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Pediatric differentiated thyroid carcinoma: An update from the APSA Cancer Committee

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ABSTRACT

Background: Differentiated thyroid carcinomas (DTCs) are rare in young children but represent almost 10% of all malignancies diagnosed in older adolescents.
Methods: This article reviews the recent literature describing surgical therapeutic approaches to pediatric DTC, associated complications, and long-term recurrence and survival outcomes.
Results: Similar to adult thyroid cancers, pediatric DTCs are more common in females and are associated with thyroid nodules, family history of thyroid cancer, radiation exposure, iodine deficiency, autoimmune thyroid disease, and genetic syndromes. Management of thyroid cancers in children involves ultrasound imaging, fine needle aspiration, and surgical resection with treatment decisions based on clinical and radiological features, cytology and risk assessment.
Conclusions: Total thyroidectomy and compartment based resection of clinically involved lymph node basins form the cornerstone of treatment of DTC. There is an evolving literature regarding the use of molecular genetics to inform treatment strategies and the use of targeted therapies to treat iodine refractory and surgically unresectable progressive disease.
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Level of evidence: This is a review article of previously published Level 1–5 articles that includes expert opinion (Level 5).

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Fewer than 2% of thyroid cancers develop in children, but the reported incidence has increased 2.3-fold over the last 40 years and there are important clinical and molecular features distinguishing differentiated thyroid cancer (DTC) in children from adults [1–3]. These differences were first formally recognized in 2015, when the American Thyroid Association (ATA) published guidelines outlining the evaluation and treatment of thyroid nodules (TNs) and DTC in children [3]. However, because of the rarity of DTC in children, coupled with the lack of granularity in national administrative databases, many recommendations within those guidelines were formulated by expert consensus. This summary article will review the current recommendations of the ATA as well as more recent progress into the epidemiology and molecular genetics of DTC that has further advanced our understanding of the disease.

1. Methods

This article reviews the most recent literature describing surgical therapeutic approaches to pediatric DTC, associated complications, and long-term recurrence and survival outcomes. A search using PubMed, Medline, Embase, Web of Science, and Clinical Trials was performed for articles between 1990 and 2019 on Differentiated Thyroid Cancer. Search term limiters were “human” and “English language”. Preference was given to those articles which distinguished pediatric thyroid cancer from adult.

2. Background

Histologically, pediatric DTC arises from the thyroid follicular cell and follows the same classification observed for adults. Papillary thyroid cancer (PTC) and PTC variants [follicular variant (fvPTC), diffuse sclerosing variant (dsvPTC), cribriform-morula variant (usually associated with *APC* mutations), solid variant, and tall cell variant], as well as follicular thyroid cancer (FTC) comprise the category of differentiated thyroid cancers. Clinically, pediatric PTC is more likely to present with regional lymph node involvement, extrathyroidal extension, and pulmonary metastases than adult onset PTC [4–10]. In spite of this, children are less likely to die from disease, with disease-specific mortality less than 3% [10,11].

2.1. Incidence

Comprising almost 60% of all cases, PTC was the most common type of pediatric thyroid cancer in a recent SEER database analysis, followed by fvPTC (23%), FTC (10%) and medullary thyroid cancer (MTC, 8%) [12]. As patients transitioned into adolescence, the incidence of PTC and fvPTC increased while MTC declined. Age-standardized DTC incidence rates (per million) are 0.04 for ages 0–4 years, 0.43 for ages 5–9 years, 3.50 for ages 10–14 years, and 15.6 for 15–19 year old children [13]. After the first decade of life, the female:male preponderance increases to 4.4:1 per 100,000. Notably, DTC is the second most common cancer of adolescent girls [14] .

2.2. Thyroid cancer in the pediatric patient with a thyroid nodule

Pediatric thyroid nodules have historically been attributed a higher risk of malignancy (22%–26%) than thyroid nodules found in adults (5%–15%) [3,15]. More recent epidemiologic studies, however, have identified thyroid nodules (TNs) in 0.2%–5% of children and small colloid cysts in more than half of children, suggesting that the rate of thyroid cancer in small, asymptomatic nodules may be lower than has been traditionally reported [16,17]. Family history of TN or thyroid cancer, radiation exposure, iodine deficiency, autoimmune thyroid disease (AIT), goiter, elevated serum thyrotropin (TSH), and several genetic syndromes increase the risk for both TN and DTC. A family history of benign thyroid disease increases the risk for pediatric DTC 2.5-fold, while a family history of DTC increases the risk 4 fold [18,19]. DTC develops in ~2% of children exposed to 10–30 Gy head/neck radiation each year with incidence peaking 15–30 years after exposure [20]. Up to a third of patients with autoimmune thyroid disease (AIT), including Hashimoto's thyroiditis and Graves' disease, develop thyroid nodules, with estimated malignancy rates of 10%–35% [21–23]. A variety of genetic disorders may predispose to TN and DTC including: familial adenomatoid-polyposis (*FAP*), Carney complex, Werner syndrome, *DICER1* syndrome, *PTEN* hamartoma tumor syndrome (PHTS), McCune–Albright, and Peutz–Jeghers syndromes [3]. Interestingly, the *DICER1* locus is in the region of the *MNG1* (multinodular goiter) locus on chromosome 14 and approximately 75% of women and 17% of men with *DICER1* mutations develop multinodular goiter (MNG) by age 40. Additionally, mutations in *DICER1* confer a 16-fold increased risk for DTC [24]. Early-onset, familial, or male MNG should trigger kindred evaluation for other *DICER1*-associated tumors (pleuropulmonary blastoma, cystic nephroma, ovarian Sertoli–Leydig cell tumor, and nasal chondromesenchymal hamartoma) [24].

2.2.1. Evaluation of a thyroid nodule

2.2.1.1. Imaging. Following detection or suspicion of a TN, a dedicated thyroid and neck ultrasound (US) should be performed [3]. The US should comment on features of TN composition, echogenicity, margins, presence or absence of calcifications, shape, and vascularity of the TN [25]. Common ultrasonographic features of PTC include: hypoechogenicity, invasive margins, increased intranodular blood flow, microcalcifications, and abnormal cervical lymph nodes

[26,27] . Diffuse sclerosing variant PTC (dsvPTC) is a widely invasive form of DTC more common in children than adults. On US, dsvPTC is characterized by diffuse thyroidal enlargement with abundant microcalcifications [28]. In contrast to malignant nodules, benign TNs are more often isoechoic, partially cystic, with sharp or noninfiltrative margins, absent calcifications, and lack of flow on Doppler [29,30].

Several scoring systems facilitate selection of TNs that require fine needle aspiration (FNA) in adults, but the higher incidence of DTC in pediatric TN limits extrapolation of these criteria to children [31–33]. 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 [32]: TI-RADS 1 (0 points) = benign; TI-RADS 2 (2 points) = not suspicious; TI-RADS 3 (3 points) = mildly suspicious; TI-RADS 4 (4–6 points) = moderately suspicious; and TI-RADS 5 (≥7 points) = highly suspicious (Fig. 1) [32,34]. In adults, fine needle aspiration (FNA) is recommended for TI-RADS 3, 4 and 5 if the nodule is greater than or equal to 2.5 cm, 1.5 cm, or 1 cm, respectively, although no such size criteria have been validated in the pediatric population [35]. Two small retrospective series have evaluated the use TI-RADS scoring in children, providing positive (71.7%) and negative (80.0%) predictive values that identify most but not all malignant TNs [36,37] . Current ATA Pediatric Guidelines were formulated prior to the development of the TI-RADS scoring system and recommend using US-guided FNA for vascular, calcified, solid, and/or pericapsular nodules and clinical context rather than size alone [3,38].

Suggest.

2.2.1.2. Fine needle aspiration. FNA is an essential part of the workup of a thyroid nodule and the preferred method to diagnose DTC [39]. Prior to FNA all patients should have a serum thyroid stimulating hormone (TSH) sent to evaluate for the presence of hyperthyroidism. Hyperfunctioning nodules have a very low risk of malignancy (2%–6%); therefore, if TSH is suppressed, thyroid scan and uptake are indicated to confirm the diagnosis [40]. Thyroid lobectomy is typically recommended for patients with hyperfunctioning nodules unless the patient has bilateral nodules better treated by total thyroidectomy. For nonhyperfunctioning nodules, the sensitivity (100%), specificity (88%), and accuracy (91%) of FNA in children are similar to those of adults but there is a greater risk for false negative FNA in nodules greater than 4 cm [16,41,42]. Purely cystic nodules are rarely malignant, but aspiration can be performed for symptomatic relief (although fluid tends to reaccummulate quickly). FNA of the solid portion of a heterogeneous solid–cystic nodule should be considered if the solid component comprises more than 50% of the lesion.

FNA results are categorized according to the six tiers of The Bethesda System for Reporting Thyroid Cytopathology: (I) nondiagnostic or unsatisfactory (ND/UNS), (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 (SUS), and (VI) malignant (Table 1) [43]. The risk of malignancy in each Bethesda category appears to be higher for children than for adults [31,44–46]. One pediatric study found malignancy rates of 10% in Bethesda II, 50% in Bethesda IV, 86% in Bethesda V and 100% in Bethesda VI nodules [47]. In another study, DTC was found in 28% of Bethesda III and 58% of Bethesda IV nodules [48]. These varying results suggest FNA results must be approached with caution and interpreted in the context of institutional indices for accuracy.

2.2.2. Lymph node evaluation

Examination of the cervical lymph nodes is critically important in risk stratifying DTC and determining operative strategy. In children, nodal architecture and shape are better predictors of lymph node involvement than lymph node size [30]. Architecturally 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;

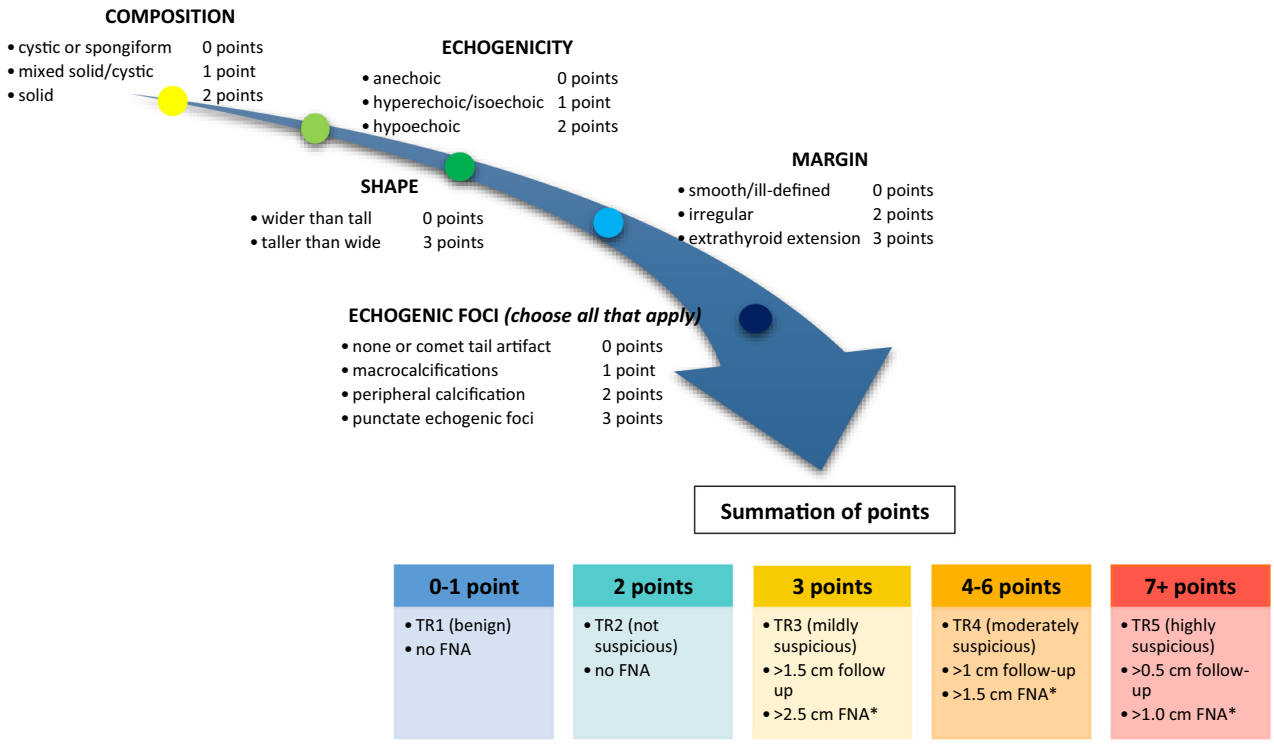

Fig. 1. TI-RADS classification and recommendations.

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	0%–44%	Molecular genetics, lobectomy if no concerning mutation, thyroidectomy if BRAF or fusion mutation
IV	Follicular neoplasm	60%–71%	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

therefore, sonographic lymph node evaluation should be performed by a radiologist or ultrasonographer with experience in pediatric head and neck imaging. A recent study found that an experienced sonographer was able to detect lymph node metastases in 45% of patients in whom prereferral imaging was read as negative for nodal involvement [49]. Following US, FNA should be performed on any suspicious lymph nodes in the lateral neck as confirmation of metastatic involvement prior to lateral neck dissection [3]. Thyroglobulin (Tg) measurement on the needle washout (made by washing the needle with 1 ml of saline into a serum collection tube after plating cells on a slide) can be helpful if cytology is nondiagnostic or indeterminate [45,50].

2.2.3. Other imaging

Additional imaging may be considered in patients with evidence of lymph node metastasis. Chest radiograph (CXR) or computerized tomography (CT) can be used to rule out macronodular lung disease and CT of the neck can aid in the assessment of anatomic relationships between important neurovascular structures of the neck and deposits of bulky disease [51,52]. Following the use of iodinated contrast agents, therapeutic radioactive iodine (RAI) should be delayed 2–3 months, until the iodine load has been cleared, as documented by measurement of urinary iodine [53]. Neither nuclear scintigraphy nor ^{18}fluorodeoxyglucose positron emission tomography (FDG-PET) plays a role during initial evaluation.

2.3. Operative recommendations for nondiagnostic, benign, and indeterminate nodules

Referral to a surgeon for thyroidectomy in patients with nondiagnostic, indeterminate or benign nodules is based on the individual DTC risk, the likelihood of false negative FNA, the risks of operative intervention, symptomatology (e.g. tracheal compression or dysphagia) and the tolerance for diagnostic ambiguity in the patient and family [3]. Patients with nondiagnostic cytology (Bethesda I) may choose repeat FNA. To avoid atypical cellular artifact owing to the previous biopsy, conventional practice has been to allow at least 3 months to pass between each biopsy attempt [54]. This practice has been challenged by recent studies in adults which have suggested that cytology can be reliably interpreted if repeated at a shorter interval, but data are lacking in children [55,56]. Other options include continued US surveillance or lobectomy.

Children with benign cytopathology (Bethesda II) should be followed by serial ultrasound, preferably done by the same ultrasonographer over time. TN growth should be tracked by US. There are no clear guidelines regarding what constitutes an abnormal rate of enlargement, but many clinicians recommend repeat FNA if the nodule enlarges more than a few millimeters over 6–12 months and/or new, concerning ultrasonographic features are detected. Operative intervention is warranted in the presence of rapid TN growth or compressive symptoms [3]. Larger lesions (>4 cm) have a higher false negative rate and lobectomy should be offered even if cytology is benign. In practice, many large nodules cause symptomatic dysphagia or airway compression or are aesthetically unappealing and patients opt for operative resection independent of cytologic categorization.

In AUS/FLUS (Bethesda III) repeat FNA may yield a diagnosis, but as many as a third of second biopsies remain AUS/FLUS [57]. Because of the increased risk for DTC in children with AUS/FLUS, lobectomy is preferred over repeat biopsy. If DTC is confirmed intraoperatively or on final histology, a completion thyroidectomy can be performed. Intraoperative frozen section may be of help in diagnosing classic PTC but has no benefit in fvPTC or FTC, as the latter requires evaluation of the entire lesion to detect vascular and/or capsular invasion [58,59].

The risk of DTC appears to be >50% in children with FN/SFN cytology (Bethesda IV) [44,47,60,61]. 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. If a *BRAF* mutation or fusion gene (*RET/PTC* or *NTRK3/ETV6*) is detected in the AUS/FLUS or FN/SFN category, total thyroidectomy is warranted based on the high risk of PTC [62,63]. On the other hand, malignancy is less likely in a TN with a *RAS* mutation or *PAX8-PPARG* rearrangement and lobectomy may be preferable [63].

Patients with bilateral TN should be considered for total thyroidectomy. For FNA suspicious for malignancy or revealing malignant cytology (Bethesda V or VI), the risk for DTC is near 100% and total thyroidectomy with or without central neck dissection is recommended [3,15].

2.3.1. Risk stratification

The ATA Pediatric Guideline used the American Joint Committee on Cancer (AJCC) TNM nomenclature to stratify children into three categories: low-, intermediate-, and high-risk for persistent postsurgical cervical disease or distant metastasis (Fig. 2). Pediatric *low-risk* includes those with disease grossly confined to the thyroid with no (N0) or unknown but unsuspected (NX) cervical nodal disease, or those with incidental nodal involvement of the central compartment (N1a) defined as microscopic metastasis to a “low” number of level VI lymph nodes. These patients are at low risk for distant metastasis but are still at risk for residual cervical disease, especially if initial surgery did not include a central node dissection. Pediatric *intermediate-risk* includes those with more extensive N1a or minimal N1b nodal involvement [3]. These patients appear to be at low risk for distant metastasis but at increased risk for persistent or recurrent cervical disease. Pediatric *high-risk* includes regionally extensive disease (extensive N1b) or locally invasive disease (T4 tumors), with or without distant metastasis [3]. Patients in this group are at the highest risk for incomplete resection, persistent disease, and distant metastasis. In spite of these definitions for risk stratification, there are no quantitative guidelines for attributing “minimal” or “extensive” nodal status.

2.4. Operative recommendations for malignant nodules and lymph node metastases

Total thyroidectomy 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 [5,64]. Total

LOW RISK
Disease confined to the thyroid (may include multiple nodules or bilateral disease if confined)
No evidence of clinical lymphadenopathy in the central neck (incidental micrometastatic disease in disease to a small number of nodes in central neck is permitted)

INTERMEDIATE RISK
PTC with extensive evidence of nodal disease in the central neck
PTC with minimal unilateral metastases to the lateral neck

HIGH RISK
PTC with macroscopic extrathyroidal extension
PTC with extensive unilateral or bilateral metastases to the lateral neck
PTC with distant metastatic disease (usually found post-operatively)

Fig. 2. Risk stratification.

thyroidectomy (TT) is recommended for children with PTC based upon the high incidence of bilateral (30%) or multifocal (65%) disease [64–69] . Patients with preoperatively detected or clinically apparent central lymph node metastases should undergo therapeutic central neck dissection (CND) of Level VI nodes (Fig. 3) [3,5,64,67]. Lesser thyroid resections than total thyroidectomy are associated with as high as 10-fold greater recurrence rates and inadequate lymph node dissections in patients with clinically positive nodes increase the need for subsequent intervention 3-fold [5,9,64,66,67]. Studies in adults have shown that compartment focused lymph node dissections reduce recurrence compared to "berry picking"; these studies have generally been extrapolated to children although primary data are lacking [70]. Several high volume centers have reported the need to reoperate for persistent as well as relapsed disease treated initially at a lower volume institution [71,72]. Although a compartment-oriented central neck lymphadenectomy theoretically increases the risks of hypoparathyroidism and recurrent laryngeal nerve injury [66,73], these complications are minimized when performed by a high-volume surgeon [69,71,72,74,75]. It is imperative that the correct operation be performed initially because anatomic planes are absent or distorted in reoperative fields, thus increasing the chance of injury [76].

Modified radical neck dissection is reserved for biopsy-proven metastatic DTC in the lateral compartment (levels II, III, IV, and V). In this setting, compartment-oriented lateral neck dissection improves disease free survival (DFS) [64,67,72]. In a report of 429 neck dissections in both pediatric and adult patients, 88% of patients who underwent lateral neck dissection had no local recurrence over the next 10 years [77].

A convincing series of data have demonstrated a volume–outcome relationship between surgeon experience at thyroidectomy and patient complications and length of stay in both adults and children [75,78]. 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 or head and neck surgeon [78–80]. Estimates of complication rates (hypocalcemia and recurrent laryngeal nerve injury) vary widely, likely reflecting both a lack of standard definitions of these complications as well as expertise of the operative team [72,81–89]. Rates of recurrent laryngeal nerve injury should be less than 3% with TT [90]. One multidisciplinary pediatric thyroid center recently reported transient complications (chiefly hypocalcemia) in 9% of children and no permanent complications [81]. Transient postoperative hypocalcemia is treated with oral calcium and calcitriol and typically resolves within a month [79,81,89,91–95].

2.4.1. Controversies in surgical management

There is no consensus on the optimal extent of resection in low and intermediate risk PTC. Most published studies are small single institution reviews and the absence of prospective randomized trials coupled with an indolent disease process has thwarted formation of an evidence-based consensus opinion. Large database studies have measured success of various operative approaches using an endpoint 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 rather than patient mortality. Furthermore, whereas the adult literature has become increasingly granular at defining recurrence and now distinguishes structural from biochemical recurrence, the pediatric literature has lagged in reporting recurrence with such granularity [96,97]. Proponents of lobectomy cite equivalent survival in patients undergoing lobectomy versus total thyroidectomy, and an increased rate of permanent hypocalcemia and permanent recurrent

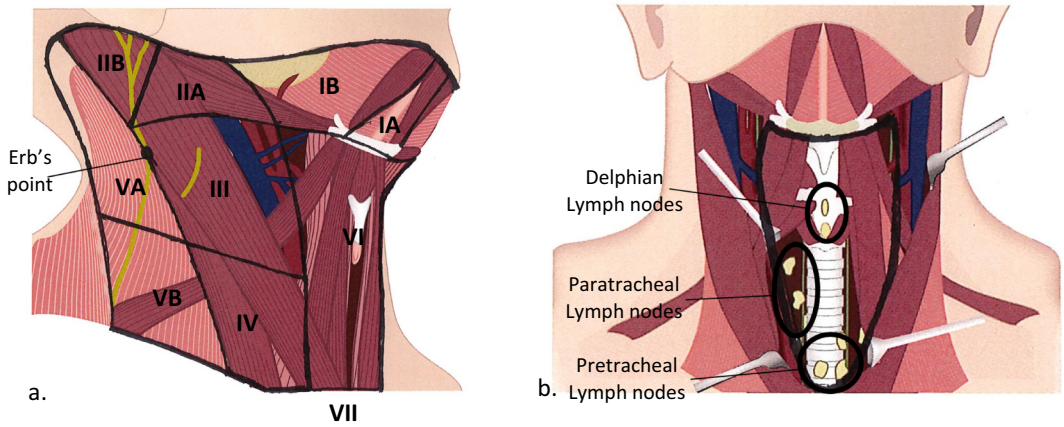

Fig. 3. (a) Cervical lymph node levels I-VII; (b) depiction of central neck lymph nodes with thyroid removed.

laryngeal nerve injury of patients undergoing total thyroidectomy [2,10]. Countering this argument is evidence for a lower recurrence rate after TT, and the observation that at least 40% of pediatric PTCs are multifocal [98,99]. Recurrence rates following thyroidectomy for PTC vary between 12% and 34%, with the majority of studies reporting rates around 20% at 10 years [5,72,87,100–102]. However, few institutional series have had sufficient patient volume to report recurrence rates based upon risk group stratification or modified by operative approach. Some experts believe a prophylactic CND should be considered for all children with PTC in order to reduce the risk of persistent or recurrent disease based on several small studies suggesting that the addition of prophylactic CND decreases recurrence rates to as low as 5% at 10 years [5,67,72,103,104]. 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 complications [105]. When considering operative strategy, the potential morbidity of bilateral CND must be weighed against the indolent nature of PTC, and prophylactic central neck dissection should be performed only by surgeons with extensive experience operating in the central neck. Since CND particularly jeopardizes the blood supply of the inferior parathyroid glands (PTs), if an inferior PT is noted to be ischemic or to have been removed *en bloc* with the nodal dissection, there may be a role for autotransplantation into the ipsilateral sternocleidomastoid muscle. McWade and colleagues have published extensively 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) and several additional groups have validated this technique [106–109].

2.5. 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 [4,5,7,8,110]. These numbers however belie high recurrence rates [111,112]. Studies with long-term follow-up indicate that children with DTC have increased mortality from second malignancies, possibly related to radioactive iodine (RAI) use [5,113,114].

2.6. 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 the fact that adolescents comprise a particularly mobile segment of the population who may have temporally and geographically dyssynchronous care. Most studies report recurrence rates of 20%–40% at 10 years unadjusted for initial stage of disease [5,87,100–102]. Children with palpable cervical nodal metastases are more likely than those without clinical node involvement to present with distant metastasis as well as experience persistent and/or recurrent disease over time [9,115]. In general, younger age, larger tumor size, solid architecture pattern, extensive tumor fibrosis, vascular invasion, disseminated psammoma bodies, extrathyroidal extension, node-positive disease with a high metastatic ratio index (MRI > 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 [72,82,100,115–121].

2.7. Postoperative staging

Following surgical resection, patients are staged based upon the operative findings to identify those with persistent disease and those at intermediate or high-risk for recurrence. For ATA pediatric low-risk patients, initial postoperative staging includes a TSH-suppressed serum thyroglobulin (Tg) [as long as Tg antibodies (Tg-Ab) are negative]. Those patients with an undetectable TSH-suppressed Tg remain assigned to the low-risk category and are followed by neck US and TSH-suppressed Tg [122–124] . Rising serum Tg indicates possible recurrence that should be confirmed by neck US, chest CT, and/or diagnostic whole-body RAI scan (DxWBS) either alone or in conjunction with single photon emission computed tomography with integrated conventional CT (SPECT/CT) to better localize disease. In children with positive Tg-Ab (common in patients with Hashimoto's thyroiditis), trending Tg is less reliable, and Tg antibody titer should be followed but is a less sensitive marker than Tg. If concern remains about residual/recurrent disease, DxWBS should be performed.

For ATA pediatric intermediate- and high risk-patients, a TSH-stimulated Tg and DxWBS are indicated to determine if treatment with ^{131}I is warranted. TSH-stimulated Tg is a reliable marker for residual disease for those without Tg antibodies [125–128]. The DxWBS is particularly useful in identifying disease in children who are Tg-Ab positive [129,130] and further assists in visualizing distant metastatic disease (most commonly pulmonary) [131]. For patients with cervical RAI uptake, SPECT/CT imaging may help distinguish regional lymph node metastases from remnant thyroid tissue [132–134].

2.8. 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 [3]. ^{131}I therapy is indicated for patients with pulmonary metastases or small volume nonresectable residual cervical disease [10,135]. Most experts also advocate ^{131}I therapy for children with extensive regional nodal involvement (extensive N1a or N1b disease) [136]. 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 to adults with persistent DTC [10,11,137].

RAI uptake is facilitated by a hypothyroid state: TSH should be greater than 30 μIU/ml, which can typically be achieved after 2 weeks of thyroid hormone withdrawal [138]. A low-iodine diet should also be followed for 2 weeks prior to therapy. Of note, RAI should be deferred for 2–3 months after exposure to iodinated CT contrast, and urine iodine excretion should be confirmed to be less than 75 μg/L prior to administration [53]. Recombinant human TSH (rhTSH, Thyrogen) which stimulates iodine uptake in remnant thyroid or residual micrometastatic disease, is an alternative to thyroid hormone withdrawal and commonly used in adults to avoid the unpleasant side effects of hypothyroidism. While not FDA-approved for patients <18 years of age, several small studies in children suggest rhTSH prior to ^{131}I therapy is both efficacious and safe for remnant ablation; there are no data on use for therapeutic intent in those classified as ATA “intermediate” or “high” risk [67,139,140].

2.9. TSH 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. The ATA recommends initial TSH suppression based upon risk stratification. In intermediate and high risk disease in which unresected micrometastatic disease is likely, TSH suppression to <0.1 μIU/ml is suggested. In children with no evidence of disease after a period of postoperative surveillance (also undefined, but likely at least 6 months) TSH may be kept in the low-normal range [3] . If Tg rises while the patient is on levothyroxine, disease relapse is likely to become clinically apparent [128,141–143]. The decision to pursue further therapy is based upon 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 [128,141].

2.10. Treatment for persistent or recurrent PTC

Given long term survival rates approaching 100%, treatment for persistent or recurrent disease should be individualized and careful consideration given to the potential risks and benefits of therapy. Patients with small cervical foci (i.e. <1 cm) 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 posttherapy targeted ^{131}I effects for years and an undetectable Tg level should not be the focus of treatment efforts. As many as a third of patients exhibit persistent, but stable, disease following RAI. Therapy should be considered only in those who show signs of progression [3].

An increasing number of multikinase inhibitors (TKIs) that target protein tyrosine kinase dependent pathways are being developed for adult patients with iodine refractory disease [144]. The DECISION trial, a multicenter phase III study of sorafenib to treat relapsed disease, reported a 12% response rate and an increase in median progression free survival (PFS) from 5.8 to 10.8 months [145]. The phase 3 SELECT trial using Lenvatinib also increased PFS for FTC and PTC [146]. Sorafenib and Lenvatinib have been approved for compassionate use in a small number of children with DTC [147–150]. Sorafenib was used without complication for 24 months to treat pulmonary metastases in an 11-year-old male [149]. His pulmonary metastases initially regressed and subsequently remained stable during the two years of therapy. Likewise, Mahajan et al. reported favorable responses to Lenvatinib in three children with progressive pulmonary metastases causing respiratory distress [150]. All three children were able to be weaned from oxygen with no further progression of disease.

2.11. Papillary thyroid microcarcinoma (PTMC)

In adults, papillary thyroid microcarcinoma (PTMC) is defined as DTC < 1 cm in diameter, and is felt to represent a more indolent form of DTC which may be treated by thyroid lobectomy, ethanol injection, or even close observation. PTMC in children, however, remains a largely unstudied entity. There is not even a consensus definition of PTMC across all pediatric age groups given the relatively smaller size of the thyroid in prepubescent children compared to older adolescents and adults [151]. Using a cutoff of 1 cm, analysis of the Surveillance, Epidemiology, and End Results (SEER) database found a PTMC prevalence of 8.4% over the period 1988–2009 with incidence increasing with age [110,151,152].

The natural history of PTMC is not well-defined, but patients are commonly considered low-risk for recurrence. However, in comparing PTMC in children with adults, pediatric PTMC is more likely to have metastatic lymph node involvement. Two pediatric studies found lower, but still frequent, rates of cervical node disease in PTMC compared with larger tumors: 31.47% vs 47.6% ($p < 0.001$) in the SEER database and 60% vs 95.2% ($p = 0.001$) in a Greek cohort [151,152]. The latter study found lower rates of extrathyroidal extension (8.8% vs 33%, $p = 0.017$) and capsular invasion (14.7% vs 45.6%, $p = 0.005$) in children with PTMC compared with DTC >1 cm [151]. However, this study compared PTMC with an aggregate of low, intermediate, and high risk PTC confounding the interpretation of these results. Of the 17 children with PTMC captured by this study, all underwent TT without prophylactic CND and there were no local or distant recurrences. In the SEER study, 70% of patients underwent TT and 35% (52% of the TT patients) received RAI [152]. Recurrence data are not available but in small series nodal spread did not impact survival. Based on these limited data in children with PTMC, some experts argue that lobectomy with isthmusectomy may be adequate for unifocal pediatric PTMC provided that US shows absence of disease in the contralateral lobe and normal regional lymph nodes. There are no large series or prospective data to support this approach, and providers who elect this management must ensure close patient follow-up and involve the patient and family in the decision making process [74,153].

2.12. Follicular thyroid carcinoma (FTC)

Fewer than 10% of pediatric DTCs are follicular carcinomas. The diagnosis of FTC is based on the identification of capsular and/or vascular invasion on permanent histologic sectioning. The 2015 American Thyroid Association Guidelines divide FTCs into those with capsular invasion (CI) alone, minimal (<4 vessels) vascular invasion (VI), and extensive VI (≥4 vessels) [31]. As opposed to PTCs which are frequently multifocal, FTCs are typically unifocal tumors without extrathyroidal extension. Any patient with multifocal FTC should be evaluated for PHTS or a DICER1 mutation [24,154,155]. 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 having FTC should raise the possibility that the lesion is an fvPTC [156].

FTCs have a different sonographic appearance than PTCs. They are frequently larger, isoechoic, and often demonstrate a hypoechoic rim [157,158]. Because of the need for permanent histology to evaluate for CI or VI, FNA cytology is largely unhelpful in diagnosing FTC.

The recommended treatment for angioinvasive FTC (≥4 vessels VI) or FTC ≥4 cm is total thyroidectomy and RAI [159–161]. Treatment of minimally invasive FTC (MI-FTC) is controversial as it seems to mimic a benign lesion [162]. Robinson et al. evaluated 419 benign adenomas, 21 MI-FTC, and 41 FTCs with capsular invasion in adults [163]. Over 16 years, disease-free survival was 100% in the adenoma group, 100% in the MI-FTC group, and 36.6% in the CI-FTC group ($P < 0.0001$) suggesting that MI-FTCs could be treated by thyroid lobectomy alone. Studies of MI-FTC in children have also demonstrated indolent behavior and have suggested that lobectomy followed by close follow-up and TSH suppression may be sufficient [156]. However, a separate study which included children with MI-FTC with vascular invasion observed recurrence in 3 of 9 children. Although approximately one-third of patients recur, 30-year disease-specific survival is 100% [164].

2.13. Complications of DTC treatment

Complications of therapy can be related to either operative intervention or RAI ablation therapy. The most common operative complications include hypocalcemia, respiratory complications, vocal cord paresis/paralysis, postoperative infection, and bleeding [165]. A number of studies have demonstrated reduction in complication rates in high volume centers [78,80,166,167] . In a cross-sectional analysis of the Healthcare Cost and Utilization Project which draws from the National Inpatient Sample, pediatric patients undergoing total thyroidectomy had a general complication rate of 17.6% and an endocrine specific (including hypocalcemia, voice disturbance, and recurrent laryngeal nerve injury) complication rate of 16.3%, but these numbers were reduced by more than half to 8.7% and 5.6% if performed by a high volume surgeon [78].

Rates of transient hypocalcemia vary widely across studies, owing in part to a lack of consensus in defining the condition, but range from 7% to 59% [78,81,92,93,95,168–171]. Calcium levels may take several months to recover following thyroidectomy and a diagnosis of permanent hypoparathyroidism should not be made before the sixth postoperative month, based on a need for continued calcium +/− calcitriol supplementation [92]. The reported incidence of permanent hypoparathyroidism also varies, running higher in population-based or multicenter pediatric studies (5.5%–25%) [165,172,173] and lower in single-institution studies (1.5%–8.0%) [81,88,89,92–94]. Central neck dissection in theory increases the risk of both 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 [89,92,95,173]. Several authors suggest obtaining either intraoperative or postoperative intact parathyroid hormone (intact PTH) level to help prognosticate need for and likely duration of calcium supplementation [169,174]. A recent study found that a four hour postoperative PTH level less than 10 pg/dl was 90% specific and 81% sensitive in identifying those patients who reported symptoms of hypocalcemia at the four hour time point of blood collection. None of 26 patients with a 4 h PTH level greater than 10 pg/dl ever experienced symptoms of hypocalcemia and fewer than 20% received any postoperative calcium supplementation [175].

The risk of recurrent laryngeal nerve injury also varies widely in published reports but a recent analysis of 1654 patients undergoing total thyroidectomy in the KID database identified a recurrent laryngeal nerve injury rate of 1.8% [165]. This rate represented children with both benign and malignant disease. Higher rates have been published in institutional case series. Young children seem particularly at risk for nerve injury with a reported incidence of vocal cord paralysis of 14.3% in children <1 year [87,100,165]. However, several recent retrospective studies from high volume institutions report inadvertent nerve injury rates of 0.4%–2.8% based upon loss of signal during intraoperative nerve monitoring or postoperative laryngoscopy [69,71,72]. Injuries to other regional nerves during lateral neck dissection (including the sympathetic chain, vagus, spinal accessory nerve, and hypoglossal nerve) are rare events [71,88,176,177].

Complications of RAI therapy include both short term effects: nausea/emesis (42%), sialadenitis (29%), dry mouth (17%) and transient bone marrow (BM) suppression (10%); as well as less common long term consequences: permanent BM suppression (4%), pulmonary fibrosis (5%), second malignancies (4%), and altered fertility (4%) [178]. Over a third of adult survivors of pediatric DTC receiving RAI reported moderate to severe xerostomia [179]. A cumulative ^{131}I dose of greater than 200 mCi was more likely to lead to salivary dysfunction. Lemon drops delayed 24 h after therapy may reduce the risk of salivary damage (whereas earlier administration of lemon drops may perpetuate damage) [180].

Children with diffuse pulmonary metastases and high RAI uptake in the lung are at risk for posttreatment pulmonary fibrosis [181,182]. Dosimetry may inform dosing to help limit radiation exposure to the adjacent normal lung parenchyma [180,181].

Childhood survivors of DTC who have received RAI or radiation have an apparent increase in second malignancies with a cumulative incidence of second malignancy of 12% which steadily increased over 40 years and is more than four-fold greater than the untreated population [183]. The salivary glands, mouth, and kidneys are at greatest risk for the development of secondary cancer [183].

2.14. Future directions: molecular genetics

Molecular genetic testing provides techniques to better characterize TN; however, data in children are limited. In adults, genetic profiling is used to distinguish benign from malignant nodules with Bethesda class III or IV cytology. 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 [63]. 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) [63]. 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 [63,184,185]. *RET/PTC1* and *RET/PTC3* are the most common rearrangements in both sporadic and radiation-induced pediatric PTCs. The *BRAF* gene is the most common location for a point mutation in pediatric PTC [63,186]. 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 [187]. 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 [188–191]. As genetic testing becomes routinely incorporated into the early diagnostic testing, staging, operative decision making, and adjuvant therapy plans may be based upon individual precision medicine, incorporating these tumor specifics into clinical care.

3. Conclusion

DTC is rare in young children but increases in frequency through adolescence such that it is the second most common pediatric malignancy found in adolescent females. The majority of DTCs in the pediatric population are papillary thyroid carcinomas. Compared to PTC in adults, PTC in children appears to bear a more locally aggressive phenotype with more frequent spread to local and regional lymph nodes and higher rates of recurrence. Operative resection remains the foundation of treatment, and local recurrence is directly affected by operative approach to regional metastatic disease. Preoperative evaluation with dedicated thyroid and bilateral neck ultrasound with FNA of suspicious nodules and lymph nodes should guide the operative approach. Total thyroidectomy 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 central neck dissection for patients with microscopic but not clinically evident disease in the central neck requires further investigation. Evidence of lateral lymph node involvement should be addressed with modified radical neck dissection. Use of lobectomy for microcarcinoma, the administration of RAI in minimal residual disease, 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.

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