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Pediatric thyroid cancer: Recent developments

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Thyroid cancer is rare in children but its incidence is increasing. Recent data have clarified important similarities and differences between thyroid cancers originating in childhood and in adulthood. The genetic drivers of pediatric thyroid cancers are similar to those in adult tumors but comprise more gene fusions and fewer point mutations. Clinically, despite frequent metastatic spread, pediatric thyroid cancer has an excellent prognosis and mortality is rare. Therefore, treatment approaches must weigh carefully the morbidity of thyroid cancer treatments against their benefits. Current key questions include which children require total thyroidectomy rather than more limited—and safer—lobectomy, and in which children does the benefit of radioactive iodine therapy outweigh its risk of inducing a secondary malignancy. Finally, molecular therapies targeting genetic drivers of thyroid cancer now provide effective treatment for children with progressive, radioiodine-refractory disease, as well as opportunities to explore novel neoadjuvant uses that facilitate therapeutic surgery or radioactive iodine.

Abbreviations: ALK, anaplastic lymphoma kinase; APC, adenomatrous polyposis coli protein; BRAF, B-Raf proto-oncogene serine/threonine kinase; DICER1, Dicer 1 ribonuclease; DTC, differentiated thyroid carcinoma; FAP, familial adenomatous polyposis; FTC, follicular thyroid carcinoma; HRAS, HRas proto-oncogene; KRAS, KRas proto-oncogene; MET, mesenchymal epithelial transition proto-oncogene; MTC, medularly thyroid carcinoma; NRAS, NRas proto-oncogene; NTRK, neurotrophic receptor tyrosine kinase; PAX8, paired box 8; PPARG, peroxisome proliferator-activated receptor gamma; PTC, papillary thyroid carcinoma; PTEN, phosphatase and tensin homolog; RAI, radioactive iodine; RET, rearranged during transfection; TERT, telomerase reverse transcriptase; TP53, tumor protein p53.

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Introduction

Pediatric thyroid cancer has many similarities to adult thyroid cancer, but also important differences related to molecular pathophysiology, clinical presentation, management, and prognosis. Because thyroid cancer is rare in children, historically the care of children with thyroid cancer was guided primarily by extrapolation from adult literature. Over the past few years, research on pediatric thyroid cancer has expanded significantly, deepening our understanding of its particularities and leading to improved care for children with this disorder. This review presents an update on pediatric thyroid cancer with a focus on recent developments and current clinical questions in the field, distinctions from adult thyroid cancer, and opportunities for future advancement.

Epidemiology

Thyroid cancer is much less common in children than in adults, occurring in 1.2 per 100,000 individuals under 20 years of age in the United States between 2015 and 2019 [1]. However, the incidence of thyroid cancer increases with age: although very rare prior to age 15 years (0.4 per 100,000), thyroid cancer is now the most commonly diagnosed malignancy in adolescents aged 15–19 years (3.5 per 100,000) [1]. As in the adult population, in recent decades the global incidence of thyroid cancer in children has risen [2], with increases by up to 9.5% per year in the United States [3]. One likely contributing factor is increased detection by diagnostic imaging of small tumors: in a study of over 270,000 Japanese children, systematic population-based ultrasound screening diagnosed thyroid cancer at a rate 30–50 times higher than the typical baseline rate, implying the possible existence of a large reservoir of subclinical pediatric thyroid cancer [2,4]. Whether this result is generalizable to other populations remains to be determined, but multiple studies indicate that the rising incidence of pediatric thyroid cancer comprises tumors of all sizes and stages, including large or invasive cancers, indicating that the incidental detection of small, low-risk tumors does not account fully for the observed rise in pediatric thyroid cancer incidence [3,5,6]. What other factors may be driving this rise remains a question for additional study.

Pathophysiology

The vast majority of pediatric thyroid cancers are differentiated thyroid cancers (DTCs) derived from thyroid follicular cells (95%) [2]. Most differentiated thyroid cancers in children are papillary carcinomas (PTCs, about 90%) and most of the remainder are follicular carcinomas (FTCs, 8–9%) [6]. Medullary thyroid carcinoma (MTC), which derives from thyroid C-cells and is pathophysiologically distinct from follicular cell-derived cancers, comprises about 4% of childhood thyroid cancers overall, but many of these cases are diagnosed in younger children due to active surveillance of genetically at-risk individuals [7]. Other tumor types such as anaplastic thyroid carcinoma, primary thyroid lymphoma, and tumors metastatic to the thyroid are extremely rare in childhood. The remainder of this review will focus on pediatric follicular cell-derived DTC, since these represent the vast majority of thyroid cancers in children and have unique pathophysiology that determines their clinical presentation and management (Table 1).

Most DTCs in childhood arise sporadically due to somatic genetic changes that lead to oncogenesis, primarily through alterations in the mitogen-activated protein kinase and phosphoinositide 3-kinase signaling pathways [8]. Typically, each cancer is driven by a single genetic variant, most commonly a single-gene alteration or a gene fusion. The Cancer Genome Atlas, published in 2015, provided the most comprehensive initial survey of the genetics of adult PTC [9]. The rarity of thyroid cancer in children delayed similar efforts to characterize its molecular landscape, but a series of recent studies using comprehensive next-generation genetic sequencing have identified a genetic driver variant in 85% or more of pediatric PTCs (Table 2) [8,10–15]. In over half of cases the primary driver is a gene fusion, most commonly including the tyrosine kinases rearranged during transfection (*RET*), neurotrophic receptor tyrosine kinase 1 (*NTRK1*), or *NTRK3* (Table 1), or more rarely other tyrosine kinase partners such as anaplastic lymphoma kinase (*ALK*) or mesenchymal epithelial transition proto-oncogene (*MET*). Mutations in B-Raf proto-oncogene serine/threonine kinase (*BRAF*), which are present in up to 60% of adult

Table 1
Characteristics of pediatric and adult papillary thyroid cancer.

	Pediatric	Adult
Predominant genetic drivers	Gene fusions (*RET*/*NTRK*) Less commonly, *BRAF* V600E	*BRAF* V600E Less commonly, gene fusions
Extent of initial surgery currently recommended	Total thyroidectomy	Lobectomy or total thyroidectomy (low-risk) Total thyroidectomy (high-risk)
Metastasis at presentation		
Regional lymph nodes	60–80%	20–50%
Distant	5–25%	2–5%
Mortality		
All stages	<1%	1–2%
Regional metastasis	<1%	2–3%
Distant metastasis	1–7%	25–40%

Abbreviations: *BRAF*, B-Raf proto-oncogene serine/threonine kinase; *NTRK*, neurotrophic receptor tyrosine kinase; *RET*, rearranged during tranfection.

PTCs [9], are far less common in pediatric PTC, occurring only in around one-quarter of cases. In fact, the prevalence of BRAF-driven cancers appears to increase along the age spectrum, since among pediatric patients younger age is associated with a higher likelihood of *RET* or *NTRK* fusion-driven DTC compared to *BRAF* [12,16]. It is also notable that pediatric DTCs do not appear to harbor coexisting variants in telomerase reverse transcriptase (*TERT)* or tumor protein p53 (*TP53*), both of which are associated with more aggressive disease and poorer outcomes when present in adult PTC [9,17,18] This difference may partially explain the very low mortality rate among children even when PTC is advanced or distantly metastatic at diagnosis.

FTC in children is rare, and consequently its genetics remain less thoroughly investigated. Existing reports have documented a genetic profile similar to that of adult FTC, including variants in HRas proto-oncogene (*HRAS*), NRas proto-oncogene (*NRAS*), KRas proto-oncogene (*KRAS*), and phosphatase and tensin homolog (*PTEN*), as well as paired box 8-peroxisome proliferator-activated receptor gamma (*PAX8-PPARG*) fusions [13–15,19]. Mutations in Dicer 1 ribonuclease (*DICER1*), which encodes an enzyme responsible for processing microRNAs, appear to be relatively common in pediatric FTCs [13,14] but also occur in some pediatric PTCs and poorly differentiated thyroid carcinomas [20,21] as well as benign thyroid nodules [20]. Germline pathogenic variants in *DICER1* cause a syndrome of predisposition to tumors of the lung, brain, ovary, kidney, and multiple other tissue, in addition to the thyroid. Therefore, identification of a *DICER1* variant by somatic testing of a pediatric thyroid tumor should prompt consideration of germline *DICER1* testing to determine whether surveillance for other tumors is necessary. Conversely, children with germline *DICER1* variants should undergo routine thyroid ultrasound surveillance for the early detection of thyroid cancer that may develop.

DICER1 represents one of several genes in which germline variants predispose to thyroid cancer as well as tumors in other organs. Pathogenic variants in *PTEN* cause PTEN hamartoma tumor syndrome (including the variants Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome), which is characterized by macrocephaly, neurological disorders (including autism or seizures), cutaneous lesions, and hamartomas of multiple tissues. Although thyroid cancer that arises in PTEN syndrome is usually not aggressive, it can occur in early childhood [22], so ultrasound surveillance of these children is generally recommended every 2–5 years, beginning at 7–10 years of age [23–25]. Mutations in adenomatrous polyposis coli (*APC*) cause familial adenomatous polyposis (FAP) and increase the risk of thyroid cancer. The rate of thyroid cancer in FAP may be up to 5% in adolescent females by age 18 years, but thyroid cancer in males with FAP occurs very rarely and not until adulthood [26].

Thyroid cancer surgery

Current American Thyroid Association guidelines recommend total thyroidectomy as the initial surgical approach for children with PTC (Fig. 1) [27]. These recommendations are based on several factors, including the significant rate of bilateral disease in pediatric thyroid cancers (20–40%) [28–30]

Table 2
Genetic driver variants identified in pediatric papillary thyroid cancers evaluated using comprehensive cancer panels including the most common known driver genes.

Study	n	No driver identified (15%)	Point variants (29%)			Fusions (55%)			
			BRAF	*RAS*	Other	*RET*	*NTRK1/3*	*BRAF*	Other
Prasad 2016 [10]	27	1	13	0	0	6	7	0	0
Pekova 2020 [11]	93	21	18	2	0	26	17	2	7
Stosic 2021 [8]	50	1	11	1	3	24	4	0	5
Franco 2022 [12]	66	20	14	1	0	22	9	0	0
Gallant 2022 [13]	38	1	7	1	1	23	3	1	1
Hess 2022 [14]	32	0	10	0	2	6	8	1	5
Newfield 2022 [15]	39	9	12	4	0	8	3	0	3
Total	345	53 (15%)	85 (25%)	9 (3%)	6 (2%)	105 (33%)	51 (15%)	4 (1%)	21 (6%)

Genes containing other point variants include guanine nucleotide-binding protein, alpha-stimulating activity (*GNAS*), Dicer 1 ribonuclease (*DICER1*), and phosphatase and tensin homolog (*PTEN*). Genes participating in other gene fusions include anaplastic lymphoma kinsase (*ALK*), mesenchymal epithelial transition proto-oncogene (*MET*), Ros 1 proto-oncogene (*ROS1*), THADA armadillo repeat containing (*THADA*), PTTG1-interacting protein (*PTTG1IP*), and paired box 8 (*PAX8*).

and some studies showing a lower long-term rate of disease persistence/recurrence after total thyroidectomy as compared with less complete resection [27,31–33]. Total thyroidectomy also facilitates the use of adjunctive radioactive iodine (RAI) treatment, which traditionally has been used for many pediatric DTCs due to their high prevalence of metastasis at diagnosis. Finally, the removal of all normal thyroid tissue increases the specificity of serum thyroglobulin for surveillance after DTC treatment.

In recent years, the management of adults with DTC has shifted toward less extensive surgery for low-risk cancers. For many of these cases, lobectomy is recognized to be adequate treatment based on studies demonstrating no increased risk of recurrence or mortality compared to total thyroidectomy, with a substantially lower risk of operative complications [34]. In light of this trend, it is pressing to determine whether and when more limited surgery is appropriate for some pediatric DTCs, particularly because of two factors that directly affect the balance of risk and benefit related to the extent of surgery for this population. First, the risk of complications from thyroid surgery is higher in children compared to adults [35], and second, disease-specific mortality for children with DTC is extremely low, making it even more imperative to reduce treatment-associated morbidity. It is therefore of great interest to identify a subset of pediatric patients who might appropriately be treated with lobectomy rather than total thyroidectomy.

One subpopulation that is likely to benefit from complete removal of the thyroid is children with bilateral DTC; therefore, assessing the likelihood of bilateral disease—ideally prior to initial thyroid surgery—would be useful to guide surgical decision-making in children with DTC. In one study of 115 children with DTC, tumor multifocality in the lobe containing the primary tumor was the only factor independently associated with the presence of contralateral disease, which was present in 65% of children with multifocal tumors [28]. Conversely, the risk of bilateral disease was only 12% among children with unifocal tumors and no clinical evidence of lymph node metastases (cN0). Another series of 102 children with stage T1 ($\leq$2 cm) PTC reported similar findings, including an association of multifocality with bilateral disease and a low rate of bilateral disease (5%) among children without lymph node metastases (N0) [29]. Many preoperative factors were not found to increase the risk of bilateral disease, including radiation exposure, autoimmune thyroiditis, genetic risk conditions, or family history of thyroid cancer [28–30]. In combination, these studies suggest that children with unifocal tumors and no lymph node metastases constitute a group in which lobectomy might be considered, with a low risk of leaving behind thyroid cancer in the contralateral lobe.

Of course, basing surgical management on outcome-based evidence is optimal, and until recently such data in pediatric DTC have been sparse and have tended to favor total thyroidectomy [31,32]. However, emerging data have provided support for less extensive initial surgery in some children with DTC. One single-center study examined clinical outcomes in 153 patients who underwent surgery for pediatric DTC, of whom 75% underwent lobectomy [36]. Over a median 15 years of follow-up, total thyroidectomy was not statistically associated with improved disease-free survival compared to

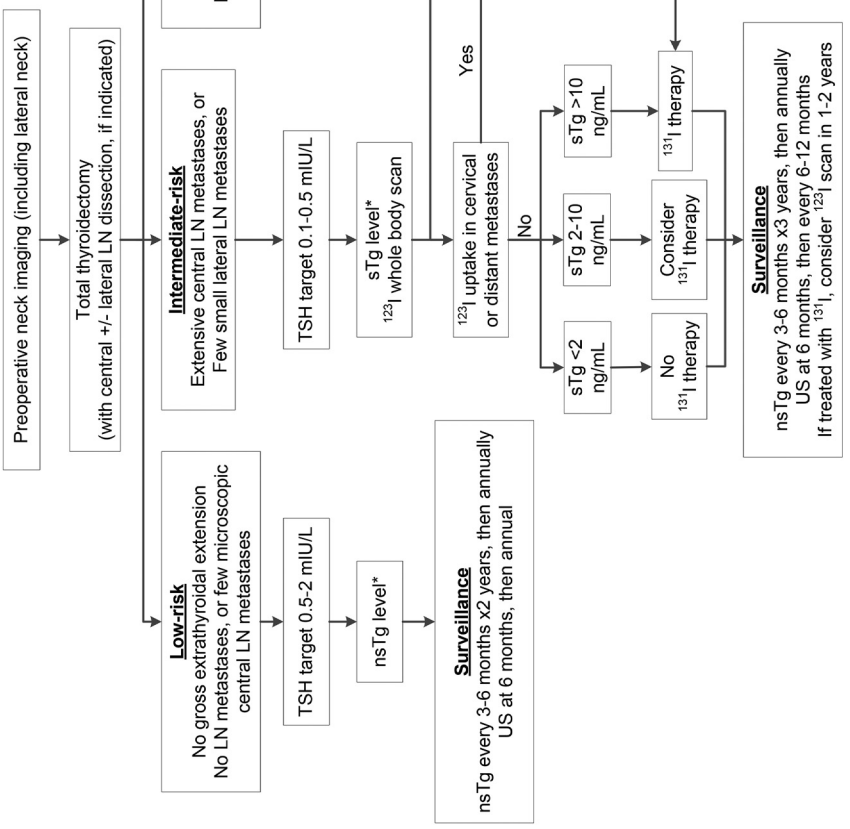

Fig. 1. Current recommendations for initial management and surveillance of pediatric differentiated thyroid cancer [27]. *Thyroglobulin values presume the absence of anti-thyroglobulin antibodies, which should be measured along with each thyroglobulin measurement. Abbreviations: LN, lymph node; nsTg, non-stimulated thyroglobulin; sTg, TSH-stimulated thyroglobulin; TSH, thyroid-stimulating hormone; US, ultrasound.

lobectomy (hazard ratio 2.12, 95% confidence interval 0.98–4.29, p = NS), but the magnitude of the association and the confidence interval suggest that total thyroidectomy may reduce recurrence risk among certain patients, presumably those with advanced disease. Among low-risk patients [defined in this cohort as having no clinical evidence of lymph node metastases (cN0) and no extrathyroidal tumor extension], those who underwent lobectomy had equivalent disease-free survival to those who underwent total thyroidectomy, with a 20-year recurrence rate around 20% in both groups [36]. However, a limitation of this study is the routine performance in this center of prophylactic lateral neck dissection even among patients undergoing lobectomy, an approach that is not consistent with consensus guidelines and that complicates the generalization of these results to current practice.

Another study utilized two large US cancer registries to investigate mortality rates from PTC in 163 children who underwent lobectomy compared with 163 propensity-matched controls who underwent total thyroidectomy [37]. In this cohort of children with low-risk thyroid cancer without nodal or distant metastases, but with tumor sizes up to 4 cm, no differences in 10-year overall or disease-specific survival were observed between the lobectomy and total thyroidectomy groups. However, the relatively short median follow-up (5–8 years) and the low mortality from pediatric thyroid cancer (2.4% in this cohort) make it difficult to detect differences in overall survival. Furthermore, this study did not evaluate the association between extent of surgery and disease recurrence, which is more common than mortality and therefore is an important long-term outcome in pediatric DTC. Nevertheless, these studies suggest that, as in adults, a subset of children with low-risk thyroid cancer might be managed effectively and safely with more limited initial surgery. It remains for future studies to validate these findings and to elaborate precisely how to define this population to balance optimally the risks and benefits of initial surgery.

Radioactive iodine therapy

Historically, adjunctive RAI therapy was administered to most children with DTC, likely due in part to their high prevalence of metastatic disease at diagnosis and relatively high risk of recurrence [32]. Although RAI therapy is recommended for children with advanced DTC, its benefit in children with lower-risk DTC is less clear. Observational studies of predominantly low-risk pediatric DTC have shown conflicting results, with some studies demonstrating an association of RAI therapy with lower risk of disease recurrence and others finding no association [31,32]. Meanwhile, in adult patients, RAI therapy for low-risk thyroid cancer does not appear to improve outcomes and is not recommended [34]. In part, this recommendation derived from growing recognition of the risk of secondary malignancies associated with RAI. Across ten large studies, RAI therapy for DTC was associated with an increased relative risk of 1.14–1.84 for developing a secondary malignancy [38]. This risk may be higher at RAI doses $\geq$100 mCi and among individuals exposed to RAI at younger ages. In two large studies including pediatric and adult DTC patients up to 25–29 years of age, RAI treatment was associated with a 50–60% increased relative risk of a secondary malignancy, most commonly leukemia or solid tumors of the salivary gland, breast, stomach, or uterus [39,40]. Although the absolute risk remains low, one study suggested that over a follow-up period of 20 years, one secondary malignancy could arise for every 150 young patients treated with RAI [40]. Moreover, the risk may continue to increase over time following RAI therapy [40], a factor that is more relevant for thyroid cancers diagnosed in childhood or adolescence than for cancers diagnosed in older adulthood. Fortunately, the 2015 consensus guidelines recommended for the first time that RAI not be used routinely for children with low-risk DTC, and such recommendations for both children and adults appear to have decreased the number of patients receiving RAI for localized DTC over the past several years [27,34,40]. As the long-term risks of RAI become increasingly clear, the burden becomes greater to demonstrate its beneficial effect on already-excellent pediatric outcomes, and to identify the precise subset of patients in whom this benefit may be observed, in order to justify its more selective and effective use in pediatric DTC.

Advanced disease

One of the most intriguing apparent paradoxes of pediatric DTC is its excellent prognosis despite the fact that the disease is more frequently and more widely metastatic at presentation than in adults

(Table 1). Among children diagnosed with PTC, 60–80% have metastases to cervical lymph nodes at diagnosis, as compared to 20–50% of adults [1,34,41–43]. The reported prevalence of distant metastases in pediatric PTC varies between 5 and 25%, with lower rates (5–8%) observed in multicenter registries that may lack standardized methods for detecting distant metastases [44,45], and higher rates (17–25%) observed mostly in single-center cohorts, which are often based at large referral centers and may be susceptible to referral bias [42,46–48]. The true prevalence of distant metastases in children is likely between these estimates (perhaps 10–20%) but is still substantially higher than the prevalence in adults (2–5%) [1,41].

In spite of presenting with more advanced disease, children with DTC have a 30-year disease-specific survival of >99% [36,41,45,49], and even those with distant metastases rarely die of the disease (30-year disease-specific survival 93–100%) [41,45,48]. In contrast, one large single-center study demonstrated a 30-year survival from distantly metastatic PTC of only 28% in adults, compared to 100% in children in the same institution [41]. The excellent prognosis of children is even more notable when considering that those with distantly metastatic DTC are rarely cured of their disease. In four recent studies of pediatric DTC with distant metastases, comprising a total of 216 patients who received a median of 2–3 RAI treatments delivering median cumulative doses of 238–317 mCi, complete resolution of DTC was achieved in only 0–22% of patients [42,46–48]. Although reduction of disease burden was observed in a substantial number of patients, particularly those with small (<1 cm) lung nodules, these observations reinforce that, in most children with distantly metastatic DTC, RAI is not a curative therapy, and that distant metastases will become a chronic but nonfatal condition. Therefore, management of pediatric patients with distantly metastatic DTC after initial RAI therapy should weigh heavily the imperative to avoid adverse effects of further treatments, including the risk of inducing a secondary malignancy potentially more perilous than DTC itself. Thus, historical management approaches that once prioritized the eradication of nonprogressive pulmonary metastases using repeated applications of RAI therapy are no longer appropriate.

Although most children with advanced DTC have a favorable prognosis, some have progressive disease that is refractory to RAI therapy. Fortunately, systemic molecular therapies have been developed that specifically target the principle genetic drivers of pediatric DTC (*RET*, *NTRK1/3*, and *BRAF*), which collectively account for about 75% of cases (Table 1). In particular, pediatric DTCs driven by *RET* or *NTRK1/3* fusions are more likely than *BRAF*-driven tumors to exhibit invasive behavior, including

Table 3
Molecular therapies targeting the primary genetic drivers of pediatric differentiated thyroid cancer that are currently approved by the United States Food & Drug Administration.

Molecular targeted therapy	US FDA Approval		Objective response rate in DTC
	Cancer type	Patient age	
NTRK			
Larotrectinib	Any solid tumor	All ages	86% [50]
Entrectinib	Any solid tumor	≥12 years	54% [51]
RET			
Selpercatinib	Any solid tumor	≥12 years	79% [52]
Pralsetinib	Any solid tumor	≥12 years	89% [53]
BRAF			
Dabrafenib/trametinib	Any solid tumor	≥6 years	69% [55]*
Vemurafenib	Melanoma	Adults	N/A
ALK			
Crizotinib	NSCLC, ALCL, IMT	≥1 year	N/A
Ceritinib	NSCLC	Adults	N/A
Alectinib	NSCLC	All ages	N/A
Brigatinib	NSCLC	Adults	N/A
Lorlatinib	NSCLC	Adults	N/A

*Data from adults with anaplastic thyroid cancer; limited data are available for differentiated thyroid cancer.
Abbreviations: ALCL, anaplastic large cell lymphoma; DTC, differentiated thyroid cancer; IMT, inflammatory myofibroblastic tumor; N/A, not applicable (insufficient data); NSCLC, non-small cell lung cancer; US FDA, United States Food & Drug Administation.

extensive nodal and distant metastasis [12], and a *RET* or *NTRK1/3* driver variant is present in 75–85% of distantly metastatic pediatric DTCs [12,48]. Thus, the majority of advanced pediatric DTCs are potentially amenable to treatment with these agents (Table 3).

Larotrectinib is an *NTRK* inhibitor approved for patients of any age that is highly effective for the treatment of *NTRK*-driven DTC. In a pooled analysis of three clinical trials in patients with advanced DTC, the objective response rate to larotrectinib was 86% [50]. Although only two children were included in this study, both had significant disease regression on larotrectinib, including one with a complete response. In a smaller study, the *NTRK* inhibitor entrectinib also appeared effective for treating advanced thyroid cancers (objective response rate 54%), but no children were included in this study and entrectinib is not currently approved for children under 12 years [51]. Targeted *RET* inhibitors are available for the treatment of advanced *RET*-driven thyroid cancers. *RET* variants are the most common genetic cause of MTC, and the *RET* inhibitors selpercatinib and pralsetinib are effective for the treatment of advanced MTC in both adults and children [52–54]. These agents also appear highly effective for treating advanced *RET*-driven DTC, with objective response rates of 80–90% among the relatively small number of adult patients studied [52,53] and initial reports of efficacy in children with DTC [16]. Both selpercatinib and pralsetinib are currently approved for use in patients 12 years and older. For children with *BRAF*-driven DTCs, targeted therapeutic options include dabrafenib/trametinib or vemurafenib. These agents have shown some efficacy in the treatment of refractory adult anaplastic thyroid cancer and DTCs, and are approved for the treatment of refractory solid tumors in children over 6 years of age [55–57], but minimal published data are available regarding their use specifically in pediatric DTC.

The advent of targeted therapies has created exciting opportunities for the treatment of RAI-refractory DTC in children who previously had few promising options. However, questions remain about the optimal criteria and timing for initiating systemic therapy. Although these agents appear to be highly efficacious, adverse effects are common, including hypertension, gastrointestinal symptoms, myalgia, fatigue, cytopenias, and elevated liver transaminases [50,52,53,58]. In addition, development of resistance to targeted inhibitors has been reported [59,60], raising questions about the long-term durability of response. Since these systemic therapies usually are not curative and younger patients may require treatment for years or decades, these potential limitations must be weighed carefully when deciding whether to initiate systemic therapy in children with advanced DTC. Systemic therapy seems reasonable for children with progressive RAI-refractory DTC that is symptomatic or threatens significant morbidity, but whether or when to initiate therapy for nonprogressive or slowly progressive disease remains an area of uncertainty.

On a short-term basis, however, the marked reduction in tumor size often observed with use of these molecular therapies has made them a potentially useful tool for managing thyroid cancers that are surgically unresectable due to anatomic considerations, such as impingement on the trachea, esophagus, or vasculature. In some cases, identification of a targetable genetic driver has permitted initiation of specific kinase inhibition that resulted in sufficient tumor regression to allow resection of an otherwise inoperable tumor [61,62]. Although such cases are rare in pediatric DTC, neoadjuvant use of molecular therapy to facilitate additional treatment represents a promising application of this technology.

Another use of systemic therapy derives from its ability to increase RAI avidity in some DTCs. Agents targeting *BRAF*, *NTRK*, or *RET* have been reported to increase iodine uptake in previously RAI-refractory DTCs in adults and children, likely by promoting tumor redifferentiation that leads to increased expression of the sodium-iodide symporter [16,63–66]. This increased RAI avidity may then been exploited for successful administration of therapeutic RAI to previously refractory tumors. In addition to broadening the therapeutic options for patients with known RAI-refractory disease, this effect might also be employed in neoadjuvant fashion to increase the cure rate of initial RAI therapy in children with distantly metastatic DTC, for whom current approaches are rarely curative. This approach recently has been attempted in a child with encouraging results [66], and studies are now needed to define whether and how this approach might be deployed more widely to increase the currently low cure rate of distant metastases in pediatric DTC.

Summary

Recent growth in research examining thyroid cancers of childhood onset has greatly expanded our knowledge of their pathophysiology and has provided insights that should lead to improved treatment. Although pediatric thyroid cancers are similar in many ways to those in adults, the unique characteristics of children and their thyroid cancers may require distinct management approaches to balance optimal disease-related outcomes against the risks of surgical and medical therapies. The introduction of targeted molecular therapeutics holds promise for children with advanced thyroid cancer, but studies are needed to clarify the best way to deploy these agents to achieve optimal patient outcomes.

Declaration of competing interest

The authors have no conflicts of interest relevant to this work.

Practice points

- Total thyroidectomy is currently recommended for children and adolescents with differentiated thyroid cancer; however, patients with unifocal cancers and no lymph nodes metastases are at low risk of bilateral disease.
- Radioactive iodine therapy is associated with an increased risk of developing secondary malignancies.
- Most children with distantly metastatic differentiated thyroid cancer will have persistent disease after radioactive iodine therapy, but long-term mortality remains very low.
- Most pediatric thyroid cancers are driver by genetic variants involving *RET, NTRK1/3,* or *BRAF,* for which targeted molecular therapies are available to treat progressive radioiodine-refractory disease.

Research agenda

- Outcome-based studies are needed to clarify which children with thyroid cancer can be treated safely with lobectomy rather than total thyroidectomy.
- Efficacy, safety, and durability of treatment with targeted molecular therapies should be confirmed in larger numbers of children with advanced thyroid cancer.
- Neoadjuvant use of systemic therapies to enhance the efficacy of other treatment modalities (surgery or radioactive iodine) should be investigated.

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