Current Understanding and Treatment of Differentiated Thyroid Cancer in Children—A Review

Steven G Waguespack, MD[1] and Gary L Francis, MD, PhD[2]

1. Associate Professor, Department of Endocrine Neoplasia and Hormonal Disorders, Department of Pediatrics, University of Texas MD Anderson Cancer Center; 2. Professor of Pediatrics, and Chief, Division of Pediatric Endocrinology and Metabolism, Virginia Commonwealth University

DOI: 10.17925/USE.2010.06.1.84

Abstract

Differentiated thyroid cancer (DTC) often presents in children with regional lymph node metastasis accompanied by a high risk for recurrence. However, children rarely die from DTC, even those who present with distant metastatic disease. The most common presentation for DTC in children is a thyroid nodule, approximately one quarter of which are malignant. In this manuscript, we review the differential diagnosis, approach, and treatment for DTC in children with a special emphasis on future perspectives.

Keywords

Childhood, pediatric, papillary, follicular, thyroid carcinoma

Disclosure: The authors have no conflicts of interest to declare.
Received: August 19, 2010 **Accepted:** October 4, 2010 **Citation:** *US Endocrinology*, 2010;6:84–91
Correspondence: Gary L Francis, MD, PhD, Professor of Pediatrics, Chief, Division of Pediatric Endocrinology and Metabolism, Virginia Commonwealth University, 1001 E Marshall St, Richmond, VA 23298. E: glfrancis@mcvh-vcu.edu

Only 1.8% of all thyroid cancers develop in children or adolescents, but the incidence appears to be increasing.[1–3] The majority of differentiated thyroid cancers (DTCs) in children are papillary thyroid cancers (PTCs), including the follicular, tall-cell, columnar, diffuse sclerosing, and encapsulated variants.[4] Follicular thyroid cancer (FTC) is less common and includes the subtypes of Hürthle-cell (oncocytic), clear-cell, and insular (poorly differentiated) carcinoma.[4] Medullary thyroid cancer (MTC) is uncommon in this age group and is usually associated with multiple endocrine neoplasia type II.[5–8] Activation of the RAS–RAF–MEK–ERK (mitogen-activated protein kinase [MAPK]) pathway is a central feature of thyroid cancers and provides the opportunity for targeted therapies beyond surgery or radioactive iodine.[9–11]

The most common presentation for DTC in children is that of a palpable thyroid nodule (see *Figure 1*). However, PTC not infrequently presents as cervical adenopathy with or without a palpable thyroid lesion. In adults, approximately one-third of all PTC is now an incidental finding detected after imaging or surgery for an unrelated condition.[12] The prevalence of incidental PTC in children is unknown but the detection of incidental PTC is increasingly common. Occasionally, DTC is detected by the discovery of distant metastases.[13–15] During adolescence, there is a 10-fold greater incidence of DTC than in younger children and a female:male preponderance (5:1) that is not seen in younger children.[2,3,7,16–18] There are important differences in clinical behavior between PTC and FTC that affect treatment and prognosis. PTC is frequently multifocal and bilateral and metastasizes to regional neck lymph nodes (see *Figure 1*). For that reason, total thyroidectomy and central compartment lymph node dissection are generally performed for more than an incidentally-discovered PTC. Distant metastases occur in 5–10% of children and generally occur only with significant regional lymph node disease.[8,19] For that reason, whole-body radionuclide scanning is generally performed during initial post-operative staging to ascertain the presence or absence of distant metastases. Prior radiation exposure is a major risk factor for the development of PTC[20,21] and children under five years of age are the most sensitive.[22,23] Radiation-induced PTC does not appear to differ in clinical behavior compared with sporadic PTC.[24] Almost 5% of patients with PTC have a family history of PTC,[22,25] which typically presents earlier in life and may require more aggressive therapy.[26] FTC is typically unifocal and rarely metastasizes to regional lymph nodes. However, FTC commonly develops hematogenous metastases, primarily to lungs and bone. For that reason, an evaluation for distant metastases is generally performed in all children with FTC except for those with minimally invasive disease.

Unique Features of Differentiated Thyroid Cancer in Children

The evaluation, treatment, and follow-up of children with DTC have generally followed adult guidelines.[27–30] However, there are several important clinical and molecular differences in DTC that have been described in children. First, although thyroid nodules are uncommon in children, nodules are five-fold more likely to be malignant in children (26.4%) than they are in adults (5%).[31,32] Second, when controlled for histology and tumor size, children with PTC are more likely to have regional lymph node involvement (80%), extra-thyroidal extension (20%), and distant pulmonary metastasis (5–10%).[8,12,14,15,33–39] Third, despite having extensive disease, children are less likely to die from disease (2%

cause-specific mortality in recent series[39]) than adults, and many children with pulmonary metastases (30–45%) develop persistent, albeit stable, disease following radioactive iodine (RAI) therapy.[39,40] Recent molecular studies have found that BRAF mutations are the most common abnormality in adult PTC (36–83% of cases),[9] but they are rare in childhood PTC.[41] In contrast, RET/PTC rearrangements are more common in PTC from children.[7,11,42] These differences might be important in the lower disease-specific mortality observed in children with DTC.

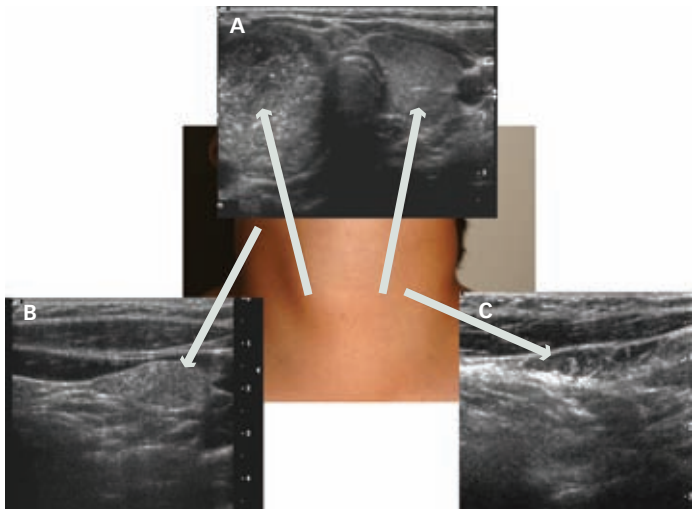
Thyroid Nodules

Thyroid nodules are uncommon in pre-pubertal children (1–1.5%) but have been reported in a fairly high proportion of adolescents (13%) when examined by ultrasound (US) or post-mortem thyroid sectioning.[31,43] Preferably under US guidance, fine-needle aspiration (FNA), is increasingly used to determine the benign or malignant nature of thyroid nodules in children.[31,44–46] As experience with FNA has increased in children, the probability of false-negative results has declined. A recent meta-analysis by Stevens et al. included 12 papers and found good sensitivity (94%), specificity (81%), and accuracy (83.6%).[47] In children with more than one nodule, selection of the nodule for FNA is often based on US features.[48] While size has not readily distinguished malignant from benign lesions in children, hypoechogenicity, irregular margins, and increased intranodal vascularization are more common among malignant lesions.[48] Molecular signatures to help improve diagnosis by FNA are also being tested but remain experimental.[49–52] Despite these advances, there remains a small probability, perhaps as high as 7%, that a malignant lesion will fail to be correctly identified by US and FNA.[53] Although limited, data suggest that close follow-up and later treatment will be successful for detecting and treating such misdiagnosed lesions. Ito et al. performed a retrospective analysis of 56 patients with PTC who underwent thyroidectomy without lymph-node dissection for a presumptive diagnosis of benign nodule.[54] Only 5.3% developed recurrent disease and none died from disease, suggesting that cancers that appear benign on FNA and US are likely to follow an indolent course that will probably not have a negative impact on survival when they are identified and treated at a subsequent date. Some, but not all, benign nodules regress spontaneously.[55] Because of that and side effects associated with thyroid-stimulating hormone (TSH) suppression, some clinicians favor TSH suppression while others do not.[31,56–60]

Pre-operative Staging of Differentiated Thyroid Cancer in Children

Pre-operative staging is necessary to direct the initial management of children with DTC. At a minimum, pre-operative studies generally include a chest radiograph (CXR) and comprehensive neck US to interrogate the contralateral thyroid lobe and the lymph nodes in the central and lateral compartments.[61] As the majority of children with PTC have cervical node involvement,[8,12,14,15,33–35] pre-operative US is paramount to identify those children who will require lymph node dissection at the time of thyroidectomy (see *Figure 1*). To facilitate surgical planning for children with bulky metastatic lymphadenopathy, many surgeons also consider computed tomography (CT) or magnetic resonance imaging (MRI) of the neck. If iodinated contrast agents are used for this procedure, therapeutic RAI will need to be delayed until total body iodine burden returns to normal (generally two to three months). Nuclear scintigraphy is not included in the pre-operative staging of the

Figure 1: A 10-year-old Boy Presented with an Asymptomatic Thyroid Mass Noticed by his Father



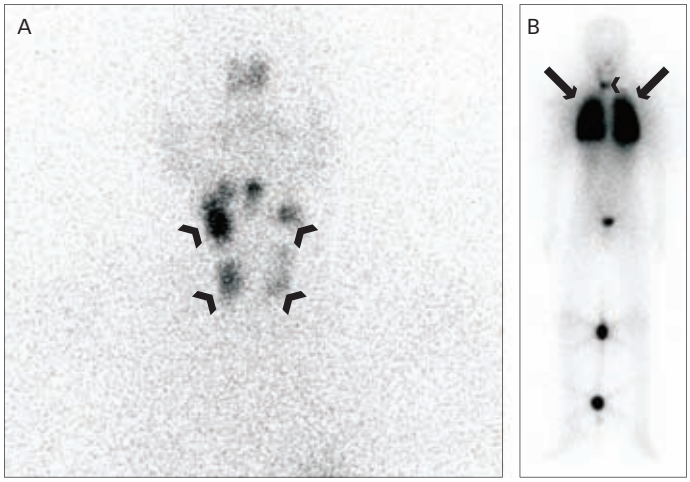
Ultrasound (US) of the thyroid (A) revealed a right lobe mass with microcalcifications consistent with a diagnosis of papillary thyroid cancer. The left lobe of the thyroid was normal in appearance. Evaluation of the lateral neck with US confirmed metastatic lymphadenopathy (B) in palpable lymph nodes in the right neck but also demonstrated a malignant-appearing lymph node (C) in the left inferior neck (subsequently confirmed on surgical pathology) that was not palpable on physical examination and would have otherwise gone undocumented.

child with an intact thyroid and a normal TSH. RAI uptake in the lungs after initial surgical therapy appears to be the most sensitive indicator of pulmonary metastases.[37] For that reason, chest CT is usually obtained only if pulmonary metastatic disease is documented after treatment with RAI. DTCs in children are well-differentiated tumors with robust RAI uptake and there appears to be no benefit from positron emission tomography (PET) scanning for this initial staging.

Several staging systems have been used to estimate the mortality risk for thyroid cancer, specifically PTC,[27,62–64] but none appears superior to the tumor–node–metastasis (TNM) classification.[65] The majority of young patients (<45 years of age) will be TNM stage I and only those few with distant metastases will be stage II. However, stage I is highly diverse and includes incidental PTC, PTC with cervical lymph node metastases, and PTC grossly invading surrounding structures such as the recurrent laryngeal nerve. Despite similar stage and low risk for mortality, the risk of recurrence is much greater for patients with cervical node involvement or local tumor invasion.[19,66] Children with PTC who have palpable cervical lymph node metastases are more likely to recur (53% versus none), persist (30% versus none), have multifocal disease (89% versus 16%), and have a higher incidence of pulmonary metastasis (20% versus none) than children without nodal disease.[19] Therefore, the absence of cervical node involvement is an important indicator of low recurrence risk.

Most children with DTC have an excellent prognosis. Cure rates are high, and 10-year survival is almost 100%.[8,18,33,36,39,40,67–69] Children diagnosed prior to age 10 may have a higher risk of recurrence and ultimately death from disease,[70–72] but not all series confirm this observation.[38,73] A recent study by Lazar et al. found that outcomes for pre-pubertal and pubertal children were similar when both groups were similarly treated.[73] They postulated that previous studies may have shown poor outcomes for pre-pubertal children because they were not

Figure 2: Diagnostic Radioactive Iodine Scans in Pediatric Papillary Thyroid Cancer



A. Bilateral macroscopic lymph node metastases (arrowheads) in a 13-year-old girl, which are best treated with surgical resection. B. Diffuse pulmonary metastatic disease (arrows) in a 12-year-old boy. Note also the residual iodine-avid neck disease (arrowhead).

treated as aggressively. For patients with stage II disease, micronodular lung metastases and iodine-avid disease confer the best prognosis.[37,68,74]

Initial Therapy for Papillary Thyroid Cancers in Children

Most surgeons perform a total thyroidectomy for children with more than incidental PTC. There are several reasons for this. First, 40% of children have multifocal PTC and a higher risk for recurrence if less than total thyroidectomy is performed.[8,12,18,27,39,69,70,75–80] Second, the majority of children with PTC have regional lymph node disease and a greater risk for distant metastasis. Total thyroidectomy will facilitate the future use of RAI when indicated. Third, assays for serum thyroglobulin (Tg) are most sensitive for detecting disease after total thyroidectomy and RAI ablation.[81–83]

Lobectomy and isthmusectomy alone may suffice in the low-risk adolescent with a small (<1cm) unifocal PTC but only if US shows no evidence of disease in the contralateral lobe or regional lymph nodes.[18,27,28,77,79] Lymph node dissection reduces recurrence risk for children with PTC and improves progression-free survival.[84,85] The extent of lymph node dissection is based on the type and clinical presentation of DTC.[63] All lymph node dissections should be comprehensive and compartment focused because the rates of recurrence are higher when 'berry picking' is performed.[86] Although total thyroidectomy and central compartment dissections are associated with greater risks of hypoparathyroidism and recurrent laryngeal nerve injury,[8,75,87] the risks should be minimized when surgery is performed by a high-volume surgeon.[79,88] After surgery, patients are evaluated for persistent disease. In patients at very low risk for recurrence (e.g. small unifocal tumors with no known lymph-node disease), this may include US of the thyroid bed and cervical lymph nodes along with a suppressed serum thyroglobulin (Tg). In recent series, such low-risk patients have been effectively followed in an expectant fashion. Post-operatively, patients at high risk for residual or recurrent disease are generally withdrawn from exogenous thyroid hormone to prepare for a stimulated-Tg and diagnostic RAI scan (see *Figure 2*). Patients with pulmonary or distant metastases are almost always treated with RAI, whereas the routine use of RAI in patients with TNM stage I disease has become more controversial.

All authors agree that RAI therapy is indicated for children with pulmonary or distant metastases as long as these are iodine avid. With this single exception, the routine prescription of RAI for children with DTC has been debated. RAI may lower recurrence and cancer-related mortality.[68,76,89] However, low-risk adults appear not to benefit from RAI.[90,91] This issue has not been well studied in children, and the possible benefits must be weighed against the potential risks of RAI on a case-by-case basis. Unfortunately, all the data available to address this issue in children are retrospective and it is unclear why RAI was prescribed for only some patients. Similar recurrence rates are commonly reported at centers in which the vast majority of children received RAI and at centers where RAI was not prescribed.[92]

Recently, data arguing against the universal prescription of RAI in children have been published by the group at Mayo Clinic.[39] In that study, children previously treated with radiation (external beam radiation [XRT], RAI, and/or radium implants) developed a variety of second cancers and had increased all-cause mortality compared with the general population.[39] Whether this results from treatment or an underlying predisposition to developing malignancy is unknown. However, concern for second cancers (chiefly leukemia but also stomach, bladder, colon, salivary gland, and breast cancer) and the knowledge that risk of death from thyroid cancer is low has tempered the routine prescription of RAI,[93–99] particularly for young children without obvious iodine-avid residual or metastatic disease. However, not all data support an increased risk of second cancers and an analysis of 30,000 cases in the Surveillance Epidemiology and End Results (SEER) database found no increase in second malignancy for patients treated with RAI.[100]

If RAI is prescribed, the TSH should be above 30μIU/ml to facilitate cellular uptake of RAI.[18,27,80,101] In patients at high risk for disease, this is commonly induced by ≥14 days of thyroid hormone withdrawal.[102] Recombinant human TSH (rhTSH) can be used for remnant ablation in low-risk patients[103,104] and may result in a lower absorbed dose to the blood.[105] However, data regarding the use of rhTSH in children are limited.[106,107] Iorcansky et al. showed that the typical adult dose (0.9mg x two doses given 24 hours apart) of rhTSH appears to be safe and generates TSH levels in children that are similar to those induced by thyroid hormone withdrawal.[108] Luster et al. used rhTSH in 100 children, most of whom (92%) received the adult dose of rhTSH.[107] No adverse events were noted.

To facilitate RAI uptake, a low-iodine diet is generally prescribed for two weeks prior to therapy. In children who received intravenous contrast during pre-operative staging, it is advisable to wait two to three months or confirm normal 24-hour urinary iodine values before performing a diagnostic thyroid scan. There are no standardized doses of RAI for children. Some adjust ^{131}I dose according to weight or body surface area (BSA) and give a fraction (e.g. child's weight in kg/70kg) based on the typical adult dose used to treat similar disease

extent.[18,101,109] Others suggest that ^{131}I doses should be based on bodyweight alone (1.0–1.5mCi/kg).[110,111] A post-treatment thyroid scan, sometimes coupled with single-photon emmission CT (SPECT) imaging to identify the exact location of suspected metastatic disease, should be obtained five to eight days after ^{131}I treatment to identify potential disease that was not apparent on the diagnostic study.[27,37] Dosimetry may be used to limit whole body retention to <80mCi at 48 hours and blood/bone marrow exposure to <200cGy[27,112,113] and is most useful in selecting appropriate doses of RAI for small children, children with diffuse lung uptake or significant distant metastases, and those undergoing multiple RAI treatments. Although total body dosimetry calculates the absorbed dose to bone marrow and blood, the lung is actually the dose-limiting organ in 10% of cases.[114] Lesional dosimetry can be performed to select effective doses of RAI for children with substantial lung involvement or an otherwise large tumor burden at distant sites, such as bone.[115–118]

Special Cases in Children

One-third of PTCs in adults are now micro-PTCs (<1cm in diameter) that are detected by imaging for unrelated conditions or after thyroid surgery for another indication.[119] The natural history of these lesions is not well understood, but adults with micro-PTC are commonly managed as low-risk patients.[120,121] Unfortunately, the clinical course is not always indolent. Lymph-node metastases have been reported in 43% of micro-PTCs and recurrence rates may be similar for micro-PTC (16.7%) and conventional PTC (21.3%).[119] Micro-PTCs with lymph node metastasis have a higher recurrence rate (18%) than do micro-PTCs without nodal metastases (1%).[122,123] Micro-PTCs showing angiolymphatic invasion have the greatest risk for recurrence,[119] and even fatal cases of micro-PTC have been reported.[124] Unfortunately, very few data address micro-PTC in children and the natural history in this population is largely unknown. Based on the widely variable clinical course of micro-PTC, many clinicians perform a dedicated US of the contralateral lobe and cervical lymph nodes. Those without involvement of the contralateral lobe or lymph nodes are generally followed expectantly after lobectomy with or without thyroid hormone suppression therapy. Those with lymph node involvement are treated as if they had conventional PTC.

FTCs are more prone to hematogenous metastasis to lungs and bones than are PTCs. The diagnosis of FTC is based on the pathologic identification of capsular and/or vascular invasion. FTCs are sub-divided into those with only capsular invasion (minimally invasive FTC) and those with capsular and widespread vascular invasion. Vascular invasion increases the risk of recurrence and metastasis. Only a few data compare outcomes for FTC and PTC in children. Mortality and recurrence rates were similar but most patients were treated with total thyroidectomy and RAI.[12] Because angioinvasion and hematogenous spread can occur even without regional lymph node disease, most patients with invasive FTC are treated with total thyroidectomy and RAI.[125] Lymph nodes in more aggressive variants of FTC are managed similarly to PTC.[63]

The management of minimally invasive FTC is controversial, even in adults, and the optimal management for children is unknown.[126,127] Many surgeons perform lobectomy alone and consider this sufficient surgery with close follow-up and possible TSH suppression. In a study of 37 patients <45 years of age with minimally invasive FTC, 10-year disease-free survival was 92% and none of the patients developed distant metastases,[126] suggesting that minimally invasive FTC might be less aggressive in young patients.

Thyroid Hormone Suppression and Follow-up

TSH suppression is almost always prescribed for post-operative DTC in children, but the optimal level of suppression is debated.[128] Some have recommended initial suppression of TSH to <0.1μIU/ml followed by relaxation of TSH to 0.5μIU/ml, once children enter remission.[110] Recent American Thyroid Association (ATA) guidelines are also followed by many practitioners.[27] Although unstudied, potential risks of long-term TSH suppression (such as negative effects on growth, cognition, bone mineralization, and the heart) are likely to be minimal in the otherwise-healthy pediatric population.

Follow-up for potential recurrence should be lifelong. Although some series suggest the majority of recurrences in young patients occur during the first decade,[12] other series have equal recurrence rates in the first and second decades,[129] and all series show some recurrence after 20–30 years.[39] Most data in children are retrospective and used diagnostic RAI scans as the 'gold standard' for detection of disease. Unfortunately, RAI scans are not the most sensitive test for detecting disease. In adults, an assessment for persistent disease usually entails measurement of a TSH-suppressed Tg, neck US, and TSH-stimulated Tg values (± diagnostic RAI scan) in patients who were previously treated with ^{131}I.[27] Patients with a negative stimulated-Tg and negative US are considered to have "no evidence of disease" and thyroid hormone suppressive therapy as well as follow-up interval are relaxed. In adults, an undetectable serum Tg is generally associated with remission[83,130,131] and Tg levels >10ng/ml (off thyroid hormone) indicate residual disease.[132] Most patients with an rhTSH-stimulated Tg value of >2ng/ml will have disease identified within five years, although some patients with a positive test may have resolution of their minimally elevated stimulated Tg.[133] Recent ATA guidelines suggest that patients with a stimulated Tg >5–10ng/ml could be empirically treated with ^{131}I, as such treatment has led to a decline in Tg in some studies.[27,134,135] A significant increase in serial Tg levels indicates disease that might achieve clinical importance and should be treated.[136,137]

It is not yet clear whether the same Tg levels have a similar prognostic value for children. Children generally have well-differentiated disease and most of the survival data for children are based on undetectable RAI diagnostic scans.[138] We do not know the serum Tg levels of these children and we do not know how aggressive we should be in treating disease detected solely by abnormal serum Tg levels. Some clinicians opt to treat young patients until there is a negative ^{131}I scan.[68] This 'treat-to-negative-scan' approach is commonly used but does not take full advantage of serum Tg and thyroid US, especially since US has detected disease in 23% of children when the Tg and scan were negative.[139] It should also be noted that Tg levels may slowly decline in children previously treated with RAI and that undetectable Tg levels in children with pulmonary metastases may not be a tenable goal for all cases.[7,67,97,140] Some children with pulmonary metastases develop stable but persistent disease after ^{131}I therapy.[141] We do not know whether

they benefit from additional therapy but in many cases the extent of disease does not appear to change during short-term follow-up.

Unfortunately, thyroglobulin antibodies (TgAb) are detected in almost 25% of patients with thyroid cancer and interfere with serum Tg assays, rendering the Tg level uninterpretable.[142] For these patients, a decline in TgAb indicates declining disease burden but it takes a median of three years to clear TgAb levels after cure of DTC.[143] A significant rise in TgAbs suggests disease progression and warrants further evaluation. Once the child becomes TgAb-negative, he or she can be followed using routine measurement of the suppressed Tg, and at least one TSH-stimulated Tg can be assessed to determine serological evidence of disease, assuming the suppressed Tg is negative.

Treatment of Residual/Recurrent Cervical Disease

Recurrent PTC develops in 30% of children and most commonly occurs in cervical lymph nodes.[39] In most cases, cervical disease can be effectively treated with repeat surgery.[144] Surgical complications are more common with re-exploration of the neck but should be minimized when the operation is performed by a high-volume surgeon. Although many patients may be cured after repeat neck surgery, not everyone will develop an undetectable Tg level.[144] Nevertheless, if cervical recurrence can be surgically removed, this is preferred over RAI, which is not particularly effective for macroscopic lymph node disease (see *Figure 2*).

Treatment of Children with Pulmonary Metastases

Up to 20% of children with DTC may have pulmonary metastases at diagnosis.[8,12,15,33,34,36–39] RAI therapy is indicated for patients with iodine-avid pulmonary metastases (see *Figure 2*), but care must be taken to select a dose that will adequately treat metastases yet not result in adverse effects such as pulmonary fibrosis. Care must also be taken not to treat the child too frequently, as death from TNM stage II DTC is unexpected during childhood and also because the response to RAI may continue beyond one year or more. Empiric dosing may not be the best approach for children with diffuse uptake on diagnostic RAI scan. Treatment dose should be determined by the extent of ^{131}I uptake, patient age, and body size and is complemented by dosimetry in some cases. Prior use of ^{131}I is also important, as uptake typically declines after each successive dose.[113] Partly based on the concerns for second malignancy in children treated with RAI, multiple high doses of ^{131}I should only be given to children who are likely to benefit from therapy.[110] Durante et al. used ^{131}I to treat 37 patients under 19 years of age with distant metastases.[145] Negative RAI scans were attained in 79%, 100% reached 10-year survival, 87% reached 20-year survival, and the relative mortality risk was 1.0. They recommended that young patients with pulmonary metastases should be treated until disappearance of ^{131}I uptake or until a cumulative dose of 22GBq (600mCi). However, it is not known how this group would have fared with less-aggressive use of RAI. Powers et al. made similar observations for children with either primary or recurrent thyroid cancer.[146–148] For patients with persistent disease who have already received more than one treatment of high-dose RAI, the decision to treat should be individualized.[145]

New Approaches for Children with Advanced Differentiated Thyroid Cancer

Very rarely, children with DTC may develop progressive life-threatening disease that is not amenable to further surgery and that no longer concentrates or responds to RAI. In such cases, systemic therapy may be considered. Although clinical trials are preferred in adults,[27,28] such trials are typically not available for children with the exception of possible phase 1 studies. Traditional cytotoxic chemotherapy has had limited success in the treatment of advanced thyroid cancer, and toxicities are considerable. Doxorubicin remains the only US Food and Drug Administration (FDA)-approved medication for this indication and has been used either as a single agent or in combination with other drugs such as cisplatin or interferon alpha-2b.[10,27,149,150]

The advent of targeted therapies in the form of oral small-molecule tyrosine kinase inhibitors has revolutionized the management of RAI-refractory DTC. A variety of agents now show promise in the treatment of this once-orphan disease.[10,151,152] To date, sorafenib has been the best studied and has shown benefit in treatment-refractory thyroid cancer in phase II clinical trials and a retrospective off-label study.[153–156] In subjects with differentiated, poorly differentiated and anaplastic thyroid carcinomas, the best response achieved with the use of sorafenib was a partial response in 11–25% and stable disease in 34–63%, giving an overall clinical benefit (partial response plus stable disease) in 59–77% of patients treated. There were no complete responses and up to 23% of subjects, chiefly those with poorly differentiated or frankly anaplastictumors, had progressive disease while taking sorafenib. It also appears that sorafenib may work more effectively for lung metastases compared with lymph node and bony metastatic disease.[155,156] The only published experience using sorafenib to treat pediatric thyroid cancer has been a single case report.[157] In that case, a 14-year-old girl with iodine non-avid progressive pulmonary metastatic disease demonstrated a partial response to treatment with sorafenib. Other oral tyrosine kinase inhibitors (TKIs) that are showing promise in the treatment of advanced DTC in adults include axitinib, motesanib, pazopanib, and sunitinib.[151,158–161,162] Although much more study is required regarding the use of these agents in children, particularly as it relates to dosing and toxicities, the use of an oral tyrosine kinase inhibitor, particularly sorafenib, may be contemplated in the very rare situation where a child warrants systemic approaches to treatment. ■

Steven G Waguespack, MD, is an Associate Professor of Internal Medicine and Pediatrics at the University of Texas MD Anderson Cancer Center in Houston, where he is also Deputy Chairman of the Department of Endocrine Neoplasia and Hormonal Disorders. Recognized as one of 'America's Top Doctors for Cancer' in endocrinology, his major clinical and research interests are thyroid cancer, pituitary tumors, and genetic syndromes of endocrine neoplasia.

Gary L Francis, MD, PhD, is a Professor of Pediatrics and Chief of the Division of Pediatric Endocrinology and Metabolism at Virginia Commonwealth University in Richmond. He is a member of the American Thyroid Association (ATA), The Endocrine Society, the Pediatric Endocrine Society, and the Society for Pediatric Research. He served on the ATA Guidelines Committee for Medullary Thyroid Cancer and is Chair of the ATA Guidelines Committee for Childhood Thyroid Cancer.

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