Advances in Differentiated Thyroid Cancer

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Thyroid Cancer—classification

- Papillary & Mixed papillary/follicular = 80%
  - Insular, tall cell, columnar cell and diffuse sclerosing variants commonly exhibit extrathyroidal invasion
- Follicular & Hurthle cell = 15%
- Medullary (Sporadic, FMTC, & MEN) = 2 - 5%
- Anaplastic & Lymphoma = Rare
- Squamous cell = Rare
- Sarcoidosis = Rare
- Metastatic lesion = Rare
DTC Incidence and Risk factors

- Incidence increasing faster than any other cancer at approximately 7%/year
  - Increased imaging
  - Environmental factors
- Risk factors
  - Age and gender
  - Exposure to external low dose radiation
  - Nodules larger than 4 cm
Thyroid nodule - Ultrasound

- Obtain in all patients with thyroid nodules
  - Size, number and cystic vs. solid characteristics
  - Suspicious features
    - Punctate microcalcifications
    - Hypoechoic and hypervascular
    - Irregular or infiltrative margins
  - Contralateral pathology
  - Local invasion into adjacent structures
  - Associated central/lateral cervical adenopathy
  - Utility of US-FNAB for non-palpable nodules/lymph nodes
- Obtain preop in all patients with known thyroid cancer
Thyroid nodule - FNAB

- Safe, easy, office-based, cost effective, etc.
- Accuracy depends on cytologist experience
- Highly sensitive & specific for papillary carcinoma
- Also useful in medullary, anaplastic, & lymphoma
- 90% satisfactory – 10% unsatisfactory
- Benign (80%), Suspicious (15%), CA (5%)
- “Follicular neoplasia" ➔ 20% thyroid carcinoma
  - $^{123}$I scan may be useful if TSH low
  - Role of FDG-PET is unknown
  - Molecular markers may provide future assistance
- False negative rate = 2-4% (? Higher in nodules > 4 cm)
Thyroid FNAB cytology classification

NCI Category I: Nondiagnostic or Unsatisfactory
- Risk of Malignancy: 1-4%
  - Benign Ultrasound
  - Repeat FNA with Ultrasound Guidance
  - Clinical Follow-Up

NCI Category II: Benign
- Risk of Malignancy: 0-3%
  - Benign

NCI Category III: Atypia or Follicular Lesion of Undetermined Significance
- Risk of Malignancy: ~5-15%
  - Benign with Suspicious Ultrasound

NCI Category IV: Follicular Neoplasm or Suspicious for a Follicular Neoplasm
- Risk of Malignancy: 15-30%

NCI Category V: Suspicious for Malignancy
- Risk of Malignancy: 60-75%

NCI Category VI: Malignant
- Risk of Malignancy: 97-99%

Papillary Thyroid Carcinoma Immunohistochemical Panel:
- CK-19
- Galectin-3
- HBME-1

Molecular Analysis:
- BRAF V600E Mutation Detection For Papillary Thyroid Carcinoma
  - Definitive Benign
  - Indeterminate
  - Definitive Malignant
  - Clinical Follow-Up
  - Surgical Follow-Up
Operative principles for thyroid nodules and DTC

- Minimum procedure should be a unilateral TOTAL lobectomy - no "nodulectomies"
- Frozen section is of controversial benefit as "follicular" tumors often require permanent pathologic exam
- Remove all thyroid tissue and enlarged central or jugular nodes in patients with known DTC (preop nodule/LN FNAB or intraop LN bx)
  - Lowest recurrence
  - Facilitation of RAI ablation when needed
  - Accurate long-term surveillance
Papillary thyroid carcinoma

- Most common thyroid malignancy (70-80%)
- Etiology: genetic, RT, ? iodine deficiency
- Papillary projections with laminated calcifications
- Peak age 30-50 years; F:M = 3:1; Muticentric in 30-60% (higher in the radiated patient)
- Initial spread via lymphatics (30-40%)
- Distant spread to bone (spine), lungs, brain, liver
Treatment and prognosis of papillary thyroid carcinoma

- Total thyroidectomy vs. Subtotal thyroidectomy
- Total ThyX with ± central/modified radical LND
- Lymph node involvement has minimal effect on prognosis; may increase local recurrence
- Lifelong T4 & Post op TB-RAI scanning/treatment
- 10 year survival > 90%; higher in occult/minimal CA
- May be aggressive in children, elderly, & male pt.s
Thyroid carcinoma & Lymph node metastases

- Central, jugular & Inf thyroid a. nodes
- Involved in 30% of papillary carcinoma
- Jugular nodal metastasis treated with modified radical neck dissection
- SCM, IJ, and accessory nerve spared
- MRND not performed prophylactically
- Central LND performed routinely with MTC
Should we perform routine prophylactic central cervical lymph node dissection for papillary thyroid carcinoma (PTC)?
Definition

- A prophylactic central neck lymph node dissection (pCLND) in PTC is defined as the resection of level VI lymph nodes in a patient with no evidence of lymph node involvement on physical examination, preoperative imaging, or intraoperative assessment.
Anatomy

- The anatomic limits of a central cervical lymph node dissection are the hyoid bone superiorly, the innominate vein interiorly, and the two carotid arteries laterally. Pretracheal, paratracheal, delphian, and perithyroidal nodes are included. This dissection requires that the ipsilateral recurrent laryngeal nerve is skeletonized within the anatomic limits described above.
Anatomy

Level VI
Where do we agree?

- High quality preoperative neck US essential
- Therapeutic central neck dissection indicated
- 30-65% of patients with PTC will have microscopic LNM
- 2006 ATA PTC treatment guidelines recommend “consideration” of pCLND
- Level I evidence does not exist and future randomized controlled trials unlikely
Main issues

- PO thyroglobulin and surveillance imaging
- RAI utilization
- Staging of PTC
- Locoregional recurrence
- Survival
- PO RLN injury and hypocalcemia
- Cost of the disease process
Modified Neck Dissection
Follicular thyroid carcinoma

- Older patient population - age 40-60 years
- M=F; incidence decreased with iodine replacement
- Angioinvasive feature & hematogenous spread
- Distant mets (lung/bone) not unusual (50%)
- Lymph node involvement rare (10-15%)
- Differentiate from adenoma by capsular, vascular, or stromal invasion
Classification of FTC

- Follicular Thyroid Carcinoma
  - Low-grade encapsulated well differentiated
  - High-grade angioinvasive
  - Hurthle cell carcinoma
Treatment & prognosis of Follicular thyroid carcinoma

- Total thyroidectomy appears to be best Rx
- "Follicular neoplasm" in preop FNAB = ipsilateral ThyX with intraop FS can be useful (20-30% CA)
- Postop TB-RAI as FTC concentrates Iodine well
- Prognosis 30-85% 10 year survival depending on the biology of the tumor.
Hurthle cell neoplasms

- Differentiate by invasion (capsular/vascular)
- Size > 2 cm = ? Carcinoma
- Adenoma = Unilateral lobectomy
- Carcinoma = Total Thyroidectomy
- FNAB & Intra op FS difficult
- “Completion” Thyroidectomy
Hurthle cell carcinoma vs. Follicular carcinoma

- Lymph node metastatic potential
- RAI resistant
- Higher mortality
- Higher local recurrence rates
Differentiated Thyroid Carcinoma Treatment principles

- Lifelong T4 supplementation & TSH suppression
- Periodic PE, TFT's, TG, & CXR
- Selective or mandatory postop RAI
- CT/MRI for high TG and negative TB RAI scan
- External RT & Chemotherapy - little or no role
TNM classification & staging

Table 1
TNM Classification System for Differentiated Thyroid Cancer

<table>
<thead>
<tr>
<th>Definition</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4a</th>
<th>T4b</th>
<th>TX</th>
<th>N0</th>
<th>N1a</th>
<th>N1b</th>
<th>NX</th>
<th>M0</th>
<th>M1</th>
<th>MX</th>
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<td>Tumor diameter 2 cm or smaller</td>
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<td>Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve</td>
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<td>Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels</td>
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<td>Primary tumor size unknown, but without extrathyroidal extension</td>
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<td>No metastatic lymph nodes</td>
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<td>Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)</td>
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<td>Metastases to unilateral, bilateral, contralateral cervical or superior mediastinal lymph node metastases</td>
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<td>Lymph nodes not assessed at surgery</td>
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<td>Distant metastases</td>
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<td>Distant metastases not assessed</td>
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<th>Stages</th>
<th>Patient age &lt; 45 years</th>
<th>Patient age 45 years or older</th>
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<td>Stage III</td>
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<td>T3, N1a, M0</td>
<td>T3, N1a, M0</td>
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<td>Stage IVA</td>
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<td>T4a, N1a, M0</td>
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<td>T1, N1b, M0</td>
<td>T2, N1b, M0</td>
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<td>T3, N1b, M0</td>
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<td>T4a,N;1b,M0</td>
<td>T4b, Any N,M0</td>
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<td>Stage IVB</td>
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<td>Stage IVC</td>
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Features suggesting aggressive thyroid carcinoma

- Incomplete resection & recurrent tumors
- Invasive large (> 5 cm) tumors
- Extensive cervical LN involvement - ? recurrence
- Older patients (> 60 years)
- Aneuploid tumors; tumor with no RAI uptake
- Distant metastases - bone, lungs, brain, liver
Thyroid nodule - evaluation

- All nodules > 1 cm
- Nodules < 1 cm with concerning features
  - Suspicious US characteristics
    - Hypervascularity, punctate microcalcifications, irregular margins, etc
  - History of radiation exposure
  - Associated cervical lymphadenopathy
  - Family history of thyroid carcinoma (MEN, medullary, DTC, etc.)
  - $^{18}$FDG-positive nodules = 33% malignant
- Nodules in children and pregnant patients
Solitary Thyroid Nodule

Clinical History
Physical Exam

Laboratory studies

Calcium
PTH
Calcitonin

Radionuclide Scanning

FNAB Cytology

TSH, T₃, T₄
Anti TPO Ab’s
Thyroglobulin

Ultrasonography
Thyroid nodule - clinical

- Dysphagia, hoarseness
- Recent onset
- Rapid onset
- Familial (sporadic/MEN)
- Airway obstruction
- Thyroid dysfunction
- Pain - thyroiditis

- Irradiation history
- Growth on Thyroxine
- Firm or fixed nodules
- Cervical adenopathy
- Solitary nodules
- Ipsilateral VC paresis
- Male gender
Thyroid nodule - evaluation

- TFT’s for all patients
  - Initial TSH suppressed → $^{123}$I thyroid scan
- Thyroglobulin levels insensitive as DTC screen
$^{123}$I thyroid scan - AFTN
Ultrasonography

I\textsuperscript{123}I Thyroid scan
Thyroid nodule - FNAB results

- Malignant
- Follicular Neoplasm
- Unsatisfactory
- Benign
- Repeat FNAB + US
- Unsatisfactory
- Observation ± T₄