Management of Differentiated Thyroid Carcinoma in Pediatric Patients

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KEYWORDS

• Thyroid cancer • Thyroid carcinoma • Papillary thyroid cancer
• Follicular thyroid cancer • Pediatric • Molecular genetics • Lymphadenectomy
• Cervical lymph node dissection

KEY POINTS

- Differentiated thyroid carcinomas (DTC) are rare in young children but represent almost 10% of all malignancies diagnosed in older adolescents.
- DTC in children is more likely to demonstrate nodal involvement and is associated with higher recurrence rates than seen in adults.
- Total thyroidectomy and compartment-based resection of involved lymph node basins form the cornerstone of treatment.

INTRODUCTION

Although fewer than 2% of thyroid cancers develop in children, thyroid cancer accounts for 6% of all childhood cancers and is the leading cause of pediatric endocrine malignancy.[1] Reported rates of pediatric thyroid cancer have more than doubled over the last 40 years, although this rise seems to be plateauing.[2] Papillary thyroid cancer (PTC), the most common subtype of thyroid cancer, accounts for the greatest increase in number of detected cases. Smaller increases have also been observed in follicular thyroid cancer (FTC).[1]

Historic recommendations for the treatment of pediatric thyroid neoplasms were derived from adult practice; however, important clinical and molecular features distinguish differentiated thyroid cancer (DTC) in children from adults.[3,4] Clinically, pediatric PTC is more likely to present with regional lymph node involvement, extrathyroidal extension, and pulmonary metastases than adult-onset PTC.[5–8] Despite this, children are less likely to die from disease, with disease-specific mortality less than 2%.[8] These

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differences were first formally recognized in 2015, when the American Thyroid Association (ATA) published guidelines outlining the evaluation and treatment of thyroid nodules (TN) and DTC in children.[4] However, because national pediatric or oncologic databases lack sufficient granularity to provide nuanced insight into pediatric thyroid cancer, coupled with the absence of a pediatric thyroid-specific database, many recommendations within those guidelines were formulated by expert consensus. This summary article reviews the current recommendations of the ATA and more recent progress into the epidemiology and molecular genetics of DTC that may inform future guidelines.

BACKGROUND AND INCIDENCE

Pediatric DTC arises from the thyroid follicular cell and its histologic classification mirrors that in adults. PTC and PTC variants (follicular variant, diffuse sclerosing variant, cribriform-morula variant, solid variant, and tall cell variant), and FTC comprise the category of DTC. PTC and its variants comprise most (>80%) pediatric thyroid cancers in a recent Surveillance, Epidemiology, and End Results database analysis, followed by FTC (10%) and medullary thyroid cancer (8%).[1] As patients transition into adolescence, the incidence and relative rates of PTC increase, whereas those of medullary thyroid cancer decline. Age-standardized DTC incidence rates (per million) are 0.04 for ages 0 to 4 years, 0.43 for ages 5 to 9 years, 3.50 for ages 10 to 14 years, and 15.6 for children 15 to 19 years.[9] After the first decade of life, the female/male preponderance increases to 4.4:1 per 100,000. DTC is the second most common cancer of adolescent girls.[10]

THYROID CANCER IN THE PEDIATRIC PATIENT WITH A THYROID NODULE

Pediatric TN demonstrate a higher risk of malignancy (20%–25%) than TN found in adults (5%–15%), although recent epidemiologic studies have identified TN in up to 5% of children suggesting that the rates of thyroid cancer in small, asymptomatic nodules may be lower than historically reported.[11,12] Most children diagnosed with thyroid disease have no identifiable risk factors, despite that several populations are at increased risk. Exposure to 10 to 30 Gy of ionizing radiation is associated with an approximately 2% annual chance of DTC, beginning 5 years after exposure and peaking at 15 to 30 years.[13] A family history of benign thyroid disease doubles the risk for pediatric DTC, whereas a family history of DTC quadruples the risk. Up to a third of patients with Hashimoto thyroiditis develop TN and these patients may have a 100-fold greater risk of thyroid malignancy than the general population.[14] A variety of genetic disorders may predispose to TN and DTC including: familial adenomatoid polyposis, Carney complex, Werner syndrome, *DICER1* syndrome, *PTEN* hamartoma tumor syndrome, McCune-Albright syndrome, and Peutz-Jeghers syndromes.[4]

EVALUATION OF A THYROID NODULE

TN most commonly present as asymptomatic masses noted by the child, parents, or a pediatrician during a well-child visit. Less commonly nodules cause symptomatic dysphagia, dyspnea, or cervical lymphadenopathy. A thorough thyroid examination includes careful palpation of the central and lateral neck. Large, firm, or fixed nodules, or those associated with lymphadenopathy are concerning for malignancy, but most malignant nodules do not exhibit these features. Following detection or suspicion of TN, a dedicated thyroid and neck ultrasound (US) should be performed.[4] Features of malignancy on US include hypoechogenicity, invasive margins, increased intranodular

blood flow, and microcalcifications.[15,16] In contrast to malignant nodules, benign TN are more often isoechoic, partially cystic, with sharp or noninfiltrative margins, absent calcifications, and lack of blood flow.[17,18] Cystic composition of greater than 50% of a nodule is the most reliable feature identifying low risk of malignancy.[19]

Several scoring systems facilitate selection of TN that should undergo fine-needle aspiration (FNA) in adults and have demonstrated good performance in the pediatric population.[20,21] The most popular of these scoring systems, the Thyroid Imaging Reporting and Data System (TI-RADS), comments on 10 US patterns to assign risk of malignancy (**Fig. 1**).[22,23] Most adult criteria contributing to risk assignation are applicable to children with several notable exceptions. In adults, FNA is recommended for TI-RADS 3, 4, and 5 categories if the nodule is greater than or equal to 2.5 cm, 1.5 cm, or 1 cm, respectively; no size criteria has been studied in children.[24] Diffuse sclerosing variant PTC is more common in the pediatric population and presents as nonnodular, diffuse infiltration of the thyroid associated with widespread microcalcifications giving a "snow-storm" appearance on US. Lateral lymph node involvement is common.[25] Current ATA Pediatric Guidelines preceded development of the TI-RADS scoring system and recommend FNA for vascular, calcified, solid, and/or pericapsular nodules based on clinical context rather than size alone.[4]

Fine-Needle Aspiration

FNA is the preferred method to diagnose DTC; however, before FNA all patients should have a serum thyroid-stimulating hormone (TSH) sent to evaluate for the presence of hyperthyroidism.[26] Hyperfunctioning "hot" nodules have a low risk of malignancy; therefore, if TSH is suppressed, a thyroid uptake scan rather than biopsy is indicated to confirm the diagnosis.[27] For the remainder of "cold" nodules, FNA is sensitive, specific, and accurate, although there is a risk for false-negative FNA in nodules greater than 4 cm.[11,28]

FNA results are categorized according to the Bethesda System for Reporting Thyroid Cytopathology: (I) nondiagnostic or unsatisfactory, (II) benign, (III) atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS), (IV) follicular/Hürthle neoplasm or suspicious for follicular/Hürthle neoplasm (FN/SFN), (V) suspicious for malignancy, and (VI) malignant (**Table 1**).[29] The risk of malignancy in each Bethesda category seems to be higher for children than for adults, although the risk varies by reporting institution, suggesting FNA results must be interpreted in the context of individual institutional indices for accuracy.[30–32]

Lymph Node Evaluation

In addition to evaluation of the nodule itself, examination of the cervical lymph nodes is essential in risk stratifying DTC and determining operative management. In children, nodal architecture and shape are better predictors of lymph node involvement than size.[18] Concerning features on US include round shape, irregular margins, calcifications, cystic change, peripheral vascularity, loss of fatty hilum, and heterogeneous echotexture. Interpretation of US images varies with expertise; therefore, sonographic lymph node evaluation should be performed by a radiologist with experience in pediatric head and neck imaging because less experienced sonographers can miss nodal involvement.[33] FNA should be performed on any suspicious lymph nodes in the lateral neck as confirmation of metastatic involvement before lateral neck dissection.[4]

Other Imaging

Additional imaging may be considered in patients with evidence of lymph node metastasis. Chest radiograph or computed tomography are used to rule out macronodular

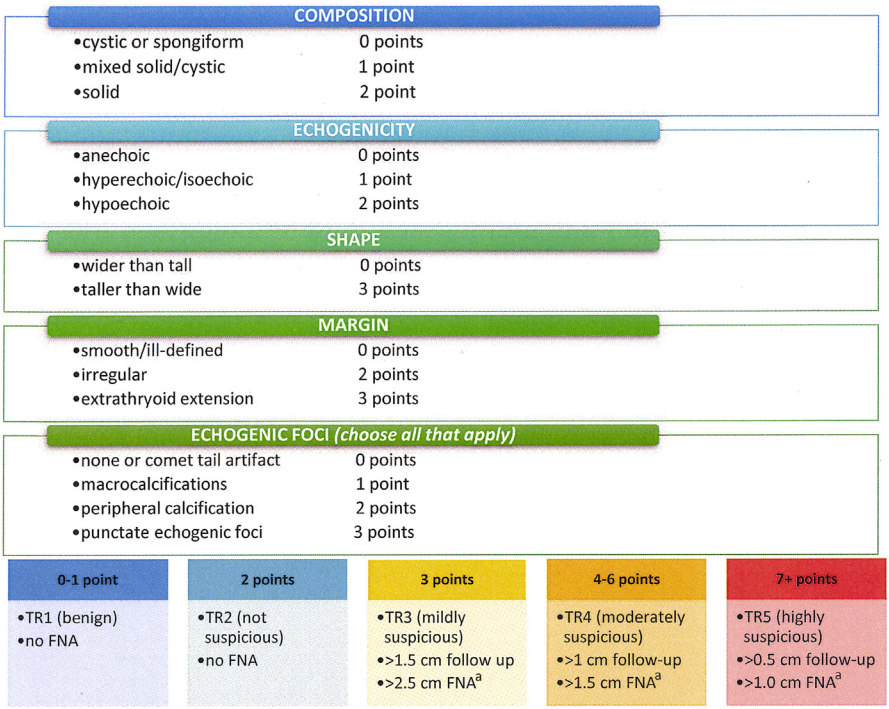

Fig. 1. TI-RADS Classification and recommendations. [a] No size criteria exist in children. (*Courtesy of* Kate Christison-Lagay, PhD, New Haven, CT.)

lung disease and computed tomography of the neck can aid in the assessment of anatomic relationships between important neurovascular structures of the neck and deposits of bulky disease.[34,35] Neither nuclear scintigraphy nor ^{18}fluorodeoxyglucose PET play a role during initial evaluation.

OPERATIVE RECOMMENDATIONS FOR NONDIAGNOSTIC, BENIGN, AND INDETERMINATE NODULES

Operative recommendations in patients with nondiagnostic, indeterminate, or benign nodules is based on individual DTC risk, the likelihood of a false-negative FNA, the risks of operative intervention, symptomatology, and patient/family tolerance for diagnostic ambiguity.[4] Patients with nondiagnostic cytology (Bethesda I) may choose repeat FNA. To avoid atypical cellular artifact because of the previous biopsy, conventional practice has been to allow at least 3 months to pass between each biopsy attempt, although several recent studies in adults have challenged the necessity of this interval.[36] Other options include continued US surveillance or lobectomy. Bedside cytologic examination of the aspirate at the time of the procedure can reduce the likelihood of an insufficient biopsy.

Children with benign cytopathology (Bethesda II) and nodules less than 4 cm should be followed by serial US tracking TN growth. Operative intervention is warranted in the presence of rapid TN growth or compressive symptoms.[4] Lesions greater than 4 cm have a higher false-negative rate and lobectomy should be offered even if cytology is

Table 1
Bethesda system for reporting thyroid cytopathology

Bethesda Category	Cytopathologic Category	Malignancy Rate, %	Suggested Treatment
I	Nondiagnostic/inadequate	1–5	Repeat FNA (other options: continued US surveillance, lobectomy)
II	Benign	0–10	Serial US if small, lobectomy if >4 cm
III	Atypia/follicular lesion of undetermined significance	20–30	Molecular genetics, lobectomy if no concerning mutation, thyroidectomy if BRAF or fusion mutation
IV	Follicular neoplasm	30–60	Molecular genetics, lobectomy if no concerning mutation, thyroidectomy if BRAF or fusion mutation
V	Suspicious for malignancy	70–86	Total thyroidectomy ± central neck dissection
VI	Malignant	97–100	Total thyroidectomy ± central neck dissection

benign. Many large nodules cause dysphagia or dyspnea or are aesthetically unappealing and patients opt for resection independent of cytology.

Because of the increased risk for DTC in children with AUS/FLUS, lobectomy is often recommended over repeat biopsy. Recently, a report from Cherella and colleagues found that almost a third of AUS/FLUS nodules were benign on repeat FNA, suggesting that repeat biopsy may be a reasonable approach.[33,37] If lobectomy is selected and DTC is confirmed intraoperatively or on final histology, a completion thyroidectomy is performed. Intraoperative frozen section may be of help in diagnosing classic PTC but has no benefit in follicular variant PTC or FTC, because the latter requires evaluation of the entire lesion to detect vascular invasion (VI) and/or capsular invasion (CI).[38,39]

The risk of DTC seems to be greater than 50% in children with FN/SFN cytology (Bethesda IV).[40–43] Lobectomy has historically been the standard of care, but the role of oncogene panels in assisting with operative planning is an area of active investigation. In high-volume centers in which oncogene panels are routinely performed on fine-needle aspirate, a positive result may augment the positive predictive value of malignancy in pediatric PTC. For example, if a *BRAF* mutation or gene fusion (*RET/PTC* or *NTRK3/ETV6*) is detected in the AUS/FLUS or FN/SFN category, total thyroidectomy (TT) is warranted based on the high risk of PTC.[44,45] However, malignancy may be less likely in a solitary, isoechoic, smooth-margined TN harboring a *RAS* mutation or *PAX8-PPARG* rearrangement. In these instances a lobectomy may be preferable.[45] For FNA suspicious for malignancy or revealing malignant cytology (Bethesda V or VI), the risk for DTC is near 100% and TT with or without central neck dissection (CND) is recommended.[46]

OPERATIVE RECOMMENDATIONS FOR MALIGNANT NODULES AND LYMPH NODE METASTASES

TT is the cornerstone of the management of DTC. The ability to achieve long-term recurrence-free survival is directly related to the adequacy of the initial operative resection.[4] Unlike the adult population in which thyroid lobectomy may be adequate for small (<4 cm) low-risk tumors, TT is currently recommended by the ATA for all children with PTC based on the high incidence of bilateral (30%) or multifocal (65%) disease.[4,47,48] Patients with preoperatively detected or clinically apparent central lymph node metastases should undergo therapeutic CND of level VI nodes (**Fig. 2**).[4,5,47] Thyroid lobectomy is associated with 10-fold greater recurrence rates and inadequate lymph node dissections in patients with clinically positive nodes increases the need for subsequent intervention three-fold.[4,5,7,47] Studies in adults have shown that compartment-focused lymph node dissections reduce recurrence compared with "berry picking"; these studies have generally been applied to children.[49] Several high-volume centers have reported the need to reoperate for persistent and relapsed disease treated less aggressively at a lower-volume institution.[50,51] Although a compartment-oriented central neck lymphadenectomy theoretically increases the risks of hypoparathyroidism and recurrent laryngeal nerve injury, these complications are minimized when performed by a high-volume surgeon.[48,50–53] It is imperative that the correct operation be performed initially because anatomic planes are absent or distorted in reoperative fields thus increasing the risk of complications.[54]

Modified radical neck dissection is reserved for biopsy-proven metastatic DTC in the lateral compartment (levels II, III, IV, and V) and improves disease-free survival.[47,51,55]

COMPLICATIONS

A convincing series of data have demonstrated a volume-outcome relationship between surgeon experience at thyroidectomy and patient complications and length of stay in children.[53,56] As a result, the ATA recommends thyroidectomy should be performed by an experienced thyroid surgeon (>30 cases/year) or as a multidisciplinary approach between a pediatric surgeon and an adult endocrine/head and neck surgeon.[56,57] In a cross-sectional analysis of the Healthcare Cost and Utilization Project, pediatric patients undergoing TT had a general complication rate of 17.6% and an endocrine-specific (including hypocalcemia, voice disturbance, and recurrent

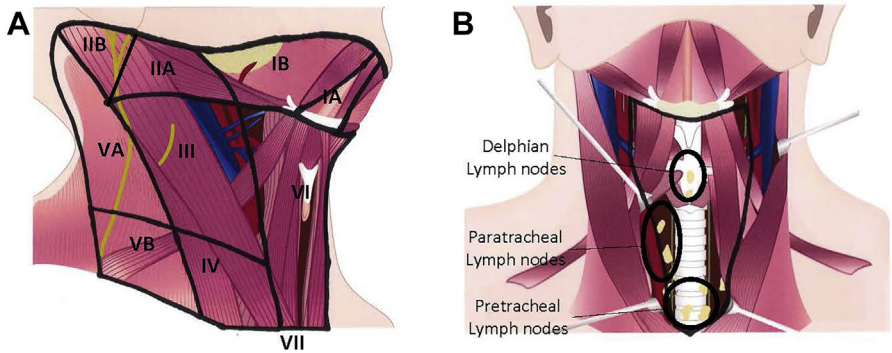

Fig. 2. (*A*) Cervical lymph node levels I-VII. (*B*) Depiction of central lymph nodes with thyroid removed. (*Courtesy of* Kate Christison-Lagay, PhD, New Haven, CT.)

laryngeal nerve injury) complication rate of 16.3%. These numbers were reduced by more than half if the operation was performed by a high-volume surgeon.[56]

A recent analysis of 1654 patients undergoing TT in the KID database identified a recurrent laryngeal nerve injury rate of 1.8%.[58] Young children seem particularly at risk for nerve injury with a reported incidence of vocal cord paralysis of 14.3% in children less than 1 year.[59,60] Several recent retrospective studies from high-volume institutions report inadvertent nerve injury rates of 0.4% to 2.8% based on loss of signal during intraoperative nerve monitoring or postoperative laryngoscopy.[48,50,51]

Rates of transient hypocalcemia ranging from 7% to 59% are widely discordant across studies, caused in part by a lack of consensus in defining metrics and study-specific variations in patient extent of disease and extent of routine surgical dissection.[56,61–63] A diagnosis of permanent hypoparathyroidism should not be made before the sixth postoperative month, based on a need for continued calcium ± calcitriol supplementation.[61] The reported incidence of permanent hypoparathyroidism also varies: running higher in population-based or multicenter pediatric studies (5.5%–25%)[58,64] and lower in single-institution studies (0.6%–8.0%).[65,66] Some centers find it useful to obtain either an intraoperative or postoperative intact parathyroid hormone level to help prognosticate need for and likely duration of calcium supplementation.[67,68]

Injuries to other regional nerves during lateral neck dissection (including the sympathetic chain, vagus, spinal accessory nerve, and hypoglossal nerve) are rare events.[50,69,70]

RISK OF RECURRENCE

The risk of recurrence in children with PTC is hard to pinpoint given the lack of standardization of treatment, the potentially long latency period to recurrence, and that adolescents comprise a particularly mobile segment of the population who may have temporally and geographically dis-synchronous care. Most studies report recurrence rates of 20% to 40% at 10 years unadjusted for initial stage of disease.[5,59,60,71] Children with palpable cervical nodal metastases are more likely than those without clinical node involvement to present with distant metastasis and experience persistent and/or recurrent disease over time.[7,72] In general, younger age, larger tumor size, solid architecture pattern, extensive tumor fibrosis, VI, disseminated psammoma bodies, extrathyroidal extension, node-positive disease with a high metastatic ratio index (>0.45), metastatic disease within the central compartment (level VI), macroscopic nodal disease, and extranodal extension are associated with a greater risk for ipsilateral or bilateral N1b disease.[51,60,72,73]

SURVIVAL

Overall survival is excellent, with 5-year survival rates of 99.8% in children with DTC confined to the thyroid and 97.1% of those with regional metastatic disease.[5,74,75] Studies with long-term follow-up indicate that children with DTC have increased mortality from second malignancies, possibly related to radioactive iodine use.[5,76,77]

RADIOACTIVE IODINE TREATMENT FOLLOWING INITIAL SURGERY

The historic practice of treating all children with DTC with ^{131}I following initial operative resection has been replaced with a stratified approach aimed at minimizing ^{131}I exposure in patients deemed low risk for persistent postsurgical disease.[4] ^{131}I therapy is indicated for patients with pulmonary metastases or small-volume nonresectable

residual cervical disease.[8,78] Most experts also advocate ^{131}I therapy for children with extensive regional nodal involvement (extensive N1a or N1b disease).[79] Up to a third of children with distant metastasis have persistent but stable disease following radioactive iodine therapy resulting in a more favorable progression-free survival in children compared with adults with persistent DTC.[8,9,80]

THYROID-STIMULATING HORMONE SUPPRESSION AND THYROGLOBULIN SURVEILLANCE

Postoperative TSH suppression is indicated for children with any type of DTC, although there is a paucity of data guiding degree of suppression. If thyroglobulin (Tg) rises while the patient is on levothyroxine, disease relapse is likely to become clinically apparent.[81,82] The decision to pursue further therapy is based on the degree of Tg elevation, the trend in Tg over time, and the results of imaging studies. When imaging fails to confirm disease, the clinical importance of biochemical recurrence in children is not yet clear.[81,82]

TREATMENT OF PERSISTENT OR RECURRENT PAPILLARY THYROID CANCER

Treatment of persistent or recurrent disease should be individualized and careful consideration given to the potential risks and benefits of therapy. Patients with small cervical foci or patients with cervical disease that cannot be visualized with cross-sectional imaging may be considered for (repeat) therapeutic ^{131}I but may also often be safely observed while maintaining TSH suppression. Macroscopic cervical disease should be removed surgically if this can be safely accomplished.

Children with pulmonary metastases may continue to experience post-therapy targeted ^{131}I effects for years and an undetectable Tg level should not be the focus of treatment efforts. A third of patients exhibit persistent, stable disease following radioactive iodine therapy; therapy should be directed at those with evidence of progression.[4]

CONTROVERSIES IN SURGICAL MANAGEMENT

There is no consensus on the optimal extent of resection of PTC sonographically confined to the thyroid. Large database studies have measured success of various operative approaches using an end point of death from disease, but outcomes in PTC are best measured by disease recurrence (a parameter not collected in national databases) over a span of decades. Furthermore, pediatric literature lacks the granularity of adult studies that distinguish structural from biochemical recurrence.[83] Proponents of lobectomy cite equivalent survival in patients, and an increased rate of permanent hypocalcemia and recurrent laryngeal nerve injury in patients undergoing TT.[3,8] Countering this argument is evidence for a lower recurrence rate after TT, and the observation that at least 40% of pediatric PTC is multifocal.[84] Few institutional series have had sufficient patient volume to report recurrence rates based on extent of disease or modified by operative approach. In addition to TT, some experts believe a prophylactic CND should be considered for all children with PTC to reduce the risk of persistent or recurrent disease. These recommendations are based on the observation of nodal involvement in more than half of resected PTC specimens in centers that routinely perform CND, and on several small studies suggesting that the addition of prophylactic CND decreases recurrence rates to 5% at 10 years.[5,47,51,85,86] CND in theory increases the risk of transient and permanent hypoparathyroidism (because the inferior parathyroids typically lie in the middle of a regional lymph node "packet" and

must be either sacrificed or reimplanted) and these sequelae are the most frequently cited counterarguments to prophylactic central neck lymphadenectomy.[61,64,66,87] In patients with unifocal lateralized disease, several studies in adults suggest that ipsilateral, prophylactic CND may provide the same benefit as bilateral CND while decreasing the rate of hypoparathyroidism, but this has not been studied in children.[88] When considering operative strategy, the potential morbidity of bilateral CND must be weighed against the indolent nature of PTC. Prophylactic CND should be performed only by surgeons with extensive experience operating in the central neck. Multiple adult groups have reported on the use of near-infrared autofluorescence to help identity (and thus preserve) parathyroid tissue (either in eutopic position or as an aide in autotransplantation), a potentially promising, although largely untested, practice in children.[89,90]

FOLLICULAR THYROID CARCINOMA

Fewer than 10% of pediatric DTC are follicular carcinomas. The diagnosis of FTC is based on the identification of CI and/or VI on permanent histologic sectioning. The 2015 ATA Guidelines divide FTC into those with CI alone, minimal (<4 vessels) VI, and extensive VI (≥4 vessels).[30] As opposed to PTC, which are frequently multifocal, FTC are typically unifocal tumors without extrathyroidal extension. Any patient with multifocal FTC should be evaluated for *PTEN* hamartoma tumor syndrome or a DICER1 mutation.[91,92] Unlike PTC, FTC spreads hematogenously to lung and bone and rarely metastasizes to regional lymph nodes. The presence of lymph node involvement in a patient diagnosed as FTC should raise the possibility that the lesion is a follicular variant PTC.[93]

FTC has a different sonographic appearance than PTC. It is frequently larger, isoechoic, and often demonstrates a hypoechoic rim.[94,95] Because of the need for permanent histology to evaluate for CI or VI, FNA cytology is largely unhelpful in diagnosing FTC.

The recommended treatment of angioinvasive FTC (≥4 vessels VI) or FTC greater than or equal to 4 cm is TT and radioactive iodine.[96,97] Treatment of minimally invasive FTC is controversial because it seems to mimic a benign lesion.[98,99] Studies of minimally invasive FTC in children have also demonstrated indolent behavior and have suggested that lobectomy followed by close follow-up and TSH suppression may be sufficient.[93] However, a separate study that included children with minimally invasive FTC with VI observed recurrence in three of nine children. Thirty-year disease-specific survival is 100%.[100]

FUTURE DIRECTIONS: MOLECULAR GENETICS AND TARGETED THERAPEUTICS

Molecular genetic testing provides techniques to better characterize TN; however, data in children are limited. Large-volume pediatric centers often use "positive" results of gene panels to inform a conversation about the likelihood of malignancy and to help tailor the surgical approach for individual children.[45] Compared with adult PTC, childhood PTC has a higher prevalence of gene rearrangements (50% in children vs 15% in adults) and a lower frequency of point mutations (30% of children vs 70% of adults).[45] Gene fusions in DTC occur most commonly between *RE*arranged during *T*ransfection (*RET*) and a variety of other genes, resulting in some 20 *RET/PTC* rearrangements.[45,101,102] *RET/PTC1* and *RET/PTC3* are the most common rearrangements in sporadic and radiation-induced pediatric PTC. The *BRAF* gene is the most common location for a point mutation in pediatric PTC.[45,103] In adults, *BRAF* mutations may be associated with more aggressive phenotype characterized by an increased

likelihood for lymph node metastasis, extrathyroidal extension, risk for recurrence, and resistance to iodine.[104] In contrast, *BRAF* mutations in children have not been associated with a greater risk for recurrence but they more frequently have metastatic lymph nodes, an observation that may have implications for the extent of initial surgical resection.[105–108] As genetic testing becomes routinely incorporated into the early diagnostic testing, staging, operative decision making, and adjuvant therapy plans may be based on individual precision medicine, incorporating these tumor characteristics into clinical care.

An increasing number of multikinase inhibitors (tyrosine kinase inhibitors) that target protein tyrosine kinase–dependent pathways are being developed for adult patients with iodine-refractory disease. Sorafenib and lenvatinib have been used in adult trials with some favorable results and have been approved for compassionate use in a small number of children with DTC.[109–112]

SUMMARY

DTC are rare in young children but represent almost 10% of all malignancies diagnosed in older adolescents, with PTC comprising most cases. Compared with PTC in adults, PTC in children is more frequently bilateral and associated with nodal metastasis and higher rates of recurrence. Operative resection remains integral to treatment, and local recurrence is directly affected by operative approach to regional metastatic disease. TT with central lymph node dissection is the treatment of choice for PTC with clinically evident lymph node involvement in the central neck. The role of prophylactic CND for patients with microscopic disease in the central neck requires further investigation. Lateral lymph node involvement should be addressed with modified radical neck dissection. The role of novel targeted therapies in high-risk patients with disseminated disease, and the use of molecular profiling of indeterminate lesions are areas of ongoing inquiry.

CLINICS CARE POINTS

- Preoperative workup of a thyroid nodule should begin with a dedicated thyroid ultrasound. Concerning features on ultrasound should prompt and extended ultrasound of the lymph nodes of the lateral neck.
- Biopsy via Fine Needle Aspiration should be performed on any concerning nodules. A minimum of thyroid lobectomy should be offered to Bethesda III/IV nodules and total thyroidectomy should be offered to Bethesda V/VI nodules.
- A compartment based lymph node dissection should be performed if positive lymph nodes are identified preoperatively.
- Radioactive Iodine should be offered to patients at risk for persistent disease.

DISCLOSURE

The authors have no relevant commercial or financial conflicts of interest. The work related to this review was unfunded.

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