PEDIATRIC

WELL-DIFFERENTIATED

THYROID CARCINOMA

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OBJECTIVES

- Overview/Background
- Epidemiology/Etiology
- Intro to Guidelines
- Workup
- Treatment
- Follow-Up
OVERVIEW/BACKGROUND

- Thyroid nodules less prevalent in pediatric population, but more likely to be malignant
- Palpable thyroid nodules in 1.5% of pediatric population (vs. 35% in adults)
- Overall malignancy rate of 26.4% vs. 5% in adults
- Typically present at more advanced stage
  - More often present with extrathyroidal involvement/metastasis

- Nearly all well differentiated cancers
  - 90% Papillary TC << Follicular TC <<<< Medullary TC and non-differentiated TC

- Long term survival >!!!90%
PTC VS FTC

PTC
- Multifocal
- Bilateral
- Frequent cervical node metastases
- Hematogenous spread to lungs in 25% of cases (typically only after significant nodal spread)
- Often non-classic cyto-architecture and histology

FTC
- Unifocal
- Unilateral
- Cervical nodal metastases uncommon
- Frequent initial hematogenous spread to lung and bones
Incidence of 0.54 per 100,000

- Incidence increased 1.1% per year between 1973-2004 SEER database
- Thought to be due to increased detection, in addition to increased radiation exposure

More common in:
- Adolescents
- Females
- Caucasians

Prepubertal vs Adolescent
- Greater family history
- Greater extrathyroidal extension
- Greater lymph node and lung metastases
ETIOLOGY

- Childhood Radiation Exposure
- Nuclear Fallout
  - Chernobyl
    - 62 fold increase in thyroid cancer
    - 10 fold increase in aggressive papillary cancer
- Exposure to diagnostic radiation
  - Prenatal exposure - 1.4 to 2.1 fold increase
  - Diagnostic CT
    - Estimated increased risk of malignancy as high as 1 additional fatal cancer per 1000 CT Scans(!)
    - Thyroid cancer induction in 65 per million
- Previous therapeutic radiation
  - 20% increased risk of thyroid nodules
  - 18 fold greater risk of thyroid cancer
  - Risk increases in a dose dependent manner, stabilizes around 30 Gy
  - Average diagnosis: 13 yrs post treatment
## Etiology

- Genetic/Familial

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene Involved</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowden</td>
<td>PTEN tumor suppressor</td>
<td>Thyroid, GI, breast, uterine tumors</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>APC gene (AD)</td>
<td>Increased risk of thyroid cancer, GI polyps with increased risk of malignant transformation</td>
</tr>
<tr>
<td>Gardner</td>
<td>APC gene (AD)</td>
<td>Increased risk thyroid cancer, jaw osteomas, GI polyps with increased risk of malignant transformation</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11 gene (AD)</td>
<td>Increased risk thyroid cancer, GI hamartomas, pigmented oral lesions</td>
</tr>
<tr>
<td>MEN 2A</td>
<td>RET proto-oncogene (AD)</td>
<td>Medullary thyroid carcinoma, pheochromocytoma, parathyroid</td>
</tr>
<tr>
<td>MEN 2B</td>
<td>RET proto-oncogene (AD)</td>
<td>Medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas, Marfanoid</td>
</tr>
</tbody>
</table>
GENETIC MUTATIONS

- PTC
  - RET/PTC
  - TRK
  - BRAF
  - RAS

- FTC
  - PAX8/PPAR-γ
  - RAS

- MTC
  - RET
Children have historically been treated based on adult guidelines. Recent ATA task force published guidelines in April 2015.
“This approach [based on adult guidelines] resulted in a high proportion of cure, but required all children to undergo therapy that included total thyroidectomy followed by RAI ablation. Unfortunately, recent studies with follow-up spanning several decades reveal an increase in all-cause mortality for survivors, predominantly due to second malignancies in children treated with radiation. These observations, coupled with a better understanding of the excellent prognosis associated with pediatric differentiated thyroid cancer, have prompted the ATA to specifically address treatment of children with benign and malignant thyroid tumors.”

“It is acknowledged by this inaugural pediatric task force that no randomized double-blind RCT exists for the treatment of DTC.”
### Box 1

**Risk factors for thyroid malignancy**

*Clinical history*
- Prior ionizing radiation exposure
- Family history of thyroid cancer
- Family history of thyroid cancer–associated conditions

*Physical examination findings*
- Palpable firm lymphadenopathy
- Hard or fixed nodules
- Features of ganglioneuromatosis (MEN 2B)

*Ultrasonography findings*
- Indistinct margins of nodules
- Microcalcifications
- Nodule growth while on levothyroxine
- Transverse blood flow pattern
- Lymph node alterations
WORK-UP

- History
  - Other head/neck lesions
  - Family history (thyroid cancer, syndromes associated with thyroid cancer)
  - Radiation history
  - Hypo/Hyperthyroidism symptoms
  - Concomitant thyroid disease

- Physical exam
  - Vital Signs (height, weight, HR, pulse pressure)
  - General: habitus (Marfanoid)
  - Neck: detailed palpation of thyroid and cervical nodes
  - Complete head and neck exam
WORK-UP

- Labs
  - TSH & T3, T4
  - Thyroid antibody panel
  - Calcitonin?
    - only if suspicious for MEN
    - Routine assessment controversial
WORK-UP

- Imaging
  - Thyroid Ultrasound
  - Thyroid Scintigraphy if patient is hyperthyroid
  - Consider CT or MRI if bulky or fixed disease, vocal cord paralysis, or to aid in surgical planning
THYROID ULTRASOUND
THYROID ULTRASOUND
WORK-UP

- Biopsy?
- US guided FNA
Indications for FNAB are not solely based on size criteria. High risk US features and high risk patient history must be taken into account.

Limited studies on Bethesda Criteria show an increased rate of malignancy.

Requires sedation

Recommend ALL be done with US guidance.
FIGURE 1

Solitary or Suspicious Thyroid Nodule Detected By Imaging or Physical Examination

TSH suppressed
Nuclear thyroid scintigraphy

Hyperfunctioning

TSH not suppressed
FNA under US guidance

Malignant

Benign

Repeat US in 6-12 mo.

Nodule stable
Repeat US every 1-2 yrs.

Nodule growing or suspicious findings
Repeat FNA &/or Surgery

Inadequate or Nondiagnostic

Repeat US & FNA in 3-6 mo.

Nodule stable &/or benign FNA
Repeat US in 6-12 mo.

Indeterminate or Suspicious

Surgery

Nodule growing &/or abnormal FNA

Benign: Check adequacy of thyroid hormone levels in 4 wks & follow clinically

Malignant: PTC/MTC

FTC
RETROSPECTIVE REVIEW OF ALL FNAB SPECIMENS FROM

- patients less than 18yo from 1998 to 2013
- N=55

Compared rates of malignancy to the published data for adults
### Table 1
The Bethesda classification, malignancy risk in adults and ATA management guidelines [6,7].

<table>
<thead>
<tr>
<th>Bethesda criteria</th>
<th>Malignancy risk (%)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Nondiagnostic</td>
<td>1–4</td>
<td>Repeat US guided FNA(^a)</td>
</tr>
<tr>
<td>II Benign</td>
<td>0–3</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>III AUS/FLUS</td>
<td>5–15</td>
<td>Repeat FNA(^a) or lobectomy</td>
</tr>
<tr>
<td>IV Suspicious for follicular neoplasm</td>
<td>15–30</td>
<td>Lobectomy</td>
</tr>
<tr>
<td>V Suspicious for malignancy</td>
<td>60–75</td>
<td>Lobectomy or total thyroidectomy</td>
</tr>
<tr>
<td>VI Malignant</td>
<td>97–99</td>
<td>Total thyroidectomy</td>
</tr>
</tbody>
</table>

### Table 3
Number and proportion of malignant thyroid nodules for each Bethesda class.

<table>
<thead>
<tr>
<th>Bethesda criteria</th>
<th>Malignant thyroid nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>I</td>
<td>0/7 (0)</td>
</tr>
<tr>
<td>II</td>
<td>0/38 (0)</td>
</tr>
<tr>
<td>III</td>
<td>2/11 (18)</td>
</tr>
<tr>
<td>IV</td>
<td>4/4 (100)</td>
</tr>
<tr>
<td>V</td>
<td>3/3 (100)</td>
</tr>
<tr>
<td>VI</td>
<td>3/3 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>12/66 (18)</td>
</tr>
</tbody>
</table>
CONCLUSIONS:

- Rate of malignancy of thyroid nodules appears to be higher in the pediatric population than adults.
- The Bethesda Criteria appear to accurately identify benign nodules, but other categories appear to have a very high rate of malignancy.
- Bethesda Group III (AUS/FLUS) poses a particular challenge.
Meta-Analysis to determine sensitivity, specificity, accuracy, PPV and NPV

12 studies identified

- 183 malignant nodules
- 347 benign nodules

Results (assuming a 20% malignancy rate)

- Sensitivity = 94%
- Specificity = 81%
- Accuracy = 83.6%
- PPV = 55.3%
- NPV = 98.2%

Conclusion

FNAB is a sensitive test in the pediatric population to help exclude the diagnosis of malignancy
MANAGEMENT

- Benign nodule
- Autonomous nodule
- Malignant nodule
  - PTC
  - FTC
- Post-Operative Staging
- Follow Up
  - Serum studies
  - Imaging studies
MANAGEMENT OF BENIGN NODULES

- Benign nodule
  - Serial US (every 6-12mo)
  - Repeat FNA if growth or suspicious features develop
  - Do not recommend for or against suppression (data conflicting)
  - Surgical Excision may be indicated for benign nodules ≤4cm due to compressive symptoms, cosmesis, patient/parent preference, or other concerns for malignancy.
MANAGEMENT OF AUTONOMOUS NODULES

- Autonomous nodule
  - Confirmed with scintigraphy
  - No need for FNA (assuming removal of nodule)
  - 5%PTC
MANAGEMENT OF PTC

- Malignant nodule
  - PTC
    - Total or near total thyroidectomy
    - Neck dissection if clinical evidence of locoregional metastases.
    - Post operative staging, treatment as indicated, and continued follow up for life
    - Treatment should occur in a center of excellence with pediatric subspecialty support
No post-operative staging system has been validated in the pediatric population.

Limited data on

- AMES (Age-Metastasis-Extent of disease-Size)
- MACIS (Metastasis-Age-Completeness of resection-Invasion-Size)

Recommend AJCC TNM adult staging

All pediatric patients are under age 45, thus all patients will be stage I or stage II.

Cannot extrapolate pediatric survival from adult survival data

However, we know the pediatric survival is good (>90%).

Use this system to stratify risk and guide post-operative therapy and follow up.

ATA Pediatric Low, Intermediate, and High risk.
### Table 1

**TNM Classification System for Differentiated Thyroid Cancer**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Patient age &lt; 45 years</th>
<th>Patient age 45 years or older</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1</strong> Tumor diameter 2 cm or smaller</td>
<td>T1 N0, M0</td>
<td>T1 N0, M0</td>
</tr>
<tr>
<td><strong>T2</strong> Primary tumor diameter &gt; 2 to 4 cm</td>
<td>T2 N0, M0</td>
<td>T2 N0, M0</td>
</tr>
<tr>
<td><strong>T3</strong> Primary tumor diameter &gt; 4 cm</td>
<td>T2 N1a, M0</td>
<td>T2 N1a, M0</td>
</tr>
<tr>
<td><strong>T4a</strong> Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve</td>
<td>T3, N1a, M0</td>
<td>T3, N1b, M0</td>
</tr>
<tr>
<td><strong>T4b</strong> Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels</td>
<td>T3, N1a, M0</td>
<td>T3, N1b, M0</td>
</tr>
<tr>
<td><strong>TX</strong> Primary tumor size unknown, but without extrathyroidal extension</td>
<td>T3, N1a, M0</td>
<td>T3, N1b, M0</td>
</tr>
<tr>
<td><strong>N0</strong> No metastatic lymph nodes</td>
<td>T3, N1a, M0</td>
<td>T3, N1b, M0</td>
</tr>
<tr>
<td><strong>N1a</strong> Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes</td>
<td>T4a, N0, M0</td>
<td>T4a, N1b, M0</td>
</tr>
<tr>
<td><strong>N1b</strong> Metastases to unilateral, bilateral, contralateral cervical or superior mediastinal lymph node metastases</td>
<td>T4a, N0, M0</td>
<td>T4a, N1b, M0</td>
</tr>
<tr>
<td><strong>NX</strong> Lymph nodes not assessed at surgery</td>
<td>T4a, N0, M0</td>
<td>T4a, N1b, M0</td>
</tr>
<tr>
<td><strong>M0</strong> No distant metastases</td>
<td>T4a, N0, M0</td>
<td>T4a, N1b, M0</td>
</tr>
<tr>
<td><strong>M1</strong> Distant metastases</td>
<td>T4b, Any N, M0</td>
<td>T4a, N1b, M0</td>
</tr>
<tr>
<td><strong>MX</strong> Distant metastases not assessed</td>
<td>Any T, any N, M1</td>
<td>Any T, any N, M1</td>
</tr>
<tr>
<td>ATA Risk Level</td>
<td>Definition</td>
<td>Initial Postoperative Staging</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>ATA Pediatric Low-Risk</strong></td>
<td>Disease grossly confined to the thyroid with N0/Nx disease or patients with incidental N1a disease (microscopic metastasis to a small number of central neck lymph nodes)</td>
<td>Tg&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>ATA Pediatric Intermediate-Risk</strong></td>
<td>Extensive N1a or minimal N1b disease</td>
<td>TSH-Stimulated Tg&lt;sup&gt;5&lt;/sup&gt; and diagnostic &lt;sup&gt;123&lt;/sup&gt;I scan in most patients (See Figure 2)</td>
</tr>
<tr>
<td><strong>ATA Pediatric High-Risk</strong></td>
<td>Regionally extensive disease (extensive N1b) or locally invasive disease (T4 tumors), with or without distant metastasis</td>
<td>TSH-Stimulated Tg&lt;sup&gt;5&lt;/sup&gt; and diagnostic &lt;sup&gt;123&lt;/sup&gt;I scan in all patients (See Figure 2)</td>
</tr>
</tbody>
</table>
RAI THERAPY

The next ATA recommendations address the specifics of RAI therapy and are outside of the scope of this lecture...
Thyroglobulin is a sensitive tumor marker

Must be measured simultaneously with Tg-Ab

Stimulated thyroglobulin requires TSH>30

Trend is more important than a single measurement

Monitor every 3-6 months
FOLLOW-UP IMAGING

- Ultrasound
  - Every 6mo, then every 6-12mo

- RAI Scan (DxWBS)
  - Initial post-operative scan
  - No need for routine surveillance scan
  - Only indicated if clinical evidence of residual/recurrent disease

- CT/MRI
  - Only if clinical concern for residual disease (i.e. rising Tg) with negative ultrasound and DxWBS

- FDG-PET/CT
  - Poorly studied, cannot be recommended
MANAGEMENT OF FTC

Malignant nodule

- FTC
  - Little data
  - Total thyroidectomy for large tumors (>4cm) and/or extensive vascular invasion (>3 vessels)
    - +/- RAI
  - Neck management for clinically evident disease
  - Lobectomy for smaller tumors (<4cm) with no or minimal vascular invasion (<3 vessels)
  - Consider PTEN mutation evaluation
Patients with DTC suffer from long-term psychosocial issues similar to other patients with chronic illnesses

Medication adherence can be a problem

Supportive counseling needed
QUESTIONS?
Thank You!!