The Treatment of Differentiated Thyroid Cancer in Children: Emphasis on Surgical Approach and Radioactive Iodine Therapy

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Pediatric thyroid cancer is a rare disease with an excellent prognosis. Compared with adults, epithelial-derived differentiated thyroid cancer (DTC), which includes papillary and follicular thyroid cancer, presents at more advanced stages in children and is associated with higher rates of recurrence.

Because of its uncommon occurrence, randomized trials have not been applied to test best-care options in children. Even in adults that have a 10-fold or higher incidence of thyroid cancer than children, few prospective trials have been executed to compare treatment approaches. We recognize that treatment recommendations have changed over the past few decades and will continue to do so.

Respecting the aggressiveness of pediatric thyroid cancer, high recurrence rates, and the problems associated with decades of long-term follow-up, a premium should be placed on treatments that minimize risk of recurrence and the adverse effects of treatments and facilitate follow-up. We recommend that total thyroidectomy and central compartment lymph node dissection is the surgical procedure of choice for children with DTC if it can be performed by a high-volume thyroid surgeon. We recommend radioactive iodine therapy for remnant ablation or residual disease for most children with DTC. We recommend long-term follow-up because disease can recur decades after initial diagnosis and therapy.

Considering the complexity of DTC management and the potential complications associated with therapy, it is essential that pediatric DTC be managed by physicians with expertise in this area. **(*Endocrine Reviews* 32: 798–826, 2011)**

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Abbreviations: AHASA, As high as safely administrable; CT, computerized tomography; DTC, differentiated thyroid cancer; dWBS, diagnostic whole-body scintigraphy; FNA, fine-needle aspiration; FNMTC, familial nonmedullary DTC; FTC, follicular thyroid cancer; MRI, magnetic resonance imaging; MTC, medullary thyroid cancer; PET, positron emission tomography; PTC, papillary thyroid cancer; RAI, radioactive iodine; rhTSH, recombinant human TSH; RLN, recurrent laryngeal nerve; SPM, second primary malignancy; Tg, thyroglobulin; TgAb, Tg antibody; THW, thyroid hormone withdrawal; WBS, whole-body scan.

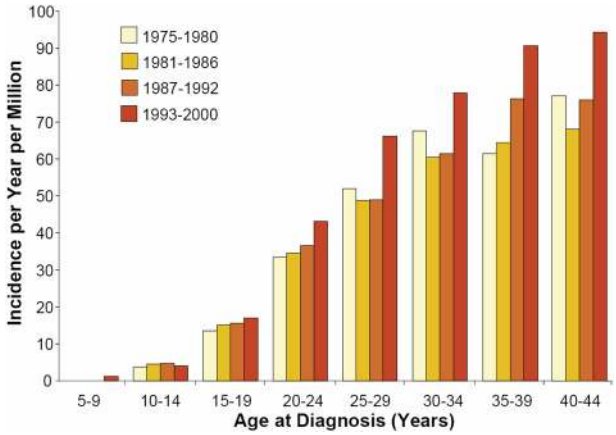

FIG. 1. The changing incidence of thyroid cancer as related to age. [Derived from (4).]

I. Introduction

Pediatric thyroid cancer is a rare and treatable disease with an excellent prognosis (1). Compared with adults, epithelial-derived differentiated thyroid cancer (DTC), which includes papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC), presents at more advanced stages of disease in children and is associated with higher rates of recurrence. Properly applied, surgery and adjuvant radioactive iodine (RAI) therapy can minimize recurrence risks.

Because of the uncommon occurrence of this disease, randomized trials have not been applied to test best-care options in children. Thus, we are left to reflect on a relatively modest number of reports about pediatric patients with DTC and more extensive studies of adults. Even in adults that have a 10-fold or more higher incidence of thyroid cancer than children, few prospective trials have been executed to compare treatment approaches.

This review considers a large number of reports pertaining to DTC presentation, therapeutic approaches, and outcomes of children with DTC. Reports for review were identified in online PubMed searches, along with reports of DTC in children referenced by other reports on the subject. We consider the experience related to the treatment of children who developed DTC after the Chernobyl nuclear reactor explosion. We consider reports of DTC and its treatment in adults because such studies greatly outnumber those in children. We consider the important recent management guidelines of the American Thyroid Association (ATA) (2), noting areas where differences in therapeutic approaches in children and adults should be appreciated. We also recognize that treatment and follow-up recommendations for DTC have changed over the past few decades and will continue to do so.

II. Thyroid Cancer in Children

Recent data from the Surveillance, Epidemiology, and End Results (SEER) registry from 1973–2004 provide contemporary insights into thyroid cancer in children (1). Thyroid cancer in the pediatric population is rare, because a total of 1753 patients with malignant thyroid neoplasms were identified with an age-adjusted annual incidence of 0.54 cases per 100,000 persons (Fig. 1). In children less than 10 yr of age, the incidence of DTC is one per 1,000,000 (1). In children from 10–14 yr of age, the incidence of DTC is one per 200,000 (1). In children from 15–19 yr, the incidence of DTC is one in 75,000 (1). After puberty, girls are four times more likely to have thyroid cancer than boys, whereas prepubertal rates are similar in boys and girls (1, 3). The incidence of pediatric thyroid cancer is increasing by an annual incidence of 1.1% per year (Fig. 1) (1, 4). The thyroid cancer types in children in the United States are PTC in 60%, follicular variant of PTC in 23%, FTC in 10%, and medullary thyroid cancer (MTC) in 5% (1).

Compared with adults, children with DTC present with more extensive disease (5–14). Lymph node involvement at diagnosis is seen in 40–90% of children (5–15), compared with 20–50% of adults (16). The prevalence of distant metastases, most commonly lung, is 20–30% in children *vs.* 2% in adults (5–14, 17). Multifocal disease is more common in children than adults and is seen in about 40% of childhood PTC cases. It is believed that proliferation of individual clones, not metastases, accounts for the multifocal nature of disease (18, 19).

As in adults, it is reasonable to apply the same definition for remission and relapse in children. Per recent guidelines (2, 20, 21), being in remission or disease free is defined as undetectable thyroglobulin (Tg) levels (<1.0 μg/liter) in the absence of Tg antibodies (TgAb), no evidence of neck disease by ultrasound, and negative diagnostic ^{131}I, ^{124}I, or ^{123}I scans. Recurrence is said to occur when cancer is detected after initial treatment was viewed to have been successful in eliminating all detectable cancer.

In general, DTC with onset at less than 10 yr of age appears to have higher recurrence and mortality rates than pre-

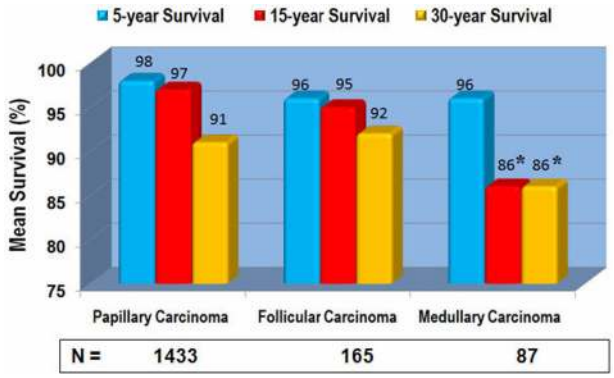

FIG. 2. The 5-, 15-, and 30-yr survival rates for papillary, follicular, and medullary thyroid carcinoma in children. *, $P = 0.006$. [Derived from (1).]

sentation at older ages (17, 22). DTC onset older than 10 yr of age behaves similarly to young adults (17). DTC is generally more widespread at presentation and more likely to recur in younger than older children (23). Other investigators, however, have found that DTC has similar biological properties in younger children and adolescents (24).

Fortunately, even in the presence of metastatic disease, long-term follow-up data show 30-yr survival rates of 90–99% for children with DTC (Fig. 2) (10, 11, 25). Even with distant metastases, mortality rates are more favorable in children than adults (26), and pulmonary metastases can remain stable for extended periods (27). The favorable prognosis reflects the fact that most young patients have well-differentiated tumor types, few have bone metastasis, and most tumors respond well to RAI therapy.

III. Risk Factors for Thyroid Cancer in Children

In most cases, specific risk factors for DTC cannot be identified in children; however, risk factors are found in a subset of patients. Exposure to low-level head and neck irradiation has been recognized for more than six decades as predisposing to DTC (28, 29). Low-level radiation doses to the thyroid of less than 30 Gy (3000 cGy or Rad) increase the risk for cancer, with the risk being higher at progressively younger ages (30–32). Above 20 yr of age, the risk of thyroid cancer after low-level irradiation is either very low or undetectable (31, 32).

Cancer risks related to low-level radiation were first observed more than half a century ago in children treated for tinea capitis and acne with irradiation (28, 29). Thyroid cancer rates were observed to increase in children exposed to the atomic blasts in Japan (33, 34). Pediatric DTC rates increased after exposure to radioactive fallout after above-ground nuclear weapon testing (35–37). Most recently, it has been suggested that childhood dental radiographs increase DTC risk 2-fold (38).

The latency period between the time of radiation exposure and cancer onset in children is typically 10–20 yr (29, 31, 32). Strikingly, more than 5000 children developed DTC after radiation exposure after the nuclear reactor explosion at Chernobyl in 1986 (39), a link first reported in 1992 (31, 40, 41). Compared with other instances of child radiation exposure, cancers were seen as early as 5 yr after the reactor explosion in the young children (42–44).

One of the largest growing groups of children at risk for thyroid cancer is childhood cancer survivors who have had head and neck irradiation. Thyroid cancers are the most common second malignancy in children who have had Hodgkin's and non-Hodgkin's lymphomas (30, 45–48). Thyroid cancer is the third most frequent malignancy in leukemia survivors (30, 45–48).

Of the children at risk for thyroid cancer, those treated for cancer before 10 yr of age are at highest risk (46, 48). The incidence of DTC increases linearly with radiation doses up to 30 Gy (3000 cGy or rad) and declines with higher doses (30, 46–48). Thyroid cancer in this group develops with a mean latency of 10 yr, with a range of 5 to more than 20 yr (30, 46–49). Considering the reported DTC latency and data showing a high occurrence of DTC in childhood cancer survivors with previous head and neck irradiation, we recommend that thyroid ultrasound studies be performed 5 yr after radiation exposure. Although we do not have data to show what the optimal times between subsequent ultrasound studies should be, based on recommendations pertaining to thyroid nodules (2) and familial DTC (50), it seems reasonable to repeat studies about every 12 months.

Practitioners who argue that palpation alone is sufficient for the follow-up of individuals who have had head and neck irradiation need to recognize that ultrasonography will detect thyroid nodules well before palpation (49, 51). It must also be recognized that earlier rather than later recognition of thyroid cancer can lead to less extensive surgery, lower administered activities of ^{131}I, and a better chance of cure.

Thyroid cancer in children can also be observed in families. Familial nonmedullary DTC (FNMTC) is diagnosed when three or more individuals in the family have DTC (52–55). Although studies are under way to identify specific genes leading to cancer risk in FNMTC, specific common molecular signatures have yet to be identified (56–58). When FNMTC is present, it is recommended that thyroid ultrasonography be performed every year or two beginning at 8 yr as part of tumor surveillance. DTC in children with FNMTC has been identified as early as 8 yr of age, and the age of cancer occurrence is generally

younger in the second generation than in the first generation (50).

Other rare genetic syndromes are associated with thyroid cancer. Cowden's syndrome is caused by mutation in the *PTEN* gene and is a rare autosomal dominant disorder associated with hamartomas of mucosal surfaces and DTC (59–61). Cancer in Cowden's syndrome has been identified as early as 8 yr (62). Gardner syndrome (familial colorectal polyposis) is an autosomal dominant condition associated with multiple polyps in the colon and other tumors including DTC (63–65). Gardner syndrome is caused by mutation in the *APC* gene located in chromosome 5q21 (63, 64).

Werner syndrome, caused by a mutation in the *WRN* gene, a DNA helicase, is a very rare autosomal recessive disorder characterized by premature aging (61). The syndrome is associated with DTC, melanomas, and sarcomas (61). Certain forms of congenital hypothyroidism, caused by mutations in the *TPO* gene, can lead to thyroid nodules goiter (66) and rarely DTC (67).

Mutations in the *RET* protooncogene typically lead to medullary carcinoma of the thyroid in multiple endocrine neoplasia 2a and 2b and isolated familial medullary carcinoma of the thyroid, which are not forms of DTC (68).

IV. Genetics of Thyroid Cancer in Children

The genetics of thyroid cancer is receiving much attention. Studies of younger *vs.* older individuals with DTC have revealed differences in gene profiling studies of tumors, but no specific gene clusters associated with DTC have been identified in the young (69).

Studies of candidate genes have revealed differences between children and adults. In adults, *RAS* mutations have been observed in 12% of adults with PTC, 29% in FTC, and 50% of patients with anaplastic cancer (70). In children, however, *RAS* mutations were not seen in children with Chernobyl-related tumors (71, 72), and only 6.5% of children with PTC in another cohort had mutations (70).

In children with DTC, gene rearrangements are more common than point mutations (73). In papillary carcinoma, *RET/PTC* rearrangements have a higher prevalence in children than in adults (47–65 *vs.* 3–34%) (74–76). There are several described *RET/PTC* rearrangements. Two specific mutations, *RET/PTC1* and *RET/PTC3*, account for 80% of the *RET* gene recombinations seen in children and adults (73). The *RET/PTC1* type rearrangement is more common in tumors with classic papillary architecture and is seen in approximately 65% of sporadic cases diagnosed in older children (73, 77). *RET/PTC3* is more common in patients with radiation-induced PTC, especially those diagnosed 4–8 yr after exposure. This mutation is associated with the solid variant of papillary carcinoma, a histological subtype rarely seen in the general population, which has a short latency period and more aggressive clinical behavior (13, 73, 77).

In follicular carcinoma, fusion of the *PAX8* and *PPARG* genes (*PAX8-PPARG*) is seen in up to 50% of adult cases, but there are no data for children (73). Point mutations seen in adult thyroid tumors, such as *RAS* and *BRAF*, are uncommon in children (73, 78, 79).

BRAF mutations (V600E) predict a more aggressive clinical course and are seen in up to 45% of adults with PTC (78, 80–82). In children with post-Chernobyl PTC, *RET* rearrangements were seen in 41% of children, V600E *BRAF* mutations were seen in 12% of children, and *RET* and *BRAF* mutations were not found to coexist (83). When the T1796A *BRAF* mutation was studied in children with PTC, the mutation was seen in 3% of young children with spontaneous PTC, in 0% of young children with post-Chernobyl PTC, and in 24% of adolescents and young adults with post-Chernobyl PTC (84). In sporadic PTC, V600E mutations were seen in 3–6% in other studies of children (78, 83, 84). Thus, in most cases, *BRAF* mutations are not present in children with DTC.

V. Nodule Evaluation

Thyroid cancer needs to be suspected when thyroid nodules are detected in children and adolescents. In a compilation of 16 different studies that examined the malignancy rate of thyroid nodules in children, 299 of 1134 nodules were malignant for an overall rate of 26% (85). Whereas the rate of thyroid cancer in published studies of children with thyroid nodules is about 26% (85), this incidence is substantially higher than one would expect based on the incidence of thyroid cancer in children. As such, it is possible that patient selection bias has skewed the results of such studies. Prospective studies of a population of healthy children are needed to fully address this issue.

When thyroid nodules are detected, serum TSH, estimated free T_4 and/or total T_4, and a neck ultrasound should be obtained. Calcitonin levels should be assessed to screen for medullary thyroid cancer, which accounts for 3–5% of pediatric thyroid cancers (1, 86). If the TSH is suppressed, a radionuclide scan may identify a hyperfunctioning nodule.

Ultrasound characteristics suggestive of malignancy include microcalcifications, indistinct margins, and a variable echotexture (20, 49, 87). Ultrasound can determine

the intrathyroidal location of nodules, identify additional nodules, and assess whether there is lymph node involvement (20, 49, 87). In children after Chernobyl, the most reliable ultrasound diagnostic criteria for malignancy were an irregular, subcapsular location and an increased intranodular vascularization by Doppler technique (88). Ultrasonographic appearance alone, however, cannot reliably distinguish between benign and malignant lesions. Thus, fine-needle aspiration (FNA) is indicated for children with thyroid nodules (20).

FNA is the most accurate means to evaluate whether a thyroid nodule is malignant (20). Reports of FNA performed in children describe similar specificity and sensitivity as adults (89–91). Difficulty arises when the FNA is nondiagnostic or the cytology is indeterminate, because malignancy can be present up to 50% of the time with such cytological features (92). If this occurs, the clinician may repeat the ultrasound study and FNA within 3–6 months or proceed to surgical removal.

The nodule size at which point FNA should be performed in children is a matter for discussion (93). In adults, recent recommendations suggest that FNA be performed when nodule diameter is or exceeds 1 cm (20). However, because about 30% of pediatric thyroid nodules are malignant, and FNA can be performed in nodules less than 1 cm, it is reasonable to biopsy smaller lesions in children if such capabilities are available, especially for nodules 0.5–1.0 cm. Ultrasound-guided FNA is recommended especially in children because of the difficulty to biopsy small nodules, which rarely can be palpated (94). When FNA is performed in children, because this is an uncommon procedure, special expertise outside pediatric departments may be needed.

VI. Thyroid Cancer Staging

There are multiple postoperative staging systems for DTC. The ATA guidelines advocate use of the American Joint Committee on Cancer (AJCC) and Union International Contre le Cancer (UICC) classification system (20). This system is used by hospital tumor registries and is clinically useful in describing the extent of disease and predicting disease mortality (20). Thyroid cancer patients under 45 yr of age, and thus all children, are classified as stage I (any tumor, any lymph node, metastasis 0) or II (any tumor, any lymph node, metastasis 1) (20).

Such staging is based on mortality and does not distinguish pediatric and adult DTC that behave differently (2, 20, 95). Fortunately, mortality is low in pediatric patients, but unfortunately, recurrence rates are high, which can be associated with morbidity. As such, labeling a pediatric patient as stage I or stage II is of little practical benefit, and the development of staging systems that consider risk of recurrence and disease and treatment related morbidity are needed. Alternatively, the response-to-therapy system estimating the risk of having persistent or recurrent disease recently proposed by Tuttle *et al.* (96) might be tested on a pediatric population.

The UICC/AJCC classification of the primary tumor carcinoma, which has been developed for adults, is also not valid for children. For example, a tumor of 1 cm size in a 10-yr-old child with a thyroid volume of approximately 8–9 ml cannot be compared with that in adults with a 2-fold higher volume (20–25 ml). Tumors of approximately 4 cm in greatest diameter, which can completely occupy one of the thyroid lobes in a child, are also less likely to still be limited to the thyroid (97). For children, the metastasis-age-completeness of resection-invasion-size (MACIS) scheme has been shown to be helpful in determining the risk of recurrence, provided that a lower cutoff score is used than that used for adults. This system, however, pertains only to PTC (25, 98).

The notion that small tumors can be labeled as low risk in children also does not apply as in adults. Adults with DTC are considered low risk if they do not have any of the following tumor characteristics (2, 20): 1) local or distant metastases; 2) residual macroscopic tumor; 3) tumor invasion of locoregional tissues or structures; 4) aggressive histology such as tall cell, insular, columnar cell carcinoma, or vascular invasion; and 5) ^{131}I uptake outside the cervical region. Most pediatric patients will present with these characteristics, and rates of recurrence for pediatric patients not treated with total thyroidectomy and RAI are 20–30% (5, 9, 12, 99–101). Thus, very few pediatric patients are low risk.

VII. Cohort Studies of Children with Differentiated Thyroid Cancer

Recognizing that thyroid cancer is rare in children, studies reporting outcomes of more than 100 children are few (5, 99–101), and there are a small number of reports with sample sizes between 25 and 100 patients (10, 12, 23, 102, 103). Outcomes of some of these studies (5, 15, 22, 26, 27, 99, 104–117) were recently independently tabulated by Thompson and Hay (9) and Luster *et al.* (12).

In general, the following observations about pediatric DTC can be made. 1) About 70% of children present with disease that is metastatic to lymph nodes. 2) About 15% of children present with distant metastatic disease, most commonly to the lungs. In more than 50% of these cases, lung tumors are micrometastases that are not apparent with chest radiographs or computerized tomography (CT) scan-

TABLE 1. Pediatric patients with thyroid cancer: large cohort studies (>100 patients)

Authors	Year	Cohort	n	Favorable effect	
				RAI	TTX
Welch Dinauer *et al.* (5)	1998	United States	170	ND	Yes
Demidchik *et al.* (99)	2007	Chernobyl	740	Yes	Yes
Handkiewicz-Junak *et al.* (100)	2007	Poland	235	Yes	Yes
Hay *et al.* (101)	2010	United States	215	No[a]	Yes

Favorable effect indicates lower rate of recurrence and/or improved disease-free survival. ND, Not possible to determine; TTX, total thyroidectomy.

[a] Possible treatment effect observed. RAI was administered to patients with more extensive disease and outcome similar to patients with less extensive disease.

ning but are apparent with RAI scans (17). 3) Recurrence rates over 5–20 yr are as high as 30%. 4) About 10–20% of children will have complications related to surgery. 5) A standardized approach to the care of children with DTC is lacking. Some children are routinely treated with RAI, whereas others are not. Some children are treated by lobectomy, and others are treated by total thyroidectomy and central compartment lymph node dissection.

Several of the large cohorts involving more than 100 children warrant discussion as detailed immediately below (Table 1).

In 1997, Welch Dinauer *et al.* (5) reviewed 170 cases of childhood DTC in the Department of Defense Automated Centralized Tumor Registry from 1953 and 1996, including 137 cases of PTC and 33 cases of FTC. In the PTC group (median follow-up, 6.6 yr), one patient died, 21 developed local recurrence, and six developed distant recurrence. Recurrence was more common in patients with multifocal or large tumors, cervical lymph node metastases, or distant metastasis at diagnosis. In the FTC group (median follow-up, 5 yr), no patient died of disease, but five developed recurrence. As with PTC, recurrence was more likely in patients with multifocal tumors.

In a subset of the above patients (118), outcome was related to the surgery performed in 37 with PTC at 21 yr of age or younger. The incidence of surgical complications and the risk of recurrence based on the extent of initial surgery and adjunctive therapy with thyroid hormone or RAI were examined (118). Patients treated with lobectomy were more likely to have recurrence than patients treated with subtotal or total thyroidectomy (118). The activities of RAI used were variable, because patients were treated in different centers in a nonstandardized manner (118). However, there were too few patients to determine whether treatment with thyroid hormone or RAI offered additional benefit (118). The authors concluded that more extensive surgery was associated with a lower risk of recurrence (118).

In 2006, Demidchik *et al.* (99) reported outcomes of 740 cases of DTC in children of Belarus. Total thyroidectomy was performed in 426 (57.6%), lobectomy in 248 (33.5%), and subtotal thyroidectomy in 58 (7.8%), and eight patients (1.1%) had partial lobectomy (99). The mean follow-up period was 9 yr. Recurrence was seen in 204 cases (27.6%), including 73 local relapses (9.9%), 90 distant metastases (12.2%), and local and distant recurrences in 41 patients (5.5%). The risk of recurrent nodal disease correlated with young age at diagnosis, multifocal carcinomas, lymph node positivity at presentation, and the lack of neck lymph node dissection. For lung metastases, the significant risk factors were female gender and young age (99). The 5- and 10-yr survival rates for the entire groups were 99.5 and 98.8%, respectively (99).

A total of 214 patients (22%) had complications related to thyroid surgery (99). Permanent recurrent laryngeal nerve (RLN) palsy occurred in 46 children (6.2%; unilateral 5.1%, bilateral 1.1%) (99). Thirteen patients (1.8%) developed transient RLN palsy (99). Tracheostomy was performed in four patients with bilateral nerve injuries. Permanent hypoparathyroidism was detected in 91 patients (12.3%). An additional 80 (10.8%) developed transient hypocalcemia (99).

A total of 464 children were treated with RAI (99). The activities of RAI used ranged from 50 MBq/kg for ablation to 100 MBq/kg for therapy of advanced disease (1.45–2.7 mCi/kg) (99); these activities were derived from standard activities of 3500 MBq (95 mCi) for ablation and 7000 MBq (190 mCi) ^{131}I for therapy in a 70-kg adult. A total of 336 children (72%) underwent ablation of thyroid remnant, and 128 (27%) received treatment for metastatic disease (99). Complete response was seen in 271 patients (58%); 159 cases (34%) had undetectable ^{131}I uptake and Tg levels between 1 and 10 ng/dl; 34 (7%) were nonresponders with ^{131}I tumor uptake apparent (99).

In 2007, Handkiewicz-Junak *et al.* (100) assessed the incidence of and predictive factors for thyroid bed recurrence or lymph node recurrence in 235 patients with DTC diagnosed at 18 yr of age or younger from 1973–2002 (100). Forty (17%) of these patients had distant metastases at diagnosis (100). During a median follow-up of 7 yr, no DTC-related deaths occurred (100). Two hundred three children (86%) remained recurrence free, and 32 children (14%) had lymph node recurrence (100). The median time from the first surgery to lymph node recurrence was 3 yr (100).

^{131}I was given after surgery to 174 children (74%) (100). Children under 12 yr of age were given 74–93 MBq/kg (2–2.5 mCi/kg). Older children were given 2.2–3.7 GBq (59–100 mCi) when no distant metastases were observed or 3.7 GBq (100 mCi) when distant metastases were present (100). Rates of thyroid bed recurrence were 20% at 10 yr in the children not treated with RAI *vs.* 1% when RAI was given (100). Rates of lymph node recur-

rence were 15% at 10 yr in the children not treated with RAI *vs.* 4% when RAI was given (100).

Risk factors for thyroid bed recurrence were less than total thyroidectomy and the lack of postsurgical radioiodine treatment (100). For nodal recurrence, risk factors were incomplete primary lymph node management. The lack of adjuvant RAI was the greatest predictor of recurrent disease after the presence of distant metastasis at presentation (100).

In 2010, Hay *et al.* (101) at the Mayo Clinic reported outcomes of 215 PTC patients younger than 21 yr old managed from 1940–2008. The patients were 3–20 yr old (median age, 16 yr); the median follow-up was 29 yr (101). Sixty-six percent had distant metastases at presentation, 5% had incomplete tumor resection, 86% had nodes removed at initial surgery, and 78% had nodal metastases (101). At 20 yr, the recurrence rates at local, regional, and distant sites were 7, 21, and 5%, respectively (101). PTC recurred in 32% by 40 yr. During 1940–1969, local and regional recurrence rates after unilateral lobectomy were significantly higher than after total thyroidectomy (101).

During 1950–2008, radioiodine remnant ablation was administered within 18 months to 32% but did not diminish the 25-yr regional recurrence rate of 16% seen after total thyroidectomy alone (101). The mean activity of ^{131}I was 79 mCi (2.9 GBq) (101). Yet, considering the incomplete thyroid resection in many patients and lack of detail provided as to who was treated with RAI, it is difficult to fully assess RAI efficacy in this cohort (101). In addition, assessment of Tg was not included as part of follow-up (101), which is a considerable limitation in determining whether recurrence has occurred or not. The Mayo Clinic data raise the possibility that RAI is indeed effective, because those receiving ^{131}I were more likely to have more extensive disease than those who did not receive it and nonetheless had a prognosis similar to those with less advanced disease who were not treated with RAI (101).

Collectively, these studies show that DTC recurrence risk can be reduced by 1) performing total thyroidectomy *vs.* lobectomy; 2) performing compartment lymph node dissection *vs.* selective or no lymph node dissection; and 3) administering RAI.

VIII. Surgical Options

The preoperative evaluation of pediatric patients with thyroid disease involves both a general examination to rule out comorbid conditions and a thyroid-focused evaluation (2, 20, 119). Thyroid assessment involves evaluation of the clinical and biochemical thyroid status combined with a detailed examination of the thyroid gland and cervical region. The neck exam focuses on thyroid size, nodularity, airway status, and an assessment of cervical lymph nodes. Ideally, surgical candidates should have their vocal cord function evaluated preoperatively, and this is essential if they have evidence of vocal cord compromise or a history of previous cervical surgery.

A neck ultrasound using a high-resolution probe (7.5 MHz or higher) should be performed to examine the contralateral thyroid lobe and the central and lateral neck compartments (120–123). Most children with PTC will have metastatic cervical lymph node disease (5, 15, 24, 43, 99, 115, 124–126). FNA before surgery of suspicious lymph nodes should be performed. Ultrasonography may not detect the full extent of lymph node involvement (128, 129). When further delineation of potential neck disease is needed, imaging using contrast-enhanced CT or magnetic resonance imaging (MRI) may be considered.

The location of lymph node compartments is important to consider in assessing the distribution of metastatic spread and operative sites. Lymph node compartments are designated I–VI (20). The central compartment (VI) is the most common site of lymph node spread (130–132) and encompasses the region between the hyoid bone and sternum and the common carotid arteries (20).

Surgical options for DTC include total thyroidectomy, near-total thyroidectomy, subtotal thyroidectomy, or lobectomy (119). Anatomically, the thyroid is divided into the right and left lobes, which are connected by the isthmus. The thyroid gland is encased by a capsule. A total thyroidectomy refers to a complete resection of the thyroid gland via an extracapsular dissection (133, 134). If it is determined intraoperatively that a complete extracapsular dissection will result in irreversible damage to either the RLN or parathyroid glands, the capsule can be entered and a small amount of thyroid tissue can be left *in situ* to avoid injury to either the RLN or parathyroid glands, a procedure referred to as a near-total thyroidectomy (133, 134).

A subtotal thyroidectomy refers to removal of the contralateral lobe, the isthmus, and the medial portion of the ipsilateral thyroid lobe (133, 134). The blood supply to the remaining thyroid tissue is left intact, along with the parathyroid gland, thus theoretically reducing the risk of postoperative hypoparathyroidism (133, 134). Additionally, dissection near the RLN is avoided, thus reducing the chance of damaging the nerve. The remaining thyroid tissue is vascularized and typically remains metabolically active, avoiding or reducing the need for thyroid hormone replacement. A lobectomy refers to an extracapsular resection of an anatomic lobe or anatomic lobe and isthmus.

In 1981, Mazzaferri and Young (135) studied 576 adult patients with PTC and a median follow-up of 10 yr and

observed that total thyroidectomy was associated with lower recurrence and mortality than subtotal thyroidectomy. Differences in outcome were not observed when cervical lymph node metastases were simply excised *vs.* more aggressive neck dissection (135).

In 2007, Bilimoria *et al.* (136) examined whether the extent of surgery affects outcomes for PTC by interrogating the National Cancer Data Base (1985–1998) that included 52,173 adults who underwent surgery for PTC. A total of 43,227 (82.9%) underwent total thyroidectomy, and 8,946 (17.1%) underwent lobectomy (136). For PTC tumors smaller than 1 cm, the extent of surgery did not impact recurrence or survival (136). For tumors that were 1 cm or larger, lobectomy resulted in higher risk of recurrence and death (136). Thus, total thyroidectomy for PTC 1.0 cm or larger improved outcomes.

In children, each of the large cohort studies, and several of the smaller sample size studies, demonstrate increased relapse rates with lobectomy *vs.* total thyroidectomy (5, 99–101, 137). Welch Dinauer *et al.* (5) observed relapse rates of about 50% with lobectomy *vs.* 14% with total thyroidectomy. Handkiewicz-Junak *et al.* (100) observed relapse rates of about 20% with lobectomy *vs.* 3% with total thyroidectomy. Hay *et al.* (101) observed relapse rates of about 30% with lobectomy *vs.* 12% with total thyroidectomy.

Each operation can be performed without lymph node dissection, the selective removal of lymph nodes that appear pathological at surgery (berry picking), or compartmental lymph node dissection, during which all lymph nodes in a region are systematically removed *en bloc*, irrespective of gross appearance (119, 138).

The extent of lymph node surgery has been the subject of attention (139, 140). Cancer recurrence most commonly occurs in lymph nodes in the laryngotracheal region (130). In children and adults, the greater the lymph node involvement in recurrent disease, the greater is the risk of distant metastasis and mortality (1, 9, 12–14). Lymph node metastasis is a pervasive component of DTC in children, because up to 90% of children with DTC will have nodal disease. Importantly, in up to 50% of cases, DTC involvement of lymph nodes is not detectable by preoperative ultrasonography (131, 141).

Gimm *et al.* (130) examined the outcome of total thyroidectomy coupled with central compartment lymph node removal in 35 adults. Twenty-four patients had lymph node metastases in the ipsilateral central compartment, including patients with T1 tumors (130). Contralateral central lymph node metastases were restricted to patients with T3 or T4 tumors (130). No patient had lymph node metastases in the contralateral cervicolateral compartment.

Machens *et al.* (142) reported on lymph node metastases in primary and reoperative thyroid cancer in adults. Between 1994 and 1999, 296 adults (134 PTC, 162 MTC) underwent total thyroidectomy and a standard resection of at least the central lymph node compartments. Of 10,446 sampled lymph nodes, 1,641 were positive. The ipsilateral lateral compartment was involved almost as often as the central compartment in primary PTC (29 *vs.* 32%) and reoperative PTC (21 *vs.* 37%). The contralateral lateral and mediastinal compartments were uncommonly affected.

In a recent study, Bonnet *et al.* (131, 141) examined lymph node disease in 115 adults presenting with PTC less than 2 cm without ultrasonographically detectable cervical lymph nodes, treated by total thyroidectomy and dissection of the central compartment. Lymph node metastases were present in 41.7% of cases (141).

An important consideration in advocating for routine central lymph node and selected lateral and contralateral lymph node compartments dissection is the increased risk of complications associated with the procedure *vs.* total thyroidectomy alone. Major potential complications include damage to the RLN and parathyroid glands, hemorrhage, and infection (143).

Pediatric data summarized by Thompson and Hay (9) and Luster *et al.* (12) revealed complication rates ranging from 0–40% for RLN injury and 0–32% for permanent hypoparathyroidism (9, 12). Recent database analysis of thyroidectomy complications in the United States showed that children aged 0–6 yr have higher complication rates (22%) than older children (15% for 7–12 yr and 11% for 13–17 yr) (144). Children had higher endocrine-specific complication rates than adults after thyroidectomy (9.1 *vs.* 6.3%) (144). Importantly, surgical outcome was significantly optimized when surgeries were performed by high-volume surgeons, defined as those performing 30 or more thyroid operations per year (144). Yet, even when surgery is performed by high-volume thyroid surgeons, complication rates reach 6% (144).

Another noteworthy consideration is the added complexity of reoperation when macroscopic residual or recurrent disease is detected. Reoperation at previous neck surgical sites is associated with substantially higher complication rates related to local scar tissue and altered postsurgical anatomy (145, 146).

Considering data from children and adults, as such, for children with DTC, we recommend total or near-total thyroidectomy along with central compartment lymph node dissection as part of the initial operation. In addition, lateral compartment dissection with lymph node removal is indicated when lymph node involvement is localized preoperatively by imaging studies and/or FNA. To minimize

the risk of complications, surgery should be performed by high-volume thyroid surgeons.

IX. Radioactive Iodine Therapy

RAI (^{131}I, also referred to as radioiodine) was observed to kill thyroid tumor cells more than 60 yr ago (147, 148). Over the decades since, RAI has gained an increasing foothold in DTC treatment because numerous reports show improved outcomes when RAI is properly applied (2, 20, 135, 149–160). Of particular importance leading to increased use of ^{131}I in DTC were the studies of Mazzaferri and Young (135) showing a very favorable impact of ^{131}I on DTC recurrence and survival in a large cohort of patients (Fig. 3). Favorable RAI efficacy in adults has been reported by other groups as well (155, 157, 159, 161). Readers are referred to interesting historical perspectives on the origins of ^{131}I therapy for DTC by the pioneers in the field (153, 162, 163).

Based on available evidence from studies of adults (2, 20, 135, 149–160), the following conclusions can be rendered: 1) RAI treatment leads to a reduced risk of recurrence and mortality in patients with DTC with postsurgical residual disease; 2) RAI benefit is clearly demonstrated in adult patients with stage III and IV disease but not in stage I; 3) RAI treatment of remnant tissue results in lower rates of DTC recurrence and metastasis; 4) relatively high cumulative activities of RAI [>300 mCi (11 GBq)] may be associated with an increased risk of second primary malignancies (SPM); 5) different approaches have been used to determine activities including empiric dosaging, blood-based upper-limit dosimetry, and tumor dosimetry; 6) RAI efficacy is dependent on factors that include tumor biology and the radiation dose to the tumor; and 7) six decades after introduction for DTC therapy, RAI use is still under refinement and viewed with controversy.

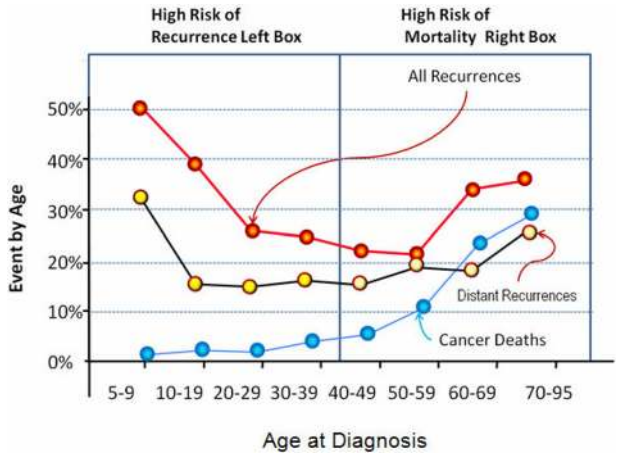

FIG. 3. Outcome event by age (percentage). The *left box* shows the group with high risk for recurrence, and the *right box* shows the group with high risk for mortality. [Derived from (127).]

Several cardinal features of RAI have been summarized by Beierwaltes (149). 1) RAI is easily administered orally. 2) Usually only one therapy course is needed. 3) Even small thyroid cancer metastases not detected by ultrasound or chest radiographs will concentrate ^{131}I selectively in a high target-to-nontarget ratio. 4) The ^{131}I in the metastasis irradiates the metastasis from the inside out, relatively selectively. 5) The ionizing radiation produced by the 609-keV β-rays (10 cGy/μCi·g) may be greater than from conventional x-rays but is confined to a smaller area because the β-radiation penetrates only a few millimeters in tissue. 6) About 85% of the nontarget ^{131}I is excreted in the urine within 1–3 d with a $t_{1/2}$ of approximately 11–15 h. 7) The target concentration of ^{131}I is retained much longer in the tumor with a $t_{1/2}$ of 1–4 d (162).

Tumor intrinsic factors influence RAI efficacy (161). Several defects are present in DTC tissue that influence RAI efficacy. Iodine uptake via the sodium-iodide symporter is always decreased compared with benign tissue of thyroid origin and is undetectable in about one third of patients (161). Iodine organification is markedly reduced in malignant thyrocytes (161). The effective half-life of iodine in tumor tissue is shorter than normal (161). Response to TSH stimulation is usually present, even in the absence of clinically evident ^{131}I uptake (161).

The issue of tumor stunning resulting in reduced efficacy of therapeutic activities of ^{131}I by dosages given for dosimetry purposes also warrants discussion. It has been suggested that less than 2 mCi (74 MBq) of ^{131}I is not associated with tumor stunning and reduced uptake of ^{131}I by tumor tissue. More recent data, however, show reduced ^{131}I uptake and tumor killing with activities as low 10–20 MBq (0.3–0.5 mCi) (164). As such, pretherapeutic activities are limited to 5–10 MBq (0.13–0.27 mCi) of ^{131}I by some groups.

X. ^{131}I Dosage Administration Strategies

There are three major approaches for choosing an appropriate ^{131}I activity for DTC treatment: 1) applying activities based on the bone marrow toxicity limited approach (160, 165); 2) applying specific activities to result in tumor ablation (159); and 3) administering fixed activities (149), also referred to as empiric dosaging, that may or may not be based on a patient's weight.

Historically, empiric fixed activities of ^{131}I were first used by Beierwaltes (162) and Beierwaltes and Johnson (166) in the late 1950s and early 1960s. Activities of 100 mCi (3.7 GBq) were used for remnant and neck residual

disease treatment, 150 mCi (5.5 GBq) for pulmonary metastases, and 200 mCi (7.4 GBq) for bony and other metastases (156, 162, 166). Such treatment resulted in a significant reduction in DTC recurrence and disease-related mortality (156, 162, 166).

Dosaging based on the administered activity that is as high as safely administrable (AHASA) was introduced by Benua *et al.* (160) in the 1960s. Blood doses of greater than 2 Gy (200 cGy or rad) at 48 h, whole-body retention of more than 120 mCi (4.44 GBq) at 48 h, or 80 mCi (2.9 GBq) retained by the lungs at 24 h were associated with bone marrow suppression and lung fibrosis (160, 163). When applied in this manner, activities up to 500 mCi (18.5 GBq) were administered to adults (160) and up to at least 550 mCi (20 GBq) in children (165). Applying this AHASA dosaging strategy, Leeper (168) observed that metastatic papillary cancer in patients less than 40 yr of age was very responsive to ^{131}I.

Recently, AHASA levels have been determined for children (169). For the treatment of distant metastases and DTC recurrence, activities up to 5 mCi/kg (200 MBq/kg) were recently found to be the lowest safe limit (169).

To better define sufficient administered activities associated with remnant and residual disease ablation, Maxon and colleagues (153, 155, 159) introduced dosimetry in the 1970s and 1980s. An absorbed dose of about 300 Gy (30,000 cGy or rad) was needed to ablate normal remnant thyroid tissue (155, 159). To ablate metastatic tumor foci in lymph nodes or distant sites, an absorbed dose of 80 Gy (8000 cGy or rad) was needed (153, 155, 159). Calculated in this manner, activities typical for individuals with regional nodal or pulmonary disease ranged from 100–200 mCi (3.7–7.4 GBq) (155, 159).

It is interesting that higher administered activities were found to ablate normal *vs.* metastatic tissue. This difference was believed to be related to a relatively uniform distribution of ^{131}I in normal residual tissue and its relatively flat, thin anatomy, resulting in β-energy of ^{131}I that would escape from the tissue without depositing much energy therein. It is also possible that some stunning of the residual tissue occurred from the diagnostic ^{131}I that was used (2–3 mCi) (H. Maxon, personal communication).

In contrast, residual nodal disease is generally limited to normal-sized nodes, within which any metastatic foci might be irregularly distributed with some distance between RAI-concentrating deposits, allowing cross-irradiation between them. In addition, the avidity of metastatic foci for ^{131}I is much less than that of normal thyroid tissue, which would minimize any stunning effect of the diagnostic study (Maxon, H., personal communication).

Although formal dosimetry is attractive, empiric dosaging is simpler and is widely used. The latter strategy, however, may result in over- or undertreatment of patients with DTC (170, 171). Considering the risk of pulmonary fibrosis associated with high lung retention [greater than 100 mCi (3.7 GBq) at 24 h] (172), dosimetry should be considered for individuals with lung metastases (173, 174).

Most recently, ^{124}I positron emission tomography (PET)/CT dosimetry has been used to calculate radioiodine therapy activities in DTC (12, 175–177). The approach uses spatial distributions of absorbed doses, dose-volume histograms, and mean absorbed dose estimates for tumors in activity calculation. When applied, the absorbed dose within individual tumors has been observed to be highly variable, ranging from 0.3–4000 cGy (rad) in the same patient (177). These observations may explain the variability in ^{131}I action and why ^{131}I therapy is not universally effective.

This approach requires serial PET or γ-camera scans as well as blood sampling for up to 5 consecutive days (12). With the ^{124}I PET data, each patient's remnant or lesion doses per mCi or GBq of administered ^{131}I is determined (12). Each patient's maximum activity of ^{131}I avoiding a more than 2-Gy dose to the blood is calculated (12). To date, this approach has been applied in a handful of children and a small number of adults (12, 165), yet it holds potential in maximizing RAI efficacy. Recently, simplified and less labor-intensive dosimetric concepts of dosimetry were introduced by Hänscheid *et al.* (178).

XI. Residual Disease Treatment and Remnant Ablation

Residual disease treatment refers to the treatment of tumor that remains after surgery. Remnant ablation refers to the treatment of normal thyroid tissue that remains after surgery (139, 179, 180).

It can be difficult to distinguish residual disease from thyroid remnant, but ^{123}I or ^{131}I pretherapy scans may provide clues. The presence of a small amount of activity at the location of the expected lateral borders of the thyroid gland and the pyramidal lobe is suggestive of thyroid remnant. The presence of uptake in neck areas not contiguous with the thyroid, the mediastinum, or lungs is indicative of residual disease. Considering patterns of lymph node drainage (131, 141, 181), activity in the region bordering the thyroid may represent residual nodal disease in addition to remnant tissue. Thus, in this setting, ^{131}I treatment of presumed remnant tissue may include residual disease.

A. Residual disease

There is general agreement that residual disease should be treated with ^{131}I in both children and adults (2, 20, 21,

151, 182–184). Residual disease therapy has been the subject of reports, a few of which deserve comment and show efficacy.

Hindié *et al.* (185) reported outcomes of 509 adult patients with DTC, of whom 74% had total thyroidectomy and RAI. Twenty patients with pulmonary metastases received RAI. When there was pulmonary disease not observed by chest x-ray, 9% of patients died of neck disease, 18% had persistent lung uptake, and 73% achieved remission at a median activity of 338 mCi (12.4 GBq) of ^{131}I (185). When pulmonary disease was detectable on chest x-ray, 22% died of disease, 55% continued to receive ^{131}I, and 22% had apparent remission after a median cumulative activity of 939 mCi (185). Overall, the 10-yr survival was 84% (185).

In 2004, Bal *et al.* (186) demonstrated RAI efficacy for pulmonary metastases in children and adults. Cumulative activities of administered ^{131}I were about 352 mCi (13 GBq) (186). After an average 3.3 courses of ^{131}I and mean duration of 33.2 months of follow-up, pulmonary lesions disappeared in 14 patients (70%), and Tg levels became undetectable (186). The majority of pediatric patients with DTC were also observed to have x-ray and CT-negative pulmonary metastasis. These metastases were ^{131}I avid and were detectable and treatable with RAI (179).

In 2006, Durante *et al.* (187) reported outcomes in 444 patients treated from 1953–1994 for distant metastases from PTC and FTC (223 had lung metastases only, 115 had bone metastases only, 82 had both lung and bone metastases, and 24 had metastases at other sites). Patients were administered 100 mCi (3.7 GBq) ^{131}I every 3–9 months during the first 2 yr and then once a year until metastatic uptake disappeared (187). In 43% of patients, disease was no longer apparent by ^{131}I whole-body scans (WBS) and radiographs, more frequently in those who were younger and had well-differentiated tumors and had a limited extent of disease. Activities of 3.7–22 GBq (100–600 mCi) were given to 96% of these individuals. Among the patients who achieved a negative study, 7% experienced tumor recurrence. Importantly, survival at 10 yr after initiation of ^{131}I treatment was 92% in patients who achieved a negative study and 19% in those who did not. These data show that ^{131}I treatment was highly effective in younger patients, and they should be treated until the disappearance of any active tissue.

In contrast, Biko *et al.* (188) showed that in 20 children with diffuse pulmonary metastases in whom ^{131}I therapy was stopped before complete remission was achieved because Tg levels or ^{131}I uptake did not notably decline further during consecutive therapies, or an elevated risk of pulmonary fibrosis was assumed, all children showed a continual decline of the tumor marker in the years afterward. The median Tg at the time of cessation of ^{131}I therapy was 56 μg/liter. After a 10-yr follow-up, Tg was less than 10 μg/liter in 18 of 20 patients with no recurrences (188). Thus, it may not be necessary to always repeatedly treat children with pulmonary metastasis, and the interventions should be weighed against potential side effects.

B. Remnant ablation

The role of remnant ablation in DTC therapy has been the subject of recent discussions, with recent recommendations for such changes (2, 189). Remnant ablation has been suggested as adjuvant therapy for patients with low risk of recurrent disease based on the notion that elimination of remaining normal thyroid tissue facilitates long-term follow-up, because Tg-producing normal tissue will not be present (20, 190, 191). Because remnant ablation also treats micrometastases, rates of disease recurrence are generally lower in patients who have received remnant ablation than those who have not (190, 191).

The notion as to whether remnant ablation should be universally performed in adults with low risk of recurrence is in flux (2, 20, 192). A European consensus report addressed this issue in 2005 (189). Adult patients with unifocal microcarcinomas, 1 cm or less, and no node or distant metastases (T1N0M0), have a 2% recurrence rate after surgery (189). Thus, it was suggested that RAI could be withheld for such patients (189). The 2009 revised ATA management guidelines for patients with thyroid nodules and differentiated thyroid cancer similarly suggest that RAI can be avoided in adults with small tumors and no lymph node spread (2). However, it is questionable whether this recommendation is applicable in children, because a 1-cm nodule in small children represents a proportionally much larger tumor than in adults.

The absolute administered activity of ^{131}I needed for remnant ablation is less than that needed for residual disease treatment. Activity-response studies by Bal *et al.* (179) revealed that 25–50 mCi (0.9–1.9 GBq) ^{131}I were sufficient to achieve remnant ablation in 90% of patients defined as a Tg below 10 μg/liter, with 10% of individuals having biochemical evidence of tissue residual. More recent studies in adults suggest that relatively low activities of ^{131}I [30 mCi (1.11 GBq)] can be used to effectively ablate thyroid tissue in about 90% of low-risk patients and is as effective as 100 mCi (3.7 GBq) with effectiveness judged as Tg of 2.0 μg/liter and a ^{131}I neck uptake of 0.1% (193, 194).

Ross *et al.* (195) recently reported recurrence of papillary microcarcinoma cancer in 6% of patients. Recurrence risks were multifocal tumors and less than a total thyroidectomy (195). RAI was not observed to reduce the risk of recurrence (195, 196). The metaanalysis by Sawka

et al. (190), however, showed that the risk of metastasis was reduced by remnant ablation.

The recommendation to withhold RAI in adults with micropapillary cancer and low-risk DTC, however, has been challenged on the following grounds (180): 1) small amounts of ^{131}I [30 mCi (1.11 GBq)] can be administered to ablate remnant tissue in 90% of the patients after thyroidectomy; 2) it is possible to use recombinant human TSH (rhTSH) in preparation for therapy to reduce total-body irradiation; 3) patients can be more reliably assured to be disease free when there is no clinical or ultrasound evidence of tumor and serum Tg is undetectable during both TSH suppression and stimulation when TgAb are not present; and 4) TSH can be maintained in the nonsuppressed ranges when the patient is disease free. As such, remnant ablation is routinely performed by some groups in adults and not by others.

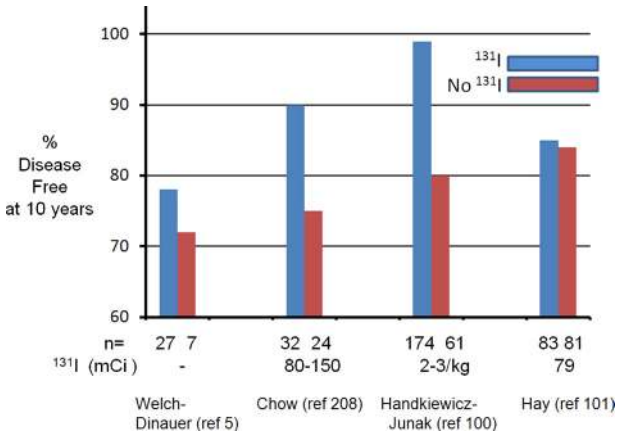

FIG. 4. Disease-free survival at 10 yr after initial therapy in children treated with or without ^{131}I in studies where data for the two different groups are presented. Numbers of children in each group and administered activities are shown. Note that patients were not randomized to be treated or not treated in these studies, and there was a bias toward treating patients with more extensive disease.

XII. RAI Use in Children

The overwhelming majority of pediatric patients will have nodal involvement (5–9, 197). In this setting, based on studies showing the potential extent of lymph node spread (132, 142, 198), it must be assumed that there will be residual lymph tissue containing micrometastases after compartment dissection. Lymph node spread is associated with increased mortality and distant metastatic spread (135, 197, 199, 200), and adjunctive RAI will reduce recurrence risk (99, 100). Thus, RAI is favored in children with DTC.

Studies of children treated with RAI are limited to a small number of reports (12, 17, 23, 99–101, 106, 107, 137, 186, 201–209). These reports include those in which outcomes with and without RAI were compared in retrospective analyses (5, 99–101, 208), studies detailing outcome in patients treated in a standardized manner without comparison groups (23, 95, 210), and reviews on the subject (12, 17, 207, 209) (Table 1 and Fig. 4). To date, randomized studies comparing RAI *vs.* no-RAI or dosage-response studies have not been performed in children, nor has the issue of remnant ablation alone been addressed.

A. RAI *vs.* no-RAI studies

Issues that engender discussion relative to children are the extent of RAI efficacy in pediatric DTC, methods of RAI dosing, and short-term and long-term consequences of RAI therapy. In the pediatric population, which is more prone than the adult population to the adverse effects of ionizing radiation (32, 211–213), the issue of RAI use in children is especially pertinent.

Welch Dinauer *et al.* (5) reported outcomes of 170 pediatric patients treated by total thyroidectomy in 82.5%, cervical node removal in 47%, and RAI in 58.4%. Any recurrence was seen in those treated by surgery alone in 32% and by surgery plus RAI in 34%. However, due to variability in surgical approaches and a possible bias in selection of ^{131}I use, it was not possible for the authors to assess RAI efficacy.

Hay *et al.* (101) report outcomes of 215 PTC patients younger than 21 yr. RAI was administered within 18 months to 32% but did not change the 25-yr regional recurrence rate of 16% after total thyroidectomy alone. The mean dosage of ^{131}I was 79 mCi (2.9 GBq). However, it is not clear whether a standardized approach was used for RAI treatment.

Other studies in which RAI was used in a standardized manner show RAI efficacy. Chow *et al.* (208) applied RAI in pediatric DTC if the tumor was greater than 1 cm, or there was cervical node disease, extrathyroidal extension, residual postoperative disease, or distant metastases. If there were no distant metastases, 80 mCi (2.9 GBq) was administered; and if distant metastases were present, 150 mCi (5.5 GBq). Rates of any recurrence were 42% when RAI was not given and 6.3% when RAI was administered, with rates of lung metastasis being 20 and 0%, respectively (208).

Demidchik *et al.* (99) reported outcomes of 740 cases of DTC in children of Belarus. A total of 464 children were treated with RAI. The activities of RAI used were 1.35–2.7 mCi/kg (50–100 MBq/kg). A total of 336 children (72%) underwent ablation of thyroid remnant, and 128 (27%) received treatment for metastatic disease. Complete response was seen in 271 patients (58%); 159 cases (34%) had undetectable ^{131}I uptake and Tg levels between 1 and 10 ng/dl; and 34 (7%) were nonresponders with persistent ^{131}I tumor uptake apparent.

Handkiewicz-Junak *et al.* (100) assessed the incidence of and predictive factors for thyroid bed recurrence or

lymph node recurrence in 235 patients with DTC diagnosed at 18 yr of age or younger from 1973–2002. ^{131}I was given after surgery to 174 children (74%). Children under 12 yr of age were given 2–3 mCi/kg (74–111 MBq/kg). Older children were given 60–100 mCi (2.2–3.7 GBq) when no distant metastases were observed or 100 mCi (3.7 GBq) when distant metastases were present. Rates of thyroid bed recurrence were 20% at 10 yr in the children not treated with RAI *vs.* 1% when RAI was given. Rates of lymph node recurrence were 15% at 10 yr in the children not treated with RAI *vs.* 4% when RAI was given.

B. Remnant ablation

Studies of RAI application for remnant ablation for low-risk DTC patients have been performed in adults (179); there have not been similar studies in children. Whereas remnant ablation is viewed as optional in adults with low-risk disease, we do not feel that these recommendations should be applied to children for several reasons. 1) Children are more prone to recurrent disease than adults. 2) Children with DTC may have thyroiditis and TgAb (10, 214, 215), which confound follow-up. 3) Long-term follow-up of children is challenging due to relocation and schooling, and many adults are unaware of the nuances of their childhood diseases. Thus, it is important to know whether a child has residual disease or not. 4) There is very little risk associated with remnant ablation in children. 5) There are few low-risk pediatric patients. 6) Knowing whether disease is not present can avoid TSH-suppressive regimens. 7) We need to recognize that medical compliance with adolescents and young adults is sporadic, and we cannot rely on TSH-suppressive therapy to prevent DTC recurrence.

C. Standardized RAI treatment cohorts

Kalemba *et al.* (210) studied 105 children with DTC, of whom 91% had total thyroidectomy and 59% had lymph node metastases. Fifty-nine percent received RAI for remnant ablation and 18% for nodal disease (210). Interestingly, complete remission with RAI was achieved in nine of 12 patients (75%) with pulmonary metastases (210).

Leboulleux *et al.* (95) detailed their approach for RAI with DTC in children. Activities administered were 1 mCi (37 MBq)/kg. The treatment was repeated every 6 months until the patient was considered cured (95). Four to six treatments resulted in cure in 80% of children (95). Of note, the TSH was kept suppressed (<0.1 mU/liter) until cure and less than 0.5 mU/liter once cured. For patients with lung disease, the risk of pulmonary fibrosis was reduced by using 1 mCi/kg or less and greater than 6-month inter-treatment intervals in children (95).

Lazar *et al.* (23) reported the following activities for young and older children with DTC: tumor limited to the thyroid gland, 30–100 mCi (1.11–3.7 GBq); tumor invading the thyroid capsule or surrounding tissues and/or with metastases in the neck or mediastinal lymph nodes, 150 mCi (5.5 GBq); and distant metastases, 175–200 mCi (6.9–7.4 GBq). This adult activity was reduced according to the patient's weight. During the median follow-up of 5 yr, the overall survival rate was 100% for prepubertal (n = 10) and pubertal (n = 17) groups, and no significant difference in evidence of residual tumor after initial therapy or the recurrence rate was seen for the two age groups (10 and 24%, respectively).

Luster *et al.* (12), as well as Biko *et al.* (188), reported the protocol used for children with post-Chernobyl DTC from Belarus. ^{131}I activities used were 1.3 mCi (50 MBq)/kg body weight for remnant ablation and 100 MBq (2.7 mCi)/kg for subsequent further therapy courses or treatment of metastases (12). These activities were derived from adult activities of 100 or 200 mCi (3.7 or 7.4 GBq), standardized for a 70-kg adult. The primary goal of the treatments was to achieve a complete biochemical remission, defined as Tg below 2 μg/liter with a negative diagnostic WBS. Failing to achieve such, the physicians strived to achieve at least a stable partial remission, which was defined as Tg below 10 μg/liter with a negative WBS. Occasionally, ^{131}I therapy was stopped before achieving any of these goals, because either the patient did not show further response to ^{131}I therapy or the risk of developing pulmonary fibrosis was deemed too high based on consecutive assessments of lung function (188). Nevertheless, these children showed a favorable clinical course of disease (188). Of 104 children treated with ^{131}I for pulmonary metastases, complete remission occurred in 28%, stable partial remission in 37%, and partial remission in 35% (12).

D. Reviews

In reviews of the subject, Hung and Sarlis (17) recommended the following activity ranges for children with DTC: 100–150 mCi for thyroid bed disease alone, 150 mCi when cervical nodes were involved, and 200 mCi for lung metastases. It was recommended that activities be adjusted for body size or that dosimetry be employed (17).

Parisi and Mankoff (209) suggested adaptation risk-stratified algorithms for adults: up to 100 mCi (3.7 GBq) for low-risk patients, 150–175 mCi (5.5–6.9 GBq) for those with lymph node metastasis, and activities up to 200 mCi (7.4 GBq) for those very-high-risk patients with large tumors, capsular invasion and extrathyroidal spread, extensive node disease, or distant metastases.

Recently, outcomes of children treated with RAI in children were the subject of a metaanalysis (207). But several

large key studies were not included in the report, and specific recommendations were not given (207).

E. Synopsis

The majority of pediatric patients with DTC present with nodal metastases, are not low risk, and should be assumed to have micrometastases. Based on the above data, we suggest that most children should be treated with RAI to ablate residual disease and reduce the risk of disease recurrence. Administered ^{131}I activities to be applied should range from 100–200 mCi (3.7–7.4 GBq) in physically mature children and may be corrected for body weight 1.35–2.7 mCi/kg (50–100 MBq/kg) in younger children. New analyses show that treatment with at least 200 MBq/kg (5.4 mCi/kg), and in most patients even much higher activities, is possible without a risk of exceeding bone marrow tolerance limits (169).

For the uncommon low-risk pediatric patient with microcarcinoma (tumor $<$ 1.0 cm) and no lymph node involvement, treatment with 30 mCi (1.1 GBq) for the purposes of remnant ablation may be administered and additional courses given if there is Tg persistence. Based on studies in adults (193, 194, 216), about 10% of patients administered ^{131}I for remnant ablation will have biochemical evidence of remaining thyroid tissue and will require retreatment. Alternatively, as suggested (2), RAI may be withheld for the child with microcarcinoma and the patient monitored for disease persistence and recurrence with Tg levels assessment and ultrasonography. If Tg levels rise in the absence of gross disease, RAI can be administered later.

XIII. Practical Issues of ^{131}I Therapy

To achieve ^{131}I uptake by remnant and residual tissue, TSH elevation is needed (155). For patients taking levothyroxine, the medication should be discontinued 2–3 wk in children and 4 wk in adults before RAI, a process termed thyroid hormone withdrawal (THW) (155, 217). Alternatively, patients can be treated with 0.7 μg/kg triiodothyronine for at least 1 month and the medication discontinued 2 wk before treatment (155). TSH levels greater than 30 mU/liter appear to be adequate to stimulate ^{131}I uptake in thyroid remnants and functional metastatic lesions (218).

A low-iodine diet should be adhered to 2 wk before treatment with ^{131}I (155). In the United States, iodine intake is about 160–177 μg/d (155, 219). After 1 wk on a low-iodine diet, urinary iodine excretion can fall 5- to 10-fold and lead to a doubling of the amount of radiation in residual tissue (155). A low-iodine diet should be prescribed for 2 wk before RAI and continued until 1 d after (155). Several web sites provide excellent details about dietary advice (http://www.thyca.org/rai.htm#diet).

Clinicians should be wary to avoid exposing the patient to iodine-containing compounds associated with clinical care. It has been recommended that the following minimal times between exposure to iodine-containing compounds and RAI treatment be observed: soaps and scrubs, 2 wk; water-soluble iv contrast agents, 4 wk; cavity-injected water-soluble contrast agents, 8 wk; and cholecystographic agents, 12 wk (155). High-iodine-content medications, including amiodarone, should be avoided (155). If there is a question as to whether the patient has iodine excess, iodine concentration can be measured in a spot urine sample (2, 20).

Another potential concern is retained gut ^{131}I (155). An effective whole-body $t_{1/2}$ of 22 h is observed in patients with large amounts of bowel ^{131}I, compared with 14 h when there is little activity in the gut (155). Thus, it is important that patients have one or two bowel movements per day. Considering that THW is associated with constipation, laxative use may be needed (155).

XIV. Recombinant Human TSH *vs.* Thyroid Hormone Withdrawal

To facilitate ^{131}I uptake by remnant tissue or residual tumor, TSH elevation is needed and can be achieved with rhTSH or THW. Patients treated with rhTSH typically receive 0.9 mg rhTSH on 2 consecutive days, and ^{131}I is given 24 or 48 h later (21).

Data in adults show that patients feel better with rhTSH *vs.* THW (220). In addition, the whole-body radiation exposure is about 30% less with rhTSH (221, 222).

Studying children, Iorcansky *et al.* (223) identified 53 children and teenagers with thyroid cancer who underwent whole-body ^{131}I scanning after THW and 19 after rhTSH treatment. The mean serum TSH at the time of ^{131}I administration was similar in patients undergoing hypothyroid preparation (mean, 188 mU/liter) and those treated with rhTSH (mean, 134 mU/liter) (223). Thus, TSH levels achieved in children after rhTSH injections were similar to values previously reported in adults (223). The authors report that dose adjustments of rhTSH are not generally required in children and teenagers undergoing rhTSH stimulation for RAI scanning or serum-stimulated Tg determinations (223).

In children, Luster *et al.* (224) reported rhTSH use in 100 DTC patients, ages 4.9-18 yr, for either treatment (40%) or diagnostic (60%) purposes. Ninety-two percent were treated using the approved adult regimen (one 0.9-mg im injection daily on 2 consecutive days), 34% including THW for less than 7 d. No clinical adverse

events occurred in 88% of rhTSH courses. Most common clinical adverse events were nausea (5% of courses) and vomiting (3%). Peak TSH concentration after rhTSH exceeded 25 mU/liter in approximately 98% of courses. Thus, rhTSH was clinically well tolerated in pediatric DTC patients and was sufficient to elevate TSH in children and adolescents.

It is important to emphasize that at present, rhTSH is not approved for children by drug-regulatory agencies in the United States or Europe. Although the use of rhTSH has the potential to reduce whole-body radiation exposure associated with ^{131}I therapy, expanded use in the pediatric population should be considered only after clinical studies show comparable efficacy to THW.

XV. Risks of RAI

The risks associated with RAI use in children and adults relate to SPM, reproductive effects, effects on salivary glands, and pulmonary fibrosis.

Studies of individuals who received diagnostic ^{131}I activities have not revealed increased SPM risks (225). Studies of individuals who received ^{131}I for the treatment of hyperthyroidism have not revealed increased cancer risks that appear to be attributable to the RAI (226–232). However, these diagnostic and hyperthyroidism-administered activities are much less than those used to treat DTC.

A. Second primary malignancies

Initial studies of the SEER database of 30,000 adult U.S. patients with DTC treated with RAI revealed no effects of ^{131}I therapy on SPM risk, but the risk of RAI exposure was only partially assessed (233). Recent reevaluation of the SEER database, however, suggested that ^{131}I may have a small carcinogenic effect with increased rates of both hematological and solid SPM in the irradiated cohort but not in the nonirradiated group after a latency period of 3 yr (234). It was also recently suggested that treatment of low-risk thyroid cancer with ^{131}I is associated with an increased risk of SPM (235).

A study by Verkooijen *et al.* (236) revealed that the SPM risk is elevated, but similarly elevated before and after ^{131}I therapy. These observations suggest a genetic predisposition for malignancies in such patients.

Rubino *et al.* (237) evaluated SPM in a European cohort of DTC patients. A total of 6841 DTC patients, diagnosed from 1934–1995, were treated at a mean age of 44 yr. Seventeen percent were treated with external radiotherapy, and 62% received ^{131}I (237). A total of 576 patients were diagnosed with a SPM. Compared with the general population, an increased risk of SPM of 27% was seen (237). This risk was dosage related; a linear dose-response relationship with ^{131}I administration was seen for all cancers combined and for leukemias. The increased risk of solid tumors and leukemia was found with ^{131}I activities higher than 200 mCi (7.4 GBq) and 100 mCi (3.7 GBq), respectively (237). At lower activities, increased SPM risks were not apparent.

Very recently in a comprehensive study, Garsi *et al.* (238) presented follow-up data of 11,007 European patients with DTC studied at an average of 14 yr after treatment. When individuals were older than 20 yr at diagnosis, the risk of SPM was about 25% higher than the general population; however, this risk was not related to ^{131}I therapy for most patients but instead to having DTC because the SPM risk without RAI was 25% (238). An RAI-related SPM risk was seen only when the cumulative dosage of ^{131}I exceeded 200 mCi (7.4 GBq) (238).

A secondary analysis of the European SPM data set was performed in a population of patients diagnosed at less than 20 yr of age by C. Rubino (personal communication). There was no evidence of an increased risk of SPM after ^{131}I treatment of DTC in children. At present, we are not aware of other studies that have performed similar analyses of ^{131}I-treated pediatric patients with a comparable population of pediatric DTC patients not treated with ^{131}I (239).

B. Reproductive risks

Potential reproductive effects of RAI therapy have been examined. The estimated doses to the gonads are 140 mGy/100 mCi (3700 MBq) to the ovaries and 85 mGy/100 mCi to the testes (240). The radiation absorbed dose to the gonads required to produce an increase in gamete mutations is estimated to be above 1 Gy (240). Importantly, no excess of malformations or cancer has been observed in offspring of individuals with this level of radiation exposure (241–243), and women and men treated with ^{131}I for DTC do not have increased rates of malformations in their offspring (242, 243).

Women treated with more than 3.7 GBq (100 mCi) ^{131}I for DTC have an increased rate of miscarriage within 1 yr of treatment (242, 243). Thus, it is recommended that pregnancy be avoided for 6–12 months after RAI therapy for DTC (242, 243). Of note, there is no evidence of long-term adverse effects on fertility related to ^{131}I use in DTC (244, 245).

In males, gonadal damage may be cumulative in those requiring multiple administrations (246). It has been suggested that sperm banking be considered in male patients with metastatic or pelvic disease or both before therapy (246). Sperm banking should be considered in patients likely to be given cumulative doses greater than 378 mCi (14 GBq) ^{131}I (246).

C. Pulmonary fibrosis

Pulmonary fibrosis is a potential concern of ^{131}I therapy in patients with diffuse lung metastases. As currently applied, RAI should not induce pulmonary fibrosis (172). In studies of 15 patients 15–60 yr of age, Rall *et al.* (172) showed that RAI did not produce fibrosis with deterioration of pulmonary function unless patients had an uptake of 100 mCi (3.7 GBq) or more of ^{131}I in lung tissue. The highest lung uptake after ^{131}I ranged from 15 to 20% (149). It is thus very unlikely to achieve activities of 100 mCi (3.7 GBq) or more in the lungs with conventional therapy (149). Biko *et al.* (188) recently showed that despite incomplete remission of thyroid cancer at the end of a session of RAI, a continuing spontaneous decline of Tg and clinical stable partial remissions can be observed in children. Therefore, if RAI is not able to completely remove lung metastases, the administration of additional RAI courses should be handled restrictively because of the risk of pulmonary fibrosis (188).

D. Other risks

Other adverse effects related to RAI include gastritis (nausea and/or vomiting), neck pain from soft tissue swelling, and sialadenitis (150, 167). Recent data suggest that radiation exposure to the salivary glands is greater when secretion is stimulated (247). Thus, the use of lozenges immediately after RAI, which had been the routine, is no longer recommended (247).

XVI. Bystander Radiation Risks

RAI poses potential risks to family members of patients treated with ^{131}I for DTC. These risks are estimated to be very low if proper precautions are followed (239, 248). It is essential that treated individuals receive instruction in posttreatment precautions to prevent the unwitting exposure of individuals to radiation exposure (249).

Recently, a joint statement on radioactive precautions after RAI therapy was issued by the ATA, The Endocrine Society, the Society of Nuclear Medicine, and The American Association of Clinical Endocrinologists (250). It was noted that the Nuclear Regulatory Commission (NRC), an agency of the Federal Government, sets the rules governing ^{131}I treatment and revises them periodically. In 1997, the NRC modified regulations to allow individualization of the procedure for preventing radiation exposure to the public after a patient is treated with ^{131}I. A goal of the rule change was to avoid the isolation of patients in hospital for prolonged periods if release to home would be safe for the patient, the patient's family, and the public. This approach enhances patient satisfaction and is the current standard of medical practice in the United States (249).

Until new regulations are released by the NRC, it is recommended that physicians and patients should continue to follow current safety procedures. These precautions are detailed at several sites http://www.thyca.org/rai.htm#after; http://www.cumc.columbia.edu/dept/thyroid/raiprep.html).

We are not aware of sites with information specific for children, but the same precautions apply. It is also important to recognize that whereas children and adults with DTC are routinely released to home after RAI treatment for DTC in the United States, in other countries, patients are hospitalized after therapy.

XVII. Levothyroxine Therapy

It is standard practice to treat thyroid cancer patients with levothyroxine postoperatively, because it is well recognized that TSH suppression can reduce rates of recurrence (251, 252). The optimal degree of TSH suppression is debated in low-risk patients, because it is not clear whether complete suppression of TSH secretion confers benefit.

In adults, the long-term impact of supraphysiological doses of thyroid hormone on bone mineral density and cardiovascular risks is well recognized (253, 254). In children, high levels of thyroid hormones can have effects on growth and can profoundly impact behavior and learning ability (255). On the other hand, children generally need considerably higher doses of levothyroxine based on body weight to completely suppress TSH compared with adults. To date, studies of effects of treatment resulting in subclinical hyperthyroidism in children treated for DTC have yet to be performed to assess impact.

In adults with low-risk disease, Biondi *et al.* (256, 257) recommend maintaining TSH levels in the low normal range (0.5–2.5 mU/liter). The ATA task force recommends more aggressive suppression (TSH, 0.1–0.5 mU/liter) (20). For high-risk adult patients, TSH values should be suppressed to below 0.1 mU/liter (20).

One scheme, proposed by Baudin *et al.* (258) for children, is to initially suppress TSH levels to under 0.1 mU/liter and then allow the TSH to rise to 0.5 mU/liter once the patient enters remission. These recommendations seem appropriate for children when one considers that most recurrent DTC develops 5 yr after initial treatment (259).

In pediatrics, it is well recognized that medical compliance can be a major problem, especially for teens and young adults, including those with serious medical conditions (260–263). Although TSH suppression is desirable, clinicians must recognize that TSH suppression may

be difficult to enforce in the pediatric population. As such, TSH-suppressive therapy cannot be practically considered to be a mainstay of therapy, supporting surgical and RAI approaches that minimize recurrence risk in children.

XVIII. Follow-Up

Follow-up care of the child with DTC involves the regular assessment of circulating thyroid hormone levels, ultrasonography of the neck, measurement of Tg, and whole-body radioiodine scans. Follow-up regimens for children with DTC have been nicely proposed by Hung and Sarlis (17) that are reasonable to follow with a few modifications.

A very pertinent issue is the criteria used to assess whether a patient is disease free. With more sensitive Tg assays, one can aim for an undetectable Tg level as indicative of a disease-free state, rather than a Tg of under 2 μg/liter, which had been standard practice.

Although a ^{131}I uptake of under 0.1% is considered an indication of being disease free, small metastases or thyroid remnants may be present with such uptake; modern γ-cameras can reliably detect thyroid remnants with an uptake as low as 0.01% (H. Hänscheid, personal communication).

In general, follow-up ultrasound and TSH-suppressed Tg level assessment is performed 6 months after initial therapy and at least annually thereafter, although following patients every 6 months for at least 5 yr after diagnosis may be preferred for patients with more advanced initial or metastatic DTC. TSH-stimulated Tg levels are assessed 6 months after initial therapy, and 6–12 months thereafter, based on the suspicion of residual disease. Assessment of free T_4, T_3, and TSH levels is indicated every 6 months and 1–2 months after dosage changes (20, 264).

A. Thyroglobulin

Assessment of Tg levels is a mainstay of DTC follow-up (2, 20, 21). rhTSH- or THW-stimulated Tg levels are considered the standard for assessing disease recurrence, and assessment is recommended every 6–12 months after diagnosis until the physician is confident the patient is disease free (2, 20, 21). Although rhTSH has been used in children and shown to have a favorable safety profile (224), rhTSH is not approved by the U.S. Food and Drug Administration for use in children less than 16 yr of age.

If the stimulated Tg is undetectable, no disease is present in most patients (20). If the level is 0.1–2.0 μg/liter, 30% will have residual disease, and follow-up neck ultrasonography is indicated (20). If the level is 2.0–10.0 μg/liter, it is likely that residual disease is present, and follow-up neck ultrasonography is indicated (20). If the Tg is over 10.0 ng/dl, follow-up neck ultrasonography and possibly CT or MRI scanning of the neck and chest are indicated. If gross cervical disease is present, reoperation is indicated (20). If not, ^{131}I treatment with 100–150 mCi (3.7–5.5 GBq) should be considered (20).

Recent data suggest that the measurement of basal Tg levels by second-generation assays shows excellent correlation with stimulated Tg levels (265). A basal Tg level less than 0.1 μg/liter correlates with a stimulated Tg level less than 2.0 μg/liter (265). Considering the expense associated with the use of rhTSH and the adverse symptoms associated with THW, assessment of basal Tg levels every 6 months seems reasonable. If basal Tg levels rise, disease recurrence needs to be considered.

A confounding factor in Tg measurement is the presence of TgAb. In adults with DTC, less than 10% of patients initially have elevated TgAb levels (266). In children, TgAb or autoimmune thyroiditis is present in 20–80% of individuals in some cohorts of children (10, 214, 215). Because of this problem, the primary tool for assessing cure or recurrence may be difficult to use in the pediatric age group. Although many TgAb-positive patients convert to being TgAb negative after treatment with surgery and RAI, 44% of patients may remain TgAb positive 5 yr after total thyroid ablation (266, 267).

B. Ultrasonography

Ultrasonography should be performed every 6 months to assess whether there is residual thyroid tissue and lymph nodes (20). As such, it is important that studies not only focus on the thyroid bed but also encompass the neck in full, examining each lymph node compartment. Because children commonly have infection-related lymphadenopathy, serial studies may be needed every 3 months to assess whether lymph nodes represent potential metastatic foci.

FNA of lymph nodes is indicated for persistent or enlarging lymph nodes (20). In addition, Tg levels can be assessed in lymph node aspirates (268, 269).

C. Diagnostic whole-body scintigraphy

^{131}I diagnostic whole-body scintigraphy (dWBS) is performed using 2–5 mCi (0.06–0.18 GBq) and is recommended at 6–12 months after diagnosis (270, 271). ^{131}I scanning is especially useful in the detection of lung metastases that are not apparent by chest radiographs or CT scanning (17). In patients with TgAb, ^{131}I scanning is especially useful in identifying potential residual disease (270, 271).

The use of dWBS in patients without lymph node or distant metastases is debated. Some groups perform at least one ^{131}I dWBS and concurrent measurement of stimulated Tg levels after the last ^{131}I therapy course to ascertain complete remnant ablation and the absence of pathological ^{131}I accu-

TABLE 2. Areas where ATA management guidelines for adults (2) do not apply to children

Recommendation no.	Recommendations
8	
Adult	BRAF mutation screening for patients with indeterminate cytology on FNA
Pediatric	Yield will be much lower in children than adults
14	
Adult	Serial ultrasound evaluations performed every 6–18 months after initial FNA with apparently benign nodules
Pediatric	Nodules should be followed every 6 months, or every 12 months at the least
25	
Adult	Total thyroidectomy considered for large tumors (>4 cm) when the FNA is suspicious for PTC
Pediatric	Exclude tumor size as a determinant for the type of operation in children
27	
Adult	Near-total or total thyroidectomy without central compartment neck dissection appropriate for T1 or T2 lesions
Pediatric	Central compartment dissection is recommended for T1 and T2 lesions, if surgery can be performed by a high-volume surgeon
31	
Adult	Use of TMN classification system and AJCC staging system
Pediatric	TNM classification system for DTC underestimates the aggressiveness of the disease, and AJCC staging system is of little utility in children, where DTC mortality is low
32	
Adult	RAI administered for T3 and T4 tumors but used selectively for T1 and T2 tumors
Pediatric	Considering high rates of lymph node involvement, higher rates of recurrence than adults, and the complicating factor of residual thyroid tissue after surgery that confounds long-term follow-up, RAI should be used for T1 and T2 tumors; if microcarcinoma is present, the patient may be closely observed without being given RAI and treatment rendered later if TG levels rise
40	
Adult	TSH suppression is recommended for high- and intermediate-risk patients and maintenance of TSH levels at the lower limit of normal for low-risk patients
Pediatric	Long-standing subclinical hyperthyroidism has adverse physical effects on the developing child and can influence academic performance; if no evidence of active disease, avoid TSH suppression (<0.5 mU/liter); TSH suppression should not be considered as a mainstay of therapy due to compliance issues

mulation. However, data suggest that ^{131}I scanning adds only a modest amount of data to the combination of Tg assessment and ultrasonography (270, 271).

D. Positron emission tomography

A subset of patients will have disease that is not ^{131}I responsive. In addition, some patients with DTC with recurrence will be Tg negative (272). These patients pose significant management and follow-up challenges. In patients with tumors that are not ^{131}I avid, [^{18}F]fluorodeoxyglucose PET scanning is useful in identifying residual disease (273, 274). In comparison with adults, this scenario is very uncommon in children.

XIX. Differences with ATA Management Guidelines

The ATA management guidelines for DTC are a benchmark for the evaluation, treatment, and follow-up of the condition (2). In general, these guidelines are applicable to children, with notable exceptions summarized below (Table 2).

The recommendation (no. 8) that BRAF mutation screening in children be considered for patients with indeterminate cytology on FNA is reasonable. However, the yield will be much lower in children than adults.

It is recommended (no. 14) that serial ultrasound evaluations be performed every 6–18 months after the initial FNA in adults with apparently benign nodules. Considering the higher risk of malignancy in children, we suggest that such nodules be followed every 6 months or at a minimum every 12 months.

The recommendation (no. 25) that total thyroidectomy be considered for large tumors (>4 cm) when the FNA is suspicious for PTC should be revised to exclude tumor size as a determinant for the type of operation in children.

The recommendation (no. 27) that near-total or total thyroidectomy without central compartment neck dissection may be appropriate for T1 or T2 lesions in adults may not apply to children, who have a much higher rate of lymph node metastasis than adults. As such, central compartment dissection is recommended for T1 and T2 lesions if surgery can be performed by a high-volume surgeon.

The TNM classification system for DTC cannot be used in children correctly, because the T category underestimates the aggressiveness of the disease (recommendation no. 31). In addition, the AJCC staging system is of modest utility in children, where DTC mortality is low. Such

mortality-based scoring systems do not reflect the risk of recurrent or persistent disease, which is a major component of pediatric DTC. It is recommended that a pediatric-specific scoring system be developed.

In adults, it is recommended (no. 32) that RAI be administered for T3 and T4 tumors but used selectively for T1 and T2 tumors. In children, considering high rates of lymph node involvement, higher rates of recurrence than adults, and the complicating factor of residual thyroid tissue after surgery that confounds long-term follow-up, we recommend that RAI be used for tumors larger than 1.0 cm. For unifocal microcarcinomas of 1.0 cm or less, RAI may be withheld and the child monitored for disease persistence. If Tg levels are detectable or rise in the absence of gross disease, RAI should be administered.

TSH suppression is recommended for high- and intermediate-risk patients and maintenance of TSH levels at the lower limit of normal for low-risk patients (recommendation no. 40). Whereas there is good evidence for the merits of TSH suppression, long-standing subclinical hyperthyroidism has adverse physical effects on the developing child and can influence academic performance. As such, TSH-suppressive therapy may have real consequences that warrant further study. Medical compliance can also be problematic in adolescents. Thus, as soon as there is no evidence of active disease, it is reasonable to avoid TSH suppression. In addition, TSH should not be considered a mainstay of therapy due to compliance issues.

Measurement of Tg for follow-up is recommended (no. 43), which we agree with. However, a notable proportion of pediatric patients may have TgAb, precluding this important follow-up tool.

XX. Suggested Areas for Future Investigation

Although we have considerable insights into DTC treatment in children, significant gaps in our knowledge remain that need to be addressed to optimize DTC treatment. 1) Recognizing the variability in DTC treatment from center to center and around the world, further examination of DTC outcome as related to different treatment practices will provide valuable information and can occur through the establishment of a worldwide DTC registry. 2) Studies are needed to assess long-term SPM risks of RAI treatment and other comorbid conditions associated with childhood DTC. 3) Formal studies of whole-body and organ-specific radiation exposure after ^{131}I in children are needed to provide insights into longer SPM risks as well. 4) Studies are needed to optimize treatment approaches to ensure success and reduce whole-body radiation exposure when ^{131}I is used by comparing outcomes of empiric dosaging *vs.* application of dosimetry and the preparative use of rhTSH *vs.* THW. 5) The genetics of DTC in children ap-

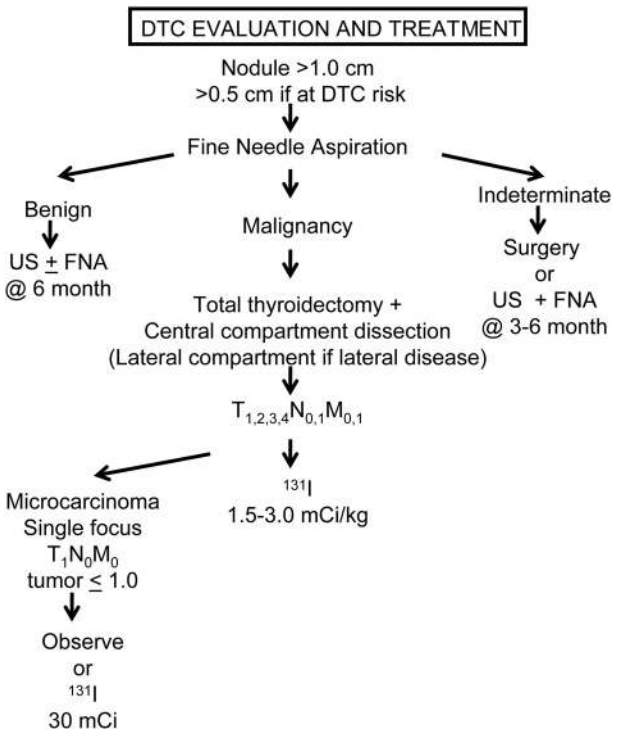

FIG. 5. Algorithm for the evaluation and treatment of DTC in children. US, Ultrasound.

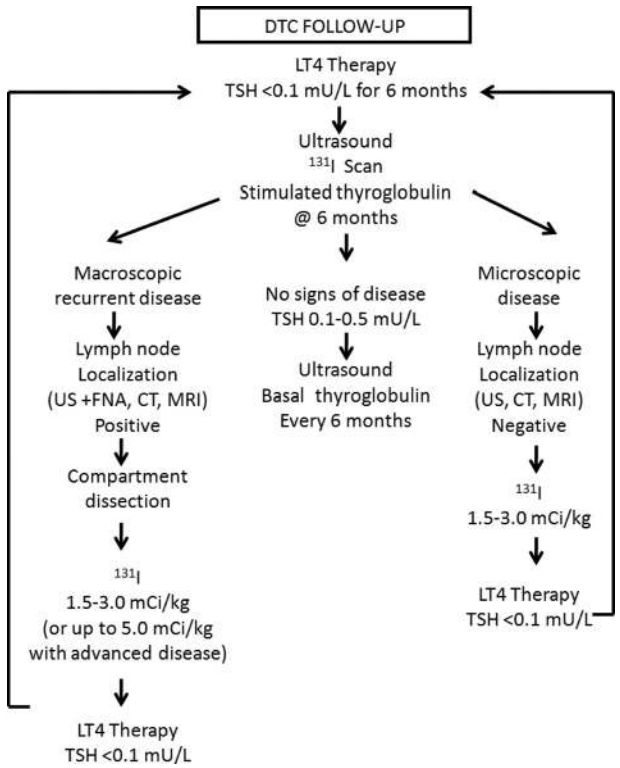

FIG. 6. Algorithm for the follow-up of DTC in children. US, Ultrasound; LT4, levothyroxine.

pear to differ from those of adults. We need to identify genetic markers that predict disease course in children with DTC. 6) A pediatric-specific DTC staging system is needed to predict clinical course. 7) We need to assess whether there are consequences of long-term TSH- suppressive therapy on the developing child.

XXI. Synopsis

DTC in children is rare, with an overall incidence of one per 100,000 individuals. DTC accounts for 95% of cases of thyroid cancer in the pediatric population, typically presents with lymph node metastases, and is associated with relatively high recurrence rates.

Ample evidence suggests that more extensive surgery is associated with lower rates of recurrence. Surgery is associated with clear and definable rates of complications that can be minimized when surgery is performed by high-volume thyroid surgeons. Evidence shows that, when properly applied, RAI is associated with lower recurrence rates. Evidence also shows that DTC is associated with an increase SPM risk, which reflects intrinsic factors related to having DTC itself. Evidence also suggests that relatively high doses of ^{131}I may contribute to an increased risk of SPM. Thus, the proven benefit of ^{131}I in preventing cancer recurrence and cancer-related deaths needs to be weighed against potential long-term risks.

Based on the constellation of the above information, the following recommendations are made for children with DTC (Figs. 5 and 6).

1) Total thyroidectomy and central compartment lymph node dissection is the surgical procedure of choice for DTC.
2) Surgery should be performed by high-volume thyroid surgeons.
3) RAI may be given for single-focus microcarcinomas without lymph node involvement with an activity of 30 mCi (1.1 GBq). Treatment should be repeated in 6–12 months if there is remaining residual thyroid or tumor tissue. Alternatively, the patient may be closely observed without being given ^{131}I and treatment rendered later if Tg levels rise.
4) RAI should be given for residual disease treatment with activities of 100–200 mCi (3.7–7.4 GBq) used or 1.3–2.7 mCi/kg (50–100 MBq/kg) for young children, for patients with nodal and distant metastases, respectively. For the treatment of distant metastases and recurrent disease, pretreatment dosimetry should be considered, and activities up to 5 mCi/kg (200 MBq/kg) may be used.
5) Whereas empiric activity selection is convenient and practical, blood-dose limiting-based or lesion-based dosimetry should be considered for children with metastatic disease to the lungs and other sites.
6) TSH levels should be maintained below 0.1 mU/liter for patients with nodal or distant metastatic disease until it is known that there is no evidence of active disease. Thereafter, the TSH may be kept at 0.1–0.5 mU/liter.
7) Long-term follow-up for the child with DTC is essential, because disease can recur decades after initial diagnosis and therapy.
8) Considering the complexity of DTC management, the potential complications associated with therapy, and the intricacies of follow-up, it is important that pediatric DTC be managed by physicians with expertise in this area.
9) Expanded research in pediatric DTC treatment is indicated because disease aggressiveness, the risks of treatment, and long-term follow-up issues cannot be directly extrapolated from the care of adults.

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