Pediatric Thyroid Cancer

Genetics, Therapeutics and Outcome

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KEYWORDS

• Thyroid nodule • Thyroid cancer • Pediatric • Child • Adolescent • Papillary • Follicular • Medullary

KEY POINTS

- Ultrasonography characteristics of the nodule should be used to decide whether a nodule should undergo fine-needle aspiration.
- In most patients, differentiated thyroid cancer is sporadic. In contrast, most pediatric patients with medullary thyroid cancer have multiple endocrine neoplasia type 2.
- Knowledge of the oncogenic driver mutation can aid in diagnosis, help stratify surgery, and be used to select systemic therapy for patients that present with morbidly advanced disease or develop progressive disease refractory to traditional therapy.
- Most pediatric patients with thyroid cancer have excellent prognosis. The goal of treating pediatric patients with thyroid cancer is to optimize outcome and reduce complications.

INTRODUCTION

Most patients with thyroid cancer are asymptomatic at the time of diagnosis even in the presence of regional or distant metastasis. More than 85% of childhood thyroid carcinomas are papillary thyroid cancer (PTC), with the remainder divided between follicular thyroid cancer (FTC) and medullary thyroid cancer (MTC), and most MTC associated with multiple endocrine neoplasia type 2 (MEN2).[1] This article reviews the cause, the clinical evaluation, the treatment, and the outcome of thyroid cancer in pediatrics.

CAUSE AND GENETICS OF DIFFERENTIATED THYROID CARCINOMA

In most pediatric patients with differentiated thyroid cancer (DTC), both PTC and FTC, the cancer is sporadic and it arises from a de novo somatic oncogenic alteration. In a

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smaller number of patients, there is an identifiable risk factor, including ionizing radiation (inhaled, ingested, or external beam) in PTC or genetic predisposition in patients with PTC, FTC, or MTC.

Radiation treatment of nonthyroid malignancy is the most common identifiable cause associated with developing PTC with increased risk, and decreased latency, associated with exposure to ionizing radiation before 10 years of age.[2–4] The overall standard incidence ratio for radiation-induced DTC ranges from 5-fold to 70-fold, with the risk limited to patients less than 16 years of age at the time of exposure.[5] The higher proliferative cellular activity in the thyroid of children or adolescents compared with adults is thought to explain the disparate effect that all forms of radiation have on radiation-induced thyroid tumorigenesis.[3]

Genetic predisposition is the second most common identifiable risk factor for the development of thyroid cancer. Predisposition can be divided into 2 broad categories: nonsyndromic (familial thyroid cancer that is not associated with a clinical phenotype and not associated with an increased risk of developing additional, nonthyroid tumors) and syndromic (thyroid cancer associated with other tumors). The former, often referred to as familial nonmedullary thyroid cancer (FNMTC), is defined by the presence of 2 or more first-degree relatives with either PTC or FTC with the inheritance pattern most consistent with an autosomal dominant mode of transmission.[6,7] Compared with sporadic DTC, FNMTC presents at a younger age and shows clinical anticipation between generations, in which subsequent generation family members may present with earlier and more invasive disease.[8] To date, a single, reliable germline locus has not been identified, necessitating thyroid ultrasonography (US) monitoring of other first-degree family members.[9,10]

Syndromic forms of thyroid cancer are associated with germline mutations in several genes, with resultant increased risk for thyroid cancer, other nonthyroid neoplasms, and phenotypic findings on physical examination. The syndromic, familial thyroid cancer predisposition syndromes are inherited in an autosomal dominant pattern and include PTEN hamartoma tumor syndrome (PHTS), familial adenomatous polyposis (FAP), DICER1 syndrome, Carney complex (CNC), and MEN2 (**Table 1**). The risk of developing thyroid cancer in syndromic DTC is approximately 10% in FAP,[11] 16% in *DICER1*-related disorders,[12] and 35% in *PTEN* hamartoma tumor syndrome.[13] In DICER1, treatment of pleuropulmonary blastoma is associated with an increased risk of developing thyroid nodules and DTC before adolescence.[14] In general, syndromic DTC is typically associated with indolent behavior and the cancers are less invasive. However, in both CNC[15] and DICER1,[16] fatal outcomes associated with poorly differentiated thyroid cancer have been reported.

For the remaining, and larger number of, patients, DTC develops sporadically, without an identifiable risk factor. In these patients, thyroid tumorigenesis and progression are most commonly associated with somatic point mutations in *BRAF*, *RAS*, *DICER1*, and *PTEN*, as well as gene fusions involving the rearranged during transfection (*RET*), neurotropic tropomyosin receptor kinase (*NTRK*) tyrosine kinases, and anaplastic lymphoma kinase (ALK) with resultant constitutive activation of the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) protein kinase B (AKT) signaling pathways.[17,18] With uncommon exceptions, these genetic alterations are mutually exclusive events, and a fairly predictable relationship exists between oncogenic genotype and histopathologic phenotype, with (1) *RET/PTC* and NTRK rearrangements and *BRAF* point mutations common in PTC; (2) paired-box gene 8 (*PAX8*)–peroxisome proliferator–activated receptor gamma (*PPARγ*) rearrangement and *DICER1* mutations common in FTC; and (3) *RAS*, *DICER1*, and *PTEN* mutations found across the spectrum of thyroid tumors, from benign follicular

Table 1
Familial thyroid cancer predisposition syndromes with additional clinical features

Predisposition Syndrome	Gene (Chromosome) with GeneReviews Link	Thyroid Phenotype	Other Features
PHTS • Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome	*PTEN* (10q23) https://www.ncbi.nlm.nih.gov/books/NBK1488/	• Thyroid adenomas and multinodular goiter • Thyroid carcinoma (PTC and FTC)	• Macrocephaly (95% or more) • Mucocutaneous lesions; papillomatous papules, trichilemmomas, acral keratoses, pigmented macules of the glans penis • Breast cancer (women only) • Endometrial carcinoma/uterine fibroids • Genitourinary tumors • Autism
DICER1 syndrome DICER1 pleuropulmonary blastoma familial tumor predisposition syndrome	*DICER1* (14q32.13) https://www.ncbi.nlm.nih.gov/books/NBK196157/	• Multinodular goiter • Thyroid carcinoma (PTC, FTC, and poorly differentiated thyroid carcinoma/rare)	• Pleuropulmonary blastoma • Sertoli-Leydig cell ovarian tumor • Cystic nephroma • Wilms tumor • Botryoid embryonal rhabdomyosarcoma • Eye and nose tumors • Pituitary blastoma
APC-associated polyposis FAP	*APC* (5q21-q22) https://www.ncbi.nlm.nih.gov/books/NBK1345/	• PTC, cribriform-morular variant	• Adrenocortical tumors • Colorectal polyps/colorectal carcinoma • Osteomas • Desmoid tumors • Pancreas adenocarcinomas • Medulloblastoma • Hepatoblastoma

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Table 1
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Predisposition Syndrome	Gene (Chromosome) with GeneReviews Link	Thyroid Phenotype	Other Features
Carney complex	*PRKAR1A* (17q24.2) and chromosome locus 2p16 (unknown gene) https://www.ncbi.nlm.nih.gov/books/NBK1286/	• Thyroid adenomas • Thyroid carcinoma (PTC FTC, and poorly differentiated thyroid carcinoma/rare)	• Mammosomatotroph • Growth hormone–secreting pituitary adenoma • Primary pigmented nodular adrenocortical disease • Large-cell calcifying Sertoli cell tumors • Spotty skin pigmentation (lentigines) • Blue nevi • Cardiac, cutaneous, or breast myxomas • Psammomatous melanotic schwannoma
MEN2A	*RET* (10q11.2) https://www.ncbi.nlm.nih.gov/books/NBK1257/	• Medullary thyroid carcinoma	• Pheochromocytoma • Parathyroid adenoma/hyperplasia • Codon-specific variants with cutaneous lichen amyloidosis and Hirschsprung disease

MEN2B	*RET* (10q11.2)	• Medullary thyroid carcinoma	Infancy • Absent tears in infancy (alacrima) • Feeding difficulties and constipation • Hypotonia Later onset • Pheochromocytoma • Mucosal neuromas: lips, tongue, and eyelids • Distinctive facies with enlarged lips • Skeletal abnormalities: joint laxity, slipped capital femoral epiphysis, pes cavus • Ganglioneuromatosis of the gastrointestinal tract • Marfanoid body habitus

Data from Adam MP, Ardinger HH, Pagon RA et al. GeneReviews [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2020. https://www.ncbi.nlm.nih.gov/books/NBK1116/. Accessed July 28, 2020.

adenomas to follicular-variant PTC (fvPTC), FTC, and poorly differentiated thyroid carcinoma.[15,16,18] In pediatrics, *RET*/*PTC* and *NTRK*-fusion genes are associated with an increased risk of invasive disease, although there are no data to suggest that these alterations are associated with increased disease-specific mortality.[17,18] In children, *BRAF* mutations do not seem to be associated with an increased risk of radioactive iodine (RAI)–refractory disease, an association that is common in adults.[17] A summary of the most common oncogenes and their association with thyroid cancer variants and clinical behavior is provided in **Table 2**.

CAUSE AND GENETICS OF MEDULLARY THYROID CARCINOMA

MTC is a malignancy that originates from the parafollicular C cells of the thyroid gland rather than the follicular cells, the origin of DTC.[19] Thus, in contrast with follicular cell–derived thyroid tumors, MTC cells are not responsive to thyroid-stimulating hormone (TSH), are not responsive to RAI therapy secondary to a lack of expression of the sodium-iodine symporter, and do not produce thyroglobulin (Tg). C cells produce calcitonin (Ctn) and carcinoembryonic antigen (CEA), both of which serve as tumor markers of MTC. With rare exceptions, MTC in children and adolescents is associated with MEN2, an autosomal dominant tumor predisposition syndrome associated with activating germline mutations in the *RET* protooncogene, designated as either MEN2A or MEN2B depending on the specific mutation.[20,21] Sporadic MTC is uncommon in the pediatric population and, similar to adults, is most commonly associated with somatic mutations of *RET* or *RAS*, with data from adults suggesting a higher rate of lymph node metastasis and decreased survival associated with *RET*-associated sporadic MTC.[19,22]

DIAGNOSTIC EVALUATION OF THYROID NODULE

Physical Examination

Physical findings related to genetic syndromes should be evaluated and recorded. PHTS is associated with macrocephaly, small benign cutaneous neoplasms on the face and neck (trichilemmomas), lipomas, and freckling of the glans penis.[23–25] Carney complex[26] and FAP[27] are associated with lentigines and MEN2B is associated with alacrima (an inability or decreased ability to produce tears); marfanoid facies (typically noted around 5 years of age); and oral mucosal neuromas, most commonly of the lips and tongue.[28]

A complete thyroid examination includes inspection and palpation of the thyroid gland as well as the lateral neck cervical lymph nodes (https://www.youtube.com/watch?v=Z9norsLPKfU). The presence of a thyroid nodule with cervical lymphadenopathy is a significant predictor for malignancy, especially if the lymph nodes are firm, immobile, and located in levels III (mid) and IV (lower) regions of the lateral neck.[29,30] In contrast, rubbery, mobile, and symmetric level II (under the mandible) lymph nodes are a common finding in otherwise healthy pediatric patients despite these lymph nodes being larger on physical and US examination.

Laboratory Evaluation

In general, there are no laboratory tests or values that can help discern the risk that a thyroid nodule is more likely to be benign or malignant. The 1 exception is that a suppressed TSH level is often associated with an autonomously functioning thyroid nodule, a nodule that carries a lower risk of malignancy in both adult and pediatric patients (1%–10%).[31] A serum Ctn level should be obtained if the patient has a family history of MEN2, clinical features suggestive of MEN2B, or if the cytology is suspicion

Table 2
Oncogenic mutation with correlation to histology and invasive potential, recommended surgical approach, and potential systemic therapy for neoadjuvant or adjuvant therapy

Somatic Driver Mutation	Histology	Invasive Potential[a]	Surgical Approach	Multikinase Inhibitor[b]	Systemic Therapy (Clinical Trials #)
Gene Fusion					
RET fusions and mutations	PTC	High	Thyroidectomy with central neck lymph node dissection; lateral neck dissection based on US and FNA	Lenvatinib Sorafenib	BLU-667 (NCT03037385) LOXO-292 (NCT03157128; NCT03899792)
	MTC	Based on RET codon	Based on calcitonin level, imaging, FNA	Vandetanib Cabozantinib	
NTRK fusion	PTC	High	Thyroidectomy with central neck lymph node dissection; lateral neck dissection based on US and FNA	Lenvatinib Sorafenib	Larotrectinib (all ages) Entrectinib (12 y and older)
ALK fusion[c]	PTC	High	Thyroidectomy with central neck lymph node dissection; lateral neck dissection based on US and FNA	Lenvatinib Sorafenib	Crizotinib (NCT02034981) Ceritinib (NCT02289144) Alectinib (NCT03194893) Ensartinib (NCT03155620)
	MTC	Limited cases	Based on calcitonin level, imaging, FNA	Vandetanib Cabozantinib	
Point Mutation					
BRAFV600E	PTC	Intermediate	Thyroidectomy with central neck lymph node dissection; lateral neck dissection based on US and FNA	Lenvatinib Sorafenib	Vemurafenib (NCT03155620) Dabrafenib with trametinib

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Table 2
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Somatic Driver Mutation	Histology	Invasive Potential[a]	Surgical Approach	Multikinase Inhibitor[b]	Systemic Therapy (Clinical Trials #)
RAS[c] PTEN DICER1[c] PAX8/PPARg[c]	PTC, FTC, and benign	Low	Lobectomy if unilateral disease Consider thyroidectomy if thyroid cancer predisposition syndrome or autoimmune thyroiditis	Lenvatinib Sorafenib	No current medical therapy
TSHR GNAS	Benign	Not applicable	Lobectomy	Not applicable	Not applicable
TERT, EIF1X, CTNNB1, AKT1, others	PTC and FTC	Limited data in pediatrics			

Abbreviations: FNA, fine-needle aspiration; TSHR, thyroid-stimulating hormone receptor.

[a] Invasive potential: (1) low, intrathyroidal; (2) intermediate, intrathyroidal and N1a; (3) high, intrathyroidal, N1a/N1b and M1.

[b] Multikinase inhibitors are selected based on thyroid cancer variant (DTC vs MTC) not oncogene. NCT01876784 and NCT03690388 are ongoing studies of refractory DTC.

[c] May be associated with poorly differentiated thyroid cancer; rare in pediatrics.

for MTC.[32] Clinicians should be aware that, in infants and young children, there is a normal physiologic increase in Ctn level, with values as high as 35 ng/L before 6 months of age that decrease into the adult range by approximately 3 years of age.[33]

Radiologic Imaging

Thyroid and neck US is the best radiologic modality to assess thyroid tissue morphology and lymph node status. Both the American Thyroid Association (ATA) adult thyroid nodule pictorial risk classification system and the Thyroid Imaging Reporting and Data System (TI-RADS) in children and adolescents may be used as a construct paradigm to stratify the nodules that should undergo further evaluation with fine-needle aspiration (FNA).[34] The US report should describe the background echogenicity of the thyroid parenchyma as well as the size, location, composition (solid, cystic, or spongiform), echogenicity (hypoechoic, isoechoic, or hyperechoic), shape (taller than wide on transverse imaging), margins (regular, infiltrative, microlobulated, or macrolobulated, and the presence or absence of extrathyroidal extension [ETE]), and the presence of echogenic foci in the nodules. Cystic composition is the single most reliable feature for assessing the risk of malignancy, with cystic composition greater than 75% associated with lower risk.[35,36] In patients with a thyroid nodule, US evaluation of the lateral neck should be performed looking for the presence of abnormal lymph nodes. Abnormal US features of lymph nodes that are consistent with thyroid cancer metastasis include rounded shape, increased echogenicity with loss of the hilum, cystic composition, echogenic foci, and increased peripheral blood flow on Doppler imaging.[37]

Most adult criteria for selecting nodules for FNA apply to children and adolescents, with the following exceptions: (1) US features and clinical context should be considered rather than size to select nodules for FNA[38]; and (2) a widely invasive form of PTC, called diffuse sclerosing variant PTC (dsvPTC), presents with nonnodular, diffuse infiltration of the thyroid associated with diffuse microcalcifications throughout the gland, a snowstorm appearance on US.[39–41] dsvPTC is commonly associated with macroscopic metastasis to lateral neck lymph nodes as well as increased thyroglobulin antibody or anti-thyroglobulin (TgAb) level.[40,42] The nonnodular appearance and the presence of increased TgAb level may mimic autoimmune hypothyroidism; however, the diffuse echogenic foci and abnormal lateral neck lymph node should help distinguish between these two conditions.

There is ongoing debate whether patients at increased risk for developing thyroid cancer should undergo monitoring by thyroid US or by physical examination. For oncology survivors treated with radiation, the most recent recommendation suggests that patients and families should be counseled about the options for surveillance but that US detects tumors at an earlier state of growth and invasiveness.[43] In familial thyroid cancer predisposition syndromes (PHTS, DICER1, and FAP), thyroid surveillance by US is recommended. However, the approach to evaluation and treatment of thyroid nodules must be considered within the context of the generally indolent behavior of DTC-predisposition syndromes.

The risk of performing thyroid US is minimal when clinicians experienced in reading thyroid US images and managing pediatric thyroid nodular disease are involved in the process. Complication from thyroid nodule aspiration are extraordinarily low and the rate of permanent complications from thyroid surgery should be less than 3% to 5% if performed by a high-volume thyroid surgeon.[44] Thus, in populations at increased risk of developing DTC, the benefit of pursuing thyroid US monitoring seems to outweigh the risk of the procedure.

Fine-Needle Aspiration

As in adults, The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is used to classify the FNA results in pediatrics with equal sensitivity, specificity, and overall accuracy.[36,45] However, although the results of the FNA are similarly used to stratify an appropriate management plan, there seems to be an increased risk of malignancy for pediatric patients with benign and indeterminate cytology. In adults, benign cytology is associated with a 0% to 3% risk of malignancy, whereas, in pediatrics, the risk of malignancy may be as high as 10%.[46] For nodules with TBSRTC category III (atypia of undetermined significance or follicular lesion of undetermined significance), category IV (follicular neoplasm), or category V (suspicious for malignancy) the risk of malignancy may be as high as 28%, 58%, and 100%, respectively.[46]

For patients with nondiagnostic cytology (TBSRTC category 1), repeat FNA may be considered but there should be a 3-month delay between FNAs to avoid potential post-FNA reactive cellular atypia.[47] Cytologic confirmation of sample adequacy at the bedside can decrease the rate of nondiagnostic results. Nodules that are category V and VI (suspicious for malignancy and malignant) correlate with a near 100% risk of PTC.[46]

In an effort to decrease reliance on diagnostic surgery, there is increasing use of supplemental molecular profile testing in pediatrics following the more widespread use of oncogene panels and gene-expression classifier testing in adults. Based on current data, oncogene panels are the only test that have clinical utility to predict an increased risk for malignancy in patients less than 19 years of age.[46] In children, the presence of a thyroid oncogene mutation or fusion (*BRAF*^{V600E}, *RET*/*PTC*, *NTRK* fusion, and others) in an indeterminate FNA specimen is associated with a near-100% likelihood of PTC.[48,49] The presence of other mutations and fusions, including *RAS*, *DICER1*, and *PTEN*, is associated with both benign and malignant disease, and, until additional molecular markers are available, diagnostic lobectomy for unilateral nodules with indeterminate oncogenes is still the best approach to determining the malignant potential (see **Table 2**).[17] For nodules with indeterminate oncogenes, or without an identifiable oncogene, microRNA testing may provide further preoperative risk stratification for identifying malignancy.[50]

SURGICAL MANAGEMENT

Thyroid surgery should be performed by a high-volume thyroid surgeon, defined as a surgeon who performs 30 or more cervical endocrine procedures annually within the age group of the patient undergoing surgery, in an effort to minimize the risk of operative complications.[38,44,51] Although the exact number of surgeries performed annually may not reflect the quality of the surgeon, it increases the likelihood that the surgeon understands the disease process in pediatric patients and is familiar with age-specific treatment recommendations. Even in the pediatric setting, the goal should be to minimize the risk of permanent surgical complications to less than 1% to 3%.[52]

Complete and accurate preoperative radiologic imaging, with FNA confirmation of at least 1 abnormal lymph node per cervical level of the neck, is critical to optimize the surgical plan and reduce the risk of an incomplete dissection that may necessitate a second operative procedure. PTC typically follows a predictable pattern of metastasis from the thyroid to the central neck (level VI) followed by spread to the lateral neck (levels II; III; IV; and, rarely, V). In general, neck US is adequate for preoperative planning. Anatomic imaging with computed tomography (CT) or MRI may be added to assess for areas not easily visualized by US.[53]

The use of intraoperative parathyroid hormone levels helps to identify patients at risk of hypoparathyroidism and to ensure early administration of calcium and calcitriol in an effort to avoid symptomatic hypocalcemia.[54] The perioperative calcium and phosphorus levels must be monitored to ensure stable values before discharge from the inpatient setting.[54,55] Early identification of hypoparathyroidism with subsequent initiation of calcitriol and calcium decreases the risk of symptomatic hypocalcemia, as well as the duration of postoperative hospitalization.[52,54,55]

Papillary Thyroid Cancer

The ATA pediatric guidelines recommend that most children with PTC undergo total or near-total thyroidectomy.[38] This recommendation is based on data showing an increased risk of bilateral disease in children, including a recent report of 172 children and adolescents where up to 40% had bilateral disease, with 23% (40 of 172) not detected on preoperative thyroid US.[56] These findings corroborate previous reports showing a lower risk of recurrence in children undergoing thyroidectomy compared with lobectomy, 6% versus 30%, respectively, over 4 decades of observation.[57]

However, lobectomy may suffice to achieve surgical remission in a subgroup of patients with noninvasive or low-invasive disease. US findings consistent with a lower risk of invasion include solid nodules that are not taller than wide on transverse imaging with smooth margins and no evidence of microcalcifications or lymphadenopathy.[58] Cytology of these lesions is often indeterminate (TBSRTC III or IV), with the final histology revealing encapsulated fvPTC,[59] minimally invasive FTC (miFTC),[38,60] or the recently designated noninvasive follicular thyroid neoplasm with papillarylike nuclear features.[61]

Prophylactic central neck lymph node dissection should be considered in pediatric patients undergoing surgery for nodules with cytology suspicious for, or consistent with, PTC (Bethesda category V and VI) secondary to a high risk of central neck (level VI) metastasis.[38] In addition, the ATA pediatric risk levels are designed to use the data obtained from the central neck lymph node dissection to stratify patients into 3 levels of persistent postoperative disease (low, intermediate, and high) for selection of patients that may benefit from RAI therapy.[38]

A therapeutic central neck dissection should be performed in all children found to have central and/or lateral neck lymph node metastases on preoperative evaluation. Lateral neck dissections should only be performed in the presence of FNA-proven metastatic lateral neck disease. When nodal dissection is performed, a complete dissection of the affected compartment should be performed, rather than "berry picking."[38]

Follicular Thyroid Cancer

In contrast with PTC, FTC is typically unifocal and shows hematogenous rather than lymphatic metastasis. Pediatric FTC is diagnosed in 10% or less of pediatric patients with DTC. FTC may develop as part of PHTS. Thus, clinicians should have a high index of suspicion in children with FTC, particularly in those with macrocephaly, lipoma, freckling of the glans penis, or a suggestive family history.[23,25,62]

FTC is typically subdivided into miFTC and widely invasive FTC (wiFTC). miFTC is defined as FTC with microscopic or no capsular invasion and/or limited vascular invasion, less than 4 vessels in or adjacent to the tumor capsule.[60] wiFTC is defined as FTC with widespread capsular invasion, widespread vascular invasion, or tumor extension into adjacent, surrounding tissue. Invasion of 4 or more vessels is associated with an increased risk of distant metastases and poorer prognosis.[63–65]

Similar to adult patients, children ultimately diagnosed with FTC typically have indeterminate FNA cytology (TBSRTC III or IV). Thus, the most initially undergo diagnostic lobectomy with consideration of total thyroidectomy for patients with underlying thyroid disease, bilateral nodules, or a known diagnosis of a thyroid tumor predisposition syndrome, such as PHTS. Frozen section cannot be used to rule out FTC because the diagnosis is based on complete histologic examination of the nodule capsule to determine whether the nodule is a follicular adenoma (no evidence of invasion) or follicular carcinoma (evidence of capsular and vascular invasion).[66] For minimally invasive FTC, lobectomy is considered sufficient to achieve surgical remission. For widely invasive FTC, completion thyroidectomy should be performed along with a postoperative RAI diagnostic whole-body scan (DxWBS) to assess for evidence of distant metastasis, most commonly to the lung or bone.[67,68]

Medullary Thyroid Cancer

For patients with MEN2, the ATA divides the germline *RET* mutations into 3 risk categories for developing MTC (highest risk, high risk, and moderate risk) and bases the recommended age for initial screening, as well as the timing of prophylactic thyroidectomy, to coincide with the goal of achieving surgical remission.[19] Total thyroidectomy is recommended as follows: within the first year of life for carriers of the highest-risk mutation (MEN2B, codon 918), at or before age 5 years for those with a high-risk mutation (MEN2A, codons 634 and 883), and for all other moderate-risk mutations when the serum Ctn level shows an increasing upward trend or at any time the parents or patient do not wish to continue with laboratory surveillance.[19] For patients with moderate-risk mutations, the course from C-cell hyperplasia to MTC may be indolent, with MTC not developing until the third, fourth, or later decades of life. Thyroid US is useful to detect the location of a thyroid nodule and to assess for regional lymph node disease. However, it is not as sensitive as serum Ctn to determine the timing of thyroidectomy to optimize surgical remission.[69] As a general rule, thyroidectomy should be scheduled once the Ctn level shows an upward trend above the normal range. A central lymph node dissection is recommended in children whose basal Ctn level is greater than 40 ng/L and in all patients that display central or lateral neck lymph node metastasis.[19,70]

In contrast with MEN2A, mutations in codon 918 (MEN2B) are more often de novo. Thus, recognition of the early clinical signs and symptoms is critically important in order to diagnose the syndrome before MTC metastasis, which may occur before 1 year of age or, more commonly, before 4 years of age.[71,72] The earliest clinical signs and symptoms of MEN2B include alacrima (the inability, or decreased ability, to make tears), constipation (associated with intestinal ganglioneuromatosis), and hypotonia (feeding difficulties with failure to thrive, club feet, hip dislocation).[28] The more classically defining symptoms, including oral and lip mucosal neuromas and elongated, marfanoid facies, are not clinically evident until school age, around 5 years of age.[28,73]

MEDICAL THERAPY

Radioactive Iodine Therapy

RAI is a highly effective, targeted medical therapy to treat persistent postsurgical disease. Over the past 5 decades, there has been a near 2-fold increase in the number of patients receiving RAI without any impact on the excellent (~98%) 20-year disease-specific survival.[74] Although there is a paucity of long-term prospective data to define the lifetime risk of RAI administered during childhood and adolescence, with increased awareness of the potential short-term and long-term risks of ^{131}I therapy there are

renewed efforts to identify which patients may (ATA pediatric intermediate and high risk) or may not (ATA pediatric low risk) benefit from ^{131}I therapy.[38,75,76]

Although there is no staging system for children and adolescents with PTC secondary to the extremely low disease-specific mortality, the American Joint Committee on Cancer (AJCC) tumor, nodes, metastases (TNM) classification system[77] is used to describe the extent of disease and stratify which patients may or may not benefit from RAI. The following is an updated version of the ATA pediatric risk levels with proposed adjustments based on recent data (**Table 3**).[38,58,78]

1. ATA pediatric low risk is defined by disease grossly confined to the thyroid with N0 (no lymph node metastasis) or less than or equal to 5 metastatic lymph nodes from the central neck (N1a).[58,78] It is difficult to assess the risk of persistent lymph node disease in patients who have no lymph nodes resected (Nx). However, the risk may be considered low if the primary tumor had no invasive potential (ie, miFTC), low-invasive potential (ie, Enc-fvPTC), or was a DTC with a low-invasive somatic oncogene (ie, *RAS*, *DICER1*, or *PTEN*).
2. ATA pediatric intermediate risk is defined by the presence of ETE (microscopic or gross); unilateral or lateral neck lymph node metastasis (N1b); or 6 to 10 metastatic lymph nodes (extensive N1a). The addition of ETE to the intermediate risk level is important if a central neck lymph node dissection was not performed because ETE has been shown to be associated with an increased risk for lymph node metastasis.[58] Clinicians should be aware that microETE was removed as a criterion for T3 tumors in the eighth edition of the AJCC TNM classification system. The synoptic pathology report must be reviewed in order to identify whether microETE was present in order to accurately interpret the risk of postoperative persistent disease.[77]
3. ATA pediatric high risk is defined by regionally extensive disease, including bilateral N1b, greater than 10 metastatic lymph nodes, and patients with distant metastasis (M1) being considered high risk for persistent postoperative disease.

For ATA low-risk patients, clinicians may consider following the TSH-suppressed Tg level with repeat neck US instead of pursuing a stimulated Tg level with DxWBS in the immediate postoperative time frame. A stimulated Tg and DxWBS can be performed

Table 3
Proposed update to the American Thyroid Association postsurgical risk levels to guide selection for radioactive iodine therapy

ATA Pediatric Risk Level	Definition	Initial Postoperative Evaluation
Low risk	Disease confined to the thyroid gland and N0 or N1a with ≤5 metastatic lymph nodes[a]	TSH-suppressed Tg
Intermediate risk	Presence of extrathyroidal extension or unilateral N1b or 6–10 metastatic lymph nodes	TSH-stimulated (>30 mIU/L) Tg and RAI DxWBS
High risk	Bilateral N1b or >10 metastatic lymph nodes or distant metastasis (M1)	TSH-stimulated (>30 mIU/L) Tg and RAI DxWBS

Abbreviations: N0, no metastatic lymph nodes; N1a, metastasis to lymph nodes limited to the central neck (level VI); N1b, metastasis to lymph nodes in the lateral neck (levels II, III, and/or IV).
[a] See text for discussion of the risk associated with Nx (no lymph nodes removed).

at a later time if there is an unexpected increased and/or increasing Tg level and no evidence of disease based on US and/or anatomic imaging (CT or MRI).[38,75,76]

For intermediate-risk and high-risk patients, a TSH-stimulated Tg level and a ^{123}I-DxWBS are recommended to search for residual or metastatic disease.[38] The use of ^{123}I is favored rather than ^{131}I because of superior imaging quality and prevention of stunning.[79]

The decision to administer ^{131}I therapy should be based on the TSH-stimulated Tg level as well as the data obtained from the ^{123}I-DxWBS. A TSH-stimulated Tg level 2 ng/mL has a 94.9% predictive value for the absence of postsurgical disease.[80] If TSH-stimulated Tg level is 2 to 10 ng/mL, ^{131}I therapy should be considered for patients with thyroid bed uptake; invasive histology, including dsvPTC, solid-variant PTC (sPTC), and widely invasive fvPTC (wi-fvPTC); evidence of gross ETE; extranodal extension; or in patients with extensive regional metastasis (extensive N1a or any N1b disease). If the TSH-stimulated Tg level is greater than 10 ng/mL, ^{131}I therapy is indicated. Repeat surgery before administration of ^{131}I should be pursued if there is evidence of persistent, macroscopic disease noted during this initial postoperative time frame because there is reduced efficacy for RAI ablation of lymph nodes larger than 1 cm.[32] The addition of single-photon emission CT with integrated conventional CT may provide more accurate anatomic localization to differentiate metastatic regional lymph node from remnant thyroid tissue.[81]

Therapeutic ^{131}I can be dosed empirically or based on bone marrow dose-limited dosimetry. There are 2 formulas to decide on empiric dosing: (1) given as a fraction of a child's weight compared with an average-sized adult (kilograms divided by 70 kg) multiplied by a typical adult dose used to treat similar disease extent,[82,83] or (2) based on millicuries/weight with a typical range between 1.0 and 3.0 mCi/Kg based on the presence of regional or distant disease.[84] Dosimetry should be considered in younger children (<10 years), those with diffuse pulmonary metastases, and those who received radiation therapy for other malignancies.[85] A posttreatment whole-body scan should be obtained 5 to 7 days after all ^{131}I treatments and is associated with a greater sensitivity for detecting persistent disease compared with the DxWBS.[86]

Even with efforts to limit the delivered activity and frequency of RAI, long-term follow-up studies are needed to confirm or refute previous reports on the risk of developing RAI-induced, second primary malignancies (SPMs).[57,74,87,88] Although the overall numbers are small, many of the SPMs are in iodine-avid glands (ie, salivary glands) or in nonavid tissues passively exposed to ^{131}I during physiologic clearance (bone marrow, colon, bladder, and others).[57,89] Thus, the challenge is to determine whether the SPM is RAI related or associated with risk factors that led to development of the thyroid malignancy. Clinicians should not fear the use of RAI. However, there is an obligation to differentiate patients who may benefit from ^{131}I therapy from patients in whom the risks of RAI outweigh the benefit. In pediatrics, the goals of achieving remission and avoiding recurrence must be balanced with the risk of complications of therapy.

PERSISTENT AND RECURRENT DISEASE

Cervical lymph nodes are the most common location for residual and recurrent PTC.[90–92] If macroscopic cervical disease is identified by imaging and confirmed via FNA, surgery is preferable to ^{131}I therapy.[93,94] Children with iodine-avid, small-volume cervical disease can be considered for therapeutic ^{131}I therapy depending on the individual risk/benefit ratio as well as the absence or presence of distant metastasis.[95]

US-guided percutaneous ethanol or radiofrequency ablation may be considered as nonsurgical treatment options in patients with a limited number of neck metastasis (1 or 2 lymph nodes) depending on the location and size of the lymph nodes.[95–97] The therapeutic success rates of ethanol injection and radiofrequency ablation have been reported to be between 70% and 98%, with decreased to absent blood flow and reduced posttreatment size of the lymph node 3 to 6 months after the procedure defining successful ablation.[95,96,98]

The lungs are the most common site for persistent or recurrent disease distal metastasis. In contrast with adults, children and adolescents with pulmonary metastasis have low disease-specific mortality, most likely secondary to the pulmonary lesions maintaining RAI avidity.[99,100] Retreatment of ^{131}I-avid pulmonary metastases should be considered in children who have shown previous improvement but continue to have persistent disease based on cross-sectional imaging obtained more than 1 to 2 years after the last RAI treatment, and sooner if there is evidence of disease progression on serial imaging obtained on a 6-month interval. The timing of additional ^{131}I should be at least 12 months from the previous treatment, with several studies showing a continuous decline in serum Tg levels for 18 to 24 months, or longer, following the previous RAI therapy.[100,101] However, up to one-third of children with significant pulmonary disease may develop stable, persistent, or progressive disease that does not respond to repeated doses of ^{131}I.[99]

Systemic Therapy for Radioactive Iodine–Refractory Differentiated Thyroid Cancer

A small proportion of children and adolescents develop progressive DTC that is refractory to ^{131}I therapy. RAI refractory (RAIR) is defined by the (1) absence of initial RAI uptake in metastasis; (2) absence of RAI uptake in metastasis after treatment with RAI; (3) presence of RAI uptake in some metastasis, but absence in others; and (4) progression despite RAI uptake in metastasis.[102] The main criteria for initiation of systemic therapy in adults are (1) large tumor burden with tumors larger than 1 to 2 cm, (2) Response Evaluation Criteria in Solid Tumors (RECIST) progressive disease over 12 months, and (3) symptomatic disease and risk of local complications.[102,103] There are no pediatric age-specific definitions for RAIR or criteria for when to initiate systemic therapy.

Over the last decade, there has been an increasing number of oral systemic therapies that have been incorporated into clinical practice for adults with similar disease. These agents target tyrosine kinase receptors or constitutively activated protein kinases in the MAPK and PI3K signaling pathways.[104] The multitargeted tyrosine kinase inhibitors (TKIs) target the vascular endothelial growth factor receptors as well as other tyrosine kinase receptors, including the epithelial growth factor receptor, fibroblast growth factor receptor, platelet-derived growth factor receptor, and RET. There are currently 4 MKIs that have received US Food and Drug Administration (FDA) approval for the treatment of advanced thyroid cancer: sorafenib and lenvatinib for DTC, and vandetanib and cabozantinib for MTC.[105] These agents are not tumoricidal but they have been shown to slow progression and to decrease tumor burden for many patients. However, in adults, the effect is often transient and many patients experience side effects, including hypertension, diarrhea, anorexia with weight loss, dermatitis, and fatigue.[105] Within pediatrics, there are several case reports where MKIs have been used; however, the data are limited and there is no consensus with regard to the timing to initiate therapy or in the selection of which oral chemotherapeutic agent should be used.[106,107]

The newer oncogene-specific targeted inhibitors have increased efficacy and less toxicity compared with the multityrosine inhibitors. Several of these agents have

been in clinical use for several years, repurposed from other cancers with similar molecular alterations. The most effective of these molecular targeted inhibitors have shown remarkable clinical efficacy with regression in tumors harboring *RET*, *NTRK*, and *ALK* fusion genes and the $BRAF^{V600E}$ mutation.[105] Larotrectinib (LOXO-101) is a selective *NTRK* inhibitor that has been approved for use in pediatric patients. The Children's Oncology Group (COG) recently opened a phase II study with larotrectinib (ADVL1823, NCT03834961) for children with previously untreated tropomyosin receptor kinase (TRK) fusion solid tumors, including thyroid cancer. This prospective study provides an opportunity to define the benefits and risks of medical therapy for children and adolescents with thyroid cancer for whom surgery caries a high risk of morbidity. In addition, the National Cancer Institute and COG Pediatric Molecular Analysis for Therapy Choice (MATCH) (NCT03155620) is a phase II study that offers access to several agents based on knowledge of the oncogenic driver mutation, including BRAF alterations (vemurafenib), ALK fusions (ensartinib), and soon to include RET mutations/fusions (LOXO 292).

Systemic Therapy for Medullary Thyroid Cancer

For patients with MTC with symptomatic or progressive metastatic disease that is not amenable to surgery, systemic treatment with receptor tyrosine kinase inhibitors or oncogene-specific targeted therapies against *RET* may be indicated (see **Table 2**). The same criteria used for initiation of systemic therapy, described earlier, should be followed for patients with MTC within the context that most patients with metastatic MTC do not achieve remission from disease. Vandetanib and cabozantinib have been FDA approved for the treatment of adults with progressive, metastatic MTC.[104,108] Limited data suggest that vandetanib is effective and well tolerated in children with advanced MTC in the setting of MEN2B.[109] The selective *RET* inhibitors (BLU-667 and LOXO-292) are currently in clinical trials, with preliminary data showing very favorable response with few side effects.[105]

FUTURE DIRECTIONS

Knowledge of the somatic oncogene driver mutation is becoming increasingly important for the diagnosis of thyroid nodules with indeterminate cytology as well as for the prediction of clinical behavior, response to therapy, and for the selection of systemic therapy.[17,18] **Table 2** summarizes a proposed oncogene-directed surgical approach, as well as potential multikinase inhibitors and oncogene-specific targeted therapy that could be used as neoadjuvant or adjuvant therapy. For patients that present with morbidly invasive disease, including evidence of recurrent laryngeal nerve paralysis, encasement of great vessels, or evidence of aerodigestive tract invasion, or with pulmonary metastasis associated with hypoxia, neoadjuvant systemic therapy should be considered. For patients with DTC, surgery and RAI should be pursued once the patient achieves improved clinical status associated with systemic therapy–induced tumor regression. For patients with MTC, surgery may be deferred if the systemic therapy is associated with significant regression because it is unlikely to achieve surgical remission once MTC metastasizes. For patients with progressive DTC or MTC that is not surgically resectable, or in patients with RAI-refractory DTC, adjuvant systemic therapy should be considered based on anatomic progression.

With the potential for significant side effects, and limited experience in using these agents in children and adolescents, multicenter collaborative studies are needed to better define the timing for initiation, selection of drug, monitoring, and adjustment

of therapy so that outcome can be optimized while minimizing the risk of side effects and adverse events.[38,105,110]

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