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# Management of Differentiated Thyroid Cancer in Children: Focus on the American Thyroid Association Pediatric Guidelines

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**First introduced in 1946, radioactive iodine (I-131) produces short-range beta radiation with a half-life of 8 days. The physical properties of I-131 combined with the high degree of uptake in the differentiated thyroid cancers (DTCs) led to the use of I-131 as a therapeutic agent for DTC in adults. There are two indications for the potential use of I-131 therapy in pediatric thyroid disorders: nonsurgical treatment of hyperthyroidism owing to Graves' disease and the treatment of children with intermediate- and high-risk DTC. However, children are not just miniature adults. Not only are children and the pediatric thyroid gland more sensitive to radiation than adults but also the biologic behavior of DTC differs between children and adults as well. As opposed to adults, children with DTC typically present with advanced disease at diagnosis; yet, they respond rapidly to therapy and have an excellent prognosis that is significantly better than that in adult counterparts with advanced disease. Unfortunately, there are also higher rates of local and distant disease recurrence in children with DTC compared with adults, mandating lifelong surveillance. Further, children have a longer life expectancy during which the adverse effects of I-131 therapy may become manifest. Recognizing the differences between adults and children with DTC, the American Thyroid Association commissioned a task force of experts who developed and recently published a guideline to address the unique issues related to the management of thyroid nodules and DTC in children. This article reviews the epidemiology, diagnosis, staging, treatment, therapy-related effects, and suggestions for surveillance in children with DTC, focusing not only on the differences between adults and children with this disease but also on the latest recommendations from the inaugural pediatric management guidelines of the American Thyroid Association.**
**Semin Nucl Med 46:147-164** 

## Introduction

Guidelines for the evaluation, treatment, and follow-up of thyroid nodules and differentiated thyroid cancer (DTC) in adults have been published by various groups.[1-3] Traditionally, the evaluation, management, and follow-up of children with thyroid cancers mirrored that of the adult guidelines. Recognizing the differences in physiology, clinical presentation, and long-term outcomes of children as compared with adults regarding DTC, the American Thyroid Association (ATA) commissioned a multidisciplinary task force consisting of an international group of endocrinologists, surgeons, nuclear medicine specialists, radiologists, as well as a molecular geneticist, to develop separate guidelines for the management of thyroid nodules and DTC in children. Acknowledging the paucity of randomized, double-blind controlled clinical trials in children with DTC as well as the relatively short length of follow-up in most reported retrospective series, this task force produced 61 graded recommendations in 34 key areas of evaluation and treatment based on available scientific evidence

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http://dx.doi.org/10.1053/j.semnuclmed.2015.10.006
0001-2998/

and expert opinion in their document titled "Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer."[4,5] As the pathophysiology, epidemiology, clinical presentation, approach to diagnosis, treatment, and surveillance of children with DTC are discussed in this article, key recommendations from these guidelines would be incorporated into the review.

## DTC: An Overview

There are four histologic types of thyroid carcinoma: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) including Hurthle cell, medullary thyroid carcinoma (MTC), and anaplastic. Papillary and follicular carcinomas, commonly referred to as the well-differentiated thyroid carcinomas (DTCs), arise from follicular cells, the cells that are involved in thyroid hormone production. The well-differentiated thyroid carcinomas are typically iodine avid.

PTC is the most common type of thyroid carcinoma in both adults and children. In adults, the papillary subtype comprises 80% of all thyroid cancers.[6] Mean age of presentation occurs in the third decade of life; peak incidence occurs at age 40 years and beyond, with an earlier peak in women than in men. Cervical lymph node metastases occur in 30%-40%; distant metastases are present in 2%-14%. Multifocal disease is common with incidences ranging from 30%-85% depending on whether routine or thin histologic sectioning has been performed. Bilateral disease is present in 33%. Overall survival in adults with PTC is 90% at 20 years.

Medullary carcinomas arise in parafollicular or C-cells of the thyroid that manufacture calcitonin. As these cancers arise in cells that are not involved in thyroid hormone production, MTCs are not iodine avid and consequently, radioiodine does not play a role in either the diagnosis or the management of these patients.[6,7]

Anaplastic thyroid carcinomas, comprising 4%-10% of thyroid cancers, are highly aggressive tumor types associated with a poor prognosis.[6] These poorly differentiated carcinomas are rarely iodine avid; thus, aggressive chemotherapy and external-beam radiation, and not radioiodine usage comprise the treatment regimen for patients with these tumors.

Thyroid cancer occurs in all age groups. An increase in overall incidence rates of DTC has been reported in both adults and children in the United States.[8] The incidence of thyroid cancer increases with age. Thyroid cancer is rare in those less than 10 years of age with an annual incidence of less than one case per million. Thyroid cancer is more common in older children and adolescents with incidence rates of 3.5 cases per million per year in those between the ages of 10 and 14 years compared with 15.4 cases per million per year in those aged 15-19 years. In those aged 25-29 years, the incidence of thyroid cancer is 60.8 cases per million per year.[9-11]

In addition to age-related differences in incidence, there are differences in the frequency of the pathologic types of thyroid cancer between children and adults. PTC is more common in children, accounting for 95% of cases of thyroid cancer, as opposed to adults, where it comprises approximately 80% of the subtypes. FTCs occur in approximately 5% in both adults and children. Anaplastic thyroid carcinoma and Hurthle cell pathologies are rare in children.[12,13]

# DTC in Children

Carcinomas comprise approximately 9.2% of cancers in children less than 20 years of age; the most common pediatric carcinomas (35%) are thyroid carcinomas.[9-11] Thyroid cancer accounts for less than 1% of cancers in those younger than 10 years, 3.6 % of cancers in those aged 10-14 years, and 7.8% of cancers in those aged 15-19 years. As in adults, DTCs are the most commonly encountered thyroid cancers, representing more than 90% of pediatric thyroid carcinomas. PTC accounts for 95% and FTC represents roughly 5% of the malignancies arising from follicular cells.[12,13] These pediatric cancers are often iodine avid and highly sensitive to thyrotropin-stimulating hormone (TSH).

Unlike adults, children typically present with advanced disease at diagnosis. Extensive regional nodal involvement occurs in 60%-80% of pediatric patients with DTC as compared with 30%-40% of adults with DTC.[14-23] There is a higher incidence of distant metastases in children as opposed to adults as well. Although bone metastases are rare ($<5\%$), lung metastases are present at diagnosis in approximately 10%-20% of children with DTC. Children have higher rates of local and distant recurrences than adults. Despite this, the prognosis in children with DTC is excellent, with a 10-year mortality of $<10\%$ and overall survival of 98%; at 20 years, overall survival is 95%.[8,14,21] The Table summarizes many of the differences between adults and children with DTC.

MTC, accounting for 5%-10% of all thyroid malignancies, is rare in children and young adults with an incidence of less than one case/million/year.[24] The biologic behavior of MTC is more aggressive than that of the DTCs but less aggressive than that of the anaplastic thyroid cancers.[25] MTC in children is typically associated with one of the following hereditary cancer syndromes: multiple endocrine neoplasia type 2a or type b and familial MTC.[26] Sporadic MTC is rare in children. A discussion of the genetics and treatment of MTC is beyond the scope of this review; the identification of RET proto-oncogene mutations as a cause of familial MTC allows for genetic testing in normal individuals who are at risk of having inherited a mutated allele. Deoxyribonucleic acid analysis in such individuals can identify, at a young age, those destined to develop MTC and allow, in the absence of other endocrine neoplasia, the performance of prophylactic thyroidectomy before the development of a thyroid malignancy.[23,27,28]

# Pathogenesis and Predisposing Factors

Most thyroid cancers have no genetic basis and arise sporadically. Ongoing research has begun to identify biologic factors underlying the behavior of thyroid cancer. As in other cancers, activation of growth-stimulating molecular pathways seems to be an important component in many thyroid cancers,

**Table** Differences Between Adults and Children With Differentiated Thyroid Cancer

| | Adults | Children |
|---|---|---|
| *Thyroid nodules* | | |
| Incidence | 10% in young adults; >50% in those >60 years | 1%-5 % |
| Percent harboring cancer | 5%-14% | 26% |
| Size criteria for FNA | >1-1.5 cm | Based on ultrasound characteristics and clinical context rather than size alone |
| *Autonomously functioning nodules* | | |
| Cancer risk | 3% | 30% (associated incidental DTC) |
| Management | I-131 radiotherapy, ethanol ablation, or surgical resection | Surgical resection (lobectomy + isthmusectomy) |
| *Frequency of pathologic subtypes* | | |
| PTC | 70%-80% | >90% |
| FTC | 15%-25% | <10% |
| Medullary thyroid cancer | 5%-8% | Rare |
| Anaplastic | 4%-10% | Rare |
| *Characteristics, PTC* | | |
| Tumor focality | | |
| Multifocal disease | 30% | 40%-65% |
| Bilateral disease | 33% | 30% |
| Tumor size | | |
| Newly diagnosed, >4 cm | 15% | 36% |
| Newly diagnosed, <1 cm | 22% | 9% |
| Frequency at presentation | | |
| Cervical lymph node metastases | 30%-40% | 60%-80% |
| Distant metastases | 2%-14% | 20%-25%, almost always lung |
| Lung metastases | 1%-7% | 20% |
| *Survival* | | |
| Overall (at 20 years) | 90% | 98% |
| In those with distant metastases | 40% at 5 years, 20% at 10 years | 96%-100% at 5 and 10 years |
| Recurrence rate, PTC (age at diagnosis) | 20% (20-50 years) | 40% (<20 years) |
| *Genetics* | | |
| Prevalence of gene rearrangements | Lower | Higher |
| BRAF mutations | Common (36%-83%) | Rare |
| RET/PTC rearrangements | Less common | More common |

particularly those with aggressive or resistant behaviors. Chromosomal rearrangements of the RET proto-oncogene have been associated with the development of PTC. In these cases, the linking of the promoter region of an unrelated gene, the PTC gene, to the carboxyl terminus of the RET proto-oncogene, results in a chimeric oncogene (RET/PTC), which promotes tumorigenesis. As compared with adults, children with DTC have a higher prevalence of RET/PTC gene rearrangements and a lower frequency of point mutations in the proto-oncogenes implicated in PTC.[29,30]

Activation of the RAS- and BRAF-signaling pathways, rearrangement of the TRK proto-oncogene, 3p25 rearrangements of peroxisome proliferator—activated receptor gamma genes, and p53 tumor suppressor gene are among other genes implicated in the tumorigenesis and biologic behavior of thyroid cancer. Occurring in 36%-86% of cases, BRAF mutations are the most common abnormality in adult PTC. In contradistinction, RAS and BRAF point mutations are uncommon in children.[30-33]

Environmental factors also play a role in the pathogenesis of thyroid cancer. Exposure to ionizing radiation is the major environmental risk factor for the development of thyroid cancer. Although the exact mechanism was unknown, the association between head and neck irradiation (XRT) and the development of thyroid cancer was first reported by Duffy and Fitzgerald in the 1950s.[34] This resulted in the abandonment of the use of radiation for the treatment of a variety of benign childhood conditions such as tinea capitus, acne, chronic

tonsillitis, and thymic hyperplasia, a practice that was prevalent at that time. The causal relationship between head and neck irradiation and the development of thyroid cancer has been confirmed in numerous subsequent studies and well documented in survivors of atomic bomb exposures in Japan and of radioactive fallout in Nevada and the Marshall Islands.[35-38] Winship and Rosvall,[39] in a review of 878 cases of pediatric cancer from the world literature ,determined that although there was an average latency period of 8.5 years between XRT and the development of thyroid cancer, the cancer risk continued for up to 30 years after radiation exposure. The risk of development of thyroid cancer was greatest when exposure to ionizing radiation occurred at a younger age, in women, when there were greater thyrotropin (TSH) levels at time of exposure, and with higher radiation rates.[40] Some of these risk factors were confirmed following the Chernobyl nuclear accident in 1986 in which a 100-fold increase in the incidence of pediatric thyroid cancer was noted in exposed populations.[41,42] The increased sensitivity of children to the tumorigenic effects of radiation, especially in those younger than 5 years, may be due to higher rates of thyroid cell replication as compared with adults.[43] Exposure of the thyroid to radiation may be accidental as occurred in Chernobyl, can be related to diagnostic medical imaging for other diseases, or can be secondary to external-beam radiotherapy for another cancer, most commonly Hodgkin disease. These types of exposures have been shown to be associated with an increased incidence of development of secondary cancers, including but not limited to thyroid cancer.[44-47] Secondary thyroid cancers were most common in survivors of leukemia and Hodgkin lymphoma.[47-49]

Similar to prior studies,[44-47] Bhatti et al[50] found that thyroid cancer risk increased linearly with thyroid radiation doses up to 20 Gy, where the relative risk peaked at 14.6 fold. A downturn in dose-response relationship was observed at thyroid radiation doses more than 20 Gy, thought attributable to cell killing. In the largest study to date of second primary thyroid cancers among childhood cancer survivors, gender, age at exposure and time since exposure were found to be significant modifiers of the radiation-related risk of thyroid cancer. These authors[50] also found an increased risk of thyroid cancer in those receiving chemotherapy, although a relatively weak one (1.6-fold increased risk), again demonstrating that the risk of a second primary thyroid cancer is typically dominated by radiation effect.

## Clinical Presentations

Differentiated thyroid carcinoma in children typically presents as an asymptomatic mass.[16,17,19] Although only 1%-5% of children have thyroid nodules compared with 4%-7% of young adults and more than 50% of persons aged 60 years or older, children with a solitary nodule are more likely to harbor a malignancy that do their adult counterparts.[51-55] Although the overall prevalence of thyroid carcinoma in a thyroid nodule is 5% in adults, the incidence of cancer in surgically removed solitary thyroid nodules in children ranges from 14%-61%, averaging approximately 26%.[56-58] The likelihood of malignancy increases if there has been rapid growth of a thyroid nodule, if the mass is hard, adherent to surrounding tissues, associated with cervical lymphadenopathy or vocal cord paralysis, or if there is a previous history of head and neck irradiation of any type.[52,59]

Cervical lymphadenopathy alone may be the initial presentation in children and adolescents with PTC. This is not unexpected given that up to 80% of children with PTC have locally metastatic disease present at the time of diagnosis. Occasionally, the diagnosis of PTC is made incidentally after the discovery of pulmonary nodules on a chest radiograph.[23]

## Diagnosis

In both children and adults, the diagnosis of DTC is based on physical examination, patient history, laboratory and imaging studies, and biopsy, preferably employing fine-needle aspiration (FNA) as opposed to excisional biopsy, as the latter often entails a lobectomy and may require a second surgery if the diagnosis of cancer cannot be made intraoperatively. When a painless thyroid nodule is first identified in a child or adolescent, serum triiodothyronine ($T_3$), thyroxine ($LT_4$), and TSH levels should be measured and a high-quality ultrasound (US) imaging of the neck performed. Given the extremely low prevalence of sporadic MTC in children and adolescents, obtaining calcitonin levels may not be cost-effective.[5]

US imaging can distinguish cystic from solid lesions, quantitate the size and number of nodules present, assess for the presence of cervical adenopathy, and be used to guide FNA.[60] Although cystic lesions are often benign, as many as 50% of malignant lesions have a cystic component[61] and up to 8% of cystic lesions represent malignancy.[62] Benign solid nodules are more likely to exhibit a homogeneous echotexture, have a translucent halo, and lack internal calcifications. The presence of indistinct margins, variable echotexture, increased intranodular blood flow, and microcalcifications in a solid nodule are findings suggestive of malignancy[60] (Fig. 1). In children as opposed to adults, PTC may present as a diffusely infiltrating disease resulting in diffuse thyroid gland enlargement, often in association with microcalcifications[5] (Fig. 2). In all children with suspicious nodules or when there is diffuse enlargement of the gland associated with microcalcifications, US of the cervical nodes should also be performed. Although helpful, imaging appearances alone cannot distinguish between benign and malignant lesions or between malignant histologies (Fig. 3). FNA is both cost-effective and highly accurate in determining if a thyroid nodule is malignant with similar specificities and sensitivities as those reported in adults and children.[3,63-65]

The 2009 ATA adult guidelines indicate that FNA is not indicated for the evaluation of a nodule $<1$ cm in size unless the patient is considered to have high risk or unless the nodule is associated with pathologic lymph nodes.[3] Although in general the pediatric task force concurred that the evaluation and treatment of thyroid nodules should be similar to those of

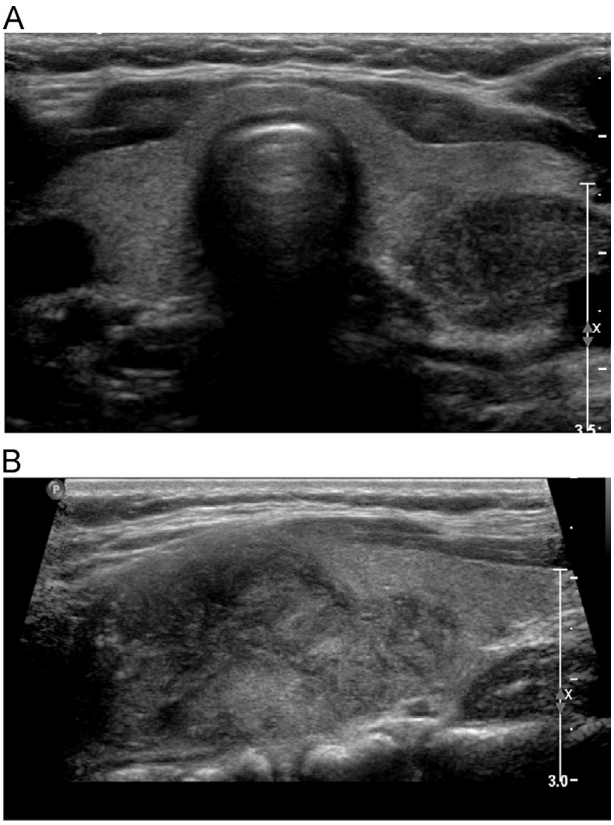


**Figure 1** Papillary thyroid carcinoma, ATA Pediatric Intermediate-Risk group. A 15-year-old girl with palpable fullness of left thyroid lobe noted on physical examination undergoes a neck US. Transverse US image (A) of the thyroid gland and longitudinal image (B) of the left lobe reveal a heterogenous, hypervascular (not shown), solid nodule measuring 4.3 × 1.7 × 1.9 cm with micorcalcifications, findings suggestive of malignancy. FNA was consistent with papillary thyroid carcinoma. No lung metastases were seen on CT (not shown). Patient underwent total thyroidectomy and lymph node sampling. Pathology demonstrated a 4-cm tumor in the left lobe with three of three sampled lymph nodes positive for disease, Stage I (T3, N1a, M0).

adults, they noted several exceptions. In contradistinction to the adult guidelines, Recommendation 5 of the current pediatric-specific ATA guidelines[5] stresses that in the growing child, US characteristics and clinical context, rather than size alone, should be used to determine if nodules warrant FNA and that US should be used to guide all FNA performed in children (Fig. 4). Further, the pediatric-specific guidelines[5] recommend that preoperative FNA of a hyperfunctioning nodule in children is not warranted as long as the lesion is surgically removed. Finally, although repeat FNA remains an option in children with insufficient or nondiagnostic cytology, it is recommended that surgery (lobectomy plus isthmusectomy) be favored over repeat FNA for all nodules with indeterminate cytology, given the apparent increased probability of malignancy in indeterminate categories in children compared with adults.[66]

Both technetium-99 pertechnetate ($TcO_4$) and Iodine-123 scanning have been used in the diagnostic evaluation of thyroid nodules, where a "cold" nodule, one with less uptake than normal thyroid tissue, may indicate a thyroid cancer.[55] Unfortunately, imaging with either of these radiotracers, while exposing the patient to ionizing radiation, is not helpful in excluding thyroid cancer as, in the absence of clinical or biochemical evidence of hyperthyroidism, most nodules would be either cold or have uptake similar to that of normal thyroid tissue. Further, only a small minority of cold nodules, when identified, are found to be thyroid cancer as opposed to more benign entities. In adults, the use of radionuclide imaging is reserved for two groups of patients with thyroid nodules: those with suspected hyperthyroidism and those with extensive multinodular goiter.[55] In adults, hot or autonomously functioning nodules are rarely malignant and treatment options include I-131 radiotherapy, ethanol injection, or surgical resection.[67]

According to the inaugural ATA pediatric guidelines, I-123 scintigraphy should be obtained only in those children with a suspicious thyroid nodule who have a suppressed TSH level [5] (Fig. 5). If the nodule is hyperfunctioning on I-123 imaging, then the child should undergo surgery, including lobectomy plus isthmusectomy, as up to 30% of children may have an incidentally discovered DTC associated with an autonomously functioning nodule as opposed to 3% of adults.[68]

## Preoperative Evaluation of the Child With Newly Diagnosed DTC

The preoperative evaluation of the child with newly diagnosed DTC should include a comprehensive neck ultrasound performed by an experienced ultrasonographer using a high-resolution probe and Doppler technique.[5] This facilitates identification of local or regional metastatic disease not appreciated on physical examination, allowing the surgeon to plan comprehensive compartment-oriented lymph node dissection during initial surgery with the goal of decreasing both recurrence rates and the need for additional surgery.[69-71] Obtaining an MR or CT of the neck with contrast can be considered in children with large fixed masses, vocal cord paralysis, or bulky metastatic lymphadenopathy or when invasion of the aerodigestive tract is of concern, although the use of iodinated contrast delays postoperative evaluation and treatment with radioactive iodine for 2-3 months. As the prevalence of lung metastases is increased in those patients with DTC and extensive cervical lymphadenopathy, either a chest x-ray or noncontrast chest CT is obtained as part of the preoperative evaluation in this select group[72,73] (Fig. 6). In patients with DTC without advanced disease, noncontrast CT is not a part of routine staging. The limited role for I-123 radionuclide scanning, recommended only if the patient presents with a suppressed TSH, has been discussed earlier. The performance of fluorine-18 fluorodeoxyglucose positron emission tomography (F18 FDG-PET or PET/CT) is not recommended in the routine evaluation of thyroid cancer but rather reserved for posttherapy surveillance in those with negative iodine scans and positive thyroglobulin levels.[74,75]

# Treatment

The goals of primary treatment of DTC are to eradicate disease and extend disease-free survival.[3] Unfortunately, all cancer

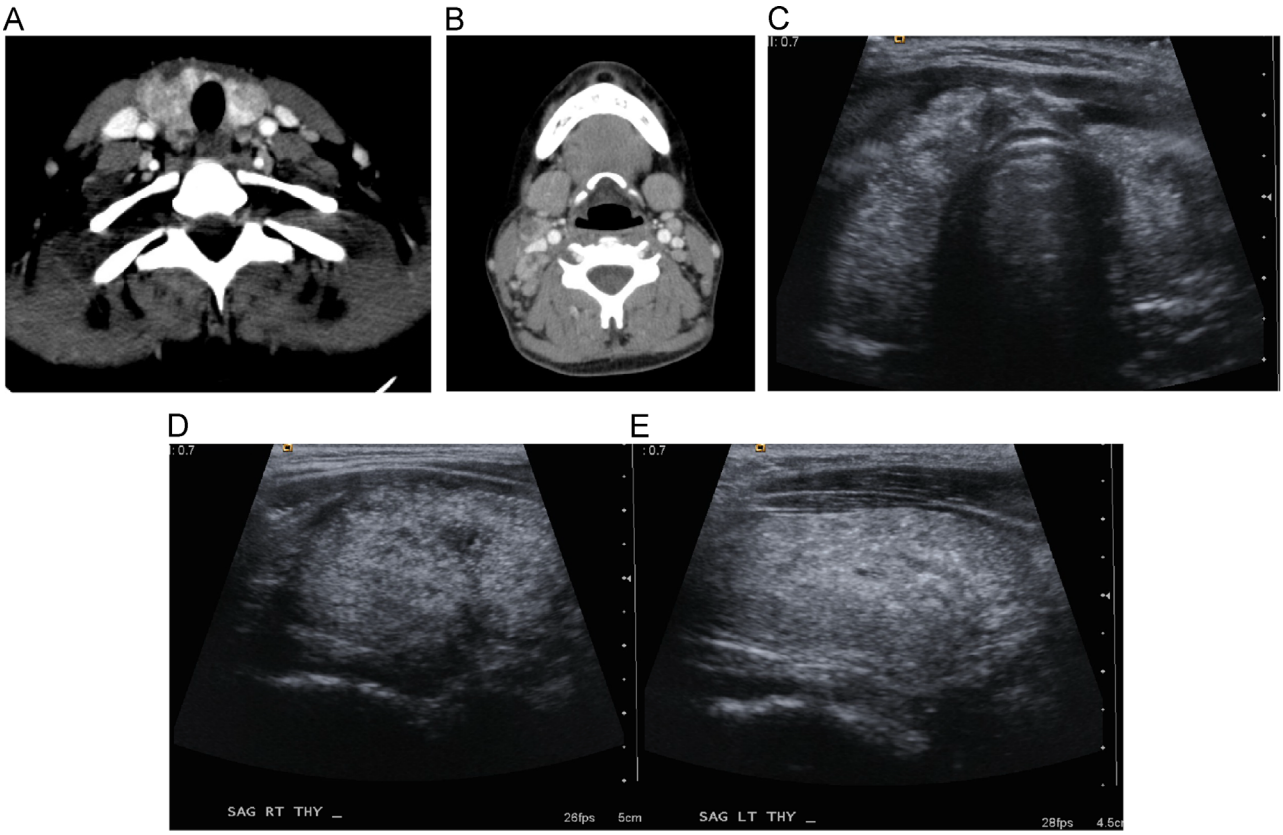


**Figure 2** Papillary thyroid carcinoma, ATA Pediatric High-Risk group. A 15-year-old girl presented with neck enlargement during routine dental examination. Contrast-enhanced CT of the neck obtained for increasing swelling and tenderness demonstrates a diffusely enlarged, heterogeneous thyroid gland (A) as well as bilateral cervical lymphadenopathy (B). US of the neck (transverse, C, and longitudinal images, D and E), obtained to guide FNA, confirms diffuse thyroid enlargement and increased echogenicity, findings suggestive of diffuse, infiltrating PTC, a presentation seen in children as opposed to adults. The patient underwent total thyroidectomy and cervical lymph node dissection. Pathology confirmed diffuse papillary thyroid carcinoma involving the left and right lobes; metastatic disease was present in 28 of 43 lymph nodes and the right recurrent laryngeal nerve was involved (Stage II; T4a, N1b, M1). Use of iodinated intravenous contrast in preoperative CT evaluation delays postoperative staging evaluation and radioiodine treatment for 2-3 months.

treatments—whether surgery, chemotherapy, or radiation—are associated with toxicities, both short term and long term, which can range from mild to debilitating, and which can affect all organ systems. The 10-year survival rate for adults with DTC exceeds 90%,[6] it approaches nearly 100% in children.[8] Although death from PTC is low, recent studies with long-term follow-up spanning decades reveal an increase in all-cause mortality for survivors of childhood DTC, predominantly due to the development of secondary malignancies in those treated with I-131 radiotherapy.[21,76,77] Awareness of the complications of treatment assumes increasing importance, making it imperative to balance the risks of treatment against potential gains from aggressive therapies and mandating discussion of these potential risks with the patient and their parent throughout the course of their initial and any subsequent treatment.

Definitive therapy for children with DTC includes surgical resection and, for those with anything other than low-risk disease, possible I-131 radiotherapy. Controversies arise regarding the type of surgery performed, who is best qualified to perform the surgery, and in those with low-risk disease, whether to use I-131 radiotherapy.

To maintain the low disease-specific mortality currently experienced by children with DTC as well as to reduce the potential complications of therapy, one of the major goals of the pediatric task force was to try to prospectively identify patients in whom I-131 therapy is indicated and to limit potential overtreatment in those who are unlikely to benefit. To these ends, the ATA pediatric task force developed three risk stratification groups for children with PTC[5] based on the use of the TNM classification system.[78] The goal of this stratification was not to define the risk of disease mortality but rather to identify patients at risk for persistent cervical disease and to determine who should undergo postoperative staging for distant metastasis.

In the ATA pediatric low-risk group,[5] disease is confined to the thyroid gland with either N0 (no regional lymph node metastases) or NX (regional lymph nodes not assessed) disease, or children with incidental N1a micrometastasis. This group is at the lowest risk for distant metastasis.

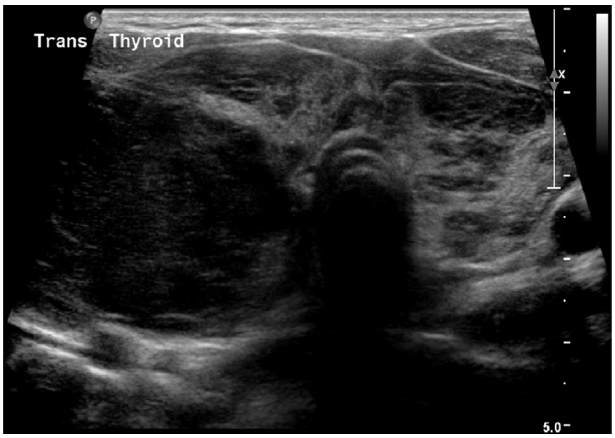


**Figure 3** Primary thyroid lymphoma. A 13-year-old boy presented with a lump in the neck shown on transverse ultrasound view to represent a large, solid nodule (n) in the right lobe of the thyroid gland. The remainder of the thyroid gland had a diffusely heterogenous echogenicity. Finding was suggestive of thyroid carcinoma and the patient underwent FNA demonstrating marginal zone lymphoma. The patient underwent total thyroidectomy. Pathology confirmed diffuse large B-cell lymphoma with chronic lymphocytic thyroiditis (Hashimoto's disease) in the remainder of the thyroid gland. This case illustrates that although extremely helpful, US imaging appearances cannot distinguish between benign and malignant histologies or between different malignant pathologies. CT of the chest and whole-body F18-FDG PET-CT (not shown) demonstrated no other sites of lymphomatous involvement. Although the performance of F18-FDG PET-CT is standard of care in the staging of lymphoma, it is not recommended in the routine evaluation of thyroid cancer. Rather, in those with thyroid cancer, F18-FDG PET-CT is reserved for posttherapy surveillance in those with negative iodine scans and positive thyroglobulin levels.

The ATA pediatric intermediate-risk group[5] includes patients with extensive N1a (metastases to level VI nodes) or minimal N1b (metastases to unilateral, bilateral, or contralateral level I, II, III, IV, or V cervical or superior mediastinal (VII) lymph nodes) disease who are at low risk for distant metastatic disease but at increased risk for incomplete nodal resection and persistent cervical disease.

The ATA pediatric high-risk group[5] includes patients with regionally extensive (extensive N1b) or locally invasive disease (T4 tumors) who are at highest risk for incomplete resection, persistent disease, and distant metastases.

## Surgery

Total or near-total thyroidectomy (as opposed to lobectomy) is recommended for children with DTC as there is an increased risk of bilateral (30%) and multifocal (65%) disease as well as an increased risk of recurrence, which would necessitate a second surgery if a total or near-total thyroidectomy had not been performed initially.[5,21,79-81] Surgical reintervention for recurrent disease in children initially treated with lobectomy alone has been associated with a higher complication rate.[82] Although performance of a lobectomy alone in those with low-risk disease is associated with fewer surgical complications, the performance of a total thyroidectomy allows use of either I-123 or I-131 to detect and I-131 to treat residual thyroid tissue and local and distant metastases. Also, serum thyroglobulin levels are more sensitive for the detection of persistent or recurrent disease when all normal thyroid tissue has been removed or ablated with I-131.[83]

Decreased disease-free survival in children has been most closely associated with the presence of persistent or recurrent local and regional disease.[21,81,83] Consequently, a central neck dissection is recommended at the time of initial surgery for those children in whom nodal metastases are identified preoperatively in either the central or lateral neck compartments.[5,84] Not only does central neck dissection decrease the risk of residual or recurrent locoregional disease but decreasing overall disease burden may potentially increase the efficacy of I-131 treatment. Although data suggest that the extent of initial surgery has the greatest effect on improving long-term disease-free survival,[21,80] the potential benefit of achieving surgical remission by decreasing the incidence of residual or recurrent locoregional disease must be balanced against the potential increased risks of a more aggressive surgery.

The most common complication of thyroidectomy, aside from postoperative pain, is either transient or permanent parathyroid dysfunction occurring with an average rate of 5%-15%. The risk of permanent hypoparathyroidism is less than 2% when surgery is performed by a high-volume endocrine surgeon.[85]

A more serious, surgery-specific complication is recurrent laryngeal nerve damage with incidence ranging from 6%-12%.[85-87] Recurrent laryngeal nerve palsy results in hoarse voice, pitch problems, and dysphagia. Extrathyroidal tumor, large tumor size, total thyroidectomy, central compartment dissection, and ipsilateral node dissection were associated with a high risk of recurrent laryngeal nerve palsy in a series by Demidchik et al,[12] although other authors did not have the same experience.[88]

Children undergoing thyroidectomy were found to have higher endocrine-specific complication rates than adults (9.1% vs 6.3%).[89] Those aged 0-6 years fared the worst, with surgical complication rates approaching 22% compared with 15% in those aged 7-12 years and 11% in those aged 13-17 years. Outcomes, including both endocrine-specific and general surgical complication rates, length of stay, and inpatient hospital costs, were optimized when surgeries were performed by a high-volume surgeon, defined as one who performs $>30$ cervical endocrine procedures per year in adults and children combined.[90] High-volume surgeons performed better than dedicated pediatric surgeons as well as general surgeons, including otolaryngologists. Moreover, surgical volume was an important predictor of pediatric outcomes regardless of surgeon specialty.[90] Given these data, the delicacy of the surgical site, and potential complications, thyroidectomy in children (where size and spacing to critical structures are much smaller than in adults) is best performed by high-volume surgeons.

## Postoperative Staging

The purpose of radioiodine scanning, the mainstay of postoperative staging for DTC, is to assess for persistent

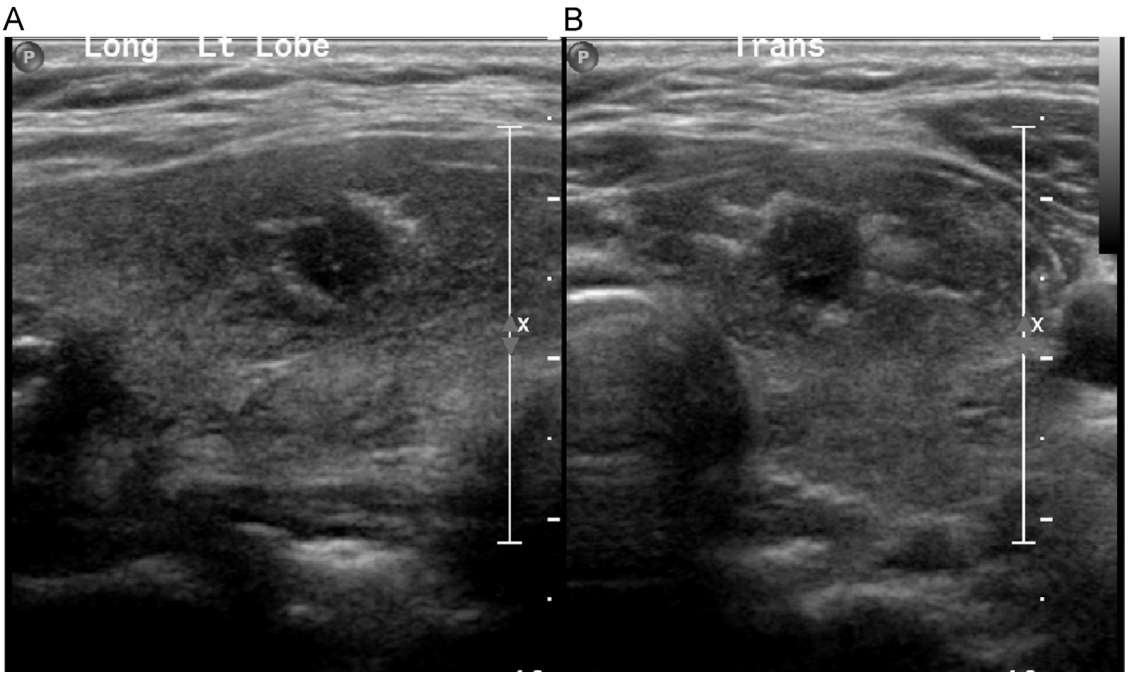


**Figure 4** Papillary thyroid carcinoma in patient with Graves disease. A 17-year-old girl with Graves' disease was referred for I-131 thyroid ablation. (A and B) Thyroid US, performed to estimate gland volume and weight to determine I-131 treatment dose, revealed a heterogeneously echogenic, ill-defined, solid nodule with microcalcifications measuring 1.5 × 0.8 cm in the left lobe (longitudinal (A) and transverse images, (B), respectively). In the pediatric population, US characteristics and clinical context, rather than size alone, should be used to determine if nodules warrant FNA. FNA was nondiagnostic. Although repeat FNA remains an option in children with insufficient or nondiagnostic cytology, surgery is favored over repeat FNA for all nodules with indeterminate cytology given the apparent increased probability of malignancy in children compared with adults. The patient underwent total thyroidectomy with lymph node sampling. Pathology was consistent with papillary thyroid carcinoma with two lymph nodes positive for metastatic involvement, Stage 1 (T1a, N1a, M0).

locoregional disease and to identify patients likely to benefit from further treatment, either I-131 radiotherapy or additional surgery.

The presence of substantial thyroid tissue at the time of scanning limits identification of sites of disease. Thus, whole-body thyroid cancer surveys are possible only after near-total thyroidectomy. The initial staging study is typically performed within 12 weeks of the surgical procedure unless the patient has received intravenous contrast during preoperative evaluation. In such cases, the initial staging study should be delayed for 2-3 months.

More extensive patient preparation is necessary for the performance of an adequate staging metastatic thyroid cancer survey (DX whole-body scanning [WBS]) as compared with iodine scintigraphy for benign disease. If the patient is on levothyroxine ($LT_4$), it should be discontinued 4-6 weeks before scheduled imaging. Supplementation with liothyronine ($T_3$) can be given up to 2 weeks before scheduled imaging to decrease the amount of time over which the patient is hypothyroid and stimulated by TSH. As children are more sensitive to the effects of hypothyroidism than adults, DX WBS using recombinant human thyrotropin stimulation (rhTSH) rather than thyroid hormone withdrawal is performed at our institution. The Food and Drug Administration has approved the use of rhTSH for use as a preparatory regimen in diagnostic scans and routine thyroid remnant ablation after surgery in adults; it is the emerging standard of care for low-risk adult patients with DTC in whom ablation is indicated. Although experience in children is limited,[91-93] our anecdotal experience, combined with previously published data, has shown that the typical adult dose of two intramuscular injections of 0.9 mg of rhTSH given 24 hours apart on each of the 2 days before I-123 administration for DX WBS is safe and adequate to achieve appropriate TSH levels. To further maximize the iodine avidity of residual thyroid cancer, a low-iodine diet is instituted 2 weeks before imaging.

As many children with thyroid cancer come from a referral population some distance from the center that would be evaluating and treating them, the time of initial DX WBS presents a convenient opportunity to discuss patient follow-up, radiation safety issues, as well radioiodine therapy, including whether I-131 treatment, if necessary, would be performed as an inpatient or as an outpatient procedure.[94]

Shortly before performing the DX WBS, the following laboratory studies should be obtained and reviewed: serum calcium, TSH, and stimulated thyroglobulin (Tg) levels and antithyroglobulin antibodies (TgAb) and complete blood counts; a negative-result pregnancy test should be confirmed in all women of childbearing age. TSH level should be greater than 30 mIU/l to ensure adequate stimulation for imaging.

Thyroglobulin, a thyroid-specific glycoprotein, is derived from two sources: normal thyroid tissue and thyroid cancer.[95]

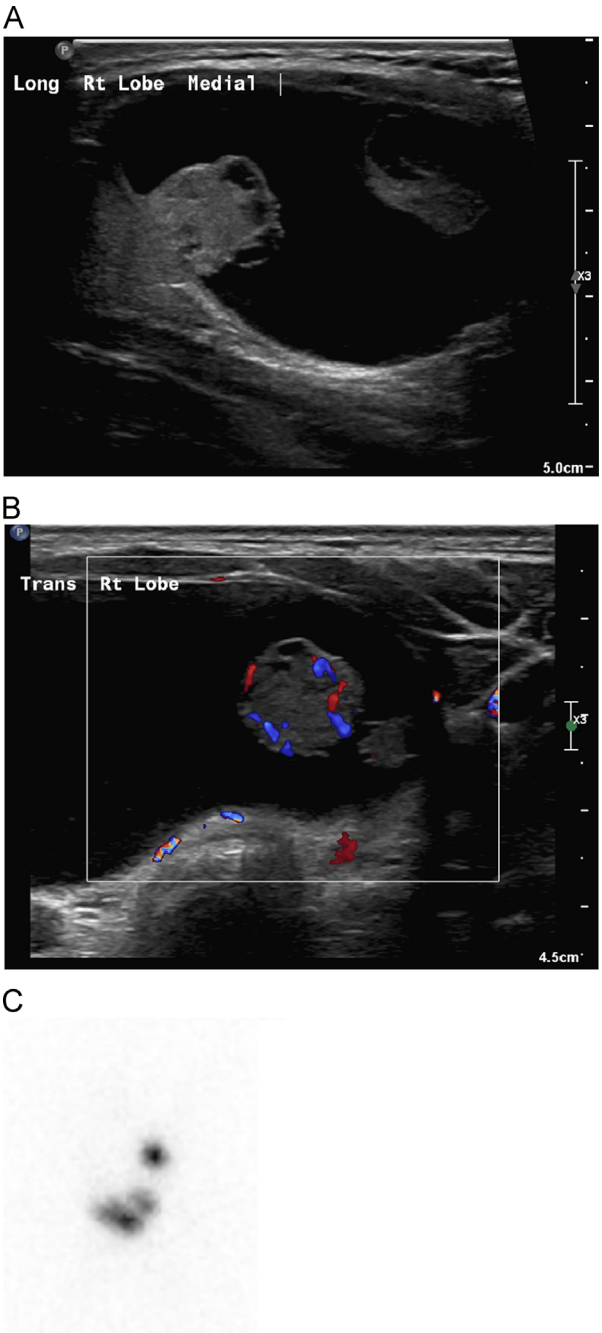


**Figure 5** Autonomously functioning nodule(s). A 15-year-old girl presented with hyperthyroidism and a suppressed TSH. Thyroid US revealed a large cystic and solid mass, measuring 5.7 × 5.6 × 3.3 cm, in the right lobe (A). The predominantly cystic mass had several peripheral nodular solid components that were hyperemic on Doppler image (B). (C) I-123 thyroid scan was performed and showed that three of the solid nodules comprising the complex mass accumulated the radiotracer with suppression of the remainder of the gland; 5- and 24-hour uptake were 15% and 25%, respectively (not shown). The patient underwent right hemithyroidectomy and pathology was consistent with follicular adenoma with hemorrhagic cystic degeneration. No DTC was revealed at pathology. Up to 30% of children may have an incidentally discovered DTC associated with an autonomously functioning nodule, as opposed to 3% of adults. Consequently, lobectomy and isthmusectomy are the recommended management for pediatric patients with autonomously functioning thyroid nodules.

In the absence of thyroid tissue, the measurement of serum thyroglobulin provides a sensitive screening tool for residual or recurrent disease in those with DTC. The measurement of nonstimulated Tg levels (Tg on $LT_4$) and the trend in those levels over time is a key component in postoperative staging, during long-term surveillance, and in the restaging of children with PTC.

Thyroglobulin levels increase after TSH stimulation. Measuring Tg levels at the time of initial and subsequent DX WBS, if performed, when there has been TSH stimulation is a key component of staging and surveillance in the ATA pediatric intermediate and high-risk groups.[5]

Previously, all children with DTC underwent a postsurgical staging DX WBS with either I-131 or I-123. In contradistinction, current pediatric guideline recommendations[5] suggest that the DX WBS can be omitted in ATA low-risk patients. Rather, this group is initially assessed and followed with neck US and serial TSH-suppressed Tg levels alone (Fig. 7). In contrast, ATA intermediate and high-risk patients should be staged with a TSH-stimulated Tg level and a DX WBS performed with I-123 whenever possible (Fig. 8). The use of I-123 rather than I-131 results in a lower patient radiation dose and improved image quality; it allows for the performance of SPECT/CT, if necessary, to distinguish remnant thyroid tissue from nodal metastases and avoids the risks of stunning that can occur with the use of I-131.[96-99]

In our center, diagnostic I-123 postsurgical scanning (DX WBS) with iodine uptake is performed at 24 hours after the oral administration of an adult-equivalent dose of 2 mCi scaled to patient weight in those who have undergone an rhTSH stimulation protocol. Anterior and posterior whole-body images are acquired with a low-energy, high-resolution collimator, with and without source markers.

Irrespective of initial risk stratification, all patients enter surveillance (discussed later) to ensure that appropriate therapy is instituted in the event that disease is subsequently identified.

## Radioiodine; I-131 Radiotherapy

Traditionally, the goals of radioiodine therapy were to ablate remnant thyroid tissue following total thyroidectomy to facilitate disease surveillance with thyroglobulin levels, imaging, or both and to treat residual thyroid cancer or its metastasis.[100,101]

Numerous authors have reported improved survival, decreased disease progression, and lower recurrence rates in those with advanced DTC who received postoperative radioactive iodine (RAI).[101-103] There is general agreement that residual disease not amenable to surgical resection and iodine-avid distant metastatic disease, particularly pulmonary metastases, should be treated with I-131 in adults and children.

However, postoperative RAI has not been clearly shown to be of benefit to those with low-risk thyroid cancer after a complete surgical resection.[104-107] Available data show that $<1\%$ of adult patients with low-risk cancer who have undetectable TSH-stimulated Tg levels and a normal neck US would have a clinical recurrence over a 10-15-year period.

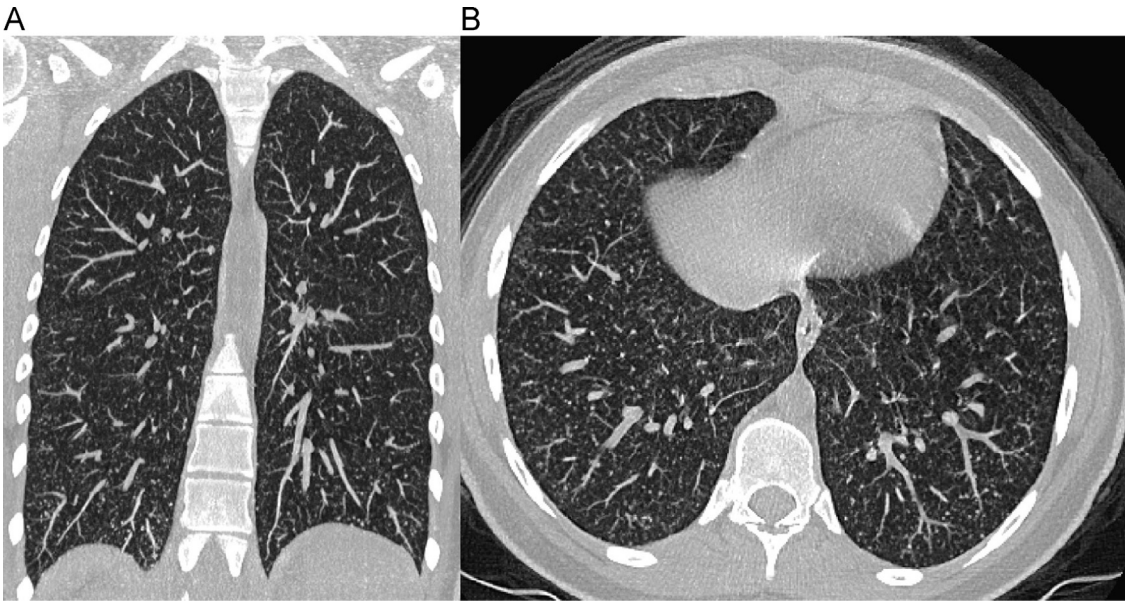


**Figure 6** Papillary thyroid carcinoma metastatic to lungs. A 15-year-old girl with PTC, Stage II (T4a, N1b, M1); this is the same patient as in Fig. 2. A 5-mm coronal (A) and axial (B) maximum-intensity-projection image from a non−contrast-enhanced CT of the lung demonstrate numerous bilateral miliary lung nodules. Pulmonary metastases occur at presentation in as many as 20% of children with PTC.

Iyer et al,[108] analyzing trends in radioiodine use over time, showed that although the use of radioiodine therapy in low-risk DTC patients aged <45 years increased from 3.3%-38.1% in the years between 1973 and 2007, the rate of overall survival remained constant. Moreover, these same authors demonstrated an increasing incidence in secondary cancers in those with low-risk DTC treated with RAI. Data such as these have led to a state of flux regarding the role of remnant ablation—that is the treatment of normal thyroid that remains following surgery—in adult patients with low-risk DTC. Although recent recommendations[3] suggest that ablative RAI can be withheld for such adult patients, there is controversy as to whether this recommendation is applicable in children. Rivkees et al[109] discuss a number of factors in children and adolescents with DTC that they feel favor the continued use of remnant ablation in this group. Not only are there fewer children with low-risk disease but also there is a higher risk of DTC recurrence in children compared with adults; additionally there are the challenges of long-term follow-up, including lack of adult awareness of their childhood diseases, and the sporadic medical compliance in this population, which precludes reliance on TSH-suppressive therapy to prevent DTC recurrence. Unfortunately, retrospective series evaluating the use of remnant ablation in children show conflicting results.[21,83,110] Despite conflicting data, current recommendations suggest that for the uncommon low-risk pediatric patient, RAI may be withheld and the patient monitored for disease persistence and recurrence with Tg levels and neck US.[3,5]

Remnant ablation, when selectively used, is easily accomplished as remnant thyroidal tissue is highly iodine avid. Controversy as to the appropriate ablation dose persists. Several studies, including level I evidence in randomized controlled trials, have demonstrated that there is little difference in efficacy between low-dose (1.1 GBq [29.7 mCi]) and high-dose (3.7 GBq [100 mCi]) I-131 radioablation irrespective of whether thyroid hormone withdrawal or rhTSH stimulation in the euthyroid state is used as the preparative regimen in those following total thyroidectomy.[104,111,112]

As opposed to remnant ablation, there is a body of evidence showing that the use of I-131 therapy decreases recurrence in those children with DTC who have residual disease.[22,73,113,114] Consequently, the ATA pediatric guidelines[5] state that I-131 is indicated for the treatment of residual nodal and locoregional disease not amenable to surgical resection as well as iodine-avid distant metastases, particularly iodine-avid pulmonary metastases, for which I-131 is considered therapeutic. These guidelines[5] further suggest that the decision to administer I-131 in those with ATA pediatric intermediate and high-risk disease initially be based on the results of the postoperative I-123 DX WBS and a TSH-stimulated Tg level in those with negative TgAb. I-131 is not indicated in those with no or minimal I-123 uptake in the thyroid bed and a stimulated Tg level <2 ng/ml unless the patient had a T4 tumor or known residual microscopic cervical disease. In those with no or minimal I-123 thyroid bed uptake but a stimulated Tg of 2-10 ng/ml, I-131 therapy with posttreatment scan or $LT_4$ suppression or both are suggested. I-131 is recommended in those with no or minimal I-123 thyroid bed uptake but a stimulated Tg >10 ng/ml as well as in those with distant metastases but no cervical uptake outside the thyroid bed. If there is cervical uptake outside the thyroid bed, either with or without distant metastases, anatomical imaging should be employed to assess for significant residual disease amenable to surgery, which would then be the next course of action. If there is no residual disease amenable to surgical debulking, then I-131 therapy with posttreatment scan is recommended in

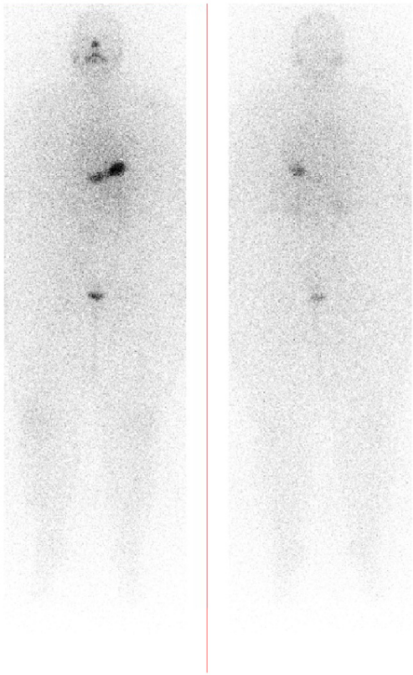

**Figure 7** Papillary thyroid carcinoma, ATA Pediatric Low-Risk group. A young woman aged 19 years with family history of thyroid cancer was found to have thyroid nodules on US (not shown). FNA was consistent with papillary thyroid carcinoma and the pateint underwent total thyroidectomy and lymph node sampling. Pathology was consistent with papillary thyroid carcinoma, multifocal (largest lesion 1.2 cm), involving the right lobe; five of five lymph nodes were negative for metastasis, Stage 1 (T1b, N0, M0). Anterior and posterior whole-body images from the staging I-123 postsurgical scan (DX WBS) demonstrate no uptake in the thyroid bed nor locoregional or distant metastases. Thyrogen-stimulated thyroglobulin level was 0.2 ng/ml (low). Therefore, I-131 ablation was not performed. After 2 years of follow-up, (both TSH-suppressed and TSH-stimulated) thyrogen levels have continued to remain low. The "ATA Pediatric Low-Risk group" is at low risk for distant metastases. According to the current guidelines, DX WBS may be omitted in this group. Rather patients are initially assessed and subsequently followed up with serial TSH-suppressed thyroglobulin level measurements and neck US imaging.

these patients. (Figure 2 in the ATA Management Guidelines for Children.[5])

Higher radioiodine doses are typically required to treat thyroid cancer as opposed to the modest doses used for remnant ablation. This is because iodine uptake in thyroid cancer is variable and substantially lower than that of normal thyroid tissue for almost all thyroid cancers. I-131 uptake is affected by a variety of factors, including serum iodide, TSH levels, tumor type, the degree of tumor differentiation, and patient age. When I-131 therapy is prescribed, the child should be on a low-iodine diet for 2 weeks before and undergo either $LT_4$ withdrawal for an appropriate amount of time (> 14 days) or receive rhTSH stimulation on each of the 2 days before planned treatment. TSH level should be obtained in the 24 hours before treatment and confirmed to be more than 30 mlU/l to facilitate uptake. A negative pregnancy test must be confirmed in all patients of childbearing age.

There are no standard doses for I-131 treatment and little in the way of prospective studies to set dosing guidelines.[100] Approaches to choosing an appropriate I-131 dose for treatment of DTC include empirical dosing, that is administering fixed I-131 activities that may or may not be based on patient weight, or the use of dosimetry, in which whole-body and blood iodine clearance measures, in addition to tumor surveys, provide estimates of the maximum tolerated dose to critical organs, typically the bone marrow or the lungs in patients with extensive pulmonary metastases. Based on the lack of data comparing empirical treatment to that informed by dosimetry, the ATA pediatric guidelines[5] do not recommend for or against either approach but rather stress that all activities of I-131 be calculated by experts with experience in dosing children.

At Seattle Children's Hospital (SCH), we typically use empirical dosing in determining the initial I-131 treatment dose. We perform dosimetry to determine I-131 dose in the following situations: patients < 10 years of age, patients who have undergone prior chemotherapy or radiation therapy or in whom thyroid cancer is a secondary tumor, in those who have extensive distant or pulmonary metastases, or when cumulative doses for thyroid cancer treatments approach 250-500 mCi (9.3-18.5 GBq). We employ the following risk-adaptive strategy for administered I-131 activities, based on adult guidelines adapted to the pediatric population and adjusted for patient weight and by additional safety factors dependent on age or antecedent treatment. Adult-equivalent doses are as follows: In those patients with lowest risk disease, an ablative dose of 30-50 mCi (1.1–1.85 GBq) may be given. In patients at higher risk for recurrence (N1 or T3), adult-equivalent doses up to 150-175 mCi (5.6-6.5 GBq) are given, depending on the extent of nodal disease and anticipated residual nodal burden. In the highest-risk patients, those with very large tumors, gross penetration of the thyroid capsule, growth into adjacent structures (T4 disease), extensive nodal disease or distant metastases (M1), and empirical adult-equivalent doses of 175-200 mCi (6.5-7.4 GBq) can be used, but with some caution particularly in younger or smaller patients.[94] However, especially for those with distant metastases, we often use dosimetry to guide safe I-131 dosing more precisely. I-131 activity treatment ranges for children with DTC recommended by Hung and Sarlis[115] are similar and as follows: 100-150 mCi (3.7-5.6 GBq) for thyroid bed disease alone, 150 mCi (5.6 GBq) when cervical nodes are involved, and 200 mCi (7.4 GBq) for lung metastases, with activities adjusted by body weight.

On the day of therapy, the pediatric radiologist or nuclear medicine specialist should ensure that the patient has complied with preparatory regimens to maximize therapeutic efficacy of I-131. A negative pregnancy test is confirmed. If the patient is capable of being treated as an outpatient (based on patient age, functional capability, and living situation), the specific release criteria mandated for outpatient therapy are reviewed with the child and their parents and the release form signed stating their ability to comply. If inpatient therapy is to be performed (mandated for doses > 230 mCi at our center), the child is admitted to a lead-lined room. In either case, patient identity is verified using two forms of identification including either a

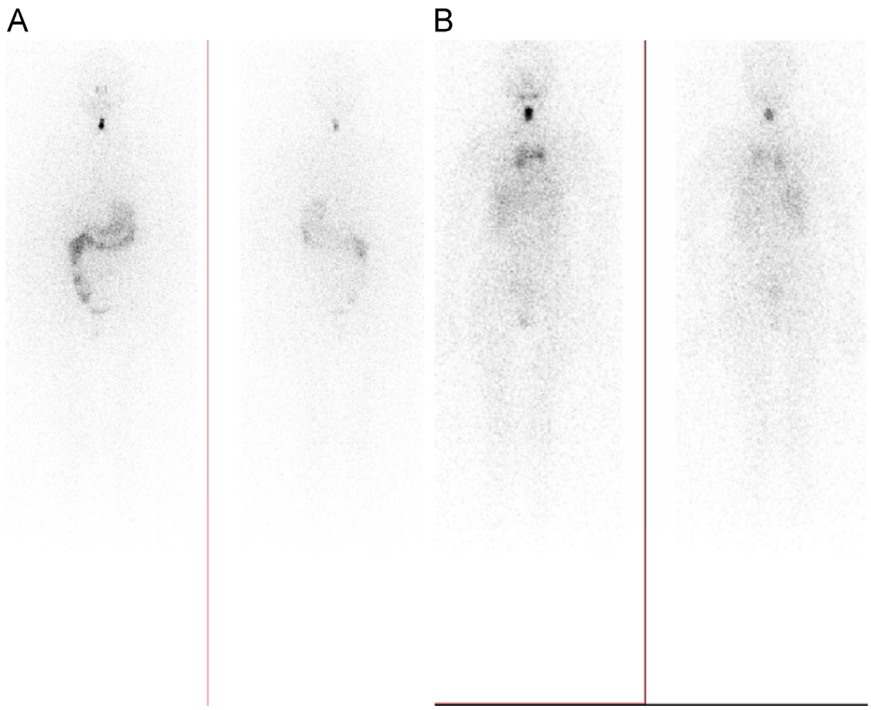


**Figure 8** Papillary thyroid carcinoma, ATA Pediatric Intermediate-Risk group. A 15-year-old girl with papillary thyroid carcinoma, Stage I (T3, N1a, M0); this is the same patient as in Fig. 1. (A) Anterior and posterior whole-body images from the staging I-123 postsurgical scan demonstrate uptake in the mid-neck. The patient was treated with I-131. (B) Anterior and posterior whole-body images from a posttreatment scan obtained 7 days following RAI administration show no additional sites of metastatic disease. There is physiological uptake in the thymus, a finding that has been reported in up to 26% of children. Diffuse liver uptake is also present, a common finding on posttherapy scans, which should not be mistaken for metastatic disease unless more focal uptake is present.

state-issued or other photo ID. Risks, benefits, and alternatives to the I-131 therapy are discussed; radiation safety precautions are reviewed. Educational materials are distributed. Written informed consent for the RAI therapy is obtained from the parent or from the patient if he or she is an emancipated minor or older than 18 years of age; assent is obtained from patients older than 12 years. Elements of the consent should include short- and long-term risks of the procedure including but not limited to sialadenitis, gastritis, neck pain or swelling, thrombocytopenia, the possibility of decreased fertility, infertility, the development of secondary malignancies, and, in those with pulmonary metastases, pulmonary fibrosis. Admonition to avoid attempts at conception for 4 months in men and pregnancy for 9-12 months in women is stressed. The need for adequate oral hydration is reiterated and for inpatients, a prophylactic intravenous line is placed. The use of lemon or sour drops commencing 24 hours after RAI administration in potentially decreasing sialadenitis is reviewed. After verifying the I-131 activity, the pediatric radiologist or nuclear medicine specialist personally witnesses or administers the radioiodine to the patient orally. Those who are candidates for outpatient treatment are discharged from the nuclear medicine department. For those being treated as inpatients, standard hospital orders are written by the admitting pediatric oncologist. Baseline patient radiation emissions are obtained by the radiation safety officer or nuclear medicine technologist immediately following the oral administration of the I-131 dose and at least twice daily thereafter. Those treated as inpatients in the state of Washington remain hospitalized until their external dose rate is less than 7 mR/h at 1 m.

All those receiving I-131 should be reimaged 7-10 days following treatment as there is a dose-related sensitivity of I-131 in disease detection.[116-118] As the dose of I-131 administered increases, so does the number of lesions detected, with posttherapy scans detecting new or additional lesions in as many as 46% of patients. Diffuse liver uptake, a common feature on posttherapy scans, should not be mistaken for metastases unless more focal uptake is present. Figure 9 shows an I-131 posttherapy scan in which diffuse pulmonary metastases, not identified on staging I-123 study, are clearly identified.

## Risks of RAI

There are both short- and long-term risks associated with therapeutic I-131 administration. Short-term risks occur during or shortly after therapy and include toxicity for tissues that retain iodine. Mild nausea or emesis from radiation gastritis occur in as many as 50% of patients;[101,102,119-121] acute sialadenitis is seen in up to 30%. Despite the use of preventative measures such as sour candies or lemon juice commencing 24 hours following I-131 dosing in conjunction with vigorous hydration for 3-5 days, permanent salivary gland dysfunction

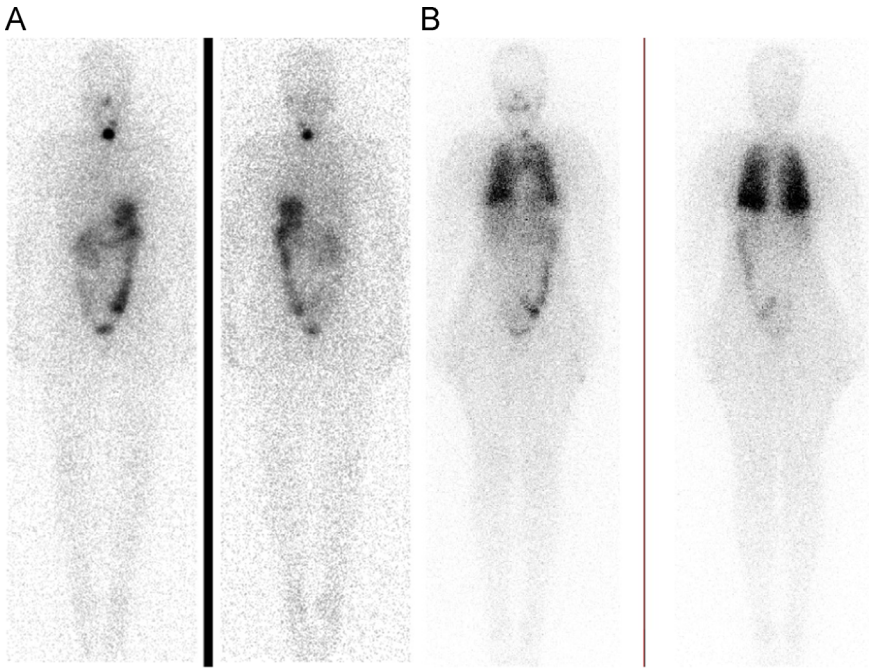


**Figure 9** Papillary thyroid carcinoma, ATA Pediatric High-Risk group. A 15-year-old girl with PTC and diffuse pulmonary metastases identified on noncontrast CT (Stage II; T4a, N1b, M1); this is the same patient as in Figures 2 and 6. (A) Anterior and posterior whole-body images from a I-131 scan, performed as part of a dosimetric study demonstrate uptake in the thyroid bed. No pulmonary uptake is seen. Patient undergoes I-131 therapy. (B) Anterior and posterior whole-body images from the posttherapy scan demonstrate diffuse uptake in the bilateral lungs as well as persistent, albeit decreased, uptake in the thyroid bed. All patients who undergo RAI should have whole-body scan at 7-10 days after treatment as there is a dose-related sensitivity of I-131 in disease detection. Posttherapy scans may detect new lesions or demonstrate known sites of disease better in more than 40% of patients.

can occur in up to 20% of patients following a single I-131 treatment and lead to lifelong xerostomia, with an increased risk not only for dental caries but also for salivary gland malignancy as well.[122-126] Pain and swelling in thyroid remnant or nodal metastases are seen in 10%-20% of cases. Although long-term bone marrow suppression is rare, transient mild leukocytopenia and thrombocytopenia occur in up to two-thirds of patients typically 4-6 weeks after treatment, with normalization within 3 months.[120,127]

In contrast to acute effects, the potential long-term hazards of I-131 therapy which are of greatest concern are genetic effects, including chromosomal damage, decreased fertility, infertility, or possible birth defects, and the development of secondary malignancies. These are considered stochastic effects with no threshold; thus, any patient receiving any dose of I-131 would be exposed to some potential risk.[128]

Short-term menstrual irregularities are fairly common, reported in up to 30%; transient amenorrhea, lasting up to 10 months in some, has been documented in 8%.[129,130] Despite this, Vini et al,[129] in a study of almost 500 women aged <40 years who underwent I-131 as treatment of thyroid cancer, found no cases of permanent ovarian failure. Smith et al[131] evaluating 154 children <28 years of age (including 68 women) concurred and found that I-131 doses up to 250 mCi (9.3 GBq) were not associated with an increased risk of infertility. Although Schlumberger et al[132,133] noted an increased risk of miscarriage in women treated with I-131 for thyroid cancer, others, in contradistinction, found no evidence of an increased risk of infertility, miscarriage, or birth defects following I-131, if conception occurred greater than 12 months after treatment.[131,134,135] Birth defects were encountered in those who conceived within 6 months of I-131 RAI.[131] Finally, it has been reported that the use of I-131 RAI is associated with an earlier onset of menopause compared with the general female population.[136] Despite some contradictory data, the current recommendation[137] is that conception should be avoided during the year following I-131 therapy.

Transient elevation of follicle-stimulating hormone persisting up to 18 months has been noted in men.[138-140] Decrease in spermatogenesis without effect on testosterone production can occur with increasing cumulative activities of I-131.[121,140,141] Not only has damage to spermatogenesis been demonstrated to be dose dependent but recent data also suggests that postpubertal testes are more susceptible to the effects of ionizing radiation than prepubertal testes.[142] Consequently, current guideline recommendations are that men avoid attempts at conception for at least 4 months following I-131 RAI and that sperm banking be considered for those receiving cumulative activities >400 mCi (14.8 GBq).[138]

In an early study, Sarker et al[143] evaluating 40 patients younger than 20 years found no overt evidence of genetic damage in those treated with high doses of I-131 for thyroid cancer. In more recent studies,[144,145] I-131 has been shown to induce an increase in the number of dicentric chromosomes in peripheral leukocytes, with aberrations of

chromosomes 1,4, and 10 most prevalent and persisting for up to 4 years.[144-146]

In 1973, Brinker et al[147] reported a 2% frequency of leukemia in patients who had undergone RAI. In 1982, Hoffmann et al[148] found that after RAI, there was an increased risk of developing cancers in salivary glands, gut, and urinary bladder, the organs that concentrate I-131. Edmonds and Smith[121] concurred reporting that children treated with RAI also had increased mortality compared with the general populace. Hay et al[21] found that the use of either I-131, external-beam radiation, or radium implants for treatment of primary thyroid cancer in children resulted in an increased risk of developing not only these cancers but leukemia and breast cancer as well. Recent studies using aggregate data[76,149] have also confirmed that I-131 radiotherapy is associated with an increased risk for the development of second malignancies as well as with an increase in overall mortality for patients with DTC. The risk for the development of secondary malignancies was found to be greater in younger patients.[149] Additionally, Rubino et al[76] discovered that the risks of secondary malignancies increased significantly with increasing cumulative amounts of RAI administered.

A significant late effect of I-131 radiotherapy is the development of pulmonary fibrosis, which occurs in those patients with thyroid cancer who have lung metastases. The risk of pulmonary fibrosis correlates with the intensity of I-131 uptake and varies inversely with the age of the patient, occurring in 10% of children but only 1% of adults with DTC.[101,120] The risk of pulmonary fibrosis has been shown to be dependent on the retained dose of I-131 in patients with DTC and pulmonary metastases and is another reason to obtain dosimetry to guide RAI dosing in this group of patients.

## Surveillance and Long-Term Follow-Up of DTC

Long-term follow-up in children with DTC includes periodic physical examinations and disease surveillance based on laboratory testing and neck US. It is important to verify that TSH is suppressed and to monitor serum thyroglobulin levels, the most important biochemical test to detect disease recurrence. At the same degree of TSH suppression, the Tg level on $LT_4$ is considered to be the best predictor of changes in tumor mass,[95,150] although a negative-result Tg on $LT_4$ does not predict a negative-result TSH-stimulated Tg.[151,152] After total thyroidectomy and RAI, in the absence of TgAb, serum thyroglobulin levels greater than 2 ng/ml with rhTSH stimulation or greater than 8-10 ng/ml following thyroid hormone withdrawal are diagnostic of tumor recurrence.[153] However, if Tg on $LT_4$ is detectable, there is no added value in performing a TSH-stimulated Tg measurement as the likelihood of persistent or recurrent disease is high.[5] TgAb, detected in up to 25% of patients with DTC, renders Tg results uninterpretable.[154,155] As such, the pediatric guidelines[5] recommend that concomitant TgAb should be measured simultaneously in all specimens sent for Tg measurement and further, that Tg and TgAb measurements be performed in the same laboratory using the same assay technique each time.

The recommended surveillance schedule[5] for children with DTC in whom there is no evidence of disease and in whom TgAb are absent is to obtain a neck US at 6 months after thyroidectomy for all ATA pediatric risk groups, then annually for 5 years for the ATA pediatric low-risk patients, as opposed to every 6-12 months for 5 years for the ATA pediatric intermediate- and high-risk groups. In addition, serum Tg level on $LT_4$ is obtained every 3-6 months for 2 years and then annually for the ATA pediatric low-risk patients, every 3-6 months for 3 years and then annually for the intermediate-risk group, and every 3-6 months for 5 years and then annually for the high-risk group. TSH-stimulated Tg +/− diagnostic I-123 scan can be considered in 1-2 years in patients treated with I-131. Longer-term follow-up (after 5 years) should be individualized and based on risk of recurrence.

A total of two separate algorithms are offered within the pediatric-specific guidelines[5]: one for use in managing those children with suspected or known residual or recurrent local disease and the other for those with known distant metastatic disease following initial therapy. These algorithms are based on evaluation of suppressed Tg levels and knowledge of previous disease extent 6-12 months following completion of primary therapy in those with suspected residual or recurrent local disease and at 12 months after initial therapy in those with known distant metastases.

The frequency of radioiodine (I-123) scanning in the long-term follow-up of children with DTC has not been well-established. Various strategies had been previously proposed[94,115] and it was suggested that, in addition to monitoring serial Tg levels, repeat DX WBS be performed at varying intervals following I-131 treatment. According to the current ATA pediatric guidelines,[5] there is no role for serial I-123 scintigraphy in children who were not previously treated with I-131; rather, serial neck US and serum Tg levels on $LT_4$ suffice. On the contrary, performing a repeat DX WBS may be of benefit in children with known iodine-avid metastases based on a prior posttherapy scan once significant time has elapsed (1-2 years) to assess response to prior I-131 treatment. There is no benefit in repeating a DX WBS once negative, unless recurrent disease is suspected clinically, based on physical examination, US, or rising LT4 levels.

## Conclusions

Despite the aggressive nature of pediatric DTC compared with adults, overall survival is excellent. However late recurrences occur, often decades after treatment, mandating lifelong surveillance. Additionally, recent data with long-term follow-up spanning decades reveal an increase in all-cause mortality for survivors of childhood DTC, predominantly due to the development of secondary malignancies in those treated with I-131 radiotherapy. These issues complicate the management of children with DTC. Although uncertainty and controversy persist in many areas (eg, the proper use of RAI; the use of novel therapies in those with iodine-unresponsive advanced disease; the interpretation of Tg and TgAb levels; and the methodology, effectiveness, and psychological effect of long-term surveillance), the inaugural pediatric management

guidelines[5] offer recommendations based on best available data to date and, as such, provide a valuable resource to all involved in the care of children with DTC.

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