Thyroid Nodules and Differentiated Thyroid Cancers in Adolescents and Young Adults

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DISCLOSURES

No Financial Disclosures

No Conflict of Interest

We will discuss FDA Approved and Non-Approved Treatments

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Objectives

- Following this presentation you will be able to:
- 1. List two major differences between DTC in children and adults
- 2. Describe the role for medical oncology in treatment of RAI-Resistant disease and MTC

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Fact 1: Thyroid Cancers (DTC and MTC) are Important Diseases among Adolescents and Young Adults (AYA)

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Cancer Among AYA

- ~ 70,000 AYA develop cancer each yr in US
- Cancer is the leading cause of death for affected AYA
- Differentiated thyroid cancer (DTC) is
  - Increasing in incidence
  - Most common invasive cancer for women 20–29 yr old
  - 2nd most common invasive cancer for adolescent girls
  - and women 30–39 and 40-49 yr old.
  - SEER database reveals
    - DTC incidence 15.6 / million for 15-19 yr old youth.
  - American Cancer Society estimates
    - 52,000 new DTC in the US during 2019
    - 4,130 new DTC in Texas (2019)

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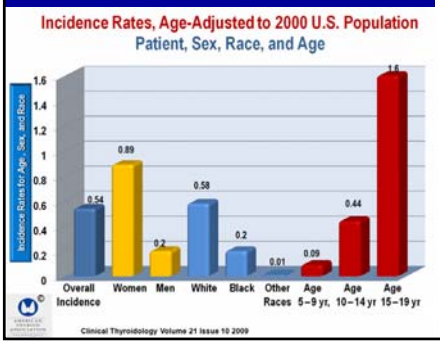
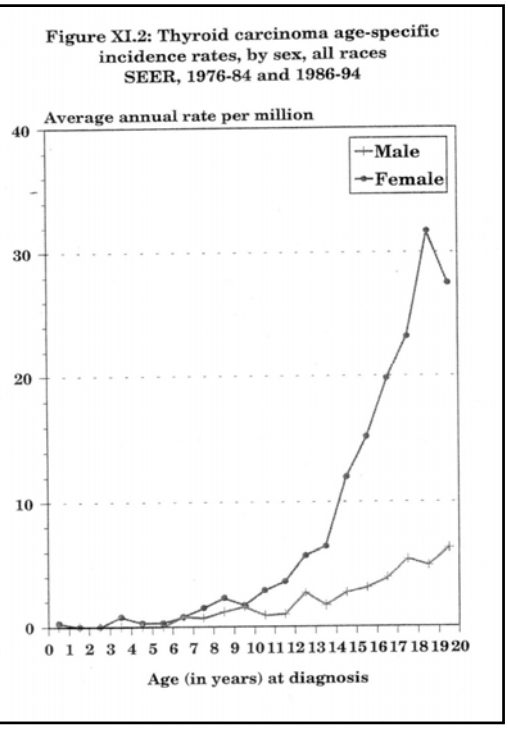
Pediatric Thyroid Cancer: Incidence





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Thyroid Cancer in Children

- 625 new cases in 2014
  - 90% DTC
- 700 neuroblastoma
- 400 osteosarcoma
- 350 rhabdomyosarcoma

- Incidence up 2.3-fold over last 40 yr

Avram et al. J Nucl Med 2014: 55(5) 705-707

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Fact 2. Adult and Pediatric Guidelines are Published BUT None Specific for AYA

Arbitrary Division at Age 18 years

- Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer The American Thyroid Association Guidelines Task Force on Pediatric Thyroid Cancer
- Francis et al. Thyroid, 2015; 25(7): 716-759

- 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer
- Haugen et al. Thyroid , 2016; 26(1):1-306

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PTC — Children vs Adults

Children present with

- Larger tumors
- Greater incidence of LN mets
- Greater incidence of lung mets
- High chance of recurrence

BECAUSE OF THAT

- Fear of recurrence
- Fear of de-differentiation
- Fear of mortality in young adults with PTC from childhood

THEREFORE

Previous Rx (TT, LN dissection and RAI for everyone)

- Goal to achieve no evidence for disease (NED)

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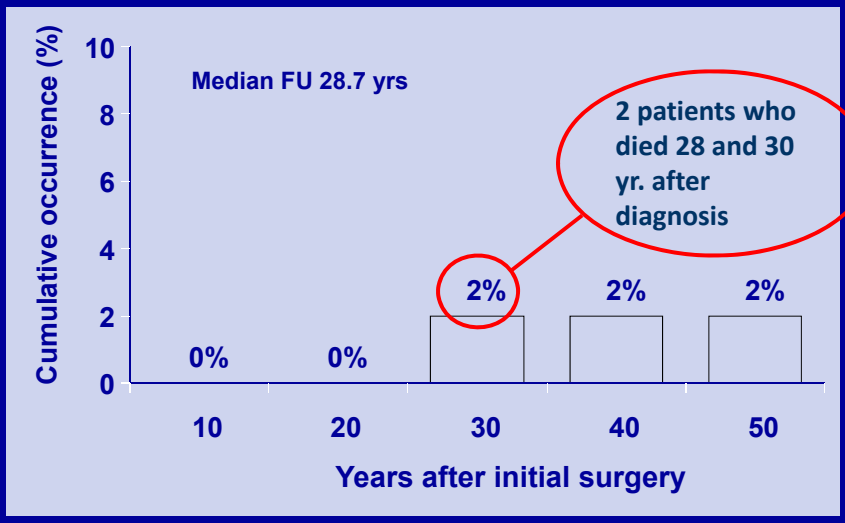
Cause-Specific Mortality in 215 PTC Patients Aged <21 Years



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Comparison and Contrast Adult v Pediatric Guidelines
Initial Thyroid Surgery for PTC

Pediatric

- TT for majority of children
  - Recurrence reduced from 35% to 6% over 40 yrs
- Central neck dissection (CND) if clinical evidence for nodes
- Prophylactic CND should be considered
- TT + prophylactic CND
  - Increased DFS 95% at 5 and 10 years

Adult

- TT if pT > 4 cm or gross extrathyroid extension or cN1 or cM1
- TT or Lobectomy if pT 1 – 4 cm no extrathyroidal extension, cN0
- Lobectomy if pT < 1 cm without extrathyroidal extension, cN0

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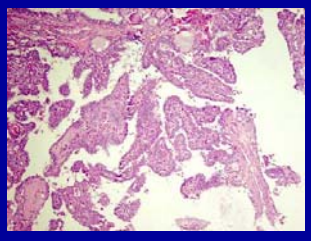
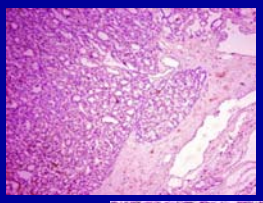
Fact 3. Thyroid Cancer is NOT One Disease

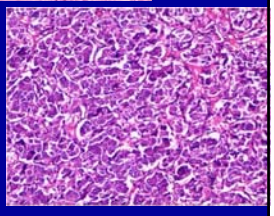
- PTC (80%)
  - Classic PTC
  - fvPTC (23%)
  - dsvPTC
  - Tall-cell
  - Hobb-nail
  - Cribriform-Morula variant
  - PTMC
  - Non-inv-fvPTC = NIFTP



- FTC (10%)
  - Minimally invasive
    - < 4 invasive areas
  - Widely invasive
    - > 4 invasive areas



- MTC (8%)
  - Highest
  - High
  - Moderate



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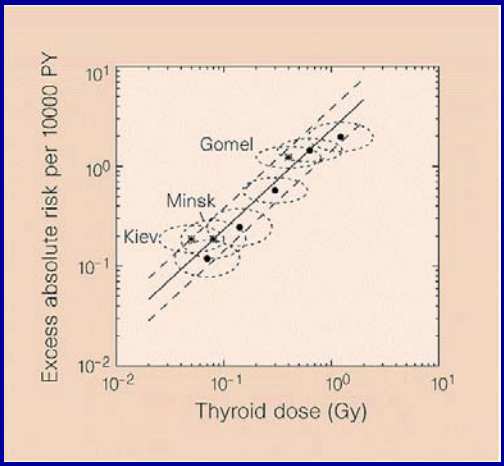
Fact 4. Dispel the Myth: Radiation Exposure at Young Age Increases Risk BUT is NOT Required



Jacob et al. Nature 998: 392: 31-32

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Areas crossed by two or more radioactive clouds during the era of nuclear testing (1951-1962) in the American Southwest.

Richard Miller, "Areas crossed by two or more radioactive clouds during the era of nuclear testing in the American Southwest, 1951-62" in Under the Cloud: The Decades of Nuclear Testing (Two- Sixty Press, 1999), between chapters 4 and 5.

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Genetic Alteration vs Absorbed Radiation

Genetic Alteration	Frequency	Gy
RET-PTC1	22%	1.04
RET-PTC3	13%	1.54
BRAF	15%	0.27
RAS	8%	0.20
PAx8-PPARγ	3%	0.62

Yuri E. Nikiforov JNCI J Natl Cancer Inst (2018) 110(4): djx209

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Fact 4. Genetic Pre-Disposition – Cancer Syndromes include Thyroid but NEED Oncology, Genetic Counseling, Life-Long Follow Up

- **Benign and malignant thyroid tumors occur in patients with**
  - **Familial adenomatoid-polyposis (FAP)**
  - **Carney complex**
  - **Endonuclease Dicer 1 (DICER1) syndrome**
  - **Phosphatase and tensin homolog hamartoma tumor syndrome (PTEN, Cowden Syndrome)**
  - **Werner syndrome.**
- **DTC has also been reported in**
  - **Beckwith–Wiedemann syndrome**
  - **Familial paraganglioma syndromes**
- **Li–Fraumeni Syndrome,**
- **McCune–Albright syndrome**
- **Peutz–Jeghers syndrome**

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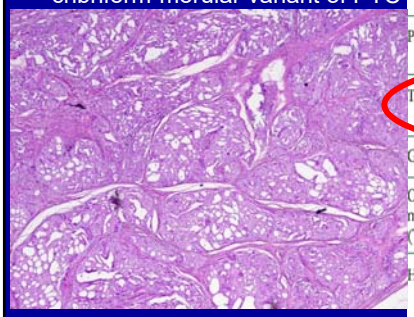
FAP

cribriform-morular variant of PTC



Cancer	Cancer Risk	Screening Recommendation
Colon	Nearly 100%	Sigmoidoscopy annually, beginning at age 10-12 years
Duodenal or periampullary	5% - 10%	Upper GI endoscopy (including side-viewing examination) every 1-3 years, start at age 20-25 years
Pancreatic	About 2%	Possibly periodic abdominal ultrasound after age 20 years
Thyroid	About 2%	Annual thyroid examination, starting at age 10 to 12 years
Gastric	About 0.5%	Same as for duodenal
CNS, usually cerebellar meduloblastoma (Turcot syndrome)	<1% but RR 92	Annual physical examination, possibly periodic head CT in affected families
Hepatoblastoma	1.6% of children <5 years of age	Possible liver palpation, hepatic ultrasound, a-fetoprotein annually during first decade of life

RR = relative risk

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Gardner Syndrome
Variant of FAP

- **Original description of Gardner's syndrome**
- **Classic triad of**
  - **Colonic polyps**
  - **Osteomas**
  - **Soft tissue tumors**
- **Other extraintestinal manifestations and endocrine tumors**
- **Thyroid cancer being the most common.**

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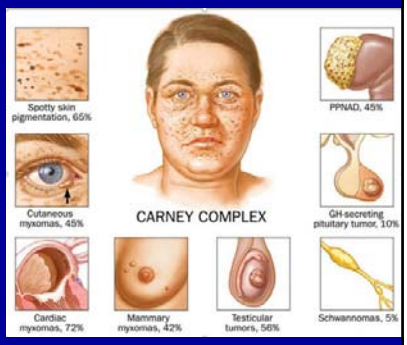
Carney Complex

- Autosomal dominant multiple neoplasia syndrome
  - Cardiac
  - Endocrine
  - Cutaneous
  - Neural myxomas
  - Pigmented lesions of the skin and mucosae
- Some similarities to McCune-Albright syndrome
- Often with large-cell calcifying Sertoli cell tumor and psammomatous melanotic schwannomas



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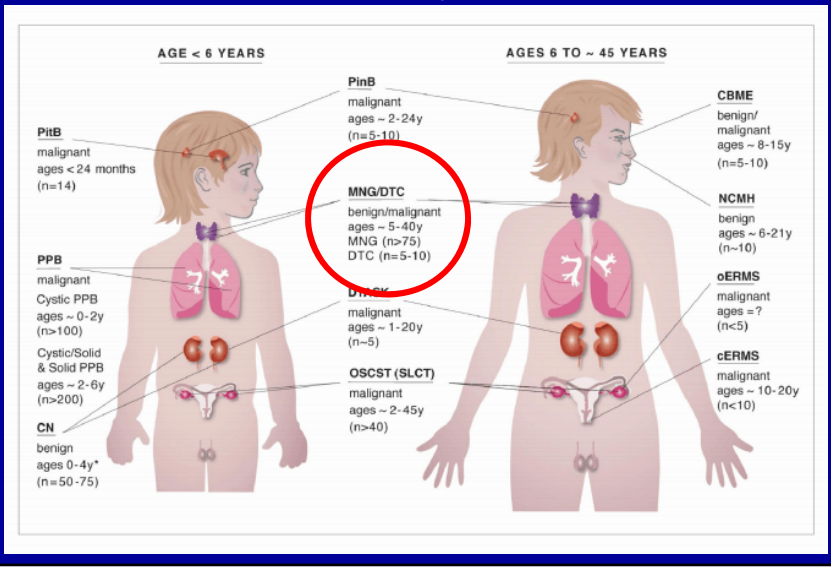
Dicer1 Syndrome

pleuropulmonary blastoma



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Cowden Syndrome

Pathognomonic criteria	Major criteria	Minor criteria
Mucocutaneous lesions:	Breast cancer	Other thyroid lesions (eg, goiter)
Trichilemmomas (facial)	Thyroid cancer	Mental retardation (IQ <75)
Acral keratoses	Macrocephaly	Hamartomatous intestinal polyps
Papillomatous lesions	Endometrial carcinoma	Fibrocystic disease of breast
Mucosal lesions		Lipomas
Lhermitte-Duclos disease (cerebellar dysplastic gangliocytoma)		Fibromas
		Genitourinary tumors

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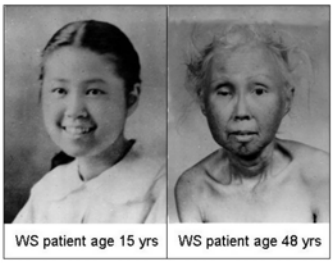
Werner Syndrome

- **The features of Werner syndrome**
- **Scleroderma-like skin changes**
- **Cataract**
- **Subcutaneous calcification**
- **Premature arteriosclerosis**
- **Diabetes mellitus**
- **Wizened and prematurely aged facies.**



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- Thyroid disease is very common in PTEN hamartoma syndrome
  - 75% prevalence
  - frequently the first organ system to be involved
- Endonuclease DICER1 syndrome
  - 75% of women 17% of men develop MNG by age 40
  - DICER1 mutations have a 16-fold increased risk of DTC.
- Early-onset, familial, or male MNG should prompt a thyroid US
- Personal and family history focused on DICER1-associated tumors
  - pleuropulmonary blastoma (PPB)
  - cystic nephroma
  - Ovarian Sertoli-Leydig cell tumor (SLCT)
  - Nasal chondromesenchymal hamartoma].

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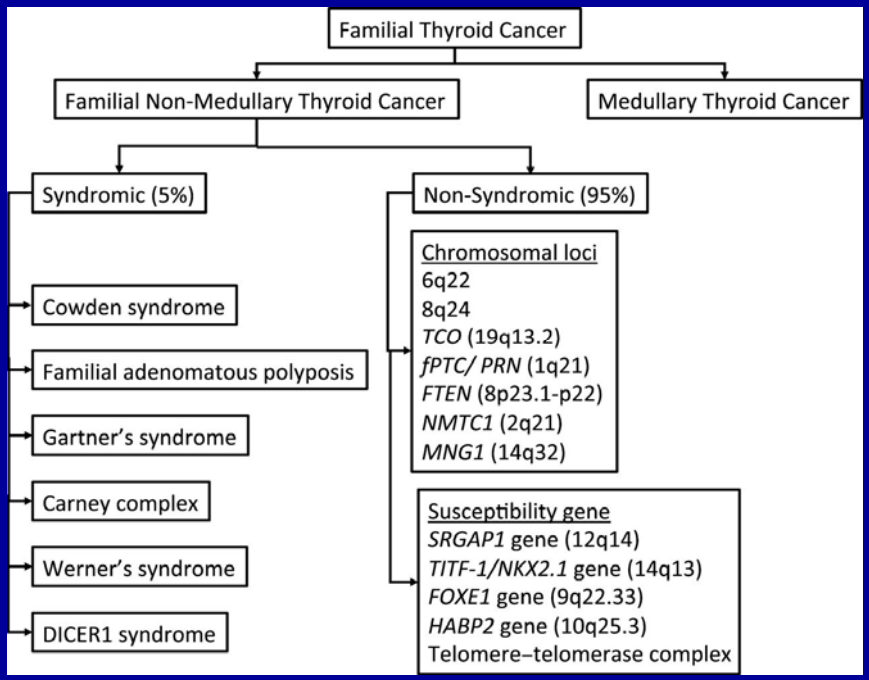

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- **Fact 5. Excluding those syndromes:**

- **Thyroid cancer is**
  - **The most heritable of all cancers that do not follow strict Mendelian inheritance**

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Hereditary PTC

- **Utah Data Base**
- **4,460 with PTC**
  - **First degree** **5.4-fold**
  - **Second degree** **2.2-fold**
  - **Third degree** **1.8-fold**
  - **Increased risk for PTC**
- **Siblings had highest risk (6.8-fold)**

Oakley et al. JAMA Otolaryngol Head Neck Surg 2013: 139(11) 1171-74

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Gene fusions in DTC

- Most common between REarranged during Transfection (RET) and a variety of other genes
  - RET/PTC1 and RET/PTC3 in sporadic and radiation-induced
- Histology associated with RET/PTC fusions include
  - Classic
  - Solid
  - Diffuse sclerosing variant PTC.
- Paired-box gene 8-peroxisomal proliferator-activated receptor gamma (PAX8/PPARγ) mutation
  - Associated with fvPTC and FTC (60%)
  - Less invasive phenotype.
- Neurotrophic tyrosine kinase (NTRK) rearrangements
  - Uncommon but may be associated with more aggressive disease.

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Point mutations in PTC

- Most common
- v-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene
  - 95% are the BRAF V600E
- In ADULTS BRAF
  - Aggressive phenotype (increased lymph node metastasis, extra-thyroidal extension, increased recurrence, and RAI resistance
- In CHILDREN BRAF V600E
  - Prevalence varies from 0 to 61%
  - Not associated with a greater risk for recurrence or mortality
  - Common in classic PTC and metastatic lymph nodes.

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Point mutations in PTC

- Point mutations in the Rat sarcoma (RAS) genes
  - Include H-RAS, N-RAS, and K-RAS
- ADULTS
  - Associated with follicular adenoma, FTC, PTC, fvPTC, and PDTC.
- CHILDREN
  - RAS mutations are less common
  - only in association with either FTC or fvPTC.
  - Codon 61 of N-RAS is the most commonly affected site in children.
- Endonuclease Dicer 1 (DICER-1) mutations in 10% of pediatric PTC
  - None of which recurred
  - Suggesting that DICER1 is another driver but associated with low risk for recurrence

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- Compared with adult PTC
- Childhood PTC has
  - Higher prevalence of gene rearrangements
    - 50% in children vs 15% in adults
  - Lower frequency of point mutations
    - 30% of children vs 70% of adults
- What Remains Unknown is THE AGE at which this transition occurs

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AYA Driver Mutations More Similar to Adults

Data from Vriens, et. al. (24)								
Group	BRAF	NRAS	KRAS	TRK	RET/PTC1	RET/PTC3	No Mutation	Multiple Mutations
AYA	46	3	2	0	2	22	34	20
>40	51	4	4	1	1	24	60	14

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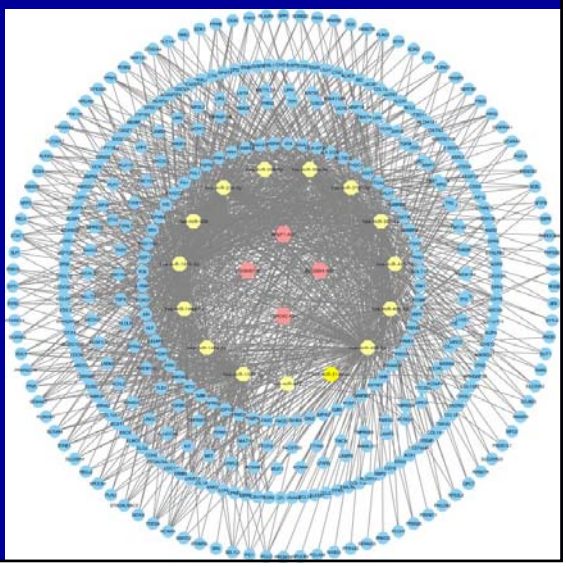
Complex Genetic Landscape of PTC

Identification of pivotal lncRNAs in papillary thyroid cancer using lncRNA–mRNA–miRNA ceRNA network Analysis.

Liang and Sun
PeerJ. 2019 Sep 19;7:e7441.



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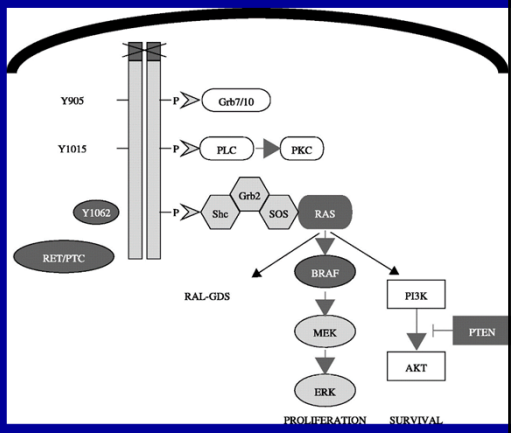
Fact 6. Driver Mutations in DTC are MOST important RAS-RAF-MEK-ERK open the Oncology Window

- RET/PTC1 or RET/PTC3 = 80% of pediatric DTC
- Both increase
  - phosphorylation and over expression of EGF-R
- BRAF V600E 45% of adult PTC
- 40% adult FTC PAX8/PPARγ



Poorten et al. Curr Opin Otolaryngol Head Neck Surg 2013: 21; 135-142

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Fact 7. Surgery +/- RAI is Effective but with Unacceptable High Complication Rates

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PTC — Children vs Adults

Children present with

- Larger tumors
- Greater incidence of LN mets
- Greater incidence of lung mets
- High chance of recurrence

BECAUSE OF THAT

- Fear of recurrence
- Fear of de-differentiation
- Fear of mortality in young adults with PTC from childhood

THEREFORE

Previous Rx (TT, LN dissection and RAI for everyone)

- Goal to achieve no evidence for disease (NED)

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PTC — Children vs Adults

BUT WHAT WE LEARNED

Disease-specific mortality is MUCH lower in children

- Greater NIS expression
- RAI sensitive
- Microscopic pulmonary metastases
- Mutations (RET/PTC or BRAF)
- Lack of progression to poorly differentiated tumors
- ? more TSH dependent
- ? more beneficial immunologic mechanisms

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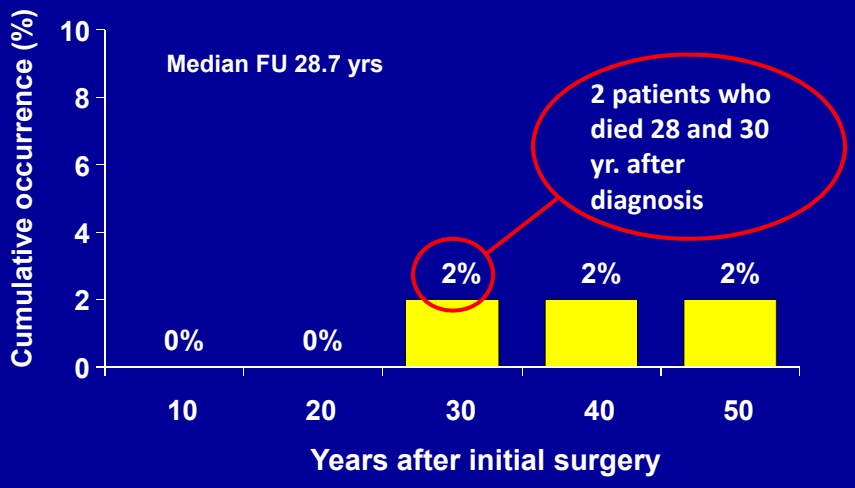
Cause-Specific Mortality in 215 PTC Patients Aged <21 Years



Hay ID et al. *World J Surg*. 34(6):1192-202; 2010

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Evolution in Care Child with PTC:

- 1934
  - Schreiner and Murphy a "fatal disease with few exceptions"
- 1946
  - RAI used for DTC
- 1952
  - Puncture of thyroid (FNA)
- 1967
  - Ultrasound (US)
- 1980s
  - Total thyroidectomy no pre-op staging
  - "Berry-picking" suspicious lymph nodes
  - RAI ablation to "all" children
  - End-point = NED
- 2015
  - Total thyroidectomy after pre-op staging
  - Compartment focused lymph node dissection in most cases
  - Reserve RAI for "high-risk" children
  - End-point of therapy may not be NED for all children
- 2020
  - An increasing role for targeted molecular therapy with multi-kinase inhibitors
  - ie: A Need for Oncologists

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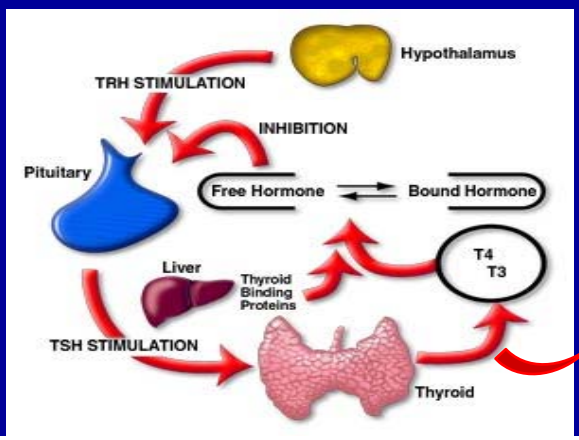

www.dpcweb.com/.../ thyroid/thyroid_function.html

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Serum Tg

- **Serum Tg proportional to volume of thyroid tissue**
- **1 ng/mL per 1 gram of thyroid mass**
- **Normal adult thyroid gland is 20-25 g, the reference range has to be generally about 20 to 25 ng/mL.**
- **Children normal thyroid = 1 gram/yr of age**

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Tg Following Thyroid Surgery

- Serum Tg falls rapidly with a half-life of 2 to 4 days
  - Any Tg released from surgery gone by one month
- TSH is the dominant influence on serum Tg level.
  - Levothyroxine Rx Tg will decline to reflect the size of the thyroid remnant plus any residual or metastatic tumor.
- Typical serum Tg < 0.5 ng/mL if TSH suppressed
- Typical thyroid remnant after near TT about 2 grams
- Serum Tg < 2 ng/mL when TSH elevated.

- Tumor recurrence with a progressive rise in Tg. Post-treatment Tg > 5 ng/mL usually recurrent DTC.

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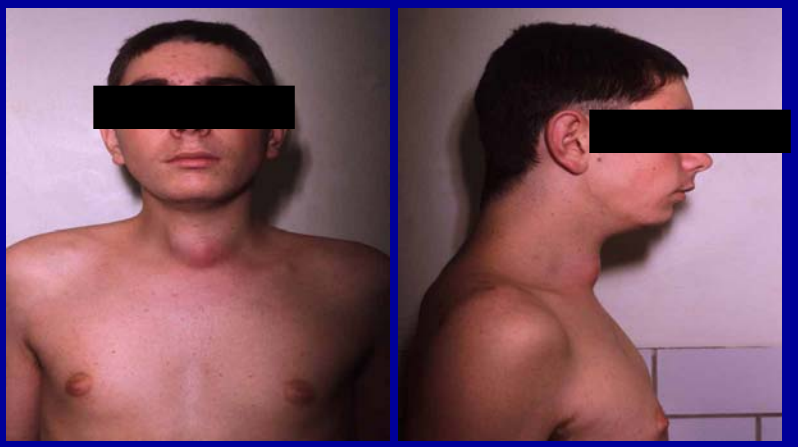

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Prevalence of Thyroid Nodules

- Prevalence: 0.2-5% in children
  - 184 nodules > 5 mm evaluated
  - 29 malignant (16%)
- Cystic lesions occur in 57% of children
- Adult prevalence = 2-6% with palpation, 19-35% with US, 8-65% in autopsy data.
- BUT
- There are groups in which nodules are more common

Mussa et al. J Pediatr 2015: 167:886-892 e881
Hayashida et al. PLoS One 2013; 8:e83220.

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Thyroid Nodules in Childhood Cancer Survivors

- **Ontaraio Canada did US**
  - **Radiation therapy > 10 yr prior**
  - **87 survivors**
- **US detected nodules in 59%**
  - **22% 5-10 mm; 19% > 10 mm**
  - **14 patients FNA**
  - **6% (n = 5) had PTC**
- **COG recommends palpation**
- **ATA Pediatric Guidelines recommend palpation**

Li et al. Thyroid 2014: 24(12) 1796-1805

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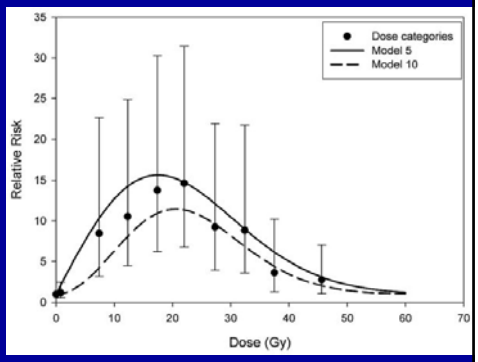
RR thyroid Cancer after Radiation Therapy

- Childhood Cancer Survivor Study
- 12,547 5-year survivors
  - Dx between 1970 and 1986
-
  - Leukemia
  - Hodgkin lymphoma and non-Hodgkin lymphoma
  - CNS cancer
  - Soft tissue sarcoma
  - Kidney cancer
  - Bone cancer
  - Neuroblastoma
- 119 Thyroid Cancers



Radiat Res. 2010 Dec; 174(6): 741–752.

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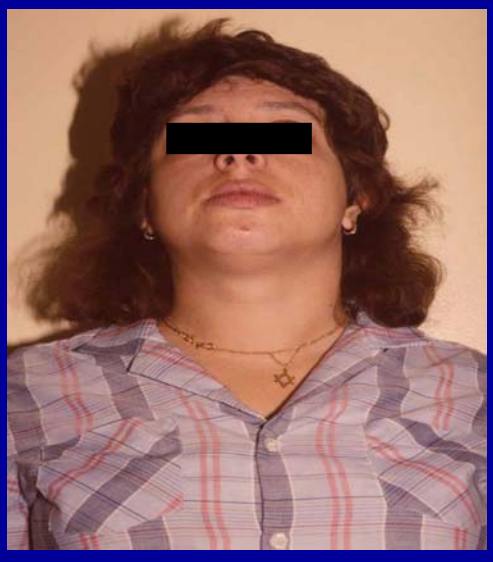

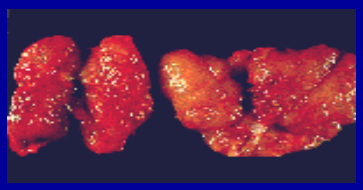

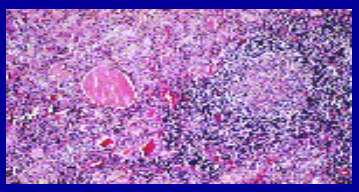

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AIT Associated Thyroid Nodules

Corrias et al, Arch Pediatr Adolesc Med 2008; 162:526

- 365 Children with autoimmune thyroid disease (AITD) Hashimoto's or Graves'
  - 3.6 – 17 yr of age
- 31.5% (n = 115) Develop Thyroid Nodules
  - 60% solitary
  - 40% multiple
  - 38 Palpable
    - 38 / 115 nodules = 33% of all nodules
    - 38 / 365 patients = 10.4% of all patients
- Radetti, et. al. J Endocr Soc, 2019. 3(3): p. 607-616.
  - 900 children with AIT
  - prevalence of TN increased
  - 9.3% at baseline to 43.9% after 10 years

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US in Children with Goiter

- 113 Korean patients < 20 yr old
- Nodules in 63.7%
  - 5.6% suspicious for malignancy
- Hypoechogenicity
  - 88.5% of AIT
  - 85.7% of Graves'

Lee et al Pediatr Radiol 2016; 46:104-111.

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Pediatric Thyroid Nodules Higher Risk of Malignancy

Table 1 Incidence of thyroid carcinoma in childhood thyroid nodules

Report	Number	%	References
1	69/138	50.0	Hayles *et al.* (1960)
2	9/44	20.4	Adams (1967)
3	9/38	23.7	Psarras *et al.* (1972)
4	12/30	40.0	Kirkland *et al.* (1973)
5	6/36	16.7	Scott & Crawford (1976)
6	10/49	20.4	Valentin *et al.* (1986)
7	12/58	20.7	Desjardins *et al.* (1987)
8	11/109	9.2	Belfiore *et al.* (1989)
9	7/32	21.9	Fowler *et. al.* (1989)
10	10/57	17.5	Raab *et al.* (1995)
11	41/148	27.7	Attie (1996)
12	17/52	32.7	Lafferty & Batch (1997)
13	26/71	36.6	Millman & Pellitteri (1997)
11	5/24	20.8	Lugo-Vicente *et al.* (1998)
12	15/93	16.1	Hung (1999)
13	7/60	11.7	Wasikowa *et al.* (1999)
14	3/31	9.7	Arda *et al.* (2001)
15	4/18	22.2	Blackburn *et al.* (2001)
16	37/155	23.9	Niedziela *et al.* (2004)
Overall	299/1134	26.4	

Niedziela M, Pathogenesis, diagnosis and management of thy nod in children. *Endo Related Cancer* Volume 13, 427-53; 2006

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Approach to Thyroid Nodule in Children

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Query Radiation Exposure and Family History

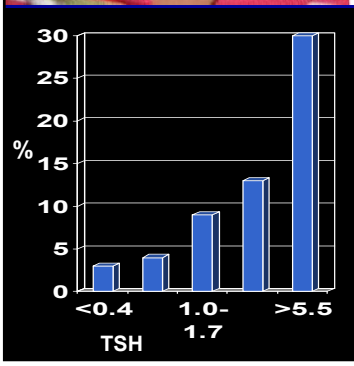
- F HX benign thyroid disease 2.5-fold
- F Hx thyroid cancer 4.0-fold
- Familial non-medullary thyroid cancer 2-5% based on > 1 affected family member
- US should be done in childhood if family member has DTC

Mihailovic et al. J Nucl Med 2014: 55;710-17

51

Serum TSH

HOWEVER
Most nodules are NOT HOT



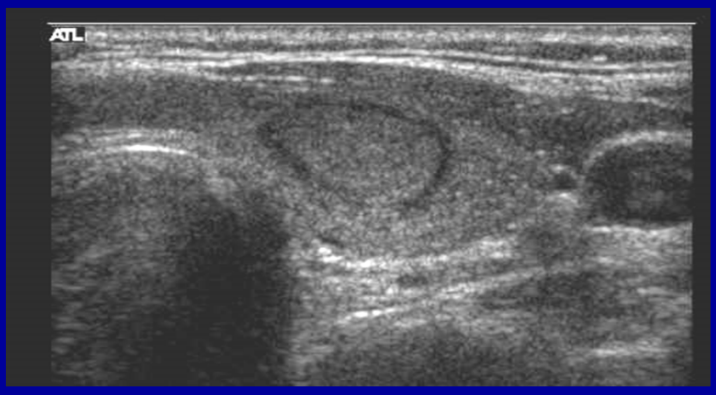
Risk of Malignancy Increases with TSH

THEREFORE
Risk of Cancer is LOW (5%) with Suppressed TSH in Child

Boelaert et al, J Clin Endocrinol Metab 91:4295, 2006
Eszlinger et al Mol Cell Endocrinol 2014: 393(1-2) 39-45
Jatana and Zimmerman Otolaryngol Clin N Am 2015: 48(1) 47-58

52

Thyroid nodule



53

Thyroid Nodules Predicting Malignancy

- 184 children and teens with nodule
  - 29 malignant, 8 FA, and 147 goitrous nodules
- US Features Associated with Malignant
  - Microcalcifications
  - Hypoechoic pattern
  - Intranodular vascularity
  - Abnormal lymph nodes
- TSH predicts malignancy
- Growth especially on L-T4 predicts malignancy

Mussa et al. J Pediatr 2015; S-0022-3476

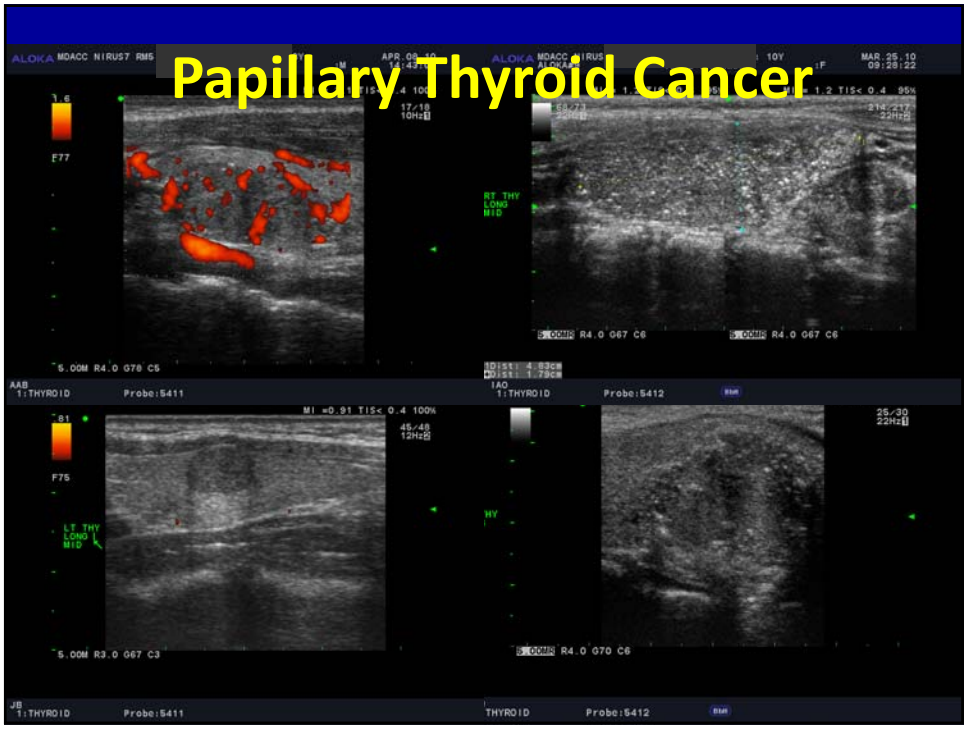
54

Richman et al.
Radiology. 2020 Feb;294(2):415-420.

- TiRADS
- ACR TI-RADS criteria for management of nodules (FNA) in adults well validated

- Pediatric study 319 patients < 19 yr old
- TiRADS would have missed 22.1% of
- Thyroid cancers

55



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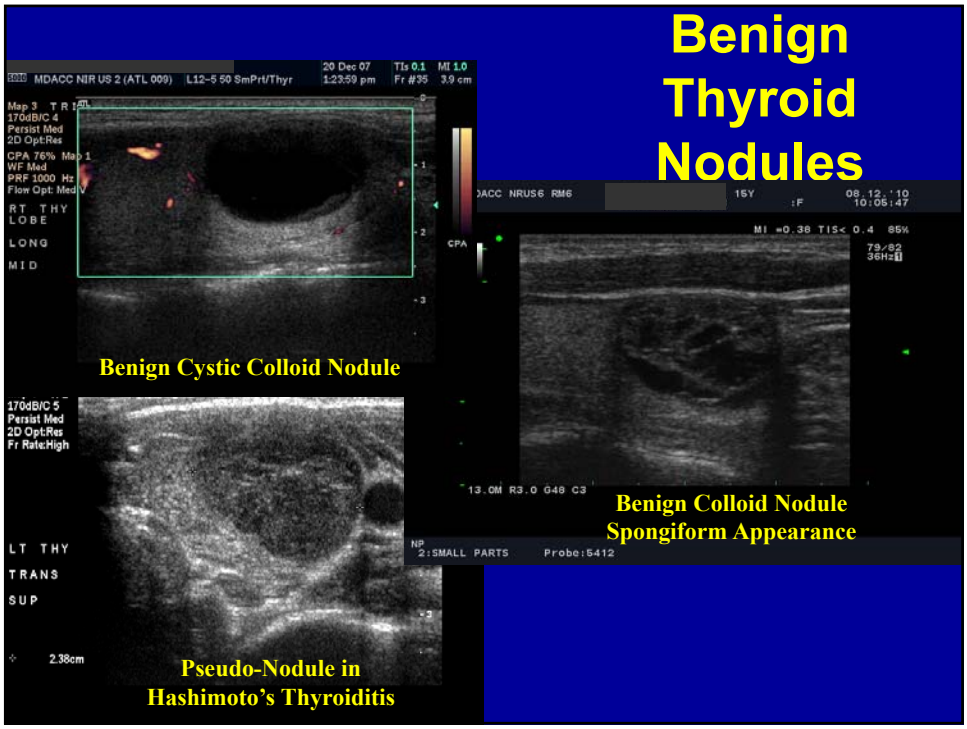

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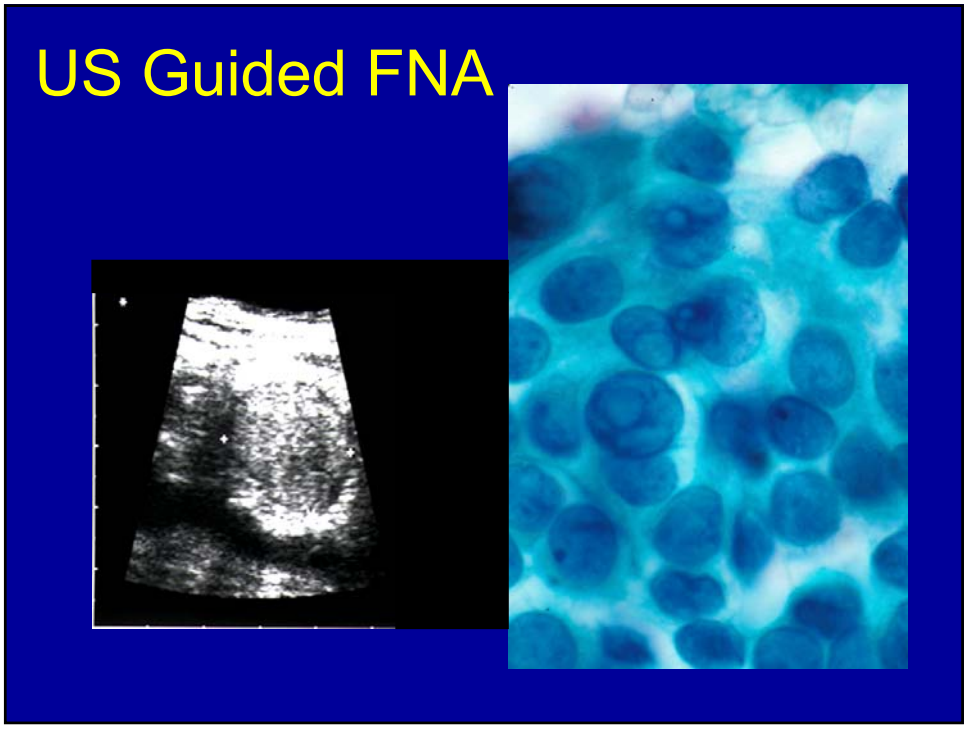

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Comparison and Contrast Adult v Pediatric Guidelines

When to Perform FNA

Pediatric

- Size is problematic due to growth of gland (1 gm/yr of age)
- Size does not correlate with cancer risk in any study of nodules in children
- FNA for:
  - all nodules > 1 cm unless purely cystic
  - 0.5-1.0 cm if suspicious US
- Small lesions more often look benign
- fvPTC (23% pediatric PTC) or FTC often look benign

Adult

- FNA if nodule:
  - > 1 cm + intermediate or suspicious US
  - > 1.5 cm + low suspicion US
  - > 2 cm with very low suspicion US no need for FNA
- Pure cyst no need for FNA

Francis et al Thyroid 2015; 25:716-759 and Haugen et al Thyroid 2016; 26:1-133
Jatana KR, Zimmerman D. Otolaryngol Clin North Am 2015; 48:47-58

59

Bethesda System for Reporting Thyroid Cytopathology

- (1) Nondiagnostic or unsatisfactory
- (2) Benign
- (3) Atypia or follicular lesion of undetermined significance (AUS/FLUS)
- (4) Follicular/Hürthle neoplasm or suspicious for follicular/Hürthle neoplasm (FN or SFN)
- (5) Suspicious for malignancy (SUSP)
- (6) Malignant

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Comparison and Contrast Adult v Pediatric Guidelines

Bethesda Classification System Used For All Ages

Pediatric (Overall DTC risk = 26%)

FNA	Cancer Risk
Nondiagnostic	"Usually benign"
Benign	5%
AUS/FLUS	28%
FN or suspicious for FN	>58%
Suspicious for CA	100%
Malignant	100%

Adult (Overall DTC risk = 5-10%)

FNA	Cancer Risk
Nondiagnostic	1-4%
Benign	0-3%
AUS/FLUS	5-15%
FN or suspicious for FN	15-30%
Suspicious for CA	60-75%
Malignant	97-99%

Buryk et al Thyroid 2015; 25:392-400 and Norlen et al J Pediatr Surg 2015; 50:1147-49

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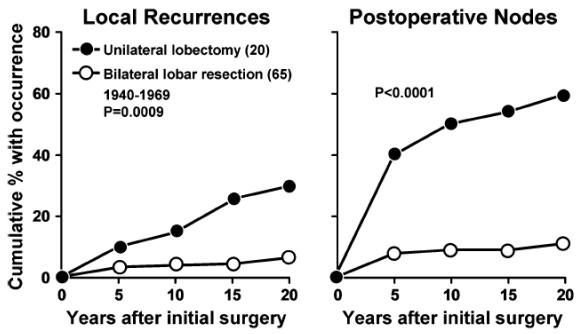
Total Thyroidectomy for Most Children

Fig. 4 Comparison of (*left panel*) local recurrences and (*right panel*) postoperative nodes in 85 PTC patients treated with either lobectomy or bilateral lobar resection at Mayo Clinic during 1940 through 1969



RECOMMENDATION 11
For the majority of children, total thyroidectomy is recommended.

Hay ID et al. *World J Surg*. 34(6):1192-202; 2010

62

What About CND for PTC in Children and Adolescents

- 83 consecutive cases < 18 yr
- 36 initial TT + CND (96%)
- Lateral neck in 57 patients ipsilateral (69%) and 35% contralateral
- 3 had no node dissection due to incidental PTC 4, 6 and 10 mm

Machens et al. J Pediatr 2010: 157(4) 648-52

63

PTC in Children and Adolescents

	age	6-11	12-15	16-18
Tumor Size		11-25	18-27	22-42
Multifocal		15%	44%	29%
Node Metastases		85%	83%	86%
# nodes		7-27	12-23	11-20
Distant mets		8%	20%	7%

Machens et al. J Pediatr 2010: 157(4) 648-52

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PTC in Children and Adolescents

# nodes	0	1-10	11-20	> 20
Tumor Size	11-32 mm	16-33 mm	18-40 mm	19-35 mm
Multifocal	20%	14%	37%	59%
Extrathyroidal extension	**10%**	**57%**	**61%**	**78%**
Distant mets	**0**	**5%**	**11%**	**30%**
Re-Operation	70%	48%	58%	59%

> 5 nodes = locoregional recurrence
> 70% of children had > 5 nodes
< TT increased recurrence by 10-fold
Incomplete node removal increased recurrence by 3-fold

Machens et al. J Pediatr 2010: 157(4) 648-52

65

Predicting Central Node Metastases in Adults

- **209 PTC:**
  - **158 node positive (N1) and 51 node negative (N0)**
- **fvPTC**
  - **7 / 158 N1 tumors (4.4%)**
  - **24 / 51 N0 tumors (47.1%)**
- **LNM more common in those with**
  - **extracapsular extension**
  - **angiolymphaatic invasion**
  - **T3 or T4 tumors**
- **BRAF**
  - **more common in classic PTC than fvPTC**
  - **No relation to central nodes**

But you do not Know this pre-op

Paulson et al. Arch Otolaryngol Head Neck Surg 2012: 138(1) 44-49

66

RCT of Prophylactic Central Neck Dissection in Adult PTC

- 181 ADULTS PTC no pre or intra operative nodes
  - Random: 88 TT and 93 TT + pCND
  - 5 yr follow-up
- No Difference in outcomes
- HOWEVER
  - TT alone higher # of ^{131}Iodine courses
  - TT+pCND higher permanent hypopara
- 50% had microscopic node disease not predicted by any pre-op feature including BRAF

Viola et al. J Clin Endocrinol Metab 2015: 100(4) 1316-24

67

Who Should Perform Surgery?

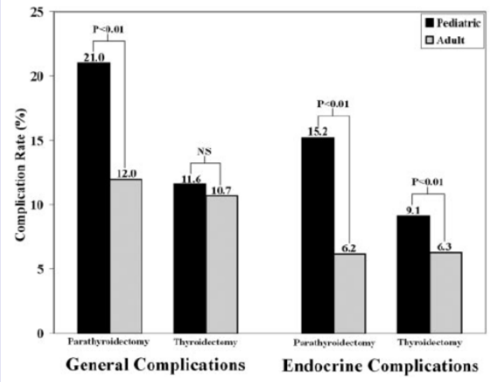

FIG. 1. Pediatric *vs.* adult general and endocrine complication rates after thyroid and parathyroid procedures, 1999–2005 (n = 97,201). NS, Not significant.

Table IV. Unadjusted clinical and economic outcomes after pediatric thyroid and parathyroid procedures by surgeon group, 1999–2005 (N = 607)

Outcome	*Surgeon group*			
	High-volume Pediatric	*Other*	P*	
Complications (%)				
General	8.7	13.4	13.2	NS
Endocrine	5.6	11.0	9.5	NS
Duration of stay (days)	1.5	2.3	2.0	<.05
Cost ($)	12,474	19,594	13,614	<.01

NS, Not significant.
*By χ^2 test or ANOVA.

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

68

ATA Pediatric Thyroid Cancer POST-OPERATIVE STAGING
Risk for Residual or Recurrent Disease

NOT risk of death

	Definition	Initial Post-op Staging
Low-Risk	Disease confined to the gland with N0/Nx disease OR incidental N1a	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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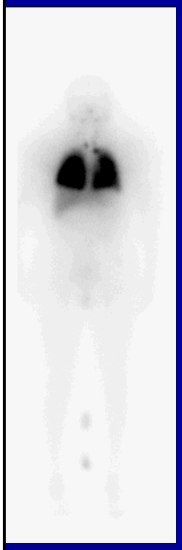
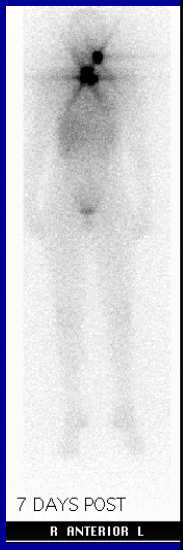
^{131}I for DTC



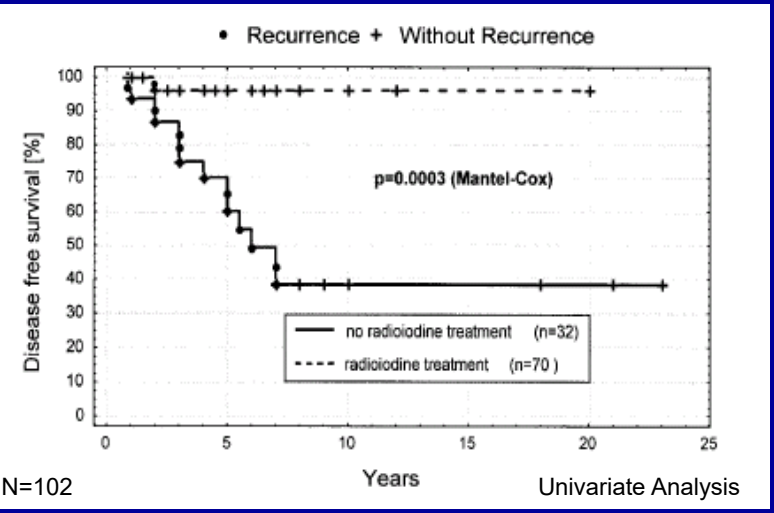
- ***Remnant Ablation*** **NO**
  - To facilitate detection of recurrent disease & initial staging
- ***Adjuvant Therapy*** **MAYBE**
  - To decrease risk of recurrence & disease-specific mortality by destroying suspected, but unproven metastatic disease
- ***RAI Therapy*** **YES**
  - To treat known disease



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

70

^{131}I Therapy in Children Appears to Increase Disease Free Survival



N=102 Univariate Analysis

Jarzab et al. European J of Nuclear Medicine 2000.

71

Lack of Impact of Ablation on Nodal Recurrence in 161 PTC Patients <21 Yrs

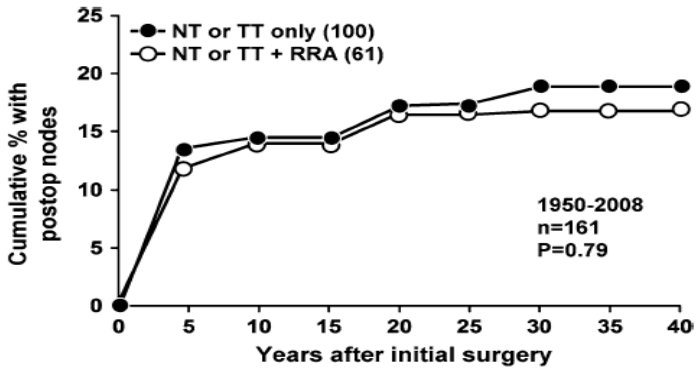


Fig. 6 Lack of impact of RRA in reducing neck nodal recurrences in PTC patients younger than 21 years of age and who had initial NT or TT at Mayo Clinic during 1950 through 2008

Hay ID et al. *World J Surg*. 34(6):1192-202; 2010

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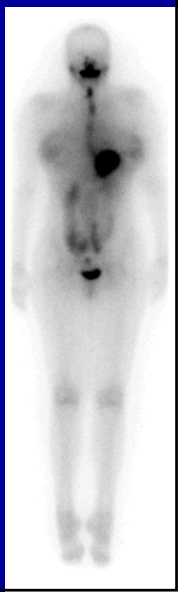
^{131}I for PTC

- **Early Side Effects**
  - Sialadenitis
  - Nausea, vomiting, diarrhea
  - Transient cytopenias
- **Late side effects**
  - Xerostomia/salivary calculi
  - Infertility (a concern for pubertal boys)
  - Pulmonary fibrosis/BM suppression
  - Malignancies---bladder, colon, breast, leukemias, salivary gland, stomach



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Risks of RAI Second Malignancy

	No RAI	RAI
All	1.05 3.5/10,000 PY	1.21 13.3/10,000 PY
Stomach	0.94	1.83
Leukemia	1.07	2.48

Brown, et al J Clin Endo Metab 93:504, 2008

74

Childhood and Adolescent PTC
Ian Hay, MD, Mayo Clinic

- **Overall survival**
- **Control**
  - **75% at 60 yr**
- **Thyroid Cancer**
  - **60% at 60 yr**
  - **P = 0.001**

- **LATER DEATHS FROM NON-THYROID CANCER**
- **9 separate types of cancer**
- **5 / 13 had I-131**
- **6 / 13 received radium or radiation therapy**
- **Only 2 / 13 (15%) never exposed to radiation**

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Comparison and Contrast Adult v Pediatric Guidelines
RAI Therapy

Pediatric

Risk Category	RAI
Low And Stim Tg < 2 ng/ml	Not Routine
Intermediate	
Stim Tg < 10 ng/ml	Rx or Follow
Stim Tg > 10 ng/ml	Rx
High	Rx locoregional Dz not amenable to surgery or distant mets Some Rx T3 tumors or extensive N1a or N1b Dz

Adult

Risk Category	RAI
Low	Not Routine
Intermediate	Consider
High	Recommend

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Comparison and Contrast Adult v Pediatric Guidelines
18 FDG-PET Scanning

Pediatric

Risk Category	RAI
Low	Insufficient Data
Intermediate	Insufficient Data
High	Insufficient Data

Adult

Risk Category	FDG-PET
Low	
Intermediate	
High	Consider in high risk with elevated Tg > 10 ng/ml and negative RAI imaging

18 FDG-PET not recommended in children
Extremely limited data
a case report and isolated cases within adult studies
unpublished data suggest low sensitivity of 18FDG-PET/CT
to identify residual disease in children that cannot
be identified via US and cross-sectional imaging (SGW).
Whether or not 18F-FDG PET has similar prognostic value
or will change management in children remains to be determined.

77

- **Who needs TT, LN dissection and RAI?**
- **Who can do just as well with less?**
- **What is a rational end-point for therapy?**
- **Do we need to achieve NED to have excellent survival?**
- **How can we tell if our therapy is working and how long will it work?**
  - **ie: Do we need annual RAI therapy?**

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ATA Pediatric Thyroid Cancer Recurrence Risk

	Initial TSH Goal	Surveillance of Patients
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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Thyroid Cancer in Children

- Review 1,800 DTC in children
- Suggest:
  - in well-operated low-risk patients stimulated Tg post op and diagnostic RAI scan
  - if NEG defer RAI therapy
- TSH suppression < 0.1 mU/L in high risk
  - and < 0.5 mU/L after remission
- Undetectable Tg = no action
- Tg < 2 ug/L = neck US
- Tg > 10 = neck US and if neg
  - then neck MR or chest CT
- Surgery if possible
- RAI in distant pulmonary metastases

Poorten et al. Curr Opin Otolaryngol Head Neck Surg 2013: 21; 135-142

80

Recurrent PTC in Children

- 227 PTC (7-20 yr old)
- 2 died of disease
- 45 recurrence
  - (36 nodes, 7 remnant, 11 distant)
- Disease specific survival
  - 10 yr = 99.3%, 20 yr = 99.3% and 30 yr = 96.5%
- DFS
  - 10 yr = 83.6%, 20 yr = 70.7% and 30 yr = 64%

Sugino et al. World J Surg 2015: 39(9) 2259-65

81

Comparison and Contrast Adult v Pediatric Guidelines
RAI Refractory Disease

Pediatric	Adult
No Definition of RAI Refractory Disease	Tumor never takes up RAI
	Tumor loses RAI uptake
	RAI uptake in some but not all lesions
	Mets progress despite RAI uptake

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Comparison and Contrast Adult v Pediatric Guidelines
Therapy for RAI Refractory Disease

Pediatric

Molecular targeted therapies may be contemplated in the rare situation where a child warrants systemic treatment. However, it is difficult to define iodine-refractory disease and iodine-refractory DTC can remain stable over years of follow up in children. For that reason, all children being considered for anti-neoplastic therapy should be referred to centers familiar with the use of these novel therapeutic agents in thyroid cancer.

Adult

Asymptomatic stable	**Follow on TSH suppression**
Isolated brain, lung, liver, bone	Stereotactic radiation or thermal
SYMPTOMATIC PROGRESSIVE not amenable to other therapies	Kinase inhibitors may be considered

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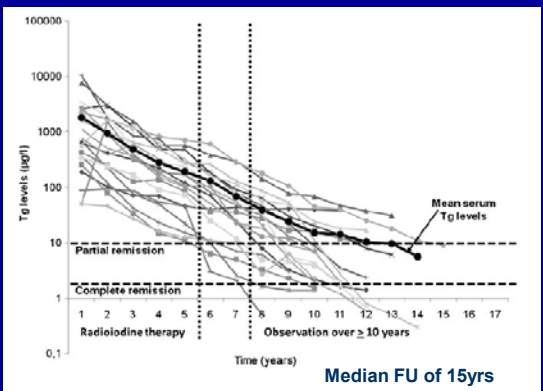
Distant Metastasis in DTC

- **Persistent but non-progressive disease frequent**
- **generally 100% 10 yr survival**
- **Delayed responses to RAI can be seen:**



Median FU of 15yrs

Tg levels in 20 children (mean age at Dx 10.4 yrs) with disseminated pulmonary mets

Mean of 5.5 RAI courses and dose of 24.2 GBq (654mCi)

LaQuaglia et al. J Ped Surg 35:955-960, 2000;
Biko et al. Eur J Nucl Med Imaging 38(4):651-5, 2011

84

Covell LL et al. Treatment of advanced thyroid cancer: role of molecularly targeted therapies. Targeted oncology. 2015;10(3):311-24.

- Adults
- TKI for treatment of poorly-differentiated thyroid cancer (PDTC).
- Advanced PTC, FTC, medullary thyroid carcinoma (MTC), and anaplastic thyroid carcinoma.
- Fails to induce remission in the majority BUT
- Significant increase in progression free survival (PFS)

85

Adult Trials

- The multicenter phase III Sorafenib trial (DECISION)
- 12% response rate
- Increase in median PFS from 5.8 to 10.8 months (78)

- Phase 3 SELECT trial using Lenvatinib
- Increased PFS for FTC and PTC.
- 75% of patients responded
- 4 / 169 achieved complete radiographic remission

- Brose MS et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014;384(9940):319-28.
- Schlumberger M et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015;372(7):621-30.

86

Sorafenib and Lenvatinib in Children

- Sorafenib and Lenvatinib have been used in a limited number of children with DTC.
- Higuchi, et al. treated an 11-year-old male with Sorafenib for 24 months without complications.
  - Pulmonary metastases initially regressed and subsequently stabilized during two years
- Mahajan, et al. reported favorable responses to Lenvatinib (14 mg/m2/day) in three children with extensive local disease and pulmonary metastases.
  - Two developed proteinuria but had clinical benefit on a lower dose, suggesting the maximum tolerable dose for children may be lower than for adults.

Higuchi Y et al. Sorafenib treatment for papillary thyroid carcinoma with diffuse lung metastases in a child with autism spectrum disorder: a case report. BMC Cancer. 2017;17(1):775.
Mahajan P et al. Response to Lenvatinib in Children with Papillary Thyroid Carcinoma. Thyroid. 2018;28(11):1450-4.

87

NTRK Fusion Tumors

- Larotrectinib, a selective inhibitor of neurotrophin tyrosine kinase (NTRK fusion)
- Data in children with PTC are very limited.
  - Drilon, et. al. treated 55 patients (age 4 mo - 76 yr)
  - 17 unique TRK fusion–positive tumor types
  - Overall response 75%
  - 55% remained progression-free
- Five had thyroid cancers
  - All five responded to therapy.
  - Adverse events were predominantly grade 1
  - No drug-related adverse event of grade 3 or 4 in > 5%
- Laetsch, et. al. treated 24 pediatric patients
  - Two with thyroid cancer.
  - Overall response was 93%

Drilon A et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med. 2018;378(8):731-9.
Laetsch TW et al. Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. Lancet Oncol. 2018;19(5):705-14.

88

Trametinib for BRAF mutant PTC

- **Trametinib effective for metastatic BRAF-mutant PTC.**
- **Both patients developed stable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria.**

White PS et al. Intermittent Dosing of Dabrafenib and Trametinib in Metastatic BRAF(V600E) Mutated Papillary Thyroid Cancer: Two Case Reports. Thyroid. 2017;27(9):1201-5.

Subbiah V et al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer. J Clin Oncol. 2018;36(1):7-13.

89

Re-Differentiation Therapy

- **MEK1/MEK2 inhibitor (selective mitogen-activated extracellular signal-regulated kinase), Selumetinib, increased RAI uptake to the threshold required for 131-I treatment in 8 of 12 adult patients, but this has not yet been studied in children.**

Ho AL et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N Engl J Med. 2013;368(7):623-32.

Nagarajah J et al. Iodine Symporter Targeting with (124)I/(131)I Theranostics. J Nucl Med. 2017;58(Suppl 2):34S-8S.

90

Mutation-Guided Re-Differentiation (Precision Therapy)

- Iravani, et. al. treated six patients (45-70 yr old)
- Tumors harboring an NRAS mutation were treated with a MEK-inhibitor (Trametinib).
- Tumors with a BRAF V600E mutation were treated with a combination of BRAF and MEK-inhibition (dabrafenib + trametinib; or vemurafenib + cobimetinib) for four weeks.
- One tumor with NRAS and all tumors with BRAF V600E mutation restored RAI uptake and proceeded to RAI therapy.

Iravani A et al. Mitogen-activated protein kinase pathway inhibition for re-differentiation of radioiodine-refractory differentiated thyroid cancer: an evolving protocol. Thyroid. 29(11) 1634-45, 2019.

91

- The NRAS demonstrated partial response
- 2 / 3 BRAF V600E mutation demonstrated partial response
- Restoration of RAI avidity
- 60% reduction in sum of lesions (SOM)
- 29-87% reduction in 18F-FDG PET uptake.

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Part 1: DTC Conclusion

- DTC is common and increasing among AYA
- Conventional Rx offers high probability for "cure"
  - BUT high (5-10%) risk for hypoparathyroidism
  - 0.5-3% risk for recurrent laryngel nerve palsy
  - Risk for pulmonary fibrosis and second malignancy
- Therefore:
- Increasing willingness to "observe" stable disease
- Consider TKI
- Consider Re-Differentiation Therapy

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Medullary Thyroid Carcinoma

- MTC = 8.1% of pediatric thyroid cancer
- Annual incidence of 0.05 / 100,000
- In children, MTC is almost always
  - Dominantly transmitted or de novo gain-of-function mutation in the REarranged during Transfection (RET) proto-oncogene and associated with multiple endocrine neoplasia (MEN) 2A or 2B.
  - Sporadic MTC is extremely uncommon in children.
  - Somatic mutations in RET and RAS are most often identified

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- Hereditary MTC
- Predictable progression from benign C-cell hyperplasia to non-invasive microscopic MTC, followed by spread to local lymph nodes, and, eventually, distant metastases
- MTC does not produce Tg or concentrate iodine
- Secrete calcitonin (Ctn) and carcinoembryonic antigen (CEA)

95

Mutations in RET are Classified:

- Highest-risk (HST)
  - MEN2B and RET M918T mutation
- High-risk (H)
  - Codon 634 (MEN2A) or A883F (MEN2B)
- Moderate-risk (MOD)
- Other codons
- However, a recent proposal:
- Split ATA MOD into
  - "moderate-high" (extracellular mutations)
  - low-moderate" (intracellular mutations)

Machens et al. Genotype-specific progression of hereditary medullary thyroid cancer. Hum Mutat 2018, 39(6):860-869

96

MEN 2A

- 95% of all MEN2
- MTC in childhood
- Later
  - pheochromocytoma (PHEO)
  - and/or hyperparathyroidism (PHPT)
- Rare variants
  - MEN2A with cutaneous lichen amyloidosis (CLA)
  - MEN2A with Hirschsprung disease (HSCR)
  - Familial medullary thyroid carcinoma (FMTC)

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MEN2A

- de novo RET mutations are rare < 10% of cases
- Thus, most kindreds are known and genetic testing for RET mutations can identify the majority of children at risk for MTC prior to the onset of disease
- Most inherited mutations occur in the extracellular, cysteine-rich domain of RET (Exons 10 and 11)
- Codon 634 (exon 11) account for the majority of classical MEN2A
- Greatest risk for early MTC in MEN2A is seen with codon 634 followed by mutations in codons 609, 611, 618, 620 or 630.

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MEN2B

- < 5% of all MEN 2
- Very early onset MTC
- 50% lifetime risk of PHEO
- Pathognomonic phenotype
  - oral and conjunctival mucosal neuromas
  - thickened lips
  - intestinal ganglioneuromatosis with megacolon
  - Marfanoid body habitus
  - high-arched palate
  - narrow long facies
  - pectus excavatum, Scoliosis, pes cavus, joint laxity, hypotonia or proximal muscle weakness
  - Symptoms that begin in infancy include constipation, feeding problems, and alacrima

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MEN2B

- De novo RET mutation in > 90%
- Most patients are diagnosed clinically,
  - based on the phenotype
  - or with dx of MTC, which is typically widely metastatic at presentation
- > 95% are M918T RET mutation
- Rarely, mutation in A883F
  - less aggressive MTC

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Prophylactic Thyroidectomy

- HST–risk: M918T mutation (MEN2B)
  - Thyroidectomy in the first year of life
- High-Risk: (MEN2A, A883F or C634F/G/R/S/W/Y)
  - Thyroidectomy ≤ age 5 yr based on Ctn levels
- MOD-Risk: (MEN2A, G533C, C609F/G/R/S/Y, C611F/G/S/Y/W, C618F/R/S, C620F/R/S, C630R/Y, D631Y, K666E, E768D, L790F, V804L, V804M, S891A, and R912P)
  - Thyroidectomy when the Ctn level exceeds normal

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Surgical Outcomes for MTC

- TT with or without central neck dissection remains the mainstay of treatment for MTC.
- None of those who presented with MTC are cured
- Majority (71%) with de novo mutations already had metastatic nodal involvement and 79% had distant metastases
- Therefore majority of MTC live with persistent disease and need medical oncology.

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TKI-Therapy

- Vandetanib and Cabozantinib are FDA-approved for adults with progressive, metastatic MTC
- Vandetanib appears to be effective in children with advanced MTC and MEN2B
- Kraft, et. al. treated 17 patients ranging from 9 – 17 years
  - 16 of whom harbored a RET M918T mutation
  - Treated for an average of 6.1 years
- The 5-year overall survival was 88.2%
- Responses were
  - partial (10/17)
  - stable disease (6/17)
  - progression (1/17)
  - Six died 0.4-5.7 years after progression

Kraft IL et al. Outcomes of Children and Adolescents with Advanced Hereditary MTC Treated with Vandetanib. Clin Cancer Res 2018, 24(4):753-765.

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Thanks for Your Attention!!!

- Summary
  - DTC is common in AYA
    - TT + RAI for most
    - TKI for persistent disease
  - MTC uncommon but
    - Majority respond to TKI
  - Immunotherapy is emerging for DTC / MTC

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