Thyroid Nodules and Cancer in children

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Objectives

• Understand the management of thyroid nodules

• Recognize characteristics of thyroid nodules that increase the risk of malignancy

• List risk factors for thyroid cancer

• Understand the management of thyroid cancer
Thyroid Embryology
The Thyroid Axis

Hypothalamus

TRH

Anterior Pituitary

TSH

Portal System

Feedback Inhibition

T3

T4

Thyroid

Peripheral Tissues

T4

T3

T3

T4
**T3 (Triiodothyronine):**
- 20% secreted by the thyroid
- 80% produced by peripheral deiodination of T4
- Mostly bound (TBG/albumin)

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**TRH (Thyroid Releasing Hormone):**
- Secreted in pulses into the Portal System of the Pituitary (not readily assayed)

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**TSH (Thyroid Stimulating Hormone):**
- 1st gen. TSH assays function in the range of 0.5-10 mIU/L
- 2nd gen. TSH assays function in the range of 0.1-10 mIU/L
- 3rd gen. assays accurately measure 0.01 mIU/L and can accurately diagnose hyperthyroidism (almost all modern labs are 3rd gen.)

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**T4 (Thyroxtine):**
- Mostly bound (TBG/albumin)
- Measured as total T4
- Free T4 (FT4)
  - Fraction of T4
  - Active hormone
Thyroid Hormone Synthesis

"Medical gallery of Mikael Häggström 2014"
The thyroid exam
The thyroid exam
A Case

• 16 yo female
  - no PMH

• Sports injury to the neck
  - CT neck showing a thyroid nodule

• Thyroid ultrasound
  - 2 cm nodule on the right
    • increased vascularity and micro-calcifications
Thyroid Nodules

• 2% of children have palpable thyroid nodules

• Ultrasound and post mortem exams
  - up to 13% of adolescents and young adults

• Thyroid is more susceptible
  - irradiation
  - carcinogenesis

• Potential for malignancy
  - 20-25%
Thyroid nodules - risk factors

- Iodine deficiency

- Radiation Exposure

- Autoimmune Thyroid disease
  - Hashimoto’s thyroiditis and Graves’ disease

- Genetic syndromes
  - Gardner, Cowden, Bannayan-Rubalcava-Riley etc
Childhood cancer survivors

• Radiation Therapy
  - Hodgkin lymphoma
  - Leukemia
  - CNS tumors

• Nodules develop
  - 2% annually

• Peak incidence: 15-25 years
Diagnostic process - nodules

- **Thyroid Function Tests**
  - TSH (Thyroid stimulating hormone)
  - Free T4
  - Thyroid antibodies
    - Thyroid peroxidase antibody
    - Anti-thyroglobulin antibody

- **Thyroid Scintigraphy**
  - if TSH is suppressed
Neck ultrasound (us)

• One or multiple nodules

• Size

• Solid, cystic or mixed appearance

• Characteristics
  - Echogenicity
  - Margins
  - Microcalcifications
  - Vascularity
Fine Needle Aspiration (FNA)

• Which nodules should be FNA’d:
  - > 1 cm
  - < 1 cm with worrisome characteristics
    • Hypoechochogenicity
    • Microcalcifications
    • Irregular borders
    • Shape taller than wide
    • Increased vascularity
    • Abnormal adjacent lymph node

• Most useful in distinguishing benign lesions from cancer

• Ultrasound guidance
  - improves diagnostic accuracy
The Bethesda System of Reporting Thyroid Cytopathology

• Nondiagnostic

• Benign

• Atypia or follicular lesion of undetermined significance

• Follicular/Hurtle cell neoplasm

• Suspicious for malignancy

• Malignant
Which Nodules should be excised

• Hyperfunctioning nodules

• Growing nodules (even if benign)

• Compressive symptoms
  - difficulty breathing or swallowing
  - snoring at night

• Atypia or follicular lesion of undetermined significance

• Nodules >4 cm
Thyroid cancer statistics

• 1.55 % of malignancies before the age of 15

• SEER registry
  - Annual incidence 0.54 cases/100,000 population
  - Prevalence 10/100,000 children

• 15-19 yo adolescents
  - 8th most common cancer both genders
  - 2nd most common among females
Predisposing Factors

• Radiation exposure

• Iodine deficiency
  - Follicular thyroid cancer

• Residence in Volcanic Areas (Hawaii, Iceland)

• Thyroid autoimmune disease
  - Hashimoto’s thyroiditis and Graves disease
Radiation Exposure

Post-Chernobyl Thyroid Carcinoma in Belarus Children and Adolescents
Figure 2. Thyroid cancer risk by radiation dose among those diagnosed with their first cancer under age 10 years and those diagnosed at age 10 years or later, the Childhood Cancer Survivor Study. (Sigurdson AJ, et al. 2005)
Thyroid Cancer Classification

Follicular origin
- Papillary: 70-80%
- Follicular: 10-20%
- Anaplastic: <2%

Nonfollicular origin
- Medullary: 5-10%
- Metastatic
- Lymphoma
Thyroid Cancer Classification

Follicular origin
- Papillary: PTC
- Follicular: FTC
- Anaplastic: <2%

Nonfollicular origin
- Medullary: MTC
- Metastatic
- Lymphoma
Papillary Thyroid Carcinoma (PTC)

• Multifocal

• Bilateral

• At time of diagnosis
  - > 50% regional lymph node involvement
  - >20% lung metastases

• Usually slow-growing

• Mortality rates < 1% 10 years after treatment
Follicular Thyroid Carcinoma (FTC)

• Unifocal

• Unilateral

• Regional Lymph node involvement
  - less common

• Hematogenous spread
  - More common
  - Lungs and Bones
Molecular genetics

• BRAF mutations
  - B-raf protein controls cell growth
  - 38-83% in adult cases
  - dedifferentiated/aggressive thyroid cancers

• RET/PTC rearrangements
  - RET proto-oncogene controls cell growth, survival and differentiation
  - more common in children
  - differentiated thyroid cancers
Treatment

• Total thyroidectomy

• Lymph node dissection
  - On a case by case basis

• Radioactive iodine ablation (RAI)
  - On a case by case basis

• L-thyroxine treatment
Thyroidectomy

• Total thyroidectomy is recommended
  - Decreased rates of recurrence
  - Better utilization of
    • RAI for imaging and/or treatment
    • Thyroglobulin as a marker for persistent or new disease

• Complications
  - Transient Hypocalcemia
  - Permanent Hypoparathyroidism
  - Recurrent laryngeal nerve damage
Radioactive Iodine Treatment (RAI)

• Destroys microscopic foci of disease

• Recurrences are more likely to be detected
  - no functioning thyroid tissue remains

• Detection and treatment of cancer outside the thyroid

• Improves specificity of
  - thyroglobulin as a tumor marker
  - Whole body scanning for detection of recurrence
Radioiodine ablation reduces recurrence and mortality in stage II and stage III thyroid cancer. Long-term development of recurrent disease (left panel) or death (right panel) from thyroid cancer in patients without distant metastases at presentation, who received either 131-I ablation (red dashed lines) or no ablation (blue solid lines). (Data from Mazzaferri, EL, Jhiang, SM, Am J Med 1994; 97:418.)
Complications of RAI

• Sialadenitis

• Nasolacrimal Duct obstruction

• Gonadal Dysfunction (amenorrhea, oligospermia)

• Secondary malignancies
Secondary Malignancy post I-131

• Sodium-Iodine symporter is present
  - Salivary glands, breast tissue, GI and GU

• RR of secondary malignancy: 1.19 (SEER)

• 6,840 patient (Sweden, Italy and France)
  - Bone and soft tissue (RR:4)
  - Female Genital Organs and CNS (RR:2.2)
  - Leukemia (RR: 2.5)

• Maximum lifetime dose of RAI: 600 mCi
Radioactive Iodine Treatment

• American Thyroid Association 2009 - Adults
  - More tailored approach

<table>
<thead>
<tr>
<th>Factors</th>
<th>Description</th>
<th>RAI ablation usually recommended</th>
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<tbody>
<tr>
<td>T1</td>
<td>1 cm or less, intrathyroidal or microscopic multifocal</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>1 to 2 cm, intrathyroidal</td>
<td>Selective use*</td>
</tr>
<tr>
<td>T2</td>
<td>&gt;2 to 4 cm, intrathyroidal</td>
<td>Selective use*</td>
</tr>
<tr>
<td>T3</td>
<td>&gt;4 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;45 years old</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>≥45 years old</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Any size, any age, minimal extrathyroidal extension</td>
<td>Selective use*</td>
</tr>
<tr>
<td>T4</td>
<td>Any size with gross extrathyroidal extension</td>
<td>Yes</td>
</tr>
<tr>
<td>Nx, N0</td>
<td>No metastatic nodes documented</td>
<td>No</td>
</tr>
<tr>
<td>N1</td>
<td>&lt;45 years old</td>
<td>Selective use*</td>
</tr>
<tr>
<td></td>
<td>&gt;45 years old</td>
<td>Selective use*</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present</td>
<td>Yes</td>
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# ATA - Pediatric Thyroid Cancer Risk Levels

<table>
<thead>
<tr>
<th>ATA Risk Level</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Low</td>
<td>Disease grossly confined to the thyroid with N0/Nx disease or patients with incidental N1a disease</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Extensive N1a or minimal N1b disease</td>
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<tr>
<td>High</td>
<td>Regionally extensive disease (extensive N1B) or locally invasive disease with/without distant metastases</td>
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L-thyroxine supplementation
Replacement
TSH suppression

Hypothalamus

TRH

Portal System

Anterior Pituitary (hypopituitary)

TSH

Feedback Inhibition

T4

Replacement
TSH suppression
Surveillance

- Serum Thyroglobulin
- Neck Ultrasonography
- Whole body scan
- Other
  - CT Neck and Chest
  - PET-CT
## Long term follow up

<table>
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<th>ATA Risk Level</th>
<th>Definition</th>
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</table>
| Low            | US at 6 months postoperatively and then annually x 5 years.  
Unstimulated TG every 3-6 months for two years and then annually |
| Intermediate   | US at 6 months postoperatively, every 6-12 months for 5 years.  
Unstimulated TG every 3-6 months for 3 years and then annually.  
Consider TSH stimulated TG, diagnostic I 123 scan in 1-2 years in patients treated with I131 |
| High           | US at 6 months postoperatively, every 6-12 months for 5 years.  
Unstimulated TG every 3-6 months for 3 years and then annually.  
TSH stimulated TG, diagnostic I 123 scan in 1-2 years in patients treated with I131 |
Thyroid cancer survival by age

% of patients surviving

Age at diagnosis


Men
Women

Pediatrics
PTC recurrence

• Up to 35% 3-33 years after treatment

• Tumor stage at diagnosis - TNM

• Increased risk
  - Thyroid capsule invasion
  - Soft tissue invasion
  - Positive surgical margins
Poorer prognosis:

- Age >45
- Large tumors
- Multifocal tumors
- Male sex
- Distant metastases
- De-differentiated tumors
Other treatment options

• Tyrosine Kinase inhibitors
  - Sorafenib - approved by the FDA for use in adults
  - Case reports in children with metastases

• External beam radiation
  - Not proven effective for lung metastases

• Doxorubicin +/- cisplatin and interferon-α
  - Not effective

• Consensus on management is needed
What we know from the literature

• Limited data for children

• Multidisciplinary approach

• High volume thyroid surgeons
  - 30 cervical endocrine procedures annually
Thyroid Tumor Board established in 2012

- **Endocrinology**
  - Ioanna Athanassaki, MD
  - Nidhi Bansal, MD
  - Jake Kushner, MD
  - David Paul, MD

- **Pediatric Surgery**
  - Monica Lopez, MD
  - Jed Nuchtern, MD
  - David Wesson, MD

- **Radiology**
  - Nadia Mahmood, MD
  - Robert C. Orth, MD, PhD
  - Victor Seghers, MD

- **Interventional Radiology**
  - Christopher I. Cassady, MD
  - Jose Hernandez, MD
  - Kamlesh U. Kukreja, MD
  - Sheena A. Pimpalwar, MD

- **Pathology**
  - Choladda Curry, MD
  - Andrea Diaz, MD
  - Norma Quintanilla, MD

- **Hematology-Oncology**
  - Muali Chintagumpala, MD
  - Surya P. Rednam, MD
  - Jodi A. Muscal, MD
  - Rajkumar Venkatramani, MD

- **Otolaryngology**
  - Matthew Sitton, MD

- **Research and Outcomes**
  - Kathleen E. Carberry, RN, MPH
The Thyroid Tumor Board at TCH

- Every case is discussed
  - individualized treatment plan

- Calcium protocol initiated pre-op
  - to avoid need for IV calcium

- Thyroidectomies performed by specific surgeons
  - to increase expertise

- Clinical practice guidelines

- Outcome measures
Back to our case

• Fine needle aspiration
  - Papillary thyroid cancer

• Treatment
  - Total thyroidectomy with central and lateral neck dissection
  - High risk disease (ATA)
  - Received radioactive iodine
  - L-thyroxine suppressive therapy

• 2 year follow up: no evidence of recurrence
Take home points

• When should a thyroid ultrasound be done
  - Growing goiters
  - Asymmetric goiters
  - Neck mass/nodule
  - Persistent cervical lymphadenopathy
Take home points

• When should you refer a case to us
  - Any nodule
  - If suspicious characteristics are present
    • call us

• How do you refer a case to us
  - Website
  - Clinic number 832-822-3670
  - Thyroid tumor coordinator 832-822-4856
Thank You!