

# Thyroid Cancer: It's Not Just for Adults

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We have no conflicts of interest to disclose



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## Objectives

- Describe the clinical presentation of thyroid cancer in children and young adults
- Discuss the clinical course and management of thyroid cancer in children
- Explain the follow-up management of thyroid cancer in children



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## The Thyroid gland

- The thyroid is a butterfly-shaped gland located in the front of the neck just above the trachea
- The thyroid produces and releases into the circulation at least two potent hormones, thyroxine (T4) and triiodothyronine (T3).
- Para thyroid glands are 4 small gland located on the back of the thyroid which regulate calcium levels in the body



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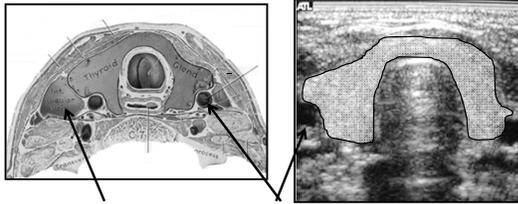
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## The Thyroid Gland



JUGULAR VEIN

CAROTID ARTERY



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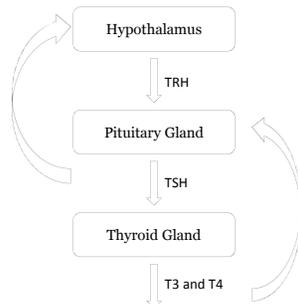
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## Thyroid Function

- Action of Thyroid Hormones
  - Maturation and differentiation
  - Neurological function
  - Growth
  - Metabolism
  - Skeletal muscle
  - Cardiovascular system
  - Reproduction



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## Thyroid Tumors

- Incidence:
  - Annually 2.0 cases per 1 million people per year in children younger than 15 years of age
  - Accounting for 1.5% of all cancers in this age group
  - Thyroid cancer incidence is higher in children aged 15-19 years of age (17.6 cases per 1 million people)



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## Incidence

- From 1990 to 2009, incidence rates for differentiated thyroid carcinomas increased in children adolescents and young adults in the United States
- More thyroid carcinomas occur in females than in males



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## Risk Factors

- External beam radiation (Hodgkins Disease)
- Exposure to atomic fallout
- Possibly RAS mutations (may be an early event in thyroid tumorigenesis)
- Iodine deficiency (follicular)



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## Histology

### Adenomas

- Benign
- Well circumscribed and encapsulated nodules
- May cause enlargement of all or part of the gland
- May extend to both sides of the neck
- Transformation to a malignant carcinoma may occur in some cells

### Carcinomas

- Papillary carcinoma (60-75%)
- Follicular carcinoma (10-20%)
- Medullary carcinoma (5-10%)
- Anaplastic carcinoma (<1%)



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## Histology

- Papillary and follicular carcinoma are often referred to as differentiated thyroid carcinoma (DTC)



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## Pathogenesis: Radiation

- Previous radiation the neck: excessive frequency of thyroid adenoma and carcinoma
- Thyroid gland in children compared with that in adults is more susceptible to carcinogenic effects of radiation (which may be reason that children with thyroid cancer tend to present with advanced disease)



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## Pathogenesis: Genetics

- Gardner Syndrome: familial adenomatous polyps in the GI tract and papillary thyroid cancer which is an autosomal dominant disorder by a mutation in the APC gene
- Cowden Syndrome: autosomal dominant inherited PTEN gene
  - Hamartoma of skin and other tissues
  - Predisposition to thyroid cancer
    - Macrocephaly 100%
    - Autism or developmental delay 82%
    - Penile freckling or other benign skin lesions 60%
    - Vascular features (arteriovenous malformations or hemangiomas) 29%
    - Gastrointestinal polyps 14%



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## Pathogenesis: Genetics

- Carney complex type I
  - PPNAD: primary pigmented nodular adrenocortical disease
  - Endocrine tumors: pituitary adenomas, papillary or follicular thyroid cancer
  - Non-endocrine tumors: cardiac and cutaneous myxomas and breast adenomas
  - Mutation in protein kinase A regulatory subunit 1 alpha gene
  - Autosomal dominant
- Werner syndrome (MEN1)
  - Connective tissue disease causing symptoms of premature aging (progeria)
  - Increased risk for osteosarcoma, soft tissue sarcomas
  - Characterized by presence of tumors in parathyroid, pancreatic islet cells, anterior pituitary and follicular and papillary thyroid cancer
  - Autosomal dominant



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## Pathogenesis: RET/MEN syndromes

- Multiple endocrine neoplasia type 2A and 2B
  - Associated with medullary thyroid cancer
  - Transmitted autosomal dominant fashion
  - Caused by germline mutations of the RET protooncogene
- MEN2A (2 or more)
  - Medullary thyroid carcinoma
  - Pheochromocytoma
  - Parathyroid disease
- MEN2B
  - Medullary carcinoma
  - Parathyroid hyperplasias
  - Adenomas
  - Pheochromocytomas
  - Mucosal neuromas
  - Ganglioneuromas
  - More aggressive



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## Benign nodules

- Most thyroid nodules in children are benign
- Causes include: inflammatory lesions, benign thyroid adenomas (usually follicular adenomas), thyroid cysts, toxic adenoma
- Risk factors include:
  - Prior history of thyroid disease
  - Exposure to radiation
  - Genetic disorders



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## Diagnosis and evaluation: Benign nodules

- Typically found on physical exam by physician, patient/family, or incidentally noted during imaging
- Ultrasound
- Fine needle aspiration (FNA) is performed to determine if nodule is benign or malignant
  - Specimens read as “nondiagnostic” or “unsatisfactory” or “atypia or follicular lesion of undetermined significance” should undergo repeat FNA



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## Follow-up: Benign nodules

- Periodic neck palpation
- Periodic ultrasound evaluation
- Significant increase in size may lead to consideration of a repeat FNA or surgical excision (usually lobectomy) because a small percentage of these “benign nodules” harbor cancer



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Types of Thyroid Cancer:  
Papillary thyroid carcinoma

- 60-75%
- Very high rate of lymph node metastasis (70-90%)
- Slow growing
- Lung metastasis 25%
- Benign course with 10 year survival rate more than 95%



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Clinical Presentation:  
Papillary thyroid carcinoma

- Male
- History of external radiation to the head and neck
- Exposure to nuclear fallout
- History of rapid growth of the nodule
- Firm or fixed mass
- Hoarseness
- Dysphagia
- Cervical adenopathy



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Diagnosis and Evaluation:  
Papillary thyroid carcinoma

- History taking and physical examination
  - History of radiation to head, neck & upper chest
  - History of hoarseness or difficulty swallowing
  - Lymphadenopathy
  - Rapid growth suggests carcinoma
  - Hard, fixed nodule suggests carcinoma



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## Diagnosis and Evaluation: Papillary thyroid carcinoma

- Labs
  - TSH and Free T4
  - Thyroglobulin (Tg)
    - Not a measure of thyroid function
    - Nondiagnostic when thyroid gland is still present
    - Used for monitoring patients after total/partial thyroidectomy



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## Diagnosis and Evaluation: Papillary thyroid carcinoma

- Neck ultrasound
  - Determine number and size of nodules
  - Determine characteristics of nodule/nodules
- Fine needle aspiration
  - Palpable/nonpalpable nodule measuring >1cm
  - Nodule < 1 cm and US highly suspicious for cancer



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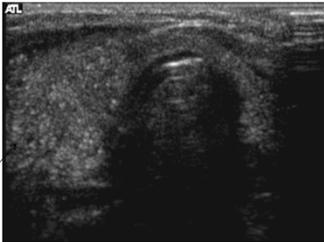
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## Papillary Carcinoma



Punctate calcifications



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## Diagnosis and Evaluation: Papillary thyroid carcinoma

- Dosimetry I131
  - I131 taken orally in a diagnostic dose
  - I131 emit gamma rays that can be imaged
  - Imaging and blood work done throughout the week of dosimetry
  - Precautions



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## Treatment: Surgical Papillary thyroid carcinoma

- Total/partial thyroidectomy
  - Possible lymph node dissection
- Postoperative management
  - Risk of edema
  - Neck drain
  - Monitor for signs of hypothyroidism
  - Pain management
  - **RISK OF HYPOCALCEMIA**
    - Obtain immediate postoperative Calcium level
    - Follow serum Calcium every 6 hours
    - Administer calcium if Calcium <8.0



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## Treatment: RAI Papillary thyroid carcinoma

- Radioactive Iodine (I-131 RAI treatment)
  - Placed on low iodine diet 1-2 weeks prior to dosimetry
    - Iodine can prevent the thyroid from taking up the I-131
  - Ablate residual thyroid tissue with RAI only in patients who have extension of disease seen on dosimetry
  - Radiation precautions: 24 hour hospital isolation



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Treatment: thyroid hormone replacement/suppression  
Papillary thyroid carcinoma

- Replace the function of the thyroid gland
- Prevents recurrence or progression
- Dose adjusted on TSH/Free T4 levels
- Brand/generic considerations
- Take same time every day; ideally on an empty stomach



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Follow-Up:  
Papillary thyroid carcinoma

- Monitor TG levels
- Monitor TSH/Free T4 levels
- Physical exam
- Ultrasound
- Dosimetry with RAI if residual disease is noted
- Dosimetry with Thyrogen
- Thyrogen stimulation



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Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

- Thyroid tumors currently diagnosed as non-invasive EFVPTC have very low risk of adverse outcomes
- EFVPTC indolent behavior and genetically different than infiltrative tumors
- Reclassified: non-invasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP)
- Tumor is completely surrounded by capsule of fibrous tissue

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### Diagnostic Criteria for NIFTP

- Encapsulation or clear demarcation
- No vascular or capsular invasion
- No tumor necrosis
- No high mitotic activity

### Clinical Management

- Lobectomy

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### Types of Thyroid Cancer: Follicular thyroid carcinoma

- 10-20%
- Usually encapsulated
- Higher incidence of bone and lung metastasis
- May be sporadic or familial
- Generally benign
- 10 year survival rate of more than 95%



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### Clinical Presentation: Follicular thyroid carcinoma

- Male
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- Total/partial thyroidectomy
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Treatment: RAI  
Follicular thyroid carcinoma

- Effect of RAI can take up to one year; dosimetry should not be performed before this
- Second dose given if disease still seen at one year dosimetry



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Treatment: RAI  
Follicular thyroid carcinoma

- Side effects
  - Early: pain and swelling of salivary glands
    - Nausea and vomiting
    - Transient loss of taste and smell
    - Transient bone marrow suppression
    - Pulmonary fibrosis
  - Larger cumulative lifetime RAI doses:
    - Permanent bone marrow suppression
    - Increase in the development of leukemias



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Follow-Up:  
Follicular thyroid carcinoma

- Monitor TG levels
- Monitor TSH/Free T4 levels
- Physical exam
- Ultrasound
- Dosimetry with RAI if residual disease is noted
- Thyrogen stimulation



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Types of Thyroid Cancer:  
Medullary thyroid carcinoma (MTC)

- 5%-10%
- Originates from the calcitonin-secreting parafollicular C cells
- Usually familial



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Clinical Presentation:  
Medullary thyroid carcinoma

- Solitary nodule
- Discovered incidentally when family member diagnosed with MTC
- Part of MEN2A or MEN2B



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MEN 2 Subtype	Medullary Thyroid Carcinoma	Pheochromocytoma	Parathyroid Disease
MEN2A	95%	50%	20%-30%
MEN2B	100%	50%	Uncommon
Familial Medullary Thyroid Carcinoma	100%	0%	0%




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**Diagnosis and evaluation:  
Medullary thyroid carcinoma**

- Generally children with MTC:
  - no clinical symptoms
  - thyroid nodule
  - palpable cervical lymphadenopathy
  - OR they are a member of a kindred affected with MTC and are found to have a positive RET germline mutation or increased plasma calcitonin levels.
- Calcitonin levels why




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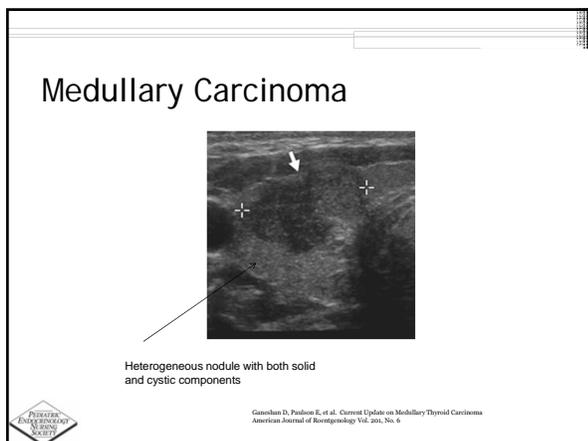
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Treatment:

Medullary thyroid carcinoma

- Total thyroidectomy: prophylactic thyroidectomy when RET mutation if confirmed
  - MEN2A: by 5 years of age
  - MEN2B: first year of life
- Thyroid hormone replacement
- No role for RAI



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Follow-up:

Medullary thyroid carcinoma

- Monitor TSH/Free T4 levels
- Monitor calcitonin levels
  - Imaging studies (US, CT/MRI) of calcitonin becomes detectable
- MEN2 syndromes: should be screened for pheochromocytoma (plasma metanephrines) starting at age 10
- MEN2 syndromes/FMTC: genetic screening for other family members



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Types of Thyroid Cancer:

Anaplastic thyroid carcinoma

- <1%
- Most advanced and aggressive thyroid cancer
- Least likely to respond to treatment
- At time of diagnosis, 50% harbor metastases in the lung, bone and brain
- RARE in pediatric age group



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Treatment:

Anaplastic thyroid carcinoma

- Surgical excision is first line of therapy
- RAI and thyroid hormone suppression therapy ineffective
- Multidrug chemotherapy (doxorubicin or paclitaxel based) has minimal/no impact in prolonging survival
- These tumours are very resistant to therapy



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Comparison of Thyroid Carcinoma Characteristics in Children and Adolescents and Adults

Characteristic	Children and Adolescents (%)	Adults (%)
Papillary	67-98	85-90
Follicular	4-23	<10
Medullary	2-8	3
Poorly differentiated	<0.1	2.7

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Comparison of Thyroid Carcinoma Characteristics in Children and Adolescents and Adults

Characteristic	Children and Adolescents (%)	Adults (%)
Multicentric	30-50	40-56
Lymph node involvement	30-90	5-55
Extra thyroid extension	24-51	16-46
Vascular invasion	<31	14-37
Distant metastases	10-20	5-10

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## Specific Guidelines for Childhood Cancer Survivors

- Risk factors
  - RT to: head, neck, chest, mantle, craniospinal, or total body irradiation
  - **Greater risk:** treatment prior to age 10 years
  - **Greatest risk:** total dose of radiation to thyroid 20-29 Gy, with a downturn risk after 29Gy
  - Radiation dose to thyroid gland  $\leq 20$ Gy + treatment with alkylating agents = increased thyroid cancer risk



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## Specific Guidelines for Childhood Cancer Survivors

- Screening for at risk survivors
  - Children's Oncology Group (COG) recommends annual exam of thyroid gland with careful palpation
  - US screening controversial due to likelihood of detection of small nodules of uncertain clinical significance which may result in unnecessary and invasive procedures



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## Conclusion



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### Case Study #1

- KM, 14 year old girl diagnosed with Hashimoto's in August 2009
- Right thyroid nodule noted in March 2010
- Thyroidectomy 6/10/10
- 100 mCi I 131 on 8/30/10
- Dosimetry repeated July 2011 and revealed no evidence of active disease
- Followed with physical exam and Tg levels every 6 months, US annually
- US on July 17, 2014 showed a persistent right lobe nodule and new submandibular lymph nodes
- Based on US results, underwent Thyrogen stimulated thyroglobulin study which showed suppressed baseline and Thyrogen stimulated Tg levels
- On Synthroid replacement/suppression



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### Case Study #2

- Mr. G diagnosed with metastatic medullary carcinoma
- Referred to genetics; positive for the MEN2A/FMTC (V804M) mutation
- Family tested and children, AG and EG, were both found to be positive for the same mutation
- AG underwent thyroidectomy in May 2008 at age 3, calcitonin level has been normal, plasma metanephrine screening started at age 10
- EG underwent thyroidectomy in March 2012, at age 4, calcitonin level have been normal



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### Case Study #3

- HC presented in January 1999 at the age of 6 with 2 week history of SOB and developed stridor and wheezing
- Imaging revealed mass
- Open biopsy on 1/19/99 revealed papillary carcinoma of the thyroid
- Thyroidectomy on 1/22/99
- RAI 30 mCi on 2/10/99, 200 mCi on 8/16/99 and 200 mCi on 8/2/00
- Followed with Thyrogen stim, US, physical exam, Tg



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### Case Study #3 (continued)

- Developed jaw pain in April 2009, with cervical lymphadenopathy, drenching night sweats, lightheadedness, swelling of left scrotum
- CBC in May 2009 showed pancytopenia and peripheral blasts
- Bone marrow showed ALL
- Treated with chemotherapy, whole brain radiation and testicular radiation
- Completed treatment in June 2015



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### Case Study #3 (continued)

- Thyroid US annually
- Tg level annually
- Continues on replacement/suppression with Synthroid
- Followed by leukemia team for possible recurrence of his ALL
- Transitioned from our team to the ALTFU



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### Resources

- [www.thyroid.org](http://www.thyroid.org): American Thyroid Association: organization devoted to thyroid biology and to prevention and treatment of thyroid disease through research, clinical care, education and public health. Resources for patients and medical professionals.
- [www.thyca.org](http://www.thyca.org): Thyroid Cancer Survivors' Association: website created and maintained by thyroid cancer survivors. Contains detailed recipes that follow a low iodine diet and several other resources for patients and medical professionals



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## Resources

- [www.checkyourneck.com](http://www.checkyourneck.com): Light of Life Foundation; contains detailed recipes that follow a low iodine diet
- [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org): Long Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. Represent a statement of consensus from a panel of experts in the late effects of pediatric cancer treatment. The screening recommendations are appropriate for asymptomatic survivors of childhood, adolescent, or young adult cancers.



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