Pediatric Thyroid Nodules and Differentiated Thyroid Cancer: Exploring the New Management Guidelines

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Objectives

- **Describe the importance of the inaugural pediatric specific American Thyroid Association (ATA) management guidelines.**
- **How guidelines may impact healthcare delivery.**
- **Identify key features of clinical presentation of pediatric thyroid nodules and differentiated thyroid cancer.**
- **Describe the treatment and long-term outcomes of children with papillary thyroid cancer (PTC).**

Guideline Development

- Task force commissioned by ATA
  - International community of experts
  - Variety of disciplines
    - Endocrinology
    - Molecular biology
    - Nuclear medicine
    - Radiology
    - Surgery

Francis, Waguespack, Bauer, *et al.* ATA Pedi Guidelines *Thyroid* 2015

Guidelines Document

- Contribution from all authors
- Primarily written by chair and co-chairs
- Pediatric Endocrine Society
  - Co-developed
  - Endorsed
- Approval
  - ATA Board of Directors and membership
  - PES Drug and Therapeutics Committee & Board of Directors

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Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Task Force on Pediatric Thyroid Cancer

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american thyroid association — DEDICATED TO SCIENTIFIC INQUIRY, CLINICAL EXCELLENCE, EDUCATION AND COLLABORATION

PES Pediatric Endocrine Society

Guiding Questions

- Task force developed clinically relevant questions pertaining to management of thyroid nodules and differentiated thyroid cancer (DTC).

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Guidelines Focus

- Thyroid nodules
- PTC primary focus
- FTC separate guidelines

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Guideline Recommendations

- Scientific evidence
- Expert opinion
- Graded using a modified schema
  - United States Preventive Services Task Force

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Guideline Recommendations

- Evaluation and management of thyroid nodules;
  - Role of interpretation of ultrasound
  - Fine needle aspiration cytology
  - Management of benign nodule
- DTC
  - Evaluation; pre-operative staging
  - Treatment;
    - Surgical management
    - Post-operative staging
    - Role of radioactive iodine therapy
    - Goals for thyrotropin suppression
  - Follow-up

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QUESTION A1

- Why do we need specific guidelines for children with thyroid nodules and thyroid cancer?

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Why Pediatric Specific Guidelines?

- Previous American Thyroid Association (ATA) guidelines;
  - Focused on management and treatment of adult thyroid nodules and thyroid cancer
  - Guidelines applied to thyroid neoplasia in children
  - High proportion of children were cured
  - All required total thyroidectomy and radioactive iodine (RAI)
  - Goal eliminate disease; negative whole body RAI scan and undetectable serum thyroglobulin (Tg)

Francis, Waguespack, **Bauer, *et al.* ATA Pedi Guidelines *Thyroid* 2**015

Why Pediatric Specific Guidelines?

- Thyroid neoplasia in children and adolescents
  - Different pathophysiology
  - Different clinical presentation
  - Low risk for death
  - Higher risk for long-term consequences
    - Second malignant neoplasia
- Unique guidelines needed

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Why Pediatric Specific Guidelines?

- **Clinical thyroid nodules uncommon in children and have a higher risk (25%) of malignancy**
- **PTC>>FTC; rare PDTC, HCC or ATC**
- **Children with PTC more likely to have lymph node and pulmonary metastases; higher recurrence rate**
- **Despite more extensive disease, children have an excellent prognosis (2-3% long-term disease specific mortality)**
- **Cancers more differentiated & responsive to ^{131}I**

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QUESTION A2 & A3

- To what age group should these guidelines apply?
- Should treatment of children with DTC be stratified into more than one age group?

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Recommendation 1

- Pediatric age should be limited to $\leq$ 18 years

Recommendation 2

- To be incorporated into future studies "Prepubertal" and "pubertal/postpubertal"
- Increase uniformity and more accurately represent the potential influence of puberty

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QUESTION A4

- What are the goals of therapy for DTC in children?

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Thyroid Carcinoma in Children

- Papillary Thyroid Cancer
  - 90% of the thyroid cases in children
  - Radiation a major risk factor for development
  - Children <5 years of age most sensitive to effects of radiation
- Follicular Thyroid Cancer
  - 5-10%
- Medullary Thyroid Cancer
  - <5%

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Thyroid Cancer in Children Incidence

- **Incidence may be on the rise**
- **1.8% of all thyroid malignancies in U.S.**
- **Adolescents 10 fold greater incidence than younger child**
- **Female:Male predominance of 5:1 in adolescence**
- **Younger children no gender difference**

SEER data 2009-2013
Data released 4/2016

Clinical Presentation

- **Solitary thyroid mass**
- **Asymptomatic**
- **Cervical adenopathy**
  - **With or without palpable thyroid lesion**
- **Incidental finding after imaging**
- **Local or distant metastasis**

Review-Pediatric Thyroid Cancer Difference

- More wide-spread disease at presentation
- Much less likely to die of disease than adults
- Pulmonary metastasis
  - Often persistent stable disease
  - More favorable progression-free survive
- Continued clinical response
  - Declining Thyroglobulin (Tg)

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Pediatric Thyroid Cancer: Survival

- **Mean disease-specific survival 31.5 yrs**
- **After >30 years:**
  - **Pts with PTC and FTC ≥ 98% survival**
  - **Pts with MTC 92% survival at >30 yrs**
- **After >20 years**
  - **Pts with loco-regional disease ≥ 98% survival**
  - **Pts with distant metastases ~84% survival**

Hogan et al. *Journal of Surgical Research*, 156, 167-72, 2009

DTC in Children Management

- Standard treatment
  - Total thyroidectomy
  - Radioactive iodine ablation
- Survivors of childhood DTC
  - Increased risk for mortalities

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DTC in Children Management

- Primary Goal of guidelines
  - Limit use of aggressive radiation therapy
  - Limit toxicities in survivors
  - Maintain low disease-specific mortality
  - Identify those who would benefit from more aggressive therapy
  - Pre- and postoperative staging

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Recommendation 3

- Children with DTC should be cared for by teams of physicians experience in the management of DTC in children.
  - Facilitate interdisciplinary decisions
  - Optimal therapy
  - Reduce possibility that treatment and long-term follow-up will be overly aggressive or inadequate

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Approach to PTC

Treatment at high volume centers preferred!

- **Surgery (total thyroidectomy +/- lymph node dissection) by an experienced thyroid cancer surgeon**
- ***Possible* treatment with RAI (^{131}I)**
- **TSH suppression and long-term monitoring with blood tests (Tg) & imaging studies (neck US, thyroid scan, etc.)**

QUESTION B1-4

- Thyroid nodule guidelines
- How common are thyroid nodules in children and what is the risk of malignancy?
- Are there high-risk groups who might benefit from prospective screening for thyroid nodules and thyroid cancer?
- What is the optimal evaluation of children with thyroid nodules?

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Thyroid Nodules

- **Rare in children**
  - **1.5% or less of children**
  - **Increased incidence with age**
  - **Female > male**
  - **Males and children < 10 years of age: increased risk of malignancy diagnosis**
- **Prevalence in North America**
  - **75 % cystic lesions or benign adenomas**
  - **22-26 % cancerous**

Niedziela *Endo-Related Cancer* 2006; Francis, Waguespack, Bauer, *et al.* ATA Pedi Guidelines *Thyroid* 2015

Pediatric Thyroid Nodules

- **Risk factors**
  - **Radiation exposure**
  - **Autoimmune thyroid disease**
  - **Iodine insufficiency**
  - **Family history**
  - **Genetic disorders (MEN2, FNMTC, *PTEN*, *APC*, *DICER1*)**
- **Signs and Symptoms concerning for cancer**
  - **Rapid growth**
  - **Voice hoarseness, compressive symptoms**
  - **Fixed lesion**
  - **Palpable Lymphadenopathy**

Picture from SGW personal collection, with permission

Pediatric Thyroid Nodules Differential Diagnosis

- **Benign Thyroid Nodule (~75%)**
  - **Colloid nodule, AKA adenomatoid nodule**
  - **Follicular or Hürthle cell adenoma**
  - **Pseudo-nodule in thyroiditis**
- **Malignant Thyroid Nodule (~25%)**
  - **Papillary thyroid Carcinoma**
  - **Follicular Thyroid Carcinoma**
  - **Medullary Thyroid Carcinoma**
- **Other**
  - **Developmental Cysts**
  - **Dermoid Cysts**
  - **Hemiagenesis**
  - **Teratoma**
  - **Lymphoma**

*

Evaluation of Pediatric Thyroid Nodules

Ultrasound Characteristics

MALIGNANT

- **Microcalcifications**
- **Hypoechoic**
- **Irregular or jagged borders**
- **Intranodular vascular flow**

BENIGN

- **Eggshell calcifications**
- **Iso- to Hyperechoic**
- **Translucent halo**
- **Smooth border**
- **Peripheral vascular flow**

SIZE and NUMBER not good indicators

QUESTION C1-6

- Papillary thyroid cancer-initial management guidelines
- What is the optimal pre-operative evaluation for the child with newly diagnosed PTC?
- What is the recommend surgical approach for the patient with a diagnosis of PCT?
- Should central neck dissection be preformed?
- What are the indications for lateral neck dissection?
- What are the possible complications of surgery and what should be done to minimize the risk of surgery?

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Preoperative PTC Staging

- **Neck US with FNA of abnormal LNs**
- **CXR (identify macroscopic mets)**
- **Thyroglobulin and Tg Ab**
- **CT neck w/ contrast for bulky or fixed neck disease**

Waguespack and Francis, *JNCCN* 2010;8:1289–1300

Who Should Perform Surgery?

- **Children with higher surgical complication rates**
- **High volume surgeons associated with shorter length of stay and lower health care costs**

■ RECOMMENDATION 14(A)

Pediatric thyroid surgery should be performed in a hospital with the full spectrum of pediatric specialty care, to include, but not be limited to endocrinology, radiology (US and anatomic imaging), nuclear medicine, anesthesia, a high-volume thyroid surgeon, and intensive care. Pediatric thyroid surgery, especially if compartment-focused lymph node resection is indicated, should ideally be performed by a surgeon who performs at least 30 or more cervical endocrine procedures annually. Thyroid surgery performed under these guidelines is associated with lower complications rates, decreased hospital stay, and lower cost.

Recommendation rating: B

Francis, Waguespack, Bauer, *et al.* ATA Pedi Guidelines *Thyroid* 2015

Sosa JA et al. *JCEM* (93) 2008; Tuggle et al. *Surgery* 2008

QUESTION C7

- What tumor classification systems can be used for pediatric PTC?

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ATA Pediatric Thyroid Cancer Risk Levels

Define risk of residual cervical or distantly metastatic disease, NOT risk of death

	Definition
Low-Risk	**Disease confined to the gland with N0/Nx disease OR incidental N1a disease (microscopic mets to small number of central neck LNs)**
Intermediate-Risk	**Extensive N1a disease or minimal N1b disease**
High-Risk	**Extensive N1b disease or invasive (T4) tumors, with or without distant mets**

Helps to determine post-op staging, initial TSH goals, and FU

Not addressed:
- Margin status
- *BRAF* status
- Primary tumor size
- LN size

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ATA Pediatric Thyroid Cancer Risk Levels—Post-Op Staging

	Definition	Initial Post-op Staging
Low-Risk	Disease confined to the gland with N0/Nx disease OR incidental N1a disease (microscopic mets to small number of central neck LNs)	Tg
Intermediate-Risk	Extensive N1a disease or minimal N1b disease	TSH-stimulated Tg and diagnostic ^{123}I scan in most patients
High-Risk	Extensive N1b disease or invasive (T4) tumors, with or without distant mets	TSH-stimulated Tg and diagnostic ^{123}I scan in all patients

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QUESTION C9-11

- What are the goals of ^{131}I treatment?
- What is the impact of ^{131}I therapy on recurrence and survival for children with PTC?
- Which children might benefit from therapeutic ^{131}I?

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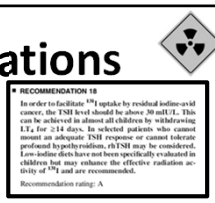
^{131}I for DTC

- ***Remnant Ablation***
  - **To facilitate future detection of recurrent disease & initial staging**
- ***Adjuvant Therapy***
  - **To decrease risk of recurrence & disease-specific mortality by destroying suspected, but unproven metastatic disease**
- ***RAI Therapy***
  - **To treat known persistent disease**

Cooper DS et al. Revised ATA Guidelines. *Thyroid.* Volume 19, Number 11; 2009

^{131}I Considerations

- **Low iodine Diet**
- **Withdrawal vs rhTSH**
- **Empiric Dosing vs Dosimetry**
- **Diagnostic & Post-treatment scans**
- **Risks vs Benefits**
- **Treatment of Lung Metastases**



RECOMMENDATION 18

In order to facilitate ^{131}I uptake by residual iodine-avid cancer, the TSH level should be above 30 mIU/L. This can be achieved in almost all children by withdrawing LT_4 for ≥14 days. In selected patients who cannot mount an adequate TSH response or cannot tolerate profound hypothyroidism, rhTSH may be considered. Low-iodine diets have not been specifically evaluated in children but may enhance the effective radiation activity of ^{131}I and are recommended.

Recommendation rating: A

Francis, Waguespack, Bauer, *et al.* ATA Pedi Guidelines *Thyroid* 2015

The Diagnostic Scan

- ^{123}I preferred over ^{131}I
- May change management:
  - Significant Iodine-avid neck disease best treated with surgery
  - Iodine-avid distant disease that may change dose
  - Iodine non-avid disease or no disease that may not require Rx
  - Caveat—Dx scan may be negative in RAI-avid disease; stim TG and clinical Hx important

QUESTION C15

- Should a posttreatment whole body scan be obtained?

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QUESTION C16

- What are the acute and long-term risks of ^{131}I therapy in children?

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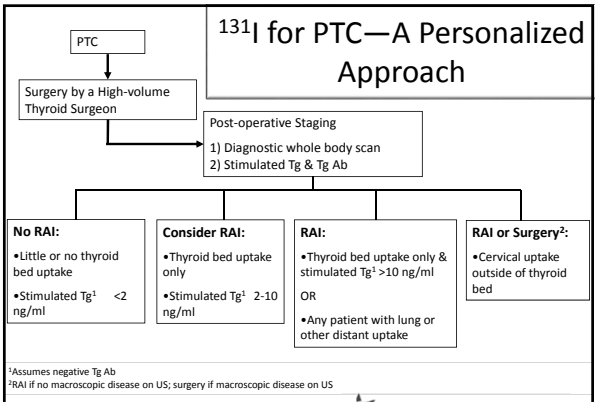
^{131}I for DTC—Side Effects

- **Early**
  - **Sialadenitis**
  - **Nausea, vomiting, diarrhea**
  - **Transient cytopenias**
- **Late**
  - **Xerostomia/salivary calculi**
  - **Lacrimal Duct Obstruction**
  - **Pulmonary fibrosis/BM suppression**
  - **Secondary Malignancies---bladder, colon, breast, leukemias, salivary gland, stomach**

^{131}I for PTC—A Personalized Approach



[1]Assumes negative Tg Ab
[2]RAI if no macroscopic disease on US; surgery if macroscopic disease on US

Waguespack & Francis, *JNCCN* 2010;8:1289–1300;
Francis, Waguespack, Bauer, *et al.* ATA Pedi Guidelines 2015

QUESTION D1-4

- Surveillance and follow-up of PTC in children
- What is the role of Tg testing..?
- What is the role of Ultrasound…?
- How are diagnostic RAI scans best used…?

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Thyroglobulin

- **Highly sensitive tumor marker**
- **Measure only once the Dx established**
- **Always check anti-Tg antibodies**
  - **Present in 37%[1]**
  - **Precludes interpretation of TG levels**
  - **Antibody levels are followed**
- **Stimulated Tg levels most sensitive but may sometimes be a false positive, esp. when <10**
- **Tg cutoffs in children not established**

[1]Arango *et al.* Endo Society Meeting 2016

Pediatric Thyroid Cancer TSH Goals and Surveillance

	Initial TSH Goal	Surveillance of Patients with No Evidence of Disease
Low-Risk	0.5-1.0 mIU/L	• US 6mo post-op and then annually x 5 yrs • Tg on LT4 q 3-6 mo for 2 yrs then annually
Intermediate-Risk	0.1-0.5 mIU/L	• US 6mo post-op and q 6-12 mo x 5yrs, then less frequently • Tg on LT4 q 3-6 mo for 3 yrs, then annually • Consider TSH-stimulated Tg ± ^{123}I scan in 1-2 yrs in pts treated with RAI
High-Risk	< 0.1 mIU/L	• US 6mo post-op and q 6-12 mo x 5yrs, then less frequently • Tg on LT4 q 3-6 mo for 3 yrs then annually • TSH-stimulated Tg ± ^{123}I scan in 1-2 yrs in pts treated with RAI

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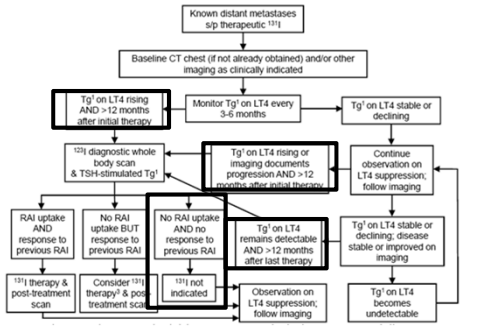
Management of Distant Metastases with RAI



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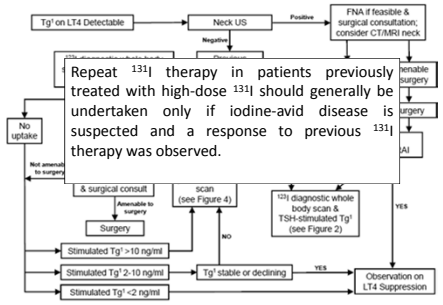
Management of Known or Suspected Residual/Recurrent Disease

(No Known Distant Metastases)



Repeat ^{131}I therapy in patients previously treated with high-dose ^{131}I should generally be undertaken only if iodine-avid disease is suspected and a response to previous ^{131}I therapy was observed.

Francis, Waguespack, Bauer, *et al.* ATA Pedi Guidelines 2015

QUESTION E1

- Follicular Thyroid Cancer
  - Rare and poorly-studied malignancy
  - Age-adjusted incidence 0.5 case/million annually
  - Prevalence appears to be declining
  - Iodine deficiency is a clear risk factor

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Summary

- **Pediatric nodules and cancer remain rare in children <age 10 but are increasing in incidence in adolescents**
- **US-guided FNA is the procedure of choice for diagnosis**
- **New guidelines provide a reference for care**
  - **Children with DTC should ideally be treated at centers with high-volume multidisciplinary teams**
  - **The role of ^{131}I in pediatric DTC is diminishing**
- **A new era of personalized medicine for thyroid cancer is upon us**

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Thank You!

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