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PEDIATRICS (L AVERILL, SECTION EDITOR)

Pediatric Thyroid Cancer: Imaging and Therapy Update

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Abstract
Purpose of Review In 2015, the management of thyroid cancer in the pediatric population was overhauled with the publication of the inaugural American Thyroid Association guidelines for children with thyroid nodules and differentiated thyroid cancer. In this article, we review these guidelines along with recent relevant literature regarding pediatric thyroid cancer, focusing on salient issues relating to imaging and radionuclide therapy.
Recent Findings The American College of Radiology recently published its inaugural recommendations for thyroid nodule imaging (TI-RADS). Regarding radionuclide therapy, recent literature has focused on ways to reduce long-term sequelae while providing optimal initial treatment.
Summary While a more standardized approach is being taken towards initial imaging of thyroid nodules and cancer, the opposite approach to treatment and surveillance is developing, with a focus on personalization.

Keywords Pediatric thyroid cancer · Children · Differentiated thyroid cancer · Radionuclide therapy

Introduction

Thyroid cancer is the most common pediatric endocrine malignancy in the United States. The most recent surveillance data estimate a thyroid cancer rate of 0.59 per 100,000 patients less than 19 years of age with a steadily rising incidence, increasing at a rate of roughly 1% per year [1]. Differentiated thyroid cancer (DTC), which consists of papillary and follicular subtypes and their respective variants, makes up the vast majority of both pediatric and adult thyroid cancers. Prior to 2015, DTC in children was managed similar to adults based on earlier guidelines from the American Thyroid Association (ATA). The practice of treating thyroid cancer patients similarly across all age groups has come under scrutiny with recent data highlighting considerable differences in the disease process, management, and long-term outcome in children versus adults. Children present with more extensive disease yet have more favorable outcomes. Children also have a longer posttreatment life expectancy and thus more time for recurrence or potential treatment effects to manifest. Recognizing the unique nature of thyroid cancer in children, the ATA adopted its first consensus guidelines for the management of thyroid nodules and DTC in children in 2015 [2•]. Of the 60 individual recommendations published, only 11 are based on the highest quality evidence. The guidelines highlight the need for more robust data to further elucidate several unresolved questions for this unique patient population. This review will focus on the role of imaging and radionuclide therapy in pediatric

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thyroid cancer, highlighting salient points from the inaugural pediatric ATA guidelines and from recent relevant studies.

Overview of Thyroid Cancer in Children

There are four primary subtypes of thyroid cancer: papillary, follicular, medullary, and anaplastic. Papillary and follicular subtypes comprise most of the cases in both adults and children, and their variants are considered well differentiated because they largely maintain the cellular make-up and function of the predecessor thyroid cell. These cells are able to use iodine to produce thyroid hormone, which makes them iodine-avid, a property that is key to radionuclide imaging and therapy.

Thyroid cancer typically presents as an asymptomatic nodule. While thyroid nodules are very common in adults, young children rarely develop thyroid nodules and the risk of malignancy in children with nodules is much higher than in adults [1, 3]. Despite the higher risk of malignancy in children with thyroid nodules, prognosis is excellent for DTC in both adults and children. Even with distant metastasis, children have 20-year overall survival rates of greater than 95% [4]. The low overall prevalence of nodules in children, coupled with excellent prognosis in pediatric DTC, precludes screening of the general population.

There are particular subsets of patients who have been identified as higher risk for developing thyroid cancer. These include children with a history of radiation exposure to the thyroid and children with family history or syndromes that increase their risk of developing thyroid cancer. Even for the higher risk group, diagnostic screening is not currently recommended. The latest ATA guidelines recommend annual physical examination to evaluate for thyroid nodules, with imaging studies pursued only in the presence of palpable nodules. There is no evidence that detection and treatment of subclinical disease affects outcome.

Along similar lines, there has been a recent shift to reclassifying certain subtypes of DTC to decrease perceived overtreatment. A rising incidence in thyroid cancer has been noted without a corresponding increase in already excellent outcomes [1]. This lead time bias is likely due to increased use of highly sensitive diagnostic equipment that has resulted in the identification and treatment of early subclinical nodules with no potential to cause harm. Therefore, the ATA has recently reclassified one of the most benign forms of papillary thyroid cancer from encapsulated follicular variant papillary thyroid carcinoma without invasion to noninvasive follicular thyroid neoplasm with papillary-like nuclear features to decrease overtreatment of papillary thyroid cancer [5]. Pediatric thyroid cancer is not immune to the evolving sentiment of reducing overdiagnosis and overtreatment. However, it is important to remember that even "low-risk" forms of pediatric thyroid cancer demonstrate much higher rates of local and distant metastasis than adults and there are no reliable data in children to confirm the safety of more conservative care plans. While the histology of pediatric thyroid cancer is very similar in children, it is not simply a miniature version of the adult disease.

Treatment and Staging of Pediatric Thyroid Cancer

The first line treatment for DTC in children is surgical resection. The ATA guidelines recommend total thyroidectomy for most children, and also that care should be provided at high volume centers by surgeons involved in at least 30 cervical endocrine procedures annually (ATA recommendations 11, 14A). However, the need for and appropriate dosing of post-thyroidectomy adjuvant therapy is not as well defined. Children who are diagnosed and treated for DTC have longer life expectancies and thus the risks of recurrent or persistent disease from presumed undertreatment is greater [6]. Conversely, due to excellent prognosis, long-term complications, such as secondary cancers from aggressive initial adjuvant therapy, also have a longer time span and thus an increased likelihood to manifest [7–9].

Recognizing the need to evaluate risks and benefits differently in children, the ATA has proposed a new tailored classification system. The new classification system is based on the tumor, node, and metastasis (TNM) staging system, and it classifies pediatric cases into low, intermediate, or high-risk based on risk of persistent cervical disease and/or distant metastasis after thyroidectomy (Table 1). For low-risk patients, postoperative staging involves evaluation of serum thyroglobulin and thyroglobulin antibody levels to assess for the presence of any residual thyroid tissue. Intermediate- and high-risk cases require both serum thyroglobulin level and radionuclide whole-body iodine scans for optimal evaluation. This is a significant departure from prior guidelines (pre-2015) based on adult patients, where all post-thyroidectomy patients were subject to adjuvant radioiodine therapy. It is important to note that while the guidelines do provide guidance for most conservative care options, data regarding the effectiveness of these approaches are severely lacking. Identification of the optimal patient-specific balance of aggressiveness of surgery and radionuclide therapy remains a key challenge.

Table 1 ATA pediatric risk classification, staging, and surveillance

ATA pediatric risk level	Definition	Initial postoperative staging	Surveillance
Low	Disease confined to the thyroid Patients with microscopic metastasis to central nodes may be included	Thyroglobulin level	US at 6 months postop then annually for 5 years Thyroglobulin while on thyroid hormone every 3–6 months for 2 years, then annually
Intermediate	Neck, metastasis to level VI Minimal metastasis to unilateral level I, II, III, IV, V, or VII	TSH-stimulated thyroglobulin + Dx I-123 scan for most	US at 6 months postop, then every 6–12 months for 5 years, then less frequently Thyroglobulin on thyroid hormone every 3–6 months for 3 years then annually TSH-stimulated thyroglobulin + I-123 scan in patients treated with I-131
High	Extensive metastasis to unilateral level I, II, III, IV, V, or VII Presence of distant metastasis	TSH-stimulated thyroglobulin + Dx I-123 scan for all	Same as for intermediate

Caption for Table 1: Adapted from Francis et al. 2015 [2•]

ATA American Thyroid Association; *US* ultrasound; *TSH* thyroid stimulating hormone

Imaging Thyroid Cancer in Children

Ultrasound

Ultrasonography is the most important imaging modality for the evaluation of thyroid nodules in both adults and children. It is widely available, relatively affordable, does not produce ionizing radiation, and provides exquisite anatomical detail. An additional advantage of ultrasound imaging is that it allows real-time image-guided fine needle aspiration (FNA) or biopsy of suspicious nodules. The ATA guidelines recommend the use of ultrasound characteristics rather than size alone in identifying nodules that require FNA and to perform all FNA for children under ultrasound guidance.

Key limitations of ultrasound evaluation are a reliance on the skillset of the operator and variability in interpretation between observers. Considering the importance of initial staging to the overall outcome and risk of recurrent or persistent disease, it is critical that optimal imaging is obtained prior to treatment. In an attempt to standardize the approach to preoperative ultrasound evaluation, the ATA put forth a statement detailing requirements for optimal preoperative imaging evaluation [10]. The availability of multifocal high-frequency linear array transducers with the ability to assess for color and power Doppler are essential. Patient positioning and scanning technique including the need to systematically assess the primary lesion as well as the central, lateral, and posterior lymph node compartments are critical. The size, location, margin, multifocality, and presence of local invasion must be assessed as these can significantly influence the surgical approach and risk of potential complications.

Classification of malignant thyroid nodules and lymph nodes can differ from one individual or institution to another and attempts have been made to standardize this process [11, 12]. The American College of Radiology's recently-released white paper called Thyroid Imaging, Reporting and Data System (TI-RADS), modeled after their successful BIRADS® system used for breast imaging, allows systematic evaluation, and the use of a standardized lexicon for thyroid nodules [13, 14•]. Recommended standardized terminology and reporting for thyroid nodules now includes a description of composition, echogenicity, shape, size, margins, and the presence or absence of echogenic foci.

With regard to nodule composition, solid nodules have a higher risk of malignancy compared with purely cystic or spongiform nodules. Unpublished data from our institution by Gannon et al. found the prevalence of pediatric thyroid cancer to be highest for solid/mostly solid thyroid nodules. Hypoechoic nodules have a high sensitivity but not specificity for malignancy. Taller-than-wide nodule shape is also considered a malignant feature. Irregular and lobulated margins are considered more suspicious for malignancy compared with smooth or ill-defined margins. The presence of extracapsular extension and punctate echogenic foci has a high specificity for malignancy. Punctate echogenic foci are particularly important to look for in children who present with diffusely enlarged thyroids without focal nodularity because these usually present with microcalcifications. These features (composition, echogenicity, shape, margin, and echogenic foci) are assigned points and accumulated to determine a TI-RADS level of 1–5. TI-RADS 3 and above then may require FNA or follow-up imaging based on a newly stratified size criteria [14•].

Notably, several studies find little correlation between nodule size and malignancy [15]. This is especially important when evaluating nodules in children who can harbor malignancy in small nodules [16, 17]. The ATA guidelines for children with thyroid nodules and DTC recommend the use of ultrasound characteristics and clinical context rather than size in identifying nodules that warrant further investigation by FNA. Furthermore, color, flow, and power Doppler assessment were not included in TI-RADS because there is inconsistent literature about its value in distinguishing benign from malignant disease [18, 19]. In our opinion, evaluation of nodule vascularity should be an integral part of the assessment of all thyroid nodules in children.

TI-RADS currently does not specify assessment of lymph nodes; however, the ATA has provided guidance for preoperative assessment of regional lymph nodes. The ATA criteria for suspicion of malignant lymph nodes includes size of more than 1 cm in maximal diameter, rounded shape (ratio of long-to-short axis less than 2), and the presence of punctate calcifications and peripheral vascularity. Of these features, the most specific marker of malignancy is the presence of punctate calcifications and the most sensitive is the presence of peripheral hypervascularity [10]. Of note, unlike thyroid nodules where cystic changes tend to be benign, in lymph nodes, cystic characteristics are associated with a higher risk of malignancy as demonstrated by Leboulleux et al. [20].

Cross-Sectional Imaging

The ATA guidelines do not recommend the routine use of other cross-sectional imaging in evaluating thyroid cancer, except in select cases. In patients with large or fixed thyroid masses, vocal cord paralysis, or bulky metastatic lymphadenopathy, contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) are recommended for optimal presurgical planning. Children are known to present with more advanced disease; therefore, a high suspicion for metastatic disease should be maintained. In cases where cross-sectional imaging is deemed necessary, CT is the preferred adjunctive imaging modality. Although CT involves exposure to ionizing radiation, it is widely available, has a much faster acquisition time, and is less prone to artifacts such as motion or air in the aerodigestive tract compared with MRI. However, the use of iodinated contrast will affect timing for potential downstream radionuclide imaging or therapy. Radioactive iodine administration generally requires a 6- to 8-week lag time after iodinated contrast for optimal thyroid uptake.

Scintigraphy

Brief Review of Iodine Tracers

Thyroid scintigraphy is the use of radionuclides to directly assess function of the thyroid and is complementary to ultrasound examination. It plays an important and continuously evolving role in the staging of DTC.

Iodine-123 (I-123) and Iodine-131 (I-131) are the most common radioiodine tracers used for thyroid scintigraphy. I-123 is an ideal tracer because of its relatively short half-life, low energy gamma emission, and low relative radiation dose; however, it is relatively expensive. I-131 produces gamma rays used for imaging and beta rays used for treatments. Used since 1946, it is one of the oldest nuclear medicine tracers. It is more widely available and less expensive but results in a higher radiation dose compared with I-123. Imaging quality for diagnostic I-131 is generally of lower resolution compared with I-123 because of lower administered dose.

Iodine-124 (I-124) is not yet widely used but potentially may become an important addition to the thyroid scintigraphy armamentarium. Unlike the other tracers mentioned, I-124 is a positron emitter and thus allows for positron emission tomography (PET) imaging. One potential role for I-124 is to prospectively determine which patients will benefit from adjuvant radioiodine I-131 therapy, and another for the determination of more individualized dosimetry calculations. Although a recent study demonstrated excellent correlation between pretherapeutic I-124 PET scans and subsequent post I-131 therapy uptake [21], a larger study found an unacceptably high false negative rate [22]. The role of I-124 in the evaluation of thyroid cancer patients is still undetermined.

Scintigraphy in Thyroid Cancer in Children

The latest ATA guidelines do not recommend routine use of radionuclide imaging for screening or preoperative assessment of thyroid cancer in adults or children. In fact, the only current indication for preoperative scintigraphy in pediatrics is for patients who present with a suppressed thyroid stimulating hormone (TSH) level and suspicion for autonomously functioning nodule. First line treatment in these cases is surgical resection rather than radioiodine ablation. Of importance, there is a high-risk of incidental DTC found in autonomously functioning nodules in children compared with adults [23]. Children with increased genetic risk for thyroid cancer also warrant careful attention.

For patients diagnosed with DTC, the ATA pediatric risk stratification is applied. Children who are considered low-risk do not undergo any pre- or postoperative

radionuclide imaging unless there is evidence of abnormal postsurgical serum markers. For cases classified as intermediate- or high-risk, additional postoperative imaging is warranted to assess disease extent and potential need for adjuvant therapy. Within 12 weeks of surgery, most intermediate-risk and all high-risk patients should undergo TSH-stimulated thyroglobulin level combined with Iodine-123 scan (ATA recommendation 15B). The postoperative staging classification then serves as a benchmark to determine long-term surveillance strategy.

Evaluation of serum thyroglobulin levels currently serves as a key gatekeeper in determining the necessity for radionuclide therapy. Thyroglobulin is a glycoprotein that is released by normal or cancerous thyroid cells, and rising levels serve as a marker for the presence of DTC cells. Although a basal level of thyroglobulin is released into the blood stream, it also can be stimulated by elevated TSH levels, ideally achieved through suppression of thyroid hormone (levothyroxine–LT4). LT4 suppression interferes with feedback mechanism via the pituitary gland, leading to symptoms of hypothyroidism in post-thyroidectomy patients. A low-iodine diet is also instituted concurrently to further increase the iodine avidity of the thyroid cells. The current recommendation is to withdraw medication and institute a low-iodine diet for 2 weeks, with the goal of achieving TSH levels of at least 30 mIU/L. For select children who are unable to achieve adequate TSH levels or are intolerant to hypothyroid symptoms, intramuscular administration of recombinant TSH (Thyrogen®, Genzyme Corp., Cambridge, MA) appears to be a safe alternative [24•].

Similar to adults, a post-thyroidectomy stimulated thyroglobulin level of more than 2 ng/mL is suggestive of persistent disease and prompts investigation with either ultrasound or radionuclide imaging. It is recommended that residual mass disease be treated with surgical resection, whereas biochemical persistence in the absence of a definite mass is optimally treated with radionuclide therapy. The guidelines allow room for discretion to consider surgery, radioactive iodine, or observation for thyroglobulin levels of 2–10 ng/mL. For thyroglobulin levels above 10 ng/mL, the consensus approach to treatment is radioiodine ablation and/or surgery once localized.

Measurement of thyroglobulin levels is often confounded by anti-thyroglobulin antibodies, which interfere with the most commonly available assays (IMA/LCMS) and make the thyroglobulin tumor marker unreliable [25]. When anti-thyroglobulin antibodies cause interference, it is possible to measure the thyroglobulin using a radioimmunoassay technique or to trend the anti-thyroglobulin antibody titers (ATA recommendation 23E), but larger prospective studies are needed to confirm the optimal plan of care.

Radionuclide Therapy

It is important to individualize the approach to therapy, including the need for detailed discussions of the benefits and risks of radioiodine therapy with patients and/or caregivers. Education and detailed discussion of radiation safety precautions are required for all patients treated in an inpatient or outpatient setting. Written informed consent is mandatory. All girls of reproductive age should obtain serum pregnancy tests, typically within 5 days of therapy. Discussion also should include the need for adequate hydration and regular bodily excretions along with instructions for how to manage radioactive waste. The use of sour candy or lemon drops, starting at least 24 h following dose administration to reduce activity of the salivary glands, commonly is recommended [26]. Following administration of I-131, all patients should receive a posttreatment whole-body scan, ideally with the addition of single-photon emission CT, to localize any focal uptake in 4–7 days (ATA recommendation 21).

The risks and efficacy associated with radionuclide therapy are proportionate to the dose given. Short-term risks including neck pain, nausea, vomiting, gastritis, and acute sialadenitis based upon the normal distribution of iodine in the body should be discussed. Longer-term risks include permanent salivary gland dysfunction and potential effects on fertility, bone marrow suppression, potential genetic defects in offspring, and disease recurrence. The development of second primary cancers in organs with increased I-131 uptake including leukemia, salivary gland, and gastrointestinal tract malignancies are reported as well. Given the higher risk of distant metastasis in children, particularly, the relative increased risk of lung metastasis, the potential to develop pulmonary fibrosis must be discussed. Also, retrospective studies link early exposure to iodine therapy to an increase in all-cause mortality [7, 8, 27].

On the other hand, inadequate treatment of the initial cancer is linked to recurrent or persistent disease [28]. Subsequent surgeries for persistent or recurrent disease are much more difficult and prone to complications [29]. Similarly, thyroid cancer cells become less iodine-avid following initial radioiodine therapy, making repeat radioiodine therapy more difficult, and requiring much higher doses with an associated increase in potential short- and long-term side effects [30]. For this reason, some advocate for a more aggressive initial approach to treatment. A recent study presented at the Society of Pediatric Radiology annual meeting in 2013 [31] evaluates the recurrence rate of thyroid cancer in pediatric patients receiving low- versus high-dose radioiodine. In this study, the 27 children included demonstrated an overall recurrence rate of 48% (13/27), with a higher rate of recurrence

in patients who received less than 100 mCi dose (69%) versus those who received a dose higher than 100 mCi (21%). This small study implies that there is an association between lower administered activity and lower efficacy in pediatric patients with DTC.

A critical limitation in the current data regarding efficacy is that historical data may be biased to include children with more aggressive disease where there is lack of clarity between recurrence and persistence. Additionally, there appears to be a latent effect from radionuclide therapy in children with continued fall in thyroglobulin levels years after radionuclide treatment in metastatic disease [32]. Considering that children treated for thyroid cancer are very unlikely to die due to their disease, close attention to long-term side effects of more aggressive treatment is important. In a study of children treated for thyroid cancer and followed for a median of 29 years, the rate of death was higher than normal for children treated for thyroid cancer, but only two (9%) of the deaths were due to thyroid cancer, whereas 15 (68%) were due to other malignancies [4]. It is very difficult to disentangle the increased risk of malignancies due to a genetic predisposition to cancer from an increased risk of cancer due to radionuclide therapy.

Given these competing forces, it is no surprise that once a decision is made to proceed with radioiodine therapy, dose selection for radioiodine therapy is a debated issue [30]. Currently, there are no clear guidelines on dose selection. Most centers use empiric treatment based on the disease staging and body weight or body surface area used in adults and adapted for the pediatric population. Others use more detailed dosimetry calculation models based upon the results of a diagnostic scan. The traditional dosimetry models rely on the as high as safely administrable (AHASA) mantra for maximal tolerated activity with the goal of limiting toxicity (to bone marrow, blood, and lung) while maximizing lesion uptake [33–35]. The introduction of new tracers with improved resolution, such as I-124 PET/CT, have led to more sophisticated personalized dosimetry models with better lesion-specific calculations [36]. The ATA guidelines are unable to recommend one method over another due to lack of available data; however, it is recommended that the treatment be provided in centers with experience treating children with thyroid cancer.

Current Challenges/Future Directions

Differentiated thyroid cancer in the pediatric population has excellent prognosis, yet longer-term studies demonstrate increased risk of recurrence, secondary malignancies, and all-cause mortality. Although there has been a general sentiment towards reducing overdiagnosis and overtreatment of thyroid cancer, children occupy a unique group given their more aggressive initial presentations and longer expected life spans. The 2015 ATA guidelines and risk stratification system represent an important first step in standardizing initial management of DTC in children, but notably most of the recommendations are based on expert opinion and must be validated by future prospective studies. Because thyroid cancer is much less common in children than adults, it is difficult for any single center to adequately study the most appropriate methods for treatment. Significant advances in the field likely will require multicenter collaborative clinical studies to determine the optimal strategy for balancing the risks of the disease with the immediate and long-term risks of treatment.

From the perspective of the radiologist, there are important gaps in identification of ultrasound features of thyroid nodules that are associated with a very low-risk of thyroid cancer, such that biopsy could be avoided. Available data are heavily biased to include children at above average risk of thyroid cancer, either by virtue, referral, or ascertainment (children with features presumed to be "low-risk" are lost to follow-up and so it is impossible to confirm that the lesion was truly benign). Therefore, the prevalence of thyroid cancer in children with thyroid nodules is very likely overestimated for all children. Further attention to molecular markers in biopsy specimens that are predictive of thyroid cancer would allow for greater personalization of care before the patient is considered for surgery.

Similarly, it is important to establish the impact of preoperative diagnostics, surgical technique, tumor stage, and iodine avidity. Given concerns for negative long-term consequences of therapies that are either too aggressive or not aggressive enough, prospective data on the outcomes of therapy will allow for much greater confidence in personalized approaches to care.

Conclusions

Management of pediatric thyroid nodules and DTC continue to evolve, and imaging and radionuclide therapy continue to play a central role in this management as part of a multidisciplinary approach. Treatment of pediatric DTC represents a unique challenge in thyroid cancer because survival rates are already excellent; the emphasis of optimizing care is on optimal quality of life for patients by reducing need for additional surgery and radionuclide therapies. Recent studies highlight the need for continued standardization of imaging technique and reporting as critical components of establishing the most effective operative plan. Similarly, the role of radionuclide therapy is shifting from "one size fits most" to a more personalized approach that is considerate of the individual needs of the

patient. These are important advancements in the field, and there remains much to be done.

Compliance with Ethics Guidelines

Conflict of Interest Nii Koney, Soran Mahmood, Anthony Gannon, Mark S. Finkelstein, and Tejal Mody each declare no potential conflicts of interest.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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