1 syndrome; 14q32; *DICER1*	Multinodular goiter, follicular adenoma, differentiated thyroid carcinoma

References: 13,14.

with fine-needle aspiration (FNA), similar to ATA adult guidelines. In a subset of patients, molecular analysis may be considered.[26] The increased risk of thyroid nodules and DTC is associated with the female gender, adolescent age, a history of exposure of ionizing radiation to the neck, and predisposing familial syndromes (Boxes 1 and 2, Tables 2 through 4).[27] Most thyroid nodules are selected for FNA based on their US characteristics. FNA specimens are reported according to The Bethesda System for Reporting Thyroid Cytology.[28] This reporting consists of 6 categories, and each is associated with a range for risk of malignancy. The categories are as follows: I, nondiagnostic; II, benign; III, atypia of undetermined significance/follicular lesion of undetermined significance; IV, follicular neoplasm; V, suspicious for malignant; and VI, malignant. Categories III and IV are considered indeterminate. In pediatric patients, up to 35% of thyroid nodules are classified as indeterminate. Pediatric patients have a higher risk of malignancy in these indeterminate classes compared with adults.[29] Options for the indeterminate nodules include excision or repeat FNA with molecular testing. Care should be taken to possibly hold an additional specimen in reserve for molecular testing if indicated and to avoid an additional FNA.

Significance and Application of Molecular Markers in Pediatric Populations

Molecular testing of thyroid FNA specimens has been shown to increase the posttest probability of thyroid malignancy on surgical resection. This is true for those cases diagnosed as Bethesda III and IV.[30] By molecular analysis, both adult and pediatric DTC show activation of the phosphatidylinositol-3-kinase/protein kinase B and mitogen-activated protein kinase signaling pathways. In pediatrics, gene fusions occur with a higher frequency compared with adults, with approximately 60% to 70% of pediatric thyroid cancers found to have a fusion oncogene compared with 15% of adults.[31,32]

Point mutations are found in approximately 30% of pediatric patients compared with 70% in adults.[32,33] *BRAF* (BRAFV600E) mutations are the most common, found in 20% to 30% of pediatric PTCs. *RAS* mutations are very uncommon in this patient group.[34,35] Other molecular alterations rarely seen in pediatric tumors include PAX8-PPARγ fusion protein, *NTRK* gene fusions, and *BRAF* gene fusions. In pediatric patients, based on limited data, a *RET*/PTC rearrangement or *NTRK* or *BRAF* gene fusions may be markers of potential aggressive behavior.[31–33,36]

Statement 3a: US examination of the thyroid and central/lateral neck is necessary in the setting of concern for thyroid cancer; US is an extension of the physical examination and can characterize the extent of thyroid pathology and regional adenopathy. Committee consensus: strongly agree (8.9).

Statement 3b: US examination provides essential information in the evaluation of pediatric patients deemed at risk for thyroid cancer (Box 1). Committee consensus: strongly agree (8.9).

Statement 3c: US-guided FNA biopsy is obtained from all pediatric patients who are considered at risk for thyroid cancer by history and/or by initial evaluation results. Committee consensus: between agree and strongly agree (8.2).

Statement 3d: Suspicious thyroid nodules and/or lymph nodes should be biopsied under US guidance to ensure precision in sampling and adequacy of the specimen. Committee consensus: between agree and strongly agree (8.4).

Statement 3e: When cytology is indeterminate (Bethesda III or IV), molecular testing can be considered. Committee consensus: agree (7.3).

Statement 3f: When cytology is insufficient (Bethesda I), biopsy should be repeated within 2 to 8 weeks. Committee consensus: between agree and strongly agree (8.0).

Statement 3g: Similar to adults, US screening for nodular thyroid disease is not recommended in the general pediatric population. Committee consensus: strongly agree (8.8).

Ultrasound

It is unclear if prospective US screening should be performed for children at increased risk for thyroid cancer, including those

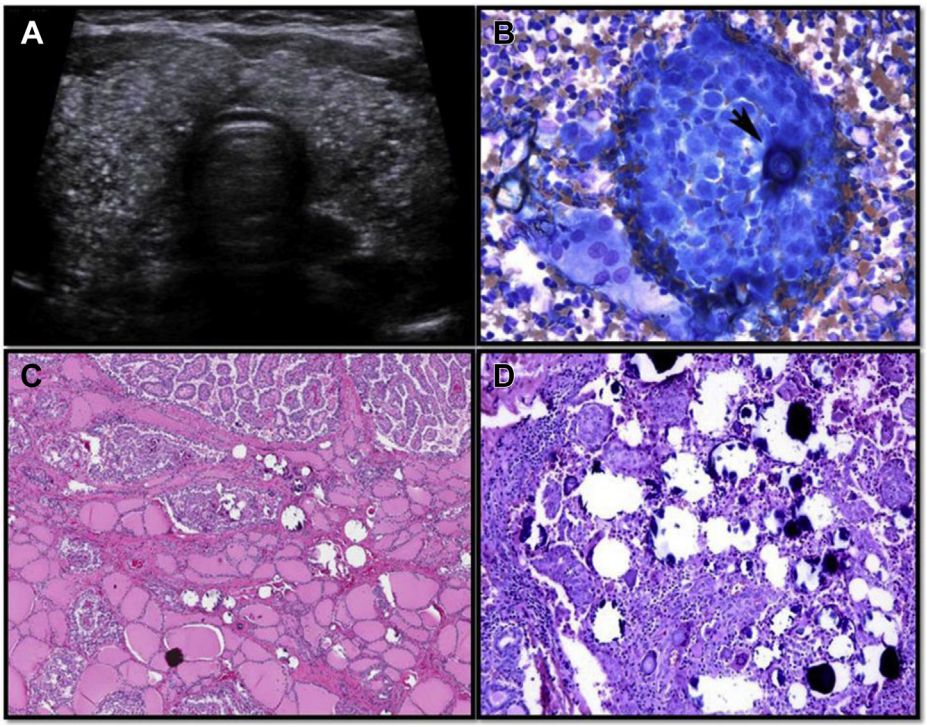

Fig. Composite figure of the diffuse sclerosing variant of papillary carcinoma cancer. *A*, Typical "snowstorm" appearance on US due to numerous microcalcifications. *B*, The air-dried fine-needle aspiration smear of diffuse sclerosing variant shows a nest of tumor cells with lamellated calcifications (psammoma body) (arrow). *C* and *D*, Histopathology (low and high magnifications, respectively) of a resection specimen shows a tumor nest with numerous psammoma bodies (within the tumor nests and intrathyroidal lymphatics) infiltrating the thyroid parenchyma.

with a history of underlying thyroid disease (family history of nonmedullary thyroid cancer, prior radiation exposure, etc.).[37] Children **at risk** should be considered for an annual physical examination of the neck (Box 1). In these children, US is the preferred first diagnostic imaging modality for assessment of palpable neck abnormalities due to ease and avoidance of exposure to radiation. Thyroid and neck US may be performed separately, based on local facilities and practices.

Because thyroid gland volume changes with age, nodule characteristics rather than size should drive the decision regarding FNA. Nodules with suspicious features, such as hypoechogenicity, solid composition, microcalcification, taller-than-wide morphology, irregular margins, and associated abnormal lymph nodes, should be biopsied.[38,39] It is important to note that diffuse sclerosing variant of papillary thyroid carcinoma (DSVPTC) typically presents with diffuse calcifications and hypervascularity throughout 1 lobe or the entire gland, rather than as a discrete nodule (Fig.). Hyperfunctioning nodules need not be biopsied due to a low risk for malignancy.

Even in young children, FNA can successfully be achieved with local anesthesia, such as after application of topical lidocaine and prilocaine ointment. Conscious sedation may occasionally be required. FNA should always be performed under US guidance to reduce the risk of sampling error. Bedside or real-time confirmation of sample adequacy can also help to assure that a successful diagnosis is made.

US should be used for preoperative planning. For the lateral neck, US and computed tomography (CT) demonstrate similar sensitivity for the detection of metastatic nodal disease; however, CT is superior to US for the central neck and should be considered in cases of bulky disease (Statement 9).[39] Cross-sectional imaging is also helpful as a map during surgery, especially in the setting of US of extensive/bulky or inferiorly extending nodal disease. Nodal classification systems are useful for multidisciplinary communication and surgical planning.[40] Nodal mapping is valuable for bulky nodal disease, allowing for a comprehensive dissection of affected neck regions.

Statement 4a: A preoperative (or prebiopsy) thyroid function panel (free thyroxine and thyroid stimulating hormone) informs preoperative management. Committee consensus: between agree and strongly agree (7.9).

Statement 4b: Preoperative treatment of vitamin D deficiency can mitigate challenges managing postoperative hypocalcemia. Committee consensus: agree (7.6).

Statement 4c: Perioperative calcium-related testing (calcium, ionized calcium, magnesium, phosphorus, intact parathyroid hormone, and 25-hydroxy vitamin D) informs patient management. Committee consensus: between agree and strongly agree (8.3).

Laboratory Evaluation and Patient Management

Laboratory evaluation of children undergoing thyroid surgery should include thyroid stimulating hormone (TSH), free thyroxine, thyroid autoantibodies, and a panel that includes calcium, albumin, phosphorus, and magnesium, as well as 25-hydroxy vitamin D and intact parathyroid hormone (parathyroid hormone; in cases of total or completion thyroidectomy). Free or total triiodothyronine may be ordered with a suppressed TSH. Thyroid function testing is ideally drawn before FNA to determine if the nodule is hyperfunctional. In cases of Graves

hyperthyroidism, 7 to 10 days before surgery, iodine drops should be started (1 to 3 drops, three times a day) to reduce thyroid gland bleeding during surgery.[41]

Because children who undergo total thyroidectomy are at risk for postoperative hypoparathyroidism, treatment with calcitriol (eg, 0.5 μg twice a day), with or without calcium carbonate, for 3 days prior to surgery can be considered. This approach has been effective for adults but not studied in children. Preoperative supplementation with vitamin D3 appears particularly prudent if a vitamin D deficiency is identified in advance.[38] Care should be exercised when using calcitriol to avoid hypercalcemia. If the patient has a low-calcium diet, supplemental calcium (500-1000 mg of elemental calcium, three times a day) may be added preoperatively.

At regular intervals after surgery, calcium levels should be followed. If hypocalcemic and not already taking calcitriol, it should be initiated (0.5 μg twice a day). Postoperatively, calcitriol may be weaned. Serum calcium and phosphorus should be monitored weekly until calcitriol is discontinued.[38,39] Pre- and postoperative calcium and calcitriol supplementation has been shown to reduce the frequency of symptomatic hypocalcemia after surgery in adults.[42,43]

Following total thyroidectomy, levothyroxine should be started the day after surgery at a weight-appropriate dose (1.5-2.0 μg/kg/day). Thyroid levels should be checked within 4 to 6 weeks after initiation and any subsequent dose changes.[1] No sooner than 6 weeks after surgery, calcitonin should be measured in individuals with medullary thyroid carcinoma and thyroglobulin (Tg) and anti-Tg antibodies in individuals with DTC. About 6 months after surgery, thyroid bed US with lymph node mapping should be obtained.[44–46]

Statement 5: Preoperative laryngeal examination, preferably by direct visualization (flexible fiberoptic laryngoscopy), is required for surgical planning. Committee consensus: strongly agree (8.6).

Preoperative Laryngeal Assessment

Flexible fiberoptic laryngoscopy. Flexible fiberoptic laryngoscopy (FFL) has long been established as a safe and effective procedure for evaluating laryngeal dynamics. This is easily performed in awake patients, from infants to adults.[47,48] This technique establishes the functional status of the vocal cords, both pre- and postoperatively. The authors recommend consistent pre- and postoperative confirmation, by either FFL or another established technique (rigid transoral laryngoscopy), of the status of vocal fold mobility in all pediatric patients undergoing thyroid surgery. Preoperative vocal cord dysfunction suggests locoregional invasion and more advanced disease and influences the discussion with the patient's family regarding the risks of surgery and possible tracheotomy. Preoperative vocal cord assessment also has implications for application and interpretation of IONM during surgery and for surgical strategy.[49,50] Postoperative vocal cord assessment is useful to definitively demonstrate whether surgery resulted in any degree of impaired vocal fold mobility. Accurate knowledge of the postoperative functional status of the vocal cords is important when considering the safety of deglutition, the potential need for voice/laryngeal interventions, and the risk of any future surgery involving the thyroid bed.

US vocal cord visualization. Transcutaneous laryngeal US has been shown to be a safe and effective alternative to FFL for the evaluation of vocal cord function. US evaluation can be useful in patients who are unable to tolerate transnasal FFL and is especially suited to pediatric patients because their laryngeal thyroid cartilage is typically noncalcified and more sonographically lucent. Providers other than otolaryngologists (eg, endocrinologists and general surgeons) may prefer US evaluation.[51–53]

Statement 6: Postoperative risk assessment and stratification is used to determine the need for and amount of postoperative radioactive iodine. Committee consensus: strongly agree (8.9).

Radioactive Iodine

Radioactive iodine (RAI) therapy has been traditionally given to children with DTC with the objectives of decreasing the rate of recurrence and eliminating residual thyroid tissue to allow better monitoring for recurrent disease using Tg. Due to the increased awareness of long-term complications from RAI, including pulmonary fibrosis, transient effects on fertility and/or menstrual cycles, and risk of salivary malignancy efforts have increased to determine which patients benefit most from this therapy and in whom it should be avoided.[1,54,55]

Occasionally, RAI is considered indicated upon return of pathology that demonstrates aggressive histology and/or large numbers of nodal metastases (>5). If the former features are discovered following a thyroid lobectomy, completion thyroidectomy with possible reoperative nodal surgery may be required to prepare the patient for subsequent RAI administration.

Both the ATA pediatric and adult guidelines stratify patients with PTC into low-, intermediate-, and high-risk groups for recurrent disease.[56] Studies of adult patients (limited pediatric data have been published) with low-risk DTC have demonstrated no improvement in survival and increased rates of second primary malignancies in those treated with RAI.[54,55] Some pediatric thyroid cancers can be intermediate- or high-risk when full histologic data are available postoperatively. In such patients, RAI is indicated due to a higher rate of recurrence.[57,58]

Thyroid cancer restaging is initially performed 6 to 8 weeks after surgery. It is recommended that ATA low-risk patients be assessed with TSH-suppressed Tg. ATA intermediate- and high-risk patients should undergo a diagnostic whole-body scan and TSH-stimulated Tg measurement to assess for persistent disease.[59] Based on available information, RAI appears to best be used in patients with N1a/N1b or greater disease and in those with nodal or locoregional disease unamenable to remedial surgery.[60,61] Patients with pulmonary metastases are also candidates for RAI therapy, but remission rates depend on the volume and distribution of metastatic disease.[62]

Postoperatively, children should undergo a thorough physical examination to assess for recurrent disease, including Tg measurements and routine US examinations of the thyroid bed and central and lateral lymph node compartments. Follow-up encounters should be adjusted based on each child's risk profile.[1,56] Providers should acquaint themselves with the risks of RAI for younger patients.

Part II: Complex Surgical Issues Unique To Pediatric Patients

The most common presentation of pediatric thyroid cancer is as a solitary thyroid nodule. Children with PTC are more likely to have an extrathyroidal extension, regional lymphadenopathy, and pulmonary metastases compared with their adult counterparts. Multifocal and bilateral PTCs are also more common in children, as is diffuse sclerosing variant, the latter posing a

greater technical challenge due to its unencapsulated, widely invasive nature.[1,63]

Statement 7a: Compartmental neck dissection is required for all biopsy-proven malignant nodal diseases (N1a or N1b). Committee consensus: between agree and strongly agree (8.2).

Statement 7b: In expert hands, elective central neck dissection is an option for patients with advanced primary disease Committee consensus: between agree and strongly agree (8.2).

Statement 7c: The benefits of an elective central neck dissection must be balanced with the low risk of missing clinically significant disease on US or during surgery and the increased risk of permanent hypoparathyroidism. Committee consensus: strongly agree (8.7).

Statement 7d: Elective lateral neck dissection is unwarranted for differentiated thyroid cancer. Committee consensus: strongly agree (9.0).

Statement 7e: Complex pediatric thyroid cancer cases are ideally referred to surgeons and centers with experience and multidisciplinary support. Committee consensus: strongly agree (8.9).

An absolute indication for a primary neck dissection is the presence of biopsy-proven nodal metastases.[64] Total thyroidectomy with elective central node dissection is controversial. Because of a greater likelihood of nodal metastases in children, consideration can be given to an ipsilateral elective central neck dissection to possibly reduce reliance on ^{131}I therapy, avoid reoperative procedures, and improve disease-free survival. These concerns are placed in equipoise with an increased risk for complications, particularly hypoparathyroidism.[65] If lifelong complications are to be avoided, operator experience is critical. Surgeons operating on children should be performing at least 30 thyroid operations per year in high-volume centers with dedicated pediatric specialists.[17,63–65]

Statement 8: Intraoperative laryngeal nerve monitoring is a beneficial guide given the thin caliper of the RLN and challenging pediatric anatomy in the setting of bulky thyroid/lymph node disease. Committee consensus: Strongly agree (8.8).

The thin caliber of the recurrent laryngeal nerves (RLNs) and external branch of the superior laryngeal nerves puts them at increased risk for injury. IONM can aid in the identification of nerves, the decision to possibly stage surgery, and the avoidance of bilateral RLN injury. Cases with extensive lymphadenopathy and/or extrathyroidal extension pose a particular risk to the RLNs as well as the parathyroid glands. Abundant thymic tissue can also make identification of these structures difficult.[66,67] IONM has been shown to be safe in the pediatric population.[62] Due to increased risk of nerve injury, postoperative laryngeal evaluation should be performed after all thyroid procedures and before pursuing contralateral surgery for children undergoing staged or completion thyroidectomy procedures.[66]

In patients with a small solitary thyroid cancer confined to 1 lobe and clinically negative nodes, consideration should be given to thyroid lobectomy, which avoids the risks of hypoparathyroidism, bilateral RLN injury, tracheotomy and, possibly, the need for lifelong levothyroxine replacement therapy.

Hypocalcemia is the most common complication after total thyroidectomy. Hypocalcemia can result in prolonged hospital admission.[68] Hypocalcemia management starts with the anticipation of the complication. It involves providing temporary or permanent calcium and calcitriol supplementation as well as the monitoring of symptoms and serum calcium levels.[69,70] Operative vigilance should be maintained for parathyroid glands, which are smaller in children. Postoperative hypocalcemia can be managed in anticipation or with the assistance of intraoperative parathyroid hormone monitoring.[71]

Techniques to Reduce Length of Stay

Length of stay (LOS) is a frequent metric used in outcome studies as a surrogate of quality related to thyroidectomy. Surgical complications, such as hypocalcemia, RLN injury, and hematoma, increase the LOS.[68] LOS after thyroidectomy ranges from the same day to several days, with reported averages in large cohorts of 1 to 3.3 days.[66–68] In several large studies, center and surgeon case volume has been demonstrated to correlate with improved outcomes and a shorter LOS.[72–78] Intraoperative parathyroid hormone measurement and early postoperative engagement by pediatric endocrinology as well as calcium supplementation may shorten hospitalization.

Life Expectancy and Length of Time to Endure Surgical Morbidities

Patients undergoing thyroidectomy for DTC have an excellent long-term prognosis. Although this is certainly good for patients, it means that the potential for living with complications of thyroid surgery for decades is very high. PTC accounts for 95% of thyroid cancers in adolescents and children. These same authors found a 98% 5-year survival rate, 97% 10-year survival rate, and 92% 30-year survival rate.[79] A review of 1690 cases of pediatric thyroid cancer from 61 European cancer registries showed a 5-year survival rate of 99% in PTC and a 5-year survival rate of 95% in medullary thyroid cancer.[80] A study of 227 patients with DTC aged 20 years or younger at the time of diagnosis showed survival rates of 99.3% at 10 years, 99.3% at 20 years, and 96.5% at 40 years.[81–83] These survival statistics emphasize the potential impact of surgical complications on the patient's quality of survivorship.

Statement 9: CT or magnetic resonance imaging should be used in cases of bulky primary and/or nodal disease, posterior thyroid masses or vocal cord paralysis on presentation. Committee consensus: strongly agree (8.6).

Cross-sectional Imaging for Bulky Lymphadenopathy

Cervical US is the most common imaging modality employed while evaluating thyroid disease in both pediatric and adult patients.[84–87] US is also well suited to evaluate the lateral neck for lymphadenopathy, and it is commonly used to provide visualization for fine-needle biopsies of both thyroid and extrathyroidal lesions. Central neck nodes can be visualized in selected patients. US alone provides sufficient imaging information in most cases. Cross-sectional imaging by CT or magnetic resonance imaging (MRI) can provide useful information beyond what is obtained by US, such as the central neck.[1,56,84,88] We chose to emphasize a few scenarios, in particular, that benefit from such imaging.

In the setting of bulky lymphadenopathy, CT or MRI can be useful to better delineate the extent of the disease.[88,89] Advanced diseases can demonstrate skull base or mediastinal involvement, invasion of the aerodigestive tract, or encasement of the carotid sheath structures. The choice of CT or MRI can be made according to factors such as whether more osseous or soft tissue detail is desired. Ultimately, imaging is left to surgeon preference. Some have argued for MRI over CT due to the necessity of waiting for

iodine-based CT contrast to clear from the body prior to RAI. However, radioiodine therapy is typically given sufficiently far after a preoperative CT, so this is rarely an issue. The potential health consequences of radiation exposure from CT imaging has discouraged its use.[89–92] Additionally, with young patients, axial imaging may require sedation or general anesthesia.[89] This is quite relevant, as recent studies have analyzed the potential impact of general anesthesia on cognitive development in young children.[93,94]

Posterior Invasive Disease and Paralyzed Vocal Cord on Presentation

In the setting of a paralyzed vocal fold on presentation or a posterior location of a thyroid mass on US, cross-sectional imaging is recommended. The additional imaging information provided can prove useful in surgical planning, particularly in relation to RLN management and monitoring. With a unilateral vocal fold paresis noted preoperatively, axial imaging detail can be useful for surgical planning on the contralateral side because efforts are made to minimize the risk of iatrogenic nerve injury that could lead to bilateral vocal fold paresis. The MRI or CT imaging detail provided with a posterior thyroid mass can inform surgical planning if it may require more than typical dissection and manipulation of the RLN.[88,95] Along with cross-sectional imaging, all of these scenarios benefit from laryngeal neuromonitoring, the details of which follow.

Statement 10: Intraoperative recurrent laryngeal nerve monitoring is used to (1) localize and protect the recurrent laryngeal and superior laryngeal nerves during surgery, (2) predict postoperative nerve dysfunction, and (3) decide on the possibility of staging surgery. Committee consensus: strongly agree (9.0).

Statement 11: Guidelines and the latest literature on nerve monitoring techniques need to be consulted for safe thyroidectomy and central neck dissection around the branches of the vagus nerve. Committee consensus: agree (7.4).

Intraoperative Nerve Monitoring

IONM of the RLNs and external branch of the superior laryngeal nerves has become increasingly common during adult thyroid and parathyroid surgery. Surgeons of all specialties are now using nerve monitoring.[50,96] Nerve stimulation can facilitate identification of the nerve, particularly during revision or technically difficult cases, as well as prognosticate postoperative nerve function.[97] IONM may be particularly useful in young children, in whom there is a higher risk of postoperative nerve paralysis and the need for tracheotomy. Recent guidelines provide guidance for the IONM management of bilateral thyroid surgery applicable to the pediatric age group.[98–101] There are various techniques for nerve monitoring if appropriately sized electromyographic monitoring endotracheal tubes are unavailable.[98]

IONM facilitates whether to stage a total thyroidectomy or to proceed with nerve sacrifice.[99,100] The negative predictive value for electromyographic loss of signal and vocal cord paralysis is 99.5%, and the positive predictive value of electromyographic loss of signal and vocal cord paralysis is 75%.[50] For nerves that are encased by a tumor, attempts to preserve the RLN should be made when there is contralateral vocal cord paralysis or when ipsilateral stimulation proximal RLN activity is present.[50,96,98] Recent guidelines provide guidance in the management of invasive scenarios and are applicable to the pediatric age group.[98] If a vocal cord is mobile preoperatively, attempts should be made to preserve an intact nerve and to avoid its sacrifice. When nerve signal is lost intraoperatively, staging surgery allows for possible recovery prior to placing the contralateral nerve at risk. Staged surgery has not been shown to negatively influence oncologic outcomes in adult patients.[102]

Diffuse Sclerosing Variant

DSVPTC is an aggressive form of PTC with a high prevalence in pediatric patients and those with a history of irradiation.[103] Other aggressive invasive variants may be encountered in this population (eg, widely invasive follicular carcinoma), but we will focus on DSVPTC as the archetype for invasive pediatric thyroid cancer. DSVPTC accounts for approximately 2% to 6% of PTCs.[104,105] DSVPTC presents with diffuse involvement of 1 or both thyroid lobes with or without a discrete mass. It has an increased incidence of extrathyroidal extension, lymph node involvement, and pulmonary metastasis.[105,106] Histologically, squamous metaplastic features, numerous psammomatous calcifications, and extensive lymphovascular involvement in a background of chronic thyroiditis characterize DSVPTC.[107]

DSVPTC has distinguishable sonographic characteristics, including diffuse thyroid enlargement, hypoechoic heterogeneous patterns, mild to profuse blood flow, and regional lymphadenopathy with suspicious features such as microcalcifications (Fig.).[108] The diffuse, scattered microcalcifications can give a “snowstorm” sonographic appearance, and the sonographic findings overlap with those of chronic thyroiditis.[103] Chereau et al reported an increased risk of locoregional recurrence and cancer-related deaths in patients with DSVPTC. Recurrence-free survival in DSVPTC appears similar to high-risk PTC (34% vs 27%).[106,107]

The FNA findings of DSVPTC include (1) solid and spherical groups of epithelial cells containing lymphocytes, (2) hobnail cells, (3) septate cytoplasmic vacuoles, (4) large unilocular vacuoles, (5) squamous differentiation, (6) abundant psammoma bodies, (7) a lymphocytic background, and (8) a relative infrequency of characteristic nuclear features of PTC.[107–110] DSVPTC has rare *BRAF* and *RAS* mutations, but a high frequency of *RET*/PTC rearrangements.[111]

Part III: Future Work

Volume Thresholds, Quality, and Safety for Pediatric Thyroid Surgery

The 2015 ATA pediatric guidelines recommend the following: “Pediatric thyroid surgery should be performed in a hospital with the full spectrum of pediatric specialty care, to include but not be limited to endocrinology, radiology (US and anatomic imaging), nuclear medicine, anesthesia, a high-volume thyroid surgeon, and intensive care” (Recommendation 14A).[1] This recommendation was developed because children are seen with unique clinical presentations and outcomes. Clinicians who are familiar with the nuances of pediatric thyroid disease may provide optimal care. This would involve providing the appropriate level of aggressiveness while giving consideration for long-term outcomes.

Providers should keep in mind the excellent prognosis associated with pediatric DTC. Additional research should focus on pediatric DTC survivorship and related issues of surveillance, complication mitigation and management, fertility, and quality of life. Multiple studies have shown reduced complications and lower costs when thyroidectomy is performed in centers that provide high-volume care.[1,65] Therefore, a multidisciplinary team-based approach should be considered in the surgery of pediatric thyroid disorders.[18,19]

Conclusion

The AACE and AHNS recommend a contemporary approach to the diagnosis and management of pediatric patients with thyroid cancer. Pediatric thyroid cancer presents with many unique

nuances, such as bulky cervical adenopathy, an increased incidence of DSVPTC, and a longer expected lifespan to contend with potential complications from thyroid surgery (hoarseness, tracheotomy, and hypocalcemia). We believe optimal outcomes and decreased morbidity will come from the use of advanced imaging, diagnostic testing, and neural monitoring of patients treated in high-volume centers by high-volume surgeons.

Disclosure

The authors have no multiplicity of interest to disclose.

Author Contributions

Drs Stack and Twining are co-first authors.

References

1. Francis GL, Waguespack SG, Bauer AJ, et al. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2015;25(7):716–759.
2. Hinson AM, Stack Jr BC. Evidence-based medicine: approach and references classification. In: Stack BC Jr, Bodenner DL, eds. *Medical and Surgical Treatment of Parathyroid Diseases. An evidence-based approach*. Springer International Publishing; 2017:11–13.
3. Stack Jr BC, Tolley NS, Bartel TB, et al. AHNS Series: do you know your guidelines? Optimizing outcomes in reoperative parathyroid surgery: definitive multidisciplinary joint consensus guidelines of the American Head and Neck Society and the British Association of Endocrine and Thyroid Surgeons. *Head Neck*. 2018;40(8):1617–1629.
4. Dalkey NC. *The Delphi Method: an Experimental Study of Group Opinion*. Rand Corporation; 1969.
5. Dalkey NC, Helmer O. An experimental application of the DELPHI method to the use of experts. *Manag Sci*. 1963;9(3):458–467.
6. Setzen G, Ferguson BJ, Han JK, et al. Clinical consensus statement: appropriate use of computed tomography for paranasal sinus disease. *Otolaryngol Head Neck Surg*. 2012;147(5):808–816.
7. Cancer stat facts: thyroid cancer. National Cancer Institute. Accessed January 1, 2020. https://seer.cancer.gov/statfacts/html/thyro.html.
8. Lee CR, Park S, Kang SW, et al. Is familial papillary thyroid microcarcinoma more aggressive than sporadic form? *Ann Surg Treat Res*. 2017;92(3):129–135.
9. Gul K, Ozdemir D, Ugras S, Inancli SS, Ersoy R, Cakir B. Coexistent familial nonmultiple endocrine neoplasia medullary thyroid carcinoma and papillary thyroid carcinoma associated with RET polymorphism. *Am J Med Sci*. 2010;340(1):60–63.
10. Richards ML. Familial syndromes associated with thyroid cancer in the era of personalized medicine. *Thyroid*. 2010;20(7):707–713.
11. Romei C, Mariotti S, Fugazzola L, et al. Multiple endocrine neoplasia type 2 syndromes (MEN 2): results from the ItaMEN network analysis on the prevalence of different genotypes and phenotypes. *Eur J Endocrinol*. 2010;163(2):301–308.
12. Dotto J, Nosé V. Familial thyroid carcinoma: a diagnostic algorithm. *Adv Anat Pathol*. 2008;15(6):332–349.
13. Nosé V. Familial non-medullary thyroid carcinoma: an update. *Endocr Pathol*. 2008;19(4):226–240.
14. Alsanea O, Clark OH. Familial thyroid cancer. *Curr Opin Oncol*. 2001;13(1):44–51.
15. Romei C, Cosci B, Renzini G, et al. RET genetic screening of sporadic medullary thyroid cancer (MTC) allows the preclinical diagnosis of unsuspected gene carriers and the identification of a relevant percentage of hidden familial MTC (FMTC). *Clin Endocrinol (Oxf)*. 2011;74(2):241–247.
16. Moses W, Weng J, Kebebew E. Prevalence, clinicopathologic features, and somatic genetic mutation profile in familial versus sporadic nonmedullary thyroid cancer. *Thyroid*. 2011;21(4):367–371.
17. Baumgarten HD, Bauer AJ, Isaza A, Mostoufi-Moab S, Kazahaya K, Adzick NS. Surgical management of pediatric thyroid disease: complication rates after thyroidectomy at the Children's Hospital of Philadelphia high-volume Pediatric Thyroid Center. *J Pediatr Surg*. 2019;54(10):1969–1975.
18. Tuttle RM, Ball DW, Byrd D, et al. Medullary carcinoma. *J Natl Compr Canc Netw*. 2010;8(5):512–530.
19. Khan A, Smellie J, Nutting C, Harrington K, Newbold K. Familial nonmedullary thyroid cancer: a review of the genetics. *Thyroid*. 2010;20(7):795–801.
20. Robenshtok E, Tzvetov G, Grozinsky-Glasberg S, et al. Clinical characteristics and outcome of familial nonmedullary thyroid cancer: a retrospective controlled study. *Thyroid*. 2011;21(1):43–48.
21. Yoo SK, Lee S, Kim SJ, et al. Comprehensive analysis of the transcriptional and mutational landscape of follicular and papillary thyroid cancers. *PLoS Genet*. 2016;12(8):e1006239.
22. Hawkins DB, Clark RW. Flexible laryngoscopy in neonates, infants, and young children. *Ann Otol Rhinol Laryngol*. 1987;96(1 pt 1):81–85.
23. Chadha NK, Lam GOA, Ludemann JP, Kozak FK. Intranasal topical local anesthetic and decongestant for flexible nasendoscopy in children: a randomized, double-blind, placebo-controlled trial. *JAMA Otolaryngol Head Neck Surg*. 2013;139(12):1301–1305.
24. Sinclair CF, Bumpous JM, Haugen BR, et al. Laryngeal examination in thyroid and parathyroid surgery: an American Head and Neck Society consensus statement: AHNS Consensus Statement. *Head Neck*. 2016;38(6):811–819.
25. İrkörücü O. Approach to the assessment of vocal cord movement by ultrasonography. *World J Surg*. 2018;42(4):1214.
26. Mostoufi-Moab S, Labourier E, Sullivan L, et al. Molecular testing for oncogenic gene alterations in pediatric thyroid lesions. *Thyroid*. 2018;28(1):60–67.
27. Wu X, Groves FD, McLaughlin CC, Jemal A, Martin J, Chen VW. Cancer incidence patterns among adolescents and young adults in the United States. *Cancer Causes Control*. 2005;16(3):309–320.
28. Baloch ZW, LiVolsi VA, Asa SL, et al. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. *Diagn Cytopathol*. 2008;36(6):425–437.
29. Monaco SE, Pantanowitz L, Khalbuss WE, et al. Cytomorphological and molecular genetic findings in pediatric thyroid fine-needle aspiration. *Cancer Cytopathol*. 2012;120(5):342–350.
30. Picarsic JL, Buryk MA, Ozolek J, et al. Molecular characterization of sporadic pediatric thyroid carcinoma with the DNA/RNA ThyroSeq v2 Next-Generation Sequencing Assay. *Pediatr Dev Pathol*. 2016;19(2):115–122.
31. Paulson VA, Rudzinski ER, Hawkins DS. Thyroid cancer in the pediatric population. *Genes*. 2019;10(9):723.
32. Bauer AJ. Molecular genetics of thyroid cancer in children and adolescents. *Endocrinol Metab Clin North Am*. 2017;46(2):389–403.
33. Ballester LY, Sarabia SF, Sayeed H, et al. Integrating molecular testing in the diagnosis and management of children with thyroid lesions. *Pediatr Dev Pathol*. 2016;19(2):94–100.
34. Parangi S, Suh H. The role of genetic markers in the evaluation and management of thyroid nodules. *Surg Clin North Am*. 2014;94(3):515–528. https://doi.org/10.1016/j.suc.2014.03.001.
35. Ronsley R, Rassekh SR, Shen Y, et al. Application of genomics to identify therapeutic targets in recurrent pediatric papillary thyroid carcinoma. *Cold Spring Harb Mol Case Stud*. 2018;4(2):a002568.
36. Dermody S, Walls A, Harley Jr EH. Pediatric thyroid cancer: an update from the SEER database 2007-2012. *Int J Pediatr Otorhinolaryngol*. 2016;89:121–126.
37. Goldfarb M, Gondek SS, Sanchez Y, Lew JI. Clinic-based ultrasound can predict malignancy in pediatric thyroid nodules. *Thyroid*. 2012;22(8):827–831.
38. Richman DM, Benson CB, Doubilet PM, et al. Thyroid nodules in pediatric patients: sonographic characteristics and likelihood of cancer. *Radiology*. 2018;288(2):591–599.
39. Cunnane M, Kyriazidis N, Kamani D, et al. A novel thyroid cancer nodal map classification system to facilitate nodal localization and surgical management: the A to D map. *Laryngoscope*. 2017;127(10):2429–2436.
40. Robbins KT, Clayman G, Levine PA, et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. *Arch Otolaryngol Head Neck Surg*. 2002;128(7):751–758.
41. Erbil Y, Giris M, Salmaslıoglu A, et al. The effect of anti-thyroid drug treatment duration on thyroid gland microvessel density and intraoperative blood loss in patients with Graves' disease. *Surgery*. 2008;143(2):216–225.
42. American Institute of Ultrasound in Medicine, American College of Radiology; Society for Pediatric Radiology, Society of Radiologists in Ultrasound. AIUM practice guideline for the performance of a thyroid and parathyroid ultrasound examination. *J Ultrasound Med*. 2013;32(7):1319–1329.
43. Lim-Dunham JE, Toslak IE, Reiter MP, Martin B. Assessment of the American College of Radiology thyroid imaging reporting and data system for thyroid nodule malignancy risk stratification in a pediatric population. *AJR Am J Roentgenol*. 2019;212(1):188–194.
44. Triana G, Valencia S, Morillo AJ. Pediatric American Thyroid Association guidelines are not completely applicable to pediatric nodule evaluation. *Radiology*. 2018;289(3):881–882.
45. Patel NA, Bly RA, Adams S, et al. A clinical pathway for the postoperative management of hypocalcemia after pediatric thyroidectomy reduces blood draws. *Int J Pediatr Otorhinolaryngol*. 2018;105:132–137.
46. Tsai SD, Mostoufi-Moab S, Bauer S, et al. Clinical utility of intraoperative parathyroid hormone measurement in children and adolescents undergoing total thyroidectomy. *Front Endocrinol (Lausanne)*. 2019;10:760.
47. Smith MM, Kuhl G, Carvalho PRA, Marostica PJC. Flexible fiber-optic laryngoscopy in the first hours after extubation for the evaluation of laryngeal lesions due to intubation in the pediatric intensive care unit. *Int J Pediatr Otorhinolaryngol*. 2007;71(9):1423–1428.
48. Williams GT, Farquharson IM, Anthony J. Fibreoptic laryngoscopy in the assessment of laryngeal disorders. *J Laryngol Otol*. 1975;89(3):299–316.
49. Schneider R, Machens A, Randolph GW, Kamani D, Lorenz K, Dralle H. Opportunities and challenges of intermittent and continuous intraoperative neural monitoring in thyroid surgery. *Gland Surg*. 2017;6(5):537–545.

50. Randolph GW, Kamani D. Intraoperative electrophysiologic monitoring of the recurrent laryngeal nerve during thyroid and parathyroid surgery: experience with 1,381 nerves at risk. *Laryngoscope*. 2017;127(1):280–286.
51. Fukuhara T, Donishi R, Matsuda E, Koyama S, Fujiwara K, Takeuchi H. A novel lateral approach to the assessment of vocal cord movement by ultrasonography. *World J Surg*. 2018;42(1):130–136.
52. Ongkasuwan J, Ocampo E, Tran B. Laryngeal ultrasound and vocal fold movement in the pediatric cardiovascular intensive care unit. *Laryngoscope*. 2017;127(1):167–172.
53. Wong KP, Woo JW, Li JYY, Lee KE, Youn YK, Lang BHH. Using transcutaneous laryngeal ultrasonography (TLUSG) to assess post-thyroidectomy patients' vocal cords: which maneuver best optimizes visualization and assessment accuracy? *World J Surg*. 2016;40(3):652–658.
54. Albano D, Bertagna F, Panarotto MB, Giubbini R. Early and late adverse effects of radioiodine for pediatric differentiated thyroid cancer. *Pediatr Blood Cancer*. 2017;64(11):e26595. https://doi.org/10.1002/pbc.26595.
55. Marti JL, Jain KS, Morris LG. Increased risk of second primary malignancy in pediatric and young adult patients treated with radioactive iodine for differentiated thyroid cancer. *Thyroid*. 2015;25(6):681–687.
56. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26(1):1–133.
57. Rivkees SA, Mazzaferri EL, Verburg FA, et al. The treatment of differentiated thyroid cancer in children: emphasis on surgical approach and radioactive iodine therapy. *Endocr Rev*. 2011;32(6):798–826.
58. Kundel A, Thompson GB, Richards ML, et al. Pediatric endocrine surgery: a 20-year experience at the Mayo Clinic. *J Clin Endocrinol Metab*. 2014;99(2):399–406.
59. Jarzab B, Handkiewicz-Junak D, Wloch J. Juvenile differentiated thyroid carcinoma and the role of radioiodine in its treatment: a qualitative review. *Endocr Relat Cancer*. 2005;12(4):773–803.
60. Chow SM, Law SCK, Mendenhall WM, et al. Differentiated thyroid carcinoma in childhood and adolescence-clinical course and role of radioiodine. *Pediatr Blood Cancer*. 2004;42(2):176–183.
61. Pawelczak M, David R, Franklin B, Kessler M, Lam L, Shah B. Outcomes of children and adolescents with well-differentiated thyroid carcinoma and pulmonary metastases following ^{131}I treatment: a systematic review. *Thyroid*. 2010;20(10):1095–1101.
62. Biko J, Reiners C, Kreissl MC, Verburg FA, Demidchik Y, Drozd V. Favourable course of disease after incomplete remission on (131)I therapy in children with pulmonary metastases of papillary thyroid carcinoma: 10 years follow-up. *Eur J Nucl Med Mol Imaging*. 2011;38(4):651–655.
63. 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;34(6):1192–1202.
64. Giordano D, Valcavi R, Thompson GB, et al. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. *Thyroid*. 2012;22(9):911–917.
65. Tuggle CT, Roman SA, Wang TS, et al. Pediatric endocrine surgery: who is operating on our children? *Surgery*. 2008;144(6):869–877 [discussion: 877].
66. 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;135(1):88–94.
67. Dralle H, Sekulla C, Lorenz K, Brauckhoff M, Machens A, German IONM Study Group. Intraoperative monitoring of the recurrent laryngeal nerve in thyroid surgery. *World J Surg*. 2008;32(7):1358–1366.
68. Maxwell AK, Shonka Jr DC, Robinson DJ, Levine PA. Association of preoperative calcium and calcitriol therapy with postoperative hypocalcemia after total thyroidectomy. *JAMA Otolaryngol Head Neck Surg*. 2017;143(7):679–684.
69. Orloff LA, Wiseman SM, Bernet VJ, et al. American Thyroid Association statement on postoperative hypoparathyroidism: diagnosis, prevention, and management in adults. *Thyroid*. 2018;28(7):830–841.
70. Stack Jr BC, Bimston DN, Bodenner DL, et al. American Association of Clinical Endocrinologists and American College of Endocrinology disease state clinical review: postoperative hypoparathyroidism definitions and management. *Endocr Pract*. 2015;21(6):674–685.
71. Lee DR, Hinson AM, Siegel ER, Steelman SC, Bodenner DL, Stack Jr BC. Comparison of intraoperative versus postoperative parathyroid hormone levels to predict hypocalcemia earlier after total thyroidectomy. *Otolaryngol Head Neck Surg*. 2015;153(3):343–349.
72. Hauch A, Al-Qurayshi Z, Randolph G, Kandil E. Total thyroidectomy is associated with increased risk of complications for low- and high-volume surgeons. *Ann Surg Oncol*. 2014;21(12):3844–3852.
73. Meltzer C, Klau M, Gurushanthaiah D, et al. Surgeon volume in thyroid surgery: surgical efficiency, outcomes, and utilization. *Laryngoscope*. 2016;126(11):2630–2639.
74. Liang TJ, Liu SI, Mok KT, Shi HY. Associations of volume and thyroidectomy outcomes: a nationwide study with systematic review and meta-analysis. *Otolaryngol Head Neck Surg*. 2016;155(1):65–75.
75. Al-Qurayshi Z, Robins R, Hauch A, Randolph GW, Kandil E. Association of surgeon volume with outcomes and cost savings following thyroidectomy: a national forecast. *JAMA Otolaryngol Head Neck Surg*. 2016;142(1):32–39.
76. Kandil E, Noureldine SI, Abbas A, Tufano RP. The impact of surgical volume on patient outcomes following thyroid surgery. *Surgery*. 2013;154(6):1346–1352 [discussion: 1352-1343].
77. Loyo M, Tufano RP, Gourin CG. National trends in thyroid surgery and the effect of volume on short-term outcomes. *Laryngoscope*. 2013;123(8):2056–2063.
78. Sosa JA, Bowman HM, Tielsch JM, Powe NR, Gordon TA, Udelsman R. The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. *Ann Surg*. 1998;228(3):320–330.
79. 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;156(1):167–172.
80. Steliarova-Foucher E, Stiller CA, Pukkala E, Lacour B, Plesko I, Parkin DM. 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(13):2150–2169.
81. Schlumberger M, De Vathaire F, Travagli JP, et al. Differentiated thyroid carcinoma in childhood: long term follow-up of 72 patients. *J Clin Endocrinol Metab*. 1987;65(6):1088–1094.
82. Sugino K, Nagahama M, Kitagawa W, et al. Papillary thyroid carcinoma in children and adolescents: long-term follow-up and clinical characteristics. *World J Surg*. 2015;39(9):2259–2265.
83. Nice T, Pasara S, Goldfarb M, et al. Pediatric papillary thyroid cancer >1 cm: is total thyroidectomy necessary? *J Pediatr Surg*. 2015;50(6):1009–1013.
84. Yeh MW, Bauer AJ, Bernet VA, et al. American Thyroid Association statement on preoperative imaging for thyroid cancer surgery. *Thyroid*. 2015;25(1):3–14.
85. Ogle S, Merz A, Parina R, Alsayed M, Milas M. Ultrasound and the evaluation of pediatric thyroid malignancy: current recommendations for diagnosis and follow-up. *J Ultrasound Med*. 2018;37(10):2311–2324.
86. Essenmacher AC, Joyce Jr PH, Kao SC, et al. Sonographic evaluation of pediatric thyroid nodules. *Radiographics*. 2017;37(6):1731–1752.
87. Stack Jr BC, Tuttle RM. Ultrasonographic characterization of cervical lymphadenopathy in chronic autoimmune thyroiditis. *Thyroid*. 2013;23(2):137–138.
88. Warren Frunzac R, Richards M. Computed tomography and magnetic resonance imaging of the thyroid and parathyroid glands. In: Buchfelder M, Guaraldi F, eds. *Imaging in Endocrine Disorders*. 45. *Front Horm Res*. Karger; 2016:16–23.
89. Callahan MJ, MacDougall RD, Bixby SD, Voss SD, Robertson RL, Cravero JP. Ionizing radiation from computed tomography versus anesthesia for magnetic resonance imaging in infants and children: patient safety considerations. *Pediatr Radiol*. 2018;48(1):21–30.
90. Tomà P, Cannatà V, Genovese E, Magistrelli A, Granata C. Radiation exposure in diagnostic imaging: wisdom and prudence, but still a lot to understand. *Radiol Med*. 2017;122(3):215–220.
91. Kutanzi KR, Lumen A, Koturbash I, Miousse IR. Pediatric exposures to ionizing radiation: carcinogenic considerations. *Int J Environ Res Public Health*. 2016;13(11):1057.
92. Darnell K, Morrison GD. Minimizing the long-term effects of ionizing radiation in pediatric computed tomography examinations. *Radiol Technol*. 2016;87(5):495–501.
93. Disma N, O'Leary JD, Loepke AW, et al. Anesthesia and the developing brain: a way forward for laboratory and clinical research. *Paediatr Anaesth*. 2018;28(9):758–763.
94. Vutskits L, Davidson A. Update on developmental anesthesia neurotoxicity. *Curr Opin Anaesthesiol*. 2017;30(3):337–342.
95. Shindo ML, Caruana SM, Kandil E, et al. Management of invasive well-differentiated thyroid cancer: an American Head and Neck Society consensus statement. AHNS consensus statement. *Head Neck*. 2014;36(10):1379–1390.
96. Barczyński M, Randolph GW, Cernea CR, et al. External branch of the superior laryngeal nerve monitoring during thyroid and parathyroid surgery: International Neural Monitoring Study Group standards guideline statement. *Laryngoscope*. 2013;123(suppl 4):S1–S14.
97. Wu C-W, Dionigi G, Barczynski M, et al. International neuromonitoring study group guidelines 2018: Part II: optimal recurrent laryngeal nerve management for invasive thyroid cancer-incorporation of surgical, laryngeal, and neural electrophysiologic data. *Laryngoscope*. 2018;128(suppl 3):S18–S27.
98. Schneider R, Randolph GW, Dionigi G, et al. International neural monitoring study group guideline 2018 part I: staging bilateral thyroid surgery with monitoring loss of signal. *Laryngoscope*. 2018;128(suppl 3):S1–S17.
99. Fundakowski CE, Hales NW, Agrawal N, et al. Surgical management of the recurrent laryngeal nerve in thyroidectomy: American Head and Neck Society Consensus Statement. *Head Neck*. 2018;40(4):663–675.
100. Salari B, Hammon RJ, Kamani D, Randolph GW. Staged surgery for advanced thyroid cancers: safety and oncologic outcomes of neural monitored surgery. *Otolaryngol Head Neck Surg*. 2017;156(5):816–821.
101. Randolph GW, Dralle H, Abdullah H, et al. Electrophysiologic recurrent laryngeal nerve monitoring during thyroid and parathyroid surgery: international standards guideline statement. *Laryngoscope*. 2011;121(suppl 1):S1–S16.

102. Sywak M, Pasieka JL, Ogilvie T. A review of thyroid cancer with intermediate differentiation. *J Surg Oncol*. 2004;86(1):44–54.
103. Kazaure HS, Roman SA, Sosa JA. Aggressive variants of papillary thyroid cancer: incidence, characteristics and predictors of survival among 43,738 patients. *Ann Surg Oncol*. 2012;19(6):1874–1880.
104. Koo JS, Hong S, Park CS. Diffuse sclerosing variant is a major subtype of papillary thyroid carcinoma in the young. *Thyroid*. 2009;19(11): 1225–1231.
105. Yun MB, Sundar PS, Lan PY, Ying SX, Hua Z. Ultrasonographic features of diffuse sclerosing variant of papillary thyroid carcinoma. *J Med Ultrasound*. 2011;19(2):41–46.
106. Chereau N, Giudicelli X, Pattou F, et al. Diffuse sclerosing variant of papillary thyroid carcinoma is associated with aggressive histopathological features and a poor outcome: results of a large multicentric study. *J Clin Endocrinol Metab*. 2016;101(12):4603–4610.
107. Lee JY, Shin JH, Han B-K, et al. Diffuse sclerosing variant of papillary carcinoma of the thyroid: imaging and cytologic findings. *Thyroid*. 2007;17(6):567–573.
108. Takagi N, Hirokawa M, Nobuoka Y, Higuchi M, Kuma S, Miyauchi A. Diffuse sclerosing variant of papillary thyroid carcinoma: a study of fine needle aspiration cytology in 20 patients. *Cytopathology*. 2014;25(3):199–204.
109. Pillai S, Gopalan V, Smith RA, Lam AK-Y. Diffuse sclerosing variant of papillary thyroid carcinoma–an update of its clinicopathological features and molecular biology. *Crit Rev Oncol Hematol*. 2015;94(1):64–73.
110. Carling T, Ocal IT, Udelsman R. Special variants of differentiated thyroid cancer: does it alter the extent of surgery versus well-differentiated thyroid cancer? *World J Surg*. 2007;31(5):916–923.
111. Youngwirth LM, Adam MA, Thomas SM, Roman SA, Sosa JA, Scheri RP. Pediatric thyroid cancer patients referred to high-volume facilities have improved short-term outcomes. *Surgery*. 2018;163(2):361–366.