



Pediatric Differentiated Thyroid Carcinoma

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Introduction

Differentiated thyroid carcinoma (DTC) is the most common endocrine malignancy, with papillary thyroid carcinoma (PTC) representing 90% or more of cases in children [1–5]. Similar to adults, children with PTC commonly present with a palpable thyroid nodule or may be identified incidentally in the context of imaging studies. Tumor size is larger in children compared with older patients (70% of children aged 0–9 years have a tumor ≥ 2 cm) [5–7]. In further contrast with adults, pediatric PTC is frequently associated with clinically apparent, malignant cervical lymphadenopathy and may present as a diffusely infiltrative carcinoma without a discrete nodule (Fig. 21.1). Rarely, children may also be diagnosed via imaging that demonstrates pulmonary metastases that may initially be attributed to an infectious etiology (Fig. 21.2). Symptoms related to neoplastic involvement of adjacent aerodigestive structures is rare (4% or less of pediatric PTC

patients) [7]. Often multifocal and bilateral, PTC is associated with regional metastases in 80% or more of childhood cases at diagnosis in some retrospective series [4, 8–15]. Children with significant cervical lymph node disease are at the highest risk of hematogenously-spread lung metastases, [10, 11] (Fig. 21.2) which have been identified in up to 25% of patients in some published pediatric case series [3, 5, 12, 16–19]. Other sites of distant metastatic disease can include the brain, bones, and other solid organs but such events are exceedingly rare in children. Paradoxically, despite having more extensive disease at diagnosis, pediatric PTC is usually a well-differentiated tumor with an indolent clinical course, which translates to an extremely low disease-specific mortality [1, 17, 20–22].

Follicular thyroid carcinoma (FTC) represents a distinct histopathological entity from PTC. In children, the diagnosis of FTC is almost always made following the pathologic identification of capsular and/or vascular invasion in a nodule surgically removed after an indeterminate fine needle aspiration biopsy (FNAB). Given the rarity of FTC in children and because it remains poorly studied in this age group, the bulk of this chapter, especially the treatment algorithms, will focus on PTC.

The excellent prognosis of pediatric DTC, in concert with substantive concerns regarding the potential for long-term sequelae related to overaggressive treatment during childhood, make the optimal management of pediatric DTC a

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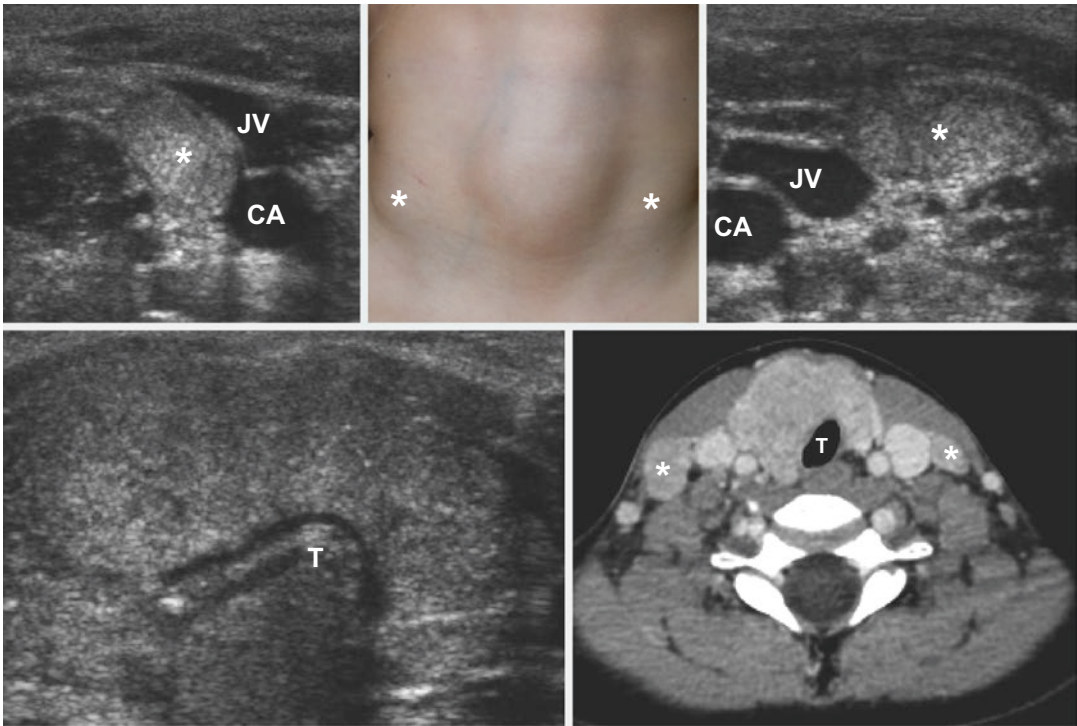


Fig. 21.1 Clinical presentation of pediatric papillary thyroid carcinoma. A 6-year-old boy with palpable cervical lymphadenopathy (asterisk) and a firm asymmetric goiter. Ultrasound demonstrates a primary tumor with scattered microcalcifications that is diffusely infiltrating both thyroid lobes and the isthmus (bottom left) as well as malig-

nant neck lymphadenopathy (asterisk) in both the right (top left) and left (top right) lateral neck. CT neck with contrast obtained as part of pre-operative staging also documents the extent of disease and its anatomic relationship to underlying aerodigestive structures such as the trachea. CA carotid artery, JV jugular vein, T trachea

challenging endeavor. Moreover, the existence of a very small population of patients with advanced disease who may benefit from systemic therapy poses a further challenge to care, given that these agents remain largely untested in children with DTC. Only recently have formal guidelines for management been developed by the American Thyroid Association (ATA) [23].

Epidemiology and Prognosis

In 2017, it is estimated that there will be 56,870 new thyroid cancer diagnosed in the United States, [24] of which 1.4% are expected to occur in individuals <20 years of age [25]. Pediatric thyroid cancer incidence is significantly lower in blacks versus whites, and the diagnosis is much more common in females [1, 6, 22, 25]. From 2010 to 2014, the age-adjusted incidence rate for

children ages 0–14 years was two case/million/year in males and five cases/million/year in females; adolescents (ages 15–19) are the most commonly affected pediatric age group (29 cases/million/year) and the female: male ratio is 5.4:1 in this population [25]. More broadly, thyroid cancer is the fifth most common cancer diagnosed in adolescence, representing 11% of all cancers [24]. In adolescents, incidence rates have been rising over the decades, [1, 6, 22, 25, 26] a trend that cannot solely be explained by an increased diagnosis of small tumors.

Children with DTC have an excellent prognosis and survival over decades is typical, even for those patients with distant metastases [1, 22]. Remission rates are high, especially in the current era of high-resolution neck ultrasonography and more comprehensive initial thyroid cancer surgery. In the pediatric population, 10-year survival is almost universally 100% [1, 19, 20, 27–32].

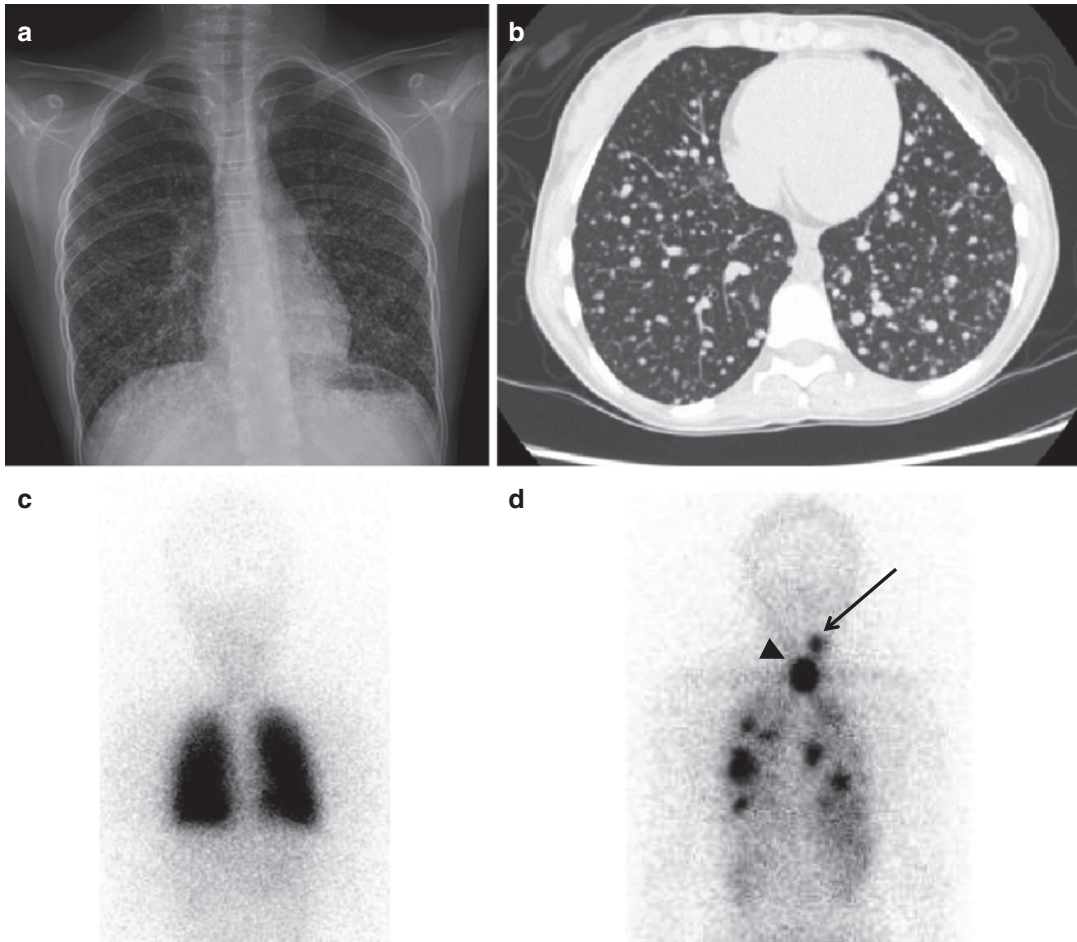


Fig. 21.2 Pulmonary metastases of pediatric papillary thyroid carcinoma. (a) Chest X-ray demonstrating a diffuse, miliary pattern of disease in a child; this pattern may initially be mistaken for an infectious etiology. (b) Axial post-contrast computed tomography image showing the micronodular pulmonary metastases typical of pediatric disease. (c)

Post-treatment thyroid scan with diffuse and intense pulmonary uptake of ^{131}I . This pattern is associated with an increased risk of pulmonary fibrosis. (d) Post-treatment thyroid scan of a different patient showing multifocal nodular pulmonary uptake, thyroid bed uptake (arrowhead), and residual cervical lymph node disease (arrow)

Children diagnosed before age 10 years appear to have a higher risk of recurrence and ultimately death from their disease, [17, 21, 33–36] although a significant difference in tumor biology between the very young and older children has not been confirmed in other studies [7, 11, 37–39]. A subgroup of pediatric patients will ultimately die of their cancer or succumb to treatment-related complications [20, 28, 29, 40, 41]. For children with distantly metastatic disease, it is those with micronodular lung metastases and iodine-avid disease who maintain the best prognosis [29, 42]. Improved risk stratification that incorporates knowledge about clinical presentation, somatic

mutational analysis, and response to treatment are needed to better identify those children who are at highest risk for ultimate disease-specific death and to avoid overzealous treatment of others who are unlikely to die from their cancer.

Risk Factors

Exposure of the thyroid to radiation (primarily in the context of medical therapy for cancer) is the major established risk factor for the development of thyroid carcinoma, although irradiation not including the thyroid region can also increase the

risk [43]. Children, particularly those younger than age 5 years, appear to be especially sensitive to the tumorigenic effects of ionizing radiation [44]. Thyroid cancer is one of the most frequently diagnosed subsequent primary malignancies in childhood cancer survivors, with at least a five-fold increase in risk [45, 46]. This risk appears to decline once the thyroid dose exceeds 2000 cGy, [44, 47] suggesting that sublethal irradiation of the thyroid imparts the greatest risk. Radiation-induced tumors do not appear to be more aggressive compared with sporadic, non-radiation induced disease [48, 49]. The latency period between radiation exposure and diagnosis is typically long, with a median time to occurrence around 19 years [45]. Surprisingly, the risk of thyroid malignancy in childhood cancer survivors appears to be increased even in those who have not received therapeutic irradiation and this may reflect, at least in part, additional increased cancer risk among recipients of alkylating chemotherapy [50, 51].

Exposure to ionizing radiation can also occur via the ingestion of radionuclides, epitomized by the large environmental exposure to radioactive iodine (RAI) resulting from the Chernobyl, and possibly, the more recent Fukushima nuclear accidents [2, 52]. Additional environmental exposures may increase the risk of thyroid cancer in children living in geographic areas with volcanic activity [53]. The small activities of $^{123}\text{I}/^{131}\text{I}$ used for diagnostic studies and the treatment of hyperthyroidism appear to be below the threshold needed for tumorigenesis [54]. The use of ^{131}I -Metaiodobenzylguanidine (^{131}I -MIBG) to treat children with neuroblastoma has also been implicated in the development of benign and malignant thyroid neoplasia, [55] although common genetic factors and mechanisms of tumorigenesis between these two malignancies may also play a role [56, 57].

There has been some conjecture regarding a link between thyroid autoimmunity and the risk of DTC. However, whether or not a strong association between autoimmune thyroid disease and DTC exists in children remains unknown. The prevalence of PTC was 3% in one study of 375 children with autoimmune thyroiditis, [58] and

another study of children with goiter did not clearly identify an increased risk of PTC in children with positive thyroid peroxidase antibodies compared with those with normal titers [59]. In a retrospective review of 32 children operated for Graves disease, DTC was identified in 22% of patients (including four diagnosed preoperatively); [60] three and two patients had lymph node and pulmonary metastases, respectively.

Although rare in the developed world, iodine deficiency is associated with an increased risk of thyroid neoplasia (specifically FTC) [61, 62] and, similar to many other cancers, obesity may be an additional risk factor [63]. Finally, although accounting for a small minority of pediatric DTC, germline variants in several genes have been associated with syndromic and non-syndromic hereditary DTC and are discussed in greater detail later in this chapter.

Histopathologic Variants

DTC comprises two major histopathologic variants, PTC and FTC, which differ in their clinical and metastatic presentations. Anaplastic (undifferentiated) thyroid carcinomas and poorly differentiated thyroid carcinomas are exceedingly rare in childhood, as are primary thyroid lymphomas and metastases to the thyroid gland.

Subtypes of PTC include classic/conventional, encapsulated, follicular (fvPTC), tall cell, oncocytic, columnar cell, diffuse sclerosing (dsPTC), hobnail, cribriform-morular and solid/trabecular variants [64, 65]. Recently, based on a retrospective analysis of clinical outcomes, the noninvasive encapsulated follicular variant of PTC has been reclassified in adults as a low risk tumor called NIFTP (noninvasive follicular thyroid neoplasm with papillary-like nuclear features [66]. It is unclear if these data can be extrapolated to pediatric patients with similar histology as no patients <age 21 years was in the NIFTP group.

In children, classic PTC is the most common variant (48%) followed by (in one recent study) dsPTC (16%), fvPTC (14.5%), encapsulated PTC (13%), tall cell PTC (13%), poorly differentiated (6.5%) and solid PTC (2%) [67]. In contrast

with adults, histologic subtype does not appear to independently predict event-free survival, [67] although some studies have shown a higher risk of recurrence in children with classic PTC compared with fvPTC [18]. Solid variant PTC is more common in children with a history of radiation exposure [64]. The diffuse sclerosing variant, characterized by diffuse and often bilateral involvement of the thyroid, demonstrates extensive squamous metaplasia, abundant psammoma bodies, stromal fibrosis, and prominent lymphocytic infiltration. It is often accompanied by chronic lymphocytic thyroiditis in the background thyroid, extensive regional nodal metastases, and a higher frequency in younger patients [68, 69].

FTC is broadly divided into minimally invasive and widely invasive forms [70]. In 2017, the World Health Organization reclassified FTC into three groups: (1) minimally invasive (capsular invasion only) (2) encapsulated angioinvasive, and (3) widely invasive [65]. Similar to adults, minimally invasive FTC in children may be a low-risk malignancy, [30, 71] but bone and lung metastases have been described in minimally invasive tumors with vascular invasion, underscoring the fact that any degree of vascular invasion may confer a risk for metastatic disease in pediatric FTC [72]. The oncocytic (Hürthle-cell) variant of FTC is rare in the pediatric population [31, 71].

Molecular Mechanisms of Disease

Somatic Genomic Alterations

Abundant work over recent decades has established the primacy of aberrations in signaling through receptor tyrosine kinase (RTK) pathways, predominantly via the cognate RAS-RAF-MEK-ERK and PI3K-AKT-mTOR pathways, in the molecular pathogenesis of DTC. Recent genomic and transcriptome analyses [73, 74] have demonstrated that activating pathogenic variants in one of these two pathways are common, identified in 96.5% of PTCs [73] and 73% of follicular thyroid neoplasms (FTC and follicu-

lar adenomas) [74]. These somatic alterations typically are mutually exclusive and the mutational burden of DTC is low compared with other carcinomas. Moreover, the relative balance of RAF- versus RAS-mediated signaling has been linked to the extent of thyrocyte differentiation and differences in expression of genes responsible for iodine uptake and metabolism, which has potential treatment implications [73].

In pediatric PTC, gene rearrangements are the most common molecular event, especially after previous radiation exposure, [75–78] but they are not limited to children with that well-established risk factor [79–81]. Fusions involving the *RE*arranged during *Transfection* (*RET*) proto-oncogene and the neurotropic tyrosine receptor kinase (*NTRK*) gene are the most common [77, 79–84]. Gene rearrangements of peroxisome proliferator-activated receptor gamma (*PPARG*) and paired box gene 8 (*PAX8*) and fusions involving the v-raf murine sarcoma viral oncogene homolog B (*BRAF*) and anaplastic lymphoma kinase (*ALK*) genes have also been identified, [77, 81, 84–87] although the *PAX8/PPARG* fusion is much more commonly associated with FTC [88]. *BRAF*^{V600E} point mutations are also prevalent, [78–81, 86, 89, 90] although not as common as in adults. Rat sarcoma (*RAS*) mutations are also identified in pediatric PTC and FTC, [77, 78, 80, 81, 86, 90] although these have also been identified among benign follicular adenomas; [74] thus, at least from a diagnostic perspective, their relevance is debatable. *BRAF* mutations are more common in older pediatric patients, [84, 86, 87, 89] and it appears that *BRAF*-mutated PTC may not be more clinically aggressive in the pediatric population, as has been suggested for adult PTC [78, 79, 81, 86, 90, 91]. *TERT* promoter, *PIK3CA*, and *PTEN* mutations are rare [89–91].

Hereditary DTC

Hereditary DTC is rare and <5% of pediatric thyroid cancers are associated with an underlying germline mutation [78]. A family history of PTC is present in 4% of pediatric cases [7].

However, in the context of the high prevalence of PTC in the population at large, the presence of a single affected 1st degree relative with PTC does not indicate a familial etiology. Multiple genes and heritable tumor syndromes have been associated with both benign and malignant thyroid neoplasia: *APC*-Associated Polyposis (*APC* gene; OMIM[Online Mendelian Inheritance in Man®] #175100), Birt-Hogg-Dubé Syndrome (*FLCN* gene; OMIM #135150), the Carney complex (*PRKARIA* gene; OMIM #160980), CHEK2-Related Cancer (*CHEK2* gene; OMIM #604373), DICER1-pleuropulmonary blastoma familial tumor predisposition syndrome (*DICER1* gene; OMIM #606241), familial non-medullary thyroid carcinoma (FNMT) (multiple genes; OMIM #188550), Li-Fraumeni syndrome (*TP53* gene; OMIM #151623), *PTEN* [phosphatase and tensin homolog] Hamartoma Tumor Syndrome (*PTEN* gene; OMIM #601728), Pendred syndrome (*SLC26A4* gene; OMIM #274600) and Werner syndrome (*WRN* gene; OMIM# 277700). Most recently, a germline compound heterozygous deletion in the *USF3* gene was identified in a Cowden syndrome-like kindred with PTC, suggesting that this gene may also be involved in the predisposition to thyroid cancer [92]. Comprehensive reviews on the individual syndromes are available elsewhere, [65, 78, 93–96] and it should be emphasized that the association of DTC with some of these tumor predisposition syndromes does not necessarily indicate causality.

The *PTEN* hamartoma tumor syndrome is one of the more common syndromic causes of multinodular goiter and DTC (primarily PTC and fvPTC, but FTC is overrepresented relative to the general population), [95, 97–99] and the youngest reported case of thyroid cancer associated with a *PTEN* mutation was in a 7-year-old [98]. A clue to this diagnosis in a child presenting with thyroid neoplasia is macrocephaly, present in 98% of children with a germline *PTEN* mutation, [99] although macrocephaly has also been reported in 42% of *DICER1* mutation carriers [100]. Multinodular goiter is predominant in patients with *DICER1* mutations, especially in females, and the risk of DTC is also increased

[101, 102]. In contrast with children at risk for hereditary medullary thyroid carcinoma, it is *not* recommended that children at risk for DTC due to an underlying disease-predisposing gene mutation undergo prophylactic thyroidectomy. In these cases, screening ultrasounds may be considered (based on expert opinion) in the *DICER1*-Syndrome, *PTEN* hamartoma tumor syndrome, Carney complex, and *APC*-associated polyposis, [95, 102–106] noting that the latter syndrome is uniquely associated with the cribriform-morular variant of PTC [107].

Evaluation, Treatment, and Follow Up

Once described as a “fatal disease with few exceptions,” [108] malignant thyroid disease is now recognized to have an excellent long-term prognosis in the majority of patients, especially in children. The evaluation and treatment of pediatric DTC has certainly evolved over the years. Historically, surgery was less-than comprehensive, relying more on palpation and limited by the lack of pre-operative high resolution ultrasonography and other cross-sectional imaging that are commonly utilized today. There has also shift in the utilization of RAI. It was once held that ¹³¹I would “clean up” whatever disease was not removed surgically and RAI was used almost universally to treat children with DTC until the thyroid scan became negative or as long as the thyroglobulin (Tg) remained detectable (once this tumor marker became available for clinical use). More recently, the concept of iodine-refractory disease in pediatric DTC has been better appreciated and current guidelines suggest a more conservative approach to RAI treatment, even among those with iodine-avid cancer [23].

Initial Work Up and Staging (Fig. 21.3)

Once the diagnosis of thyroid cancer is established, a comprehensive pre-operative assessment is critical to understand the extent of cervical disease to facilitate the optimal surgical

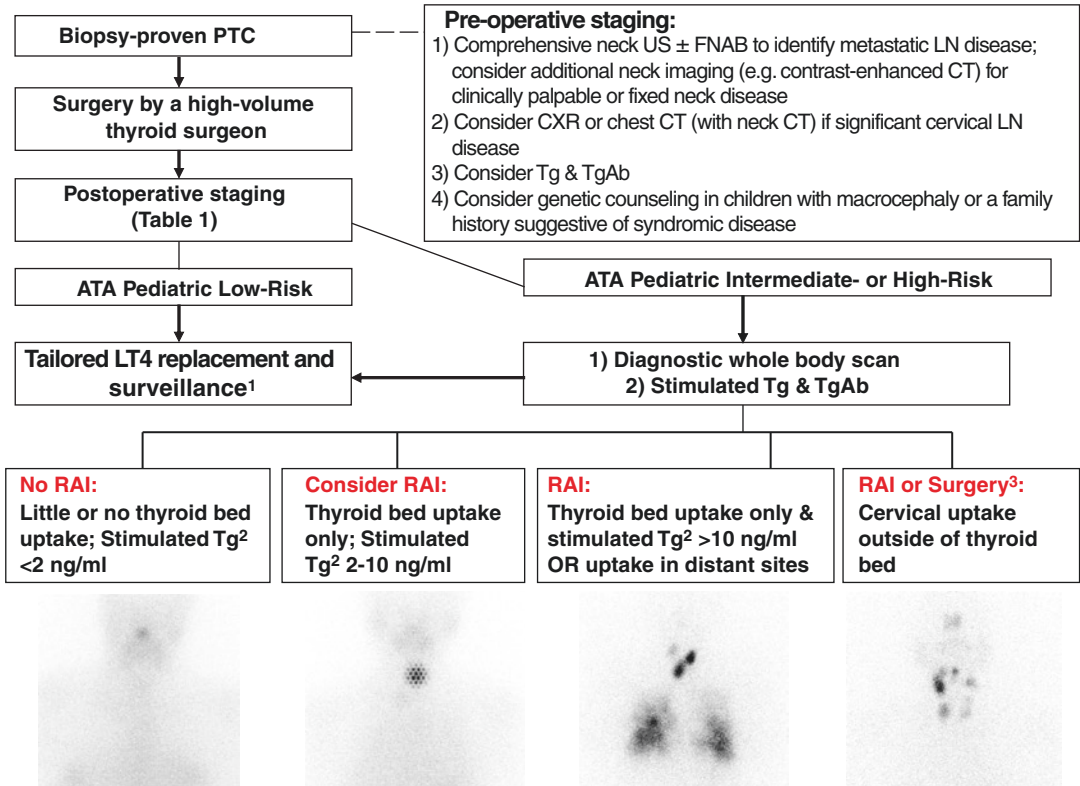


Fig. 21.3 Initial evaluation and treatment of biopsy-proven pediatric papillary thyroid carcinoma. ¹If residual/recurrent PTC is suspected during long-term follow up of low-risk patients, and assuming neck US is negative, further evaluation and treatment with RAI is recommended. ²Assumes negative TgAb; if TgAb is positive and there is no evidence of iodine-avid disease on the diagnostic scan, consideration can be given to deferring RAI treatment,

especially in intermediate-risk patients. ³RAI only if surgery deemed unsafe or not feasible. ATA American Thyroid Association, CT computed tomography, CXR chest X-ray, FNAB fine needle aspiration biopsy, LN lymph node, LT4 levothyroxine, RAI radioactive iodine (¹³¹I), Tg thyroglobulin, TgAb thyroglobulin antibody, TSH thyroid stimulating hormone, US ultrasound

approach. Universally recommended, assuming it is not already done, is a high-resolution cervical ultrasound (US) performed by an experienced ultrasonographer to interrogate the thyroid and lateral neck lymph nodes [23, 109, 110]. If suspicious adenopathy is identified, US-guided FNAB should be undertaken to confirm disease and the extent of regional metastases. In the presence of cystic lymph nodes, which are highly suggestive of PTC metastases, measurement of Tg on fluid from the needle washout may help to secure the diagnosis of malignant involvement [111, 112]. In children with bulky cervical disease, a primary tumor that appears fixed to underlying aerodigestive structures, or vocal cord paralysis, contrast-enhanced computed tomography (CT) of the

neck is recommended to help guide further the surgical approach [23, 109]. Only a minority of children will have pulmonary metastases, typically only those with bulky cervical disease, [10] and the detection of pulmonary metastatic disease does not change the initial therapeutic approach. In addition, postoperative staging with RAI, if indicated, will effectively identify most children with pulmonary metastases, even those with negative baseline radiographic imaging [16]. Therefore, current guidelines do not suggest routine chest imaging in all pediatric DTC patients, although some centers do obtain a pre-operative CXR in high risk children because the finding of a significant disease burden may alter the approach to subsequent RAI therapy [109].

However, a CXR is not sensitive enough to identify small-volume micronodular pulmonary metastases, [16] and for that reason, some also consider chest CT, especially if neck CT is also planned. Although not recommended by all, some experts do obtain baseline Tg and thyroglobulin autoantibodies (TgAb) after confirmation of DTC [109].

Surgery

The surgical approach to pediatric DTC is not significantly different from adult cases and so will not be discussed in detail. In general, given the high rate of lymph node and pulmonary metastases, total thyroidectomy is recommended in most cases [23]. However, in children with small, incidentally discovered tumors, no previous radiation exposure, and no evidence of contralateral disease or cervical lymph node disease, thyroid lobectomy \pm ipsilateral central neck dissection may result in similar long-term outcomes [7, 22, 32, 113, 114].

Current data suggest that the single most important factor for improving long-term disease-free survival is the extent of the initial surgery, with more complete surgery decreasing or eliminating persistent/recurrent disease and the need for additional treatment [11, 14, 17, 18, 20, 115–117]. Older studies, however, are confounded by the frequent prescription of RAI. Compartment-oriented neck dissection is advised for biopsy-proven lymph node disease and central neck dissection (CND), in the absence of documented lymph node metastases, can be selectively considered in children and determined by intraoperative findings, [23] recognizing that complication rates are higher with central neck dissection [118]. In the setting of a unifocal PTC > 1 cm, [119] an ipsilateral CND, with pursuit of contralateral CND only if intra-operative findings suggest central compartment disease, may help to balance the risks and benefits in pediatric patients. In every case, the decision to perform a CND should be driven by the experience of the surgeon and his or her ability to localize the parathyroid glands. Preservation of parathyroid function

(including the liberal use of parathyroid auto-transplantation) and avoidance of significant recurrent laryngeal nerve injury is paramount, even if it means leaving residual microscopic disease. Surgical complications are not insignificant in children with thyroid cancer, [2, 7, 19, 117, 118, 120] and there are lower complication rates and shorter hospital length of stay when surgery is performed by a high-volume thyroid surgeon [23, 121–125]. Therefore, it is strongly preferred that thyroid surgery, especially when lymph node dissection is required, always be performed by a surgeon experienced in the management of pediatric DTC.

Postoperative Staging

Several prognostic staging systems have been used for DTC, and a thorough discussion of this topic is beyond the scope of the current chapter. The pathological TNM (tumor-node-metastasis) classification developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) is the international reference staging system for thyroid cancer, [126] and this has recently been updated to the eighth edition, which will be implemented in January 2018. Underscoring the excellent prognosis, the highest TNM stage that anyone with pediatric-onset DTC can have is stage II, distinguished from stage I disease only by the presence of distant metastases. Therefore, most children, even those with extensive locoregional disease, are considered to have stage I disease. Another used staging system for PTC, the MACIS score, may also be useful in children and adolescents [127, 128].

Utilizing AJCC 7th edition TNM staging, a novel risk categorization for PTC (ATA Pediatric Low-, Intermediate-, and High-risk) was introduced in the inaugural ATA pediatric guidelines [23] (Table 21.1) and subsequently validated in other studies [4, 36, 39]. This risk stratification is intended to identify those at risk of persistent cervical disease and distant metastases in order to determine which patients would benefit from more intensive postoperative stag-

Table 21.1 ATA pediatric risk categories and recommendations for postoperative staging and clinical follow up^a

ATA risk level	Definition ^b	Postoperative staging ^c	TSH target ^d	Surveillance of patients with no evidence of disease ^e
ATA pediatric low-risk	Disease grossly confined to the thyroid (T1-T3) with N0/Nx disease <i>or</i> patients with incidental N1a disease (metastasis <0.2 cm to ≤5 central neck lymph nodes)	Non-stimulated Tg ^f on LT4 therapy	0.5–1.0 mIU/L	US at 6 months post-operatively and then annually for 5 years Tg ^f on LT4 every 6 months for 2 years and then annually
ATA pediatric intermediate-risk	Extensive N1a (>5 central neck lymph nodes or lymph nodes >0.2 cm) or minimal N1b disease (≤5 lateral neck lymph nodes)	TSH-stimulated Tg ^f and diagnostic ¹²³ I scan in most patients (see Fig. 21.3)	0.1–0.5 mIU/L	US at 6 months post-operatively, every 6–12 months for 5 years, and then every 2–3 years Tg ^f on LT4 every 6 months for 3 years and then annually Consider TSH-stimulated Tg ^f ± diagnostic ¹²³ I scan after 1–2 years (or longer) in patients treated with ¹³¹ I
ATA pediatric high-risk	Regionally extensive disease (extensive N1b; >5 lateral neck lymph nodes) or locally invasive disease (T4 tumors); known distant metastasis	TSH-stimulated Tg ^f and diagnostic ¹²³ I scan in all patients (see Fig. 21.3)	<0.1 mIU/L	US at 6 months post-operatively, every 6–12 months for 5 years, and then every 2–3 years Tg ^f on LT4 every 6 months for 3 years and then annually TSH-stimulated Tg ^f ± diagnostic ¹²³ I scan after 1–2 years (or longer) in patients treated with ¹³¹ I

ATA American Thyroid Association, LT4 levothyroxine, Tg thyroglobulin, TSH thyroid stimulating hormone, US ultrasound

^aAdapted from the inaugural ATA pediatric thyroid nodule and DTC guidelines [23]. These recommendations apply to pediatric papillary thyroid carcinoma and not to follicular thyroid carcinoma or other rare pathologic variants

^bUtilizing TNM staging from the American Joint Committee on Cancer, 7th edition, cancer staging manual [126]

^cPostoperative staging that is done within 12 weeks after initial definitive thyroid surgery

^dInitial targets for TSH suppression. These are subsequently adapted to the patient's disease status on long-term follow up. In higher risk patients who have no evidence of disease after 3–5 years, the TSH can be allowed to rise to the low normal range

^eSurveillance after surgery ± radioactive iodine therapy in patients who are believed to be disease-free; these recommendations do not apply to patients with known or suspected residual disease who require additional imaging and possibly treatment (see Fig. 21.4)

^fAssumes negative thyroglobulin autoantibodies (TgAb). In patients with elevated TgAb titers, serial monitoring of the antibody level (using the same assay at the same lab) may be used as a surrogate for disease trajectory, although elevated titers alone do not imply residual or recurrent disease

ing, management, and surveillance. Children with ATA Pediatric Intermediate- or High-risk PTC benefit from an initial postoperative diagnostic RAI scan and a TSH-stimulated Tg to identify persistent locoregional or distantly metastatic disease, [23, 109] whereas those in the ATA Pediatric Low-risk category can be more conservatively monitored, understanding that it is plausible for children initially identified in one risk

category to move to a different risk level after appropriate surgery and RAI and during long-term follow up (Fig. 21.3). As increasingly employed in adults, [129] dynamic risk stratification based on the response to initial therapy may also predict outcomes in pediatric DTC [4]. Limitations of the ATA pediatric risk categorization is that it does not fully incorporate the identification of extrathyroidal extension, margin

status, primary tumor and metastatic lymph node size, histologic variant or knowledge regarding tumor mutational status. Furthermore, the extent of pre-operative staging and the experience of the surgeon also impacts the validity of this system.

Radioactive Iodine Therapy

Employed for the treatment of thyroid cancer since the 1940s, RAI has had an important role in the evaluation and management of children with DTC. Almost universally administered in the past, the pendulum has now swung in the opposite direction and ^{131}I therapy is currently used much more selectively in children and only after incorporating new data obtained from initial postoperative staging [23, 109] (Fig. 21.3). This more conservative approach has, in part, arisen from knowledge that there are real long-term risks from the overzealous prescription of ^{131}I during childhood, such as pulmonary fibrosis in young children with a large lung disease burden and the potential for the late development of a second primary malignancy (primarily hematological and salivary gland malignancies) [20, 41, 42, 130–136]. Furthermore, better understanding that death from pediatric DTC remains quite rare, experts have come to realize that very aggressive treatment during childhood may not ultimately improve disease-specific survival, especially during an era when novel targeted therapeutics have become quickly incorporated into the treatment of advanced DTC.

RAI is no longer given exclusively to ablate normal remnant thyroid tissue, since the serum Tg can become undetectable within 5–7 years after no RAI therapy [137] and because the risks of routine remnant ablation largely outweigh the potential benefits in children, especially in those operated on by high-volume surgeons. Currently, surgery is preferred over RAI to treat residual/recurrent cervical disease that is amenable to surgical resection, [23, 109] and long-term control of cervical disease has been shown to be excellent in the reoperative setting [138].

The greatest challenge in pediatric DTC remains how to determine when additional ^{131}I

therapy is warranted in children with iodine-avid, distantly metastatic disease and a previous response to RAI. Repeated courses of ^{131}I can induce remission in some, but not all children, with pulmonary metastases, of whom 50% or more will have persistent disease despite RAI [42, 139–141]. Children with small-volume, iodine-avid micronodular (<1 cm) lung disease are those most likely to respond to treatment, [142] and they may ultimately become disease-free whereas others, especially those with a more extensive metastatic disease burden, may never become cancer free as assessed by Tg levels [42, 139, 142, 143].

Furthermore, the Tg response to ^{131}I treatment may not be attained for up to 15–18 months [144] and studies have shown a continued decline in serum Tg levels years after the last dose of RAI has been administered [139, 143]. Recognizing these issues and asserting that an undetectable serum Tg level should no longer be the sole goal of treatment in children with pulmonary disease, the ATA guidelines have recommended longer intervals between ^{131}I courses, suggesting that treatment be given no sooner than 12 months after the last dose [23]. In all cases, the decision to prescribe ^{131}I to any child with DTC should be individualized and incorporate knowledge regarding prognosis, tumor avidity for RAI, and previous response to therapy (Fig. 21.4).

A diagnostic thyroid scan and a stimulated Tg level (assuming the patient is TgAb negative) are recommended for children with DTC who require such staging [23, 109] (Fig. 21.3). Obtaining these data can identify those children with no evidence of disease (defined as those with an undetectable serum Tg and the absence of structurally-apparent disease) who can avoid unnecessary RAI exposure, children with extensive RAI-avid cervical disease who may benefit from re-operation, and those with RAI-avid distant metastases, who may need to have their planned administered ^{131}I activity adjusted because of either the extent of disease or the intensity of the pulmonary uptake. Diagnostic thyroid scans using ^{123}I are generally preferred [145, 146]. One challenge in young patients is the fact that iodine-avid DTC may not be visualized

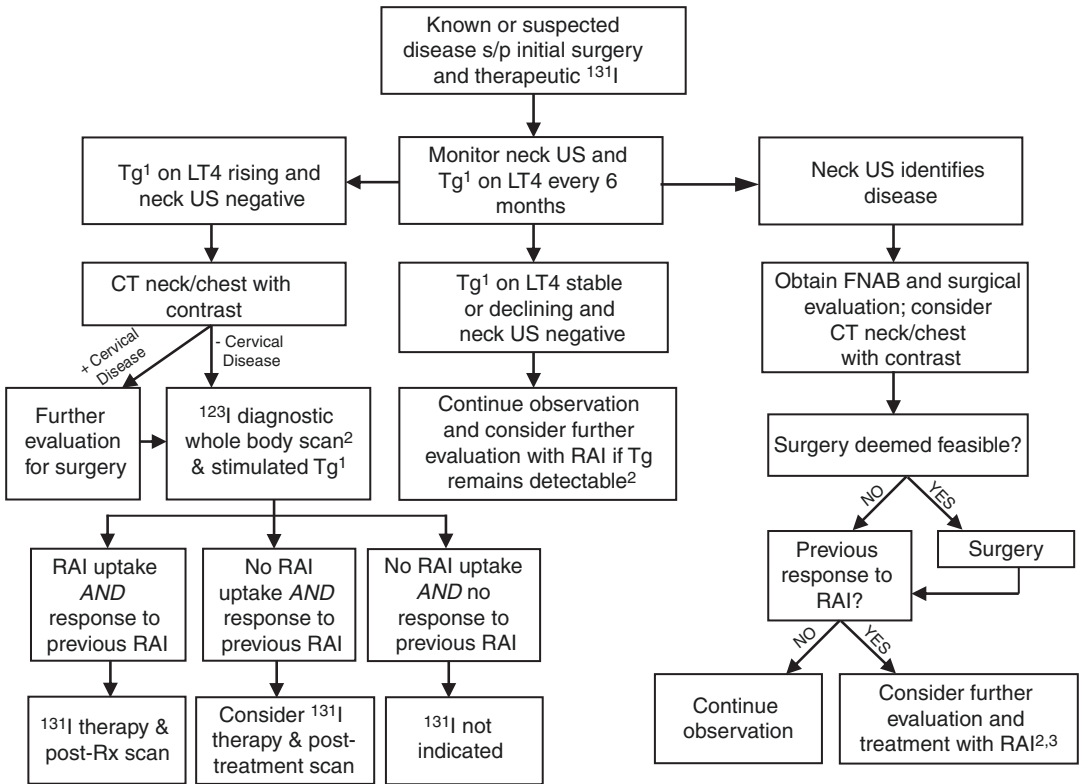


Fig. 21.4 Follow up of the pediatric patient with known or suspected residual/recurrent papillary thyroid carcinoma after initial surgery and RAI. ¹ Assumes a negative TgAb; in TgAb-positive patients, the singular presence of TgAb cannot be interpreted as a sign of disease unless the titer is clearly rising over time; a declining TgAb titer would suggest ongoing response to treatment. ²Further evaluation and treatment with RAI should only be considered after a reasonable period of time (1–2 years) has

elapsed in order not to overtreat a patient who may have a delayed clinical response to prior RAI. ³Repeated courses of ¹³¹I should be considered only if iodine-avid disease is proven/suspected and there was a previous clinical response to ¹³¹I therapy. *CT* computed tomography, *FNAB* fine needle aspiration biopsy, *LT4* levothyroxine, *RAI* radioactive iodine, *Tg* thyroglobulin, *TgAb* thyroglobulin antibody, *US* ultrasound

on the diagnostic scan [146] (Fig. 21.5). In these cases, the presence of disease is suggested by an elevated Tg out of proportion to the scan findings and what would be expected for normal remnant thyroid tissue. It has been proposed that a stimulated Tg is >10 ng/mL would be a reasonable cut-off for empirically treating patients at higher risk for residual/metastatic disease [23]. However, the exact Tg threshold above which treatment should be given has not been well studied in children. A recent study suggested that the novel application of a TSH/Tg ratio may help to inform the decision regarding ¹³¹I treatment [147]. Another study in pediatric DTC patients, already treated with surgery and RAI, showed that all children with

lung metastases had a stimulated Tg > 10 ng/mL. Thus, this cutoff may indeed be appropriate to identify higher risk patients who might benefit from further evaluation and treatment [148].

In order to facilitate RAI scanning and possible treatment, the TSH level should be above 30 mIU/mL and the ATA guidelines suggest an approach using short-term thyroid hormone withdrawal, except in select patients for whom recombinant human TSH (rhTSH) should be considered [23]. In children, an appropriately elevated TSH can almost always be achieved after 2–3 weeks of thyroid hormone withdrawal, [149, 150] which is usually extremely well-tolerated. The use of rhTSH for ¹³¹I treatment may result in a lower

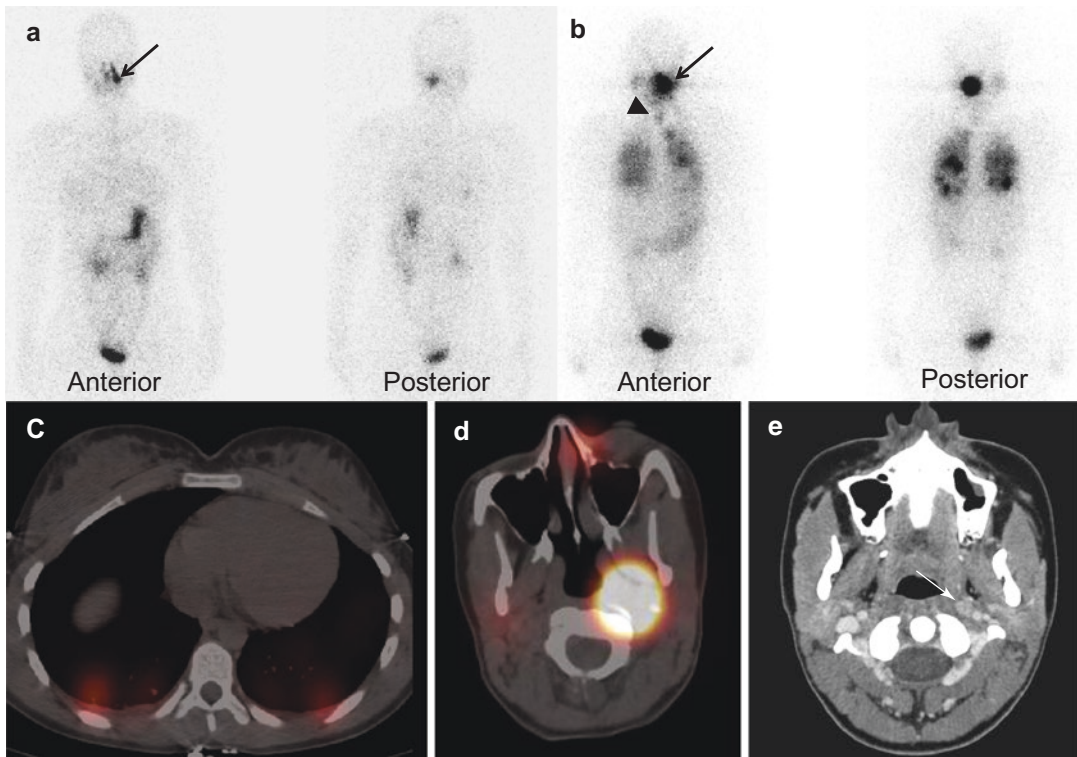


Fig. 21.5 Diagnostic (a) and post-treatment (b) radioactive iodine scans in a high-risk 15-year-old patient with a stimulated thyroglobulin of 229 ng/mL. The diagnostic ^{123}I scan (a) shows asymmetric upper cervical uptake (arrow) and subtle nodular uptake in the lungs on the posterior view. The scan obtained after treatment with high dose ^{131}I (b) demonstrates intense left upper cervical

uptake with star artifact (arrow), subtle left thyroid bed uptake (arrowhead), and diffuse and nodular uptake in the lungs. The addition of SPECT/CT imaging documents the iodine-avidity of the pulmonary metastases (c) and confirms the location of the upper cervical uptake to be in a retropharyngeal lymph node (d), which is well demonstrated (arrow) on CT neck after intravenous contrast (e)

absorbed dose to the blood compared with withdrawal [151] and its efficacy appears to be non-inferior to thyroid hormone withdrawal after 43 months of follow up [152]. A low iodine diet is generally advised for 1–2 weeks to facilitate uptake by remaining thyroid tissue; for children who received intravenous contrast during CT, it is advisable to wait 2–3 months or to confirm appropriate 24-h urine iodine levels first.

In pediatric DTC, there are no standardized approaches to determining the administered ^{131}I activity, which is generally based on a weight (child's weight in kg/70 kg) or body surface area (child's BSA $\text{m}^2/1.6 \text{ m}^2$ for females or 1.9 m^2 for males) adjustment of the typical prescribed activity used in adults for a similar extent of disease [153–155]. For example, for empiric therapy, a

child with pulmonary metastases would be administered an activity that is proportionately equivalent in an adult to a 150–200 mCi (5.55–7.4 GBq) dose (or less, if significant diffuse pulmonary uptake is present (Fig. 21.1), in order to minimize the risk of pulmonary fibrosis). Others determine the activity based on body weight alone (2.0–2.5 mCi/kg; 74–92.5 MBq/kg) [153]. Dosimetric studies to limit whole body retention at 48 h to less than 80 mCi (2.96 GBq) and blood/bone marrow exposure to less than 200 cGy should be considered in children anticipated to have significant diffuse lung uptake, patients with more widespread distant metastases, and children who may have limited bone marrow reserve due to prior cancer therapy [23, 145, 156, 157]. However, this approach is more time consuming,

is not available at all centers, and has not yet been demonstrated to improve outcomes or minimize treatment-related morbidity.

In all children treated with ^{131}I , a post-treatment scan is advised 4–7 days subsequent to therapy to identify other sites of persistent disease that were not apparent on the diagnostic study [16, 157] (Fig. 21.5). The incorporation of single-photon emission computed tomography (SPECT)/CT with nuclear scintigraphy has substantially improved our ability to localize disease and distinguish benign from malignant sites of RAI uptake [158, 159] (Fig. 21.5). One must also be aware that 50% of children may have findings on the post-treatment thyroid scan, notably thymic uptake, that are not representative of iodine-avid disease [160]. Although the empiric treatment with ^{131}I of adults who have RAI scan-negative, structural disease or Tg positive, imaging negative disease has not been proven to be effective, [161, 162] whether or not similar empiric treatment of children with an abnormal Tg and a negative diagnostic scan results in similar long-term outcomes has not been studied.

Thyroid Stimulating Hormone Suppression and Follow Up

Thyroid stimulating hormone (TSH) is believed to be a thyrocyte mitogen. The role of exogenous thyroid hormone to treat thyroid cancer in children (by lowering TSH) was first reported in 1937, [163] and TSH suppression is universally employed in the management of DTC today. All children who have undergone total thyroidectomy for malignant thyroid disease are replaced with thyroid hormone at age-appropriate doses, [164] and the degree of initial TSH suppression depends on the child's ATA risk category [23] (Table 21.1). In general, the TSH goal can be loosened and the TSH allowed to rise to the low normal range in patients who have no evidence of disease after a 1–3 year period of follow up, depending on the original extent of disease. In children who have had thyroid lobectomy, the TSH is measured 4–6 weeks after surgery and supplementation considered if the TSH is in the

upper half of the normal range or overtly elevated, understanding that thyroid hormone supplementation can be stopped and the TSH reevaluated after a period of follow up in the child who continues to have no evidence of cancer. The potential risks of TSH suppression in children (such as negative effects on growth and bone age, bone mineralization, cognition, behavior, and the heart) [165, 166] are unstudied but are assumed to be minimal in otherwise healthy children.

Follow-up of children with DTC should be lifelong, given that the probability of recurrence continues to increase over time and because clinical disease may not be identified until decades after initial treatment [20, 21, 32]. For those with persistent disease despite appropriate initial therapy, early recognition that thyroid cancer may become a chronic disease, albeit one with low morbidity and mortality, may justify a more restrained approach to treatment. In addition to tailored TSH suppression, and not dissimilar from adult recommendations, the long-term surveillance of pediatric DTC includes the periodic assessment of Tg and TgAb levels, routine neck US, and the selective use of diagnostic thyroid scans and other cross sectional imaging of the neck \pm chest [23, 129] (Table 21.1 and Fig. 21.4). The intensity and type of follow up is primarily based on the postoperative ATA pediatric risk categorization and dynamic risk re-stratification, modifying the follow-up regimen as new data become available.

In adults, ^{18}F -fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging can be helpful in the prognostic evaluation of advanced disease and the determination of who would not benefit from empiric ^{131}I [167–169]. There are no similar published studies in children, who are more likely to have well-differentiated tumors and hence unlikely to have significant FDG-avid disease, although even in the presence of FDG-avid lung disease, younger adults are still likely to demonstrate RAI uptake [170].

Even if ^{131}I therapy is not utilized, Tg levels and their trend over time serve as a useful indicator of disease status, assuming there are no interfering TgAb [137, 171, 172]. Extrapolating from adult

studies, children who have had only a lobectomy for low-risk disease should also be able to be followed similarly with Tg levels and cervical US [173]. If the TSH-suppressed Tg is undetectable after primary therapy has been completed, there appears to be very little added value in obtaining a TSH-stimulated Tg, [174–176] and there is now movement away from obtaining a routine TSH-stimulated Tg in children in the absence of other indicators of disease [23]. Nevertheless, as demonstrated in adult studies, [175–177] an undetectable TSH-stimulated Tg after initial treatment that includes total thyroidectomy and ^{131}I is highly predictive of long-term remission. Clinical recurrences primarily occur in cervical lymph nodes, [175, 176] underscoring the critical importance of cervical US during long-term disease surveillance [148] (Fig. 21.4). As alluded to earlier, the exact Tg values that indicate residual, clinically relevant disease in children that would warrant more intensive surveillance or treatment remains poorly studied in children, although a stimulated Tg >10 ng/mL is likely to represent an actionable threshold [23, 148].

In children with detectable TgAb, the antibody titer itself can be followed, and it is the trend of this analyte over time (using the same assay and lab) that is more important than its absolute value [178, 179]. Even with successful treatment of DTC, TgAb may persist for a median of 3 years after treatment [180]. Therefore, in patients with +TgAb, greater emphasis should be placed on structural and functional imaging to identify disease.

Systemic Therapy for Advanced Disease

In children, the development of progressive DTC that warrants systemic treatment outside of repeated courses of ^{131}I is very rare. The definition of RAI-refractory disease, better established in adults, [181] remains poorly defined in the pediatric population. It is now understood that RAI-refractory DTC does indeed occur in children, and contemporary guidelines clearly state that repeated courses of RAI should not be given

when there was no documented response to previous ^{131}I therapy [23]. In such cases, disease may remain quite indolent for years while continuing TSH suppression. In the rare event of a child with progressive DTC needing alternative approaches to care, consultation with providers who are experienced in the use of systemic therapy in children is recommended. A review of the currently available, molecularly targeted agents for the treatment of DTC is beyond the purview of this chapter and is covered elsewhere. Of the FDA-approved therapies, single agent sorafenib has been studied in phase I and phase II clinical trials in pediatric patients with refractory solid tumors or leukemias, [182–185] but no children with DTC were enrolled into these trials and there is only limited and anecdotal experience using sorafenib to treat advanced PTC in children [186, 187]. Lenvatinib remains largely unstudied in the pediatric population and there have been no published reports on its use in children. Currently, a phase I/II study in children, including an expanded cohort with ^{131}I -refractory DTC, is recruiting (ClinicalTrials.gov Identifier NCT02432274).

Conclusion

Rare in children but increasing in incidence, pediatric DTC presents with more locally advanced and distant disease compared with adults. Despite this more advanced clinical presentation, the prognosis for patients with pediatric-onset disease is excellent and disease-specific mortality remains low, even in the presence of pulmonary metastases. This is most likely due to the fact that DTC in children is typically a well-differentiated tumor that most often is iodine-avid and responsive to TSH suppression. Given the excellent prognosis and anticipated indolent nature of the cancer, therapy for pediatric DTC should be individualized and geared towards balancing goals of disease eradication with limiting treatment-related morbidity, particularly in non-progressive residual disease. It is preferred that, whenever possible, children with DTC be cared for at centers with established programs in the multidisciplinary manage-

ment of this disease; most critical is the identification of a high-volume surgeon to undertake such cases, which should improve oncologic outcomes and minimize postoperative complications. Therapy with ^{131}I is becoming less frequently prescribed and is now tailored to the individual patient and based on the likelihood of having disease that is expected to respond to RAI therapy, recognizing that aggressive treatment may not improve the already low disease-specific mortality observed. Further research geared towards better understanding the optimal use of RAI and predicting long-term outcomes based on clinical presentation and tumor mutational status is needed.

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