

# **Thyroid Neoplasia**

## **Background**

1. Definitions
  - Adenoma
    - Benign thyroid tumor
  - Carcinoma
    - Most common endocrine neoplasia
    - Types
      - Papillary
      - Follicular
      - Medullary
      - Anaplastic
2. Websites
  - American Thyroid Association (ATA)
    - <http://www.thyroid.org>

## **Pathophysiology**

1. Pathology<sup>1</sup>
  - Adenoma
    - Discrete solitary mass
    - Usually follicular cells
    - Non-functional, very rarely harbor carcinoma
  - Papillary CA
    - Follicular cells, solitary or multifocal
    - Age 20-40 yo
    - Mutations of tyrosine kinase receptors (RET or NTRK1) specific for papillary CA
    - Spread: lymphatic
  - Follicular CA
    - Follicular cells
    - Often mutation of RAS oncogenes
    - Spread: hematogenous, often to lungs & bones
  - Medullary CA
    - Abnormal parafollicular C cells
    - Mutation in germ-line RET proto-oncogenes
    - Secrete calcitonin, somatostatin, serotonin and VIP
    - Sporadic: 80%, 40-50 yo, mostly solitary
    - Familial: 20%, younger pts or children, often bilateral or multifocal, seen in MEN-2 (multiple endocrine neoplasia type 2)
    - Spread: lymphatic, hematogenous
    - May be part of MEN syndromes
  - Anaplastic CA
    - Undifferentiated cells
    - Highly malignant
    - Rapidly invading adjacent structures
    - Mean age 65 yo
    - Various oncogenes involved
    - Point mutation inactivating p53 common

2. Incidence/ prevalence<sup>1,2</sup>
  - Thyroid nodules
    - Baseline prevalence 3-7%
    - Incidental finding on U/S 20-76%
    - 20-48% pts w/solitary palpable nodule have additional nodules on U/S
    - Slow, progressive growth over wks-mos suggests malignancy
  - Adenoma
    - Benign thyroid nodules outnumber cancer 10:1
  - Carcinoma
    - Rare
    - 5-8% of thyroid nodules are cancerous<sup>3</sup>
    - Annual incidence has risen 2.4x (1973-2002)
      - 87% of incr due to nodules <2 cm
    - Papillary
      - Prev: 75%
      - Inc: 5.8/100,000 F; 2.5/100,000 M
    - Follicular
      - Prev: 10-20%
      - Inc: F > M
    - Medullary
      - Prev: 5%
      - Inc: F = M
    - Anaplastic
      - Prev: <5%
      - Inc: 2/1,000,000 people
3. Risk factors for malignancy<sup>2,3</sup>
  - Female > male (2.5:1)
  - Age <20, >60
  - Genetic susceptibility (1st deg relative)
  - Family hx of thyroid carcinoma
  - Family hx of thyroid cancer syndrome
    - Cowden's syndrome
    - Familial polyposis
    - Carney complex
    - MEN 2
    - Werner syndrome
  - Radiation exposure, esp. age <20
    - Therapeutic or accidental
  - Solitary firm or hard nodules
  - Multinodular goiter
    - Anaplastic carcinoma
    - May harbor both hyperfunctioning and "cold" nodules
  - Growing nodule
  - Cervical adenopathy
  - Persistent hoarseness, dysphonia, dysphagia, and dyspnea
    - Anaplastic carcinoma
  - Nodules in children
    - 2x higher risk of malignancy than adult nodules<sup>3</sup>

#### 4. Morbidity/ mortality<sup>4,5</sup>

- Prognosis
  - Worse if age >45 (most important prognostic factor)
- Adenoma
  - Resected adenomas do not recur
- Carcinoma
  - Local spread
    - Trachea
    - Esophagus
    - Recurrent laryngeal nerve
  - Mets to lymph nodes and distant sites (lungs, bone)
  - Postoperative damage
    - Recurrent laryngeal nerve
- Papillary CA
  - 10-yr survival 93%
  - 5-yr relative survival rate
    - Stage I, II = 100%
    - Stage III = 96%
    - Stage IV = 45%
  - 5-25% local recurrence
  - 10-15% distant mets (lung)
  - Recurrence more likely if
    - Age >40 yo
    - Large tumor size
    - Extracapsular extension
- Follicular CA
  - 10-yr survival rate 85%
  - 5-yr relative survival rate
    - Stage I, II = 100%
    - Stage III = 79%
    - Stage IV = 47%
  - Mets vascular (lung, liver, bone), uncommon to LNs
- Medullary CA
  - 10-yr survival (if age < 40 yo) 75%
  - 5-yr survival rate
    - Stage I = 100%
    - Stage II = 97%
    - Stage III = 78%
    - Stage IV = 24%
  - Lymph node spread common at Dx
- Anaplastic CA
  - 10-yr survival rate 14%
  - 5-yr survival rate 9%
  - 90% local or distant mets (lung >> bone > brain) at Dx

#### Diagnostics

##### 1. History<sup>1-3</sup>

- Most pts w/thyroid nodules asymptomatic
  - May complain of neck pressure or pain if spontaneous hemorrhage into nodule

- Radiation exposure (esp. head/neck)
  - Hoarseness
    - Vocal cord paralysis suggests malignancy
  - Dysphagia
  - Cough
  - CNS disturbance
    - Heat intolerance
    - Irritability
    - Insomnia
  - Frequent bowel movements
  - Wt loss
  - Infertility
  - Dyspnea (advanced Dz)
  - Family hx of thyroid Dz
2. Physical exam
- Painless thyroid nodule
  - Thyroid mass
    - May be nodular, hard or fixed
  - Cervical lymphadenopathy
    - Worse prognosis
  - Possible malignancy
    - Vocal cord paralysis
    - Lateral cervical lymphadenopathy
    - Fixation of nodule to surrounding tissues
3. Diagnostic testing
- Malignancy of nodules
    - Nonpalpable nodules have same risk of malignancy as palpable nodules of same size
    - Evaluate all nodules  $\geq 1$  cm unless risk factors present<sup>1</sup>
    - Incidental nodules found by FDG-PET for other reasons have a 33% chance of malignancy; evaluate regardless of size<sup>1</sup>
  - CT/MRI
    - Not routinely used
    - Rarely dx for malignant lesions in nodular thyroid<sup>3</sup>
    - Can be useful for suspected substernal extension of goiter
    - CT contrast medium contains iodine and reduces uptake of radioisotope
  - Calcitonin assay
    - Serum marker for Medullary thyroid carcinoma (MTC)
    - Incr in renal impairment and pts taking PPIs
    - A must if family hx of MTC or MEN2
    - 10-100 pg/mL - abnormal
    - $>100$  pg/mL highly suggestive of MTC
  - TPOab
    - High levels in presence of diffusely enlarged thyroid suggestive of autoimmune or Hashimoto's thyroiditis
  - Thyroglobulin assay
    - Not useful in work-up of thyroid nodules

## Diagnostic Algorithm

### 1. TSH normal

- Ultrasound, if nodule found → FNA
- High risk for cancer
  - Hypoechoic nodule in concert w/one pattern assoc w/malignancy (microcalcifications, irreg or microlobulated margins and chaotic arrangement of intranodular vasculature)
  - Rounded, more tall (antero-posterior) than wide (transverse) and marked hypoechoogenicity is also suggestive of malignancy
  - Presence of 2 suspicious criteria identifies 87-93% of thyroid malignancies

### 2. TSH low

- FT3, FT4
  - Central hypothyroidism will have depressed TSH and low FT4
- Radioiodine uptake scan
  - Esp. in areas of iodine poor diets
- Cold nodule
  - Risk of cancer 5-8%: Positive predictive value low → FNA
- Single hot nodule
  - Treat w/radioactive iodine or follow-up
- Multiple hot nodules
  - Ultrasound
    - Non-suspicious → radioactive iodine/follow up
    - If suspicious → FNA

### 3. TSH high

- Evaluate for hyperthyroidism
  - FT4
  - Thyroid peroxidase antibody (TPOab)
- Ultrasound
  - Non-suspicious → eval and Tx for hypothyroidism
  - Nodule found → FNA
    - Benign → no further studies
    - Non-diagnostic → repeat FNA, if repeat non-diagnostic, close follow up and/or surgery

### 4. Other

- Most common benign dx
  - Colloid nodule
    - Cystic → percutaneous ethanol injection
    - Solid → FNA
      - Non-suspicious → routine follow-up
      - Suspected malignant → 50-75% chance of malignancy at surgery
      - Malignant → >95% chance of malignancy at surgery
- Most common malignant lesion
  - Papillary thyroid carcinoma (PTC)
    - FNA
      - Indeterminant follicular neoplasia

- Radioiodine scan
  - Hot → routine follow-up
  - Cold → surgical excision
- Hurthle cell
  - If indeterminate Hurthle cell found on FNA → surgery

### **Diagnostic Classifications**

1. TNM Classification System for Differentiated Thyroid CA
2. Staging for Medullary Carcinoma

### **Differential Diagnosis**

1. Multinodal goiter
2. Thyroid adenoma
3. Thyroid cyst (cystic degeneration of adenoma)
4. Thyroid hyperplasia
5. Thyroid carcinoma
6. Non-Hodgkin's Lymphoma

### **Acute Treatment**<sup>1-3</sup>

1. Suspicious/indeterminate FNA or concerning hx → surgery
2. Pre-op staging U/S for contralateral lobe and neck nodes recommended
  - US neck, vocal cord assessment and CXR
3. Routine pre-op measurement of serum Tg
  - Not recommended
4. Post-op radioactive ablation for high-risk patients (metastatic ds, nodal ds, gross residual ds) → check baseline CBC and renal function
5. Indeterminate FNA (esp cold nodules) → surgical resection
6. Indeterminate, small (<100 mL) hot nodules
  - Radioactive ablation or surgery (if w/o suspected malignant potential)
7. RAI ablation
  - Indicated for hyperthyroidism caused by hyperfunctioning adenoma or toxic multinodular goiter (85-100% effective)<sup>3</sup>
8. Antithyroid drugs
  - Discontinue 3 wks prior to RAI ablation
  - Restart 3-5 days post ablation
9. Pre-op FNA suggestive of PTC → near-total or total thyroidectomy
  - Remove central compartment lymph nodes
  - If nodule <1 cm and no LN involvement may be treated by lobectomy plus isthmectomy
10. Advanced, poorly differentiated follicular carcinomas, medullary carcinomas and Hurthle cell carcinomas
  - Manage aggressively in concert w/multi-disciplinary teams
11. Benign nodules → follow w/serial U/S (q6-18 mo)
  - If nodule volume incr by 50% or grows by 2mm in 2 dimensions repeat FNA<sup>3</sup>
  - If no incr as noted above may follow up U/S in 3-5 yrs<sup>1</sup>
  - TSH suppression therapy more effective in small, relatively newly diagnosed nodules, colloid features on FNA and in regions w/borderline iodine deficiency

12. Adverse effects of suppression Tx
  - Oversuppression can lead to bone mineral density loss in postmenopausal women
  - 3x incr of Afib in elderly pts w/suppression Tx<sup>3</sup>
  - Routine thyroxine suppression of benign nodules not recommended in iodine sufficient populations<sup>1</sup>
13. May choose surgery after informed consent of risks and benefits
14. Laser Thermal Ablation (LTA)
  - Alternative for benign nodules in high-surgical risk pts

### **Further Management**<sup>1,3</sup>

1. Postoperative staging
  - Crucial to prognosis and follow-up care strategies (AJCC/UICC staging system recommended)
2. Permanent hypoparathyroidism or injury to recurrent laryngeal nerve occurs in <1% of cases
3. RAI ablation
  - Recommended for known distant mets, gross extrathyroid extension of tumor primary tumors >4 cm, primary tumors 1-4 cm in size w/LN mets or other high risk features
  - Remnant ablation
    - Can be performed following TSH withdrawal or rhTSH stimulation
  - Low iodine diet
    - Recommended for 1-2 wks prior to remnant ablation Tx
  - Complications of RAI ablation
    - Low-level leukopenia
    - Thrombocytopenia
    - Oligo/amenorrhea, premature menopause
    - Male infertility
  - Post-therapy scan
    - Recommended 2-10 days after remnant ablation
4. Thyroxine suppression postoperatively warranted most in pts who received radiation Tx during childhood
5. Target range of TSH following resection of thyroid cancer = 0.5mU/L
6. Suppression to < 0.1mU/L may be necessary for high-risk pts and those w/metastatic or locally invasive ds not completely resected
7. External beam irradiation
  - Recommended for primary tumors in pts >45yo w/visible extrathyroidal dz and high risk for microscopic residual dz or when further surgery or ablation likely to be ineffective
8. Adjuvant chemotherapy
  - No role in Tx of differentiated thyroid carcinoma
9. Cystic lesions
  - Recur 60-90% of time and should be referred for surgical removal or percutaneous ethanol injection (PEI) upon recurrence<sup>1</sup>
10. Malignancy must be ruled out by FNA prior to consideration
11. Refilling rate of those treated <5%

## 12. PEI

- Not indicated for
  - Toxic autonomously functioning thyroid nodules
  - Cold nodules
- Appeals to younger pts due to absence of scarring, radiation exposure and late hypothyroidism

## Long-term Care<sup>1,6</sup>

1. Algorithms exist regarding standards for f/u in first 6-12 mos post ablation and 12 mos and beyond
2. Dz free status post surgery and remnant ablation is defined as:
  - No clinical evidence of tumor
  - No imaging evidence of tumor
3. Recombinant Human Thyrotropin (rh-TSH)-stimulated serum thyroglobulin (Tg) levels
  - Used to follow low-risk DTC pts (SOR:A)<sup>6</sup>
  - rhTSH-stimulated Tg level is comparable to thyroid hormone withdrawal-stimulated Tg measurements when 2mcg/L is used as cutoff value [sensitivity and NPV of 100% and false positive rate of 9%]<sup>6</sup>
4. Serum TSH, serum Tg and antithyroglobulin antibody levels should be measured
  - q6-12 months post ablation
  - Annually thereafter (rising Tg levels over time is suspicious for growing thyroid tissue or cancer)
5. If dz free after 12 mos post ablation, rh-TSH stimulated Tg levels are drawn to confirm absence of ds; if negative can be followed by annual clinical exam plus rh-TSH stimulated Tg measurement while on thyroid replacement therapy
6. Cervical U/S following surgery should be performed at 6-12 mos and then periodically thereafter depending on clinical exam and Tg levels (FNA w/Tg washout can be considered for suspicious nodes if positive result would change mgmt)
7. Whole body RAI scan
  - Consider in pts w/intermediate-high risk of recurrence
8. FDG-PET scan may be used to stage poorly differentiated cancers, prognosis in pts w/metastatic ds, post-treatment assessment of pts w/metastatic and locally invasive dz
9. In pts w/persistent dz, TSH suppression to 0.1mU/L indefinitely if w/o contraindications
10. Pts free of dz but at high risk of recurrence should maintain TSH 0.1-0.5mU/L for 5-10 yrs following Tx
11. Pts free of dz and at low risk for recurrence should maintain TSH in low normal range (0.3-2.0mU/L)

## Prevention<sup>1,3</sup>

1. Screening U/S
  - For all pts w/Hx of childhood neck irradiation, MEN2 and familial thyroid cancer
2. No measures currently recommended to prevent post RAI ablation salivary gland damage



3. Xerostomia post RAI ablation places pt at risk for dental caries which should be addressed by dentist

### **Patient Education**

1. [www.thyroid.org/patient\\_brochure/cancer\\_of\\_thyroid.html](http://www.thyroid.org/patient_brochure/cancer_of_thyroid.html)

### **Special Populations<sup>1,3</sup>**

1. Children
  - Dx and Tx approach to one or more thyroid nodules in a child = adult (TSH, US, FNA)
2. Pregnancy
  - Euthyroid and hypothyroid pts → FNA
  - Pts w/suppressed TSH after 1st trimester can wait for FNA until postpartum and non-lactating when radionuclide scan can be performed
  - If FNA reveals papillary thyroid carcinoma in early pregnancy and significant growth occurs prior to 24 wks gestation, surgery should be performed
    - If found after 24 wks surgery can be delayed until postpartum
  - Using levothyroxine to suppress TSH to 0.1-1.0 mU/L until postpartum reevaluation is NOT recommended as no available evidence indicates effective reduction in size or growth rate occurs during pregnancy
  - RAI ablation should be postponed until 6-8 wks post lactation and recommend pregnancy avoidance for 6-12 mos post therapy

### **References**

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### **Evidence-Based Inquiries**

1. What is the best way to evaluate thyroid nodules less than 1 cm in size?

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