Update in Thyroid Cancer Management
Thyroid Surgery

“One could not cut the thyroid gland out of the living body in its sound condition without risking the death of the patient from haemorrhage.

It is a proceeding by no means to be thought of”

Liston 1846
Thyroid Surgery

“One of the most thankless, most perilous undertakings which, if not altogether prohibited, should at least be restricted”

Diffenbach 1848

“Horrid butchery ... deserving of rebuke and condemnation”

“No honest and sensible surgeon would ever engage in it”

Gross 1866
Theodor Kocher (1841-1917) “Father of the Thyroid Surgery”

Nobel Prize in Medicine 1909
"for his work on the physiology, pathology and surgery of the thyroid gland"
Thyroid Cancer

- 1% of all new malignant disease
- 0.5% in men and 1.5% in women

- 94% are differentiated carcinomas (papillary or follicular)
- 5% are medullary carcinoma
- 1% are anaplastic carcinoma
Thyroid Cancer

- Overall survival rates
  - 98% for papillary
  - 92% for follicular
  - 80% for medullary
  - 13% for anaplastic

- Poorer prognosis if
  - older age at diagnosis
  - widespread metastatic disease
Nodule Evaluation

Solitary thyroid nodule > 1 cm in diameter

Increased suspicion if:

- Age < 15 yr or > 45 yr
- Male sex
- Hx of radiation exposure
- Hx of diseases associated with thyroid cancer
- Nodule > 4 cm in diameter
- Suspicious US findings: central hypervascularity, irregular border, microcalcifications
Sonogram of the thyroid shows a 0.5 cm nodule with internal calcifications characteristic of a papillary carcinoma.
Nodule Evaluation

Highly suspicious if:

- Rapid nodule growth
- Very firm nodule
- Fixation to adjacent structures
- Family history of thyroid cancer
- Vocal cord paralysis
- Enlarged regional lymph nodes
- Symptoms of invasion into neck structures
Nodule Evaluation

TN (palpation/imaging) > 1 - 1.5 cm

Hx and Physical Serum TSH

Low TSH

Normal/High

123I, 99Tc Scan

Hot

Not

Dx U/S

Not >50% cystic Nor posterior

Elevated TSH

Eval/Rx for hypo

Eval/Rx For hyper

Pall or U/S Guided FNA

U/S Guided FNA

Other nodule >1.0-1.5 cm

U/S Guided FNA

Normal TSH

FNA not indicated

No Nodule
FNA Results

- Carcinoma: papillary, medullary, anaplastic
- Lymphoma

- Follicular neoplasm (20% cancer rate; higher if old age, male, large size, cold nodule)

- Benign

- Insufficient biopsy
Investigations

- **Chest X-ray** is mandatory
- **Ultrasonography of thyroid & neck** is valuable
- **CT/MRI** in selected cases
- **Radionuclide scans** is nonspecific and non-diagnostic, may be useful in hyperfunctioning adenoma
- **Intra-op. frozen section** not helpful in follicular lesions, may be useful in suspected papillary carcinoma
Differentiated thyroid carcinoma

- Women:men = 2:1 with a median age at diagnosis of 45 years
- Iodine insufficiency – follicular
- Radiation exposure – papillary
- Familial – 5%

- Aggressive variant:
  - tall cell and columnar cell features of papillary type
  - oxyphilic (Hürthle cell) and poorly diff. features of follicular type
Differentiated thyroid carcinoma

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Differentiated thyroid carcinoma

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Goals of Initial Therapy

- To remove primary tumor, disease that has extended beyond thyroid capsule, and involved cervical lymph nodes
- To minimize treatment- and disease-related morbidity
- To permit accurate staging of the disease
- To facilitate postoperative radioactive iodine treatment
- To permit accurate long-term surveillance
- To minimize the risk of recurrence and metastatic spread
Differentiated thyroid carcinoma

- Goals of initial therapy

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Indications for total thyroidectomy

- Age < 15 yr or > 45 yr
- Hx of radiation exposure
- Family Hx of thyroid cancer
- Diameter ≥ 4 cm
- Extrathyroidal extension
- Bilateral nodularity
- Aggressive variant
- Cervical nodal metastases
- Distant metastases
- Invasive follicular carcinoma
“If a skilled thyroid surgeon is not available, the patient should be referred to an appropriate surgeon rather than be given a subtotal thyroidectomy.”
Lobectomy + Isthmusectomy

If **ALL** of the followings present:

- Age 15 y - 45 y
- No prior radiation
- Tumor < 4 cm in diameter
- No aggressive variant
- No macroscopic multifocal disease
- Negative isthmus margin

Or

- Minimal invasive follicular cancer
- No extrathyroidal extension
- No contralateral lesion
- No cervical nodal metastases
- No distant metastases
Minimally Invasive Follicular Carcinoma

- A well-defined tumor with microscopic capsular and/or a few foci of vascular invasion

- Often requires examination of at least 10 histologic sections to demonstrate
Lymph Node Dissections:
Elective vs Therapeutic
Elective Node Dissection

“The removal of lymph nodes that are normal on physical examination and radiographic imaging”

Early detection and removal of microscopic disease in regional lymph nodes may prevent recurrence and improve survival
Elective Node Dissection

- Controversial
- Improve cause-specific survival in patients age > 60 yr or tumor with extrathyroidal invasion  
- Increased peri-operative complications
- No overall survival benefit  
**Elective Node Dissection**

- **Ipsilateral central neck dissection** (level VI) should be considered for patients with papillary carcinoma and suspected Hürthle carcinoma.

- Not necessary for:
  - follicular cancer
  - papillary and Hürthle cell cancers when followed by radioactive iodine therapy
Therapeutic Node Dissection

“The removal of regional lymph nodes that are clinically or radiographically abnormal and, therefore, proven or suspected to harbor metastatic disease”
Therapeutic Node Dissection

- **Central neck dissection** (level VI)

- **Lateral neck dissection** (levels II-V, sparing spinal accessory nerve, internal jugular vein, and SCM muscle)
  
  "laterally from carotid sheath to trapezius muscle and from subclavian vein inferiorly to hypoglossal nerve superiorly"
<table>
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<tr>
<th>Risk</th>
<th>Age</th>
<th>T-stage</th>
<th>N-stage</th>
<th>Extent of surgery</th>
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## Recommended Surgical Treatment for Follicular Carcinoma

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Differentiated thyroid carcinoma

- Goals of initial therapy
- What is the appropriate operation?
- What is the role of postoperative staging systems?
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Role of Postoperative Staging

- To permit prognostication for an individual patient
- To tailor decisions regarding postoperative adjunctive therapy
- To make decisions regarding the frequency and intensity of follow-up
- To enable accurate communication between health care professionals
- To evaluate differing therapeutic strategies in clinical studies
### Prognostic Factors for DTC

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<th>EORTC</th>
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Relationship of Recurrence and Mortality to Age and Size of Tumor
**AJCC Staging for Thyroid Cancer**

6th Edition

<table>
<thead>
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<th>Primary tumor (T)</th>
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<tr>
<td>TX: Primary tumor cannot be assessed</td>
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<tr>
<td>T0: No evidence of primary tumor</td>
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<td>T1: Tumor ≤2 cm in greatest dimension limited to thyroid</td>
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<tr>
<td>T2: Tumor &gt; 2 cm but &lt;4 cm in greatest dimension limited to thyroid</td>
</tr>
<tr>
<td>T3: Tumor &gt; 4 cm limited to thyroid or with minimal extension beyond the thyroid</td>
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<tr>
<td>T4a: Tumor any size invading subcutaneous tissue, larynx, trachea, esophagus or recurrent laryngeal nerve</td>
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<tr>
<td>T4b: Tumor invades prevertebral fascia, encases carotid artery or mediastinal vessels</td>
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<tr>
<td>N0: No regional lymph node metastasis</td>
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<td>N1: Regional lymph node metastasis</td>
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<tr>
<td>N1a: Metastasis to Level VI</td>
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<td>N1b: Metastasis to cervical or superior mediastinal lymph nodes (unilateral or bilateral)</td>
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<tr>
<td>M0: No evidence of distant metastasis</td>
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<tr>
<td>M1: Distant metastasis</td>
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# AJCC Staging for Thyroid Cancer 6th Edition

<table>
<thead>
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<th>Stage</th>
<th>PTC &amp; FC &lt;45 years</th>
<th>PTC &amp; FC &gt;45 years &amp; all medullary Ca</th>
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<td>T4, any N, M1</td>
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Differentiated thyroid carcinoma

- Goals of initial therapy

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Post Thyroidectomy Evaluation (1-12 wk)

- TSH + thyroglobulin measurement + antithyroglobulin antibodies in **ALL** cases

- Total body radioiodine scan if:
  - Residual disease in neck
  - Tumor size > 1 cm
  - Nodal metastases
  - Distant metastases
  - Aggressive histology
Whole Body $^{131}\text{I}$ Scan of Metastatic Follicular Carcinoma
Radioiodine Treatment

- Thyroid bed uptake
- Gross residual disease in neck with adequate radioiodine uptake
- Metastatic disease if radioiodine scan positive
- Thyroglobulin > 10 ng mL
Recombinant Human TSH

- TSH stimulation achieved by induction of hypothyroidism following withdrawal of thyroid hormone is uncomfortable and reduces quality of life

- Elevated TSH persists for weeks and may stimulate tumor growth
Recombinant Human TSH

- Whole-body $^{131}$I scans were of good quality for patients who received rh-TSH while continuing thyroid hormone.
  
  *Ladenson PW, et al. NEJM 1997*

- Combination of rh-TSH-stimulated whole-body scan and serum Tg detected 100% of metastatic carcinoma.
  
  *Haugen B, et al. J Clin Endocrinol Metab 1999*
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TSH Suppression

Supraphysiologic doses of T3/T4

- To prevent symptomatic hypothyroidism
- To induce a subclinical hyperthyroid state
  (suppressed TSH with normal T4 and T3 levels without signs or symptoms of thyrotoxicosis)
TSH Suppression

- Thyroid hormone suppression therapy significantly decreases risk of major adverse clinical events including disease recurrence, progression, and mortality (RR=0.73)


- No survival benefit in low-risk stage I

  *Jonklaas J, et al. Thyroid 2006*
TSH Suppression

- Oral levothyroxine (LT4)
- Starting 2 µg/kg/day of LT4, titrate based on follow-up thyroid function tests 6-8 weeks later
- Keep TSH < 0.1 mU/L in high-risk patients
  - TSH 0.1-0.5 mU/L in low-risk patients
- Patients with known or suspected residual disease and no contraindications should continue TSH suppression indefinitely
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External Beam Radiation Therapy

- Gross residual tumor with inadequate radioiodine uptake
- Extensive adjacent organ invasion
- Extensive nodal disease or extracapsular invasion
- Locoregional recurrence with negative scan
- Distant metastasis (bone, CNS) with negative scan
Chemotherapy

- Modest benefit in patients with advanced, radioiodine-resistant thyroid cancer

- Doxorubicin monotherapy may be effective in up to 40% but not durable

- Combination chemotherapy (carboplatinum and epirubicin) under TSH stimulation demonstrated complete and partial response rate of 37% in poorly differentiated carcinoma
Targeted Therapy

- **Tyrosine kinase inhibitors**: target RET/PTC oncogene, RAS, RAF, and MEK kinase

- **Modulators of growth or apoptosis**: COX2 inhibitors, retinoids, bortezomib, geldanomycin

- **Angiogenesis inhibitors**: VEGFR inhibitor

- **Immunomodulators**: dendritic cells

- **Gene therapy**: p53 tumor-suppressor gene
**Surveillance and Maintenance**

- Physical examination, TSH, Tg, anti-Tg antibodies at 6 and 12 mo, then annually if disease-free
- Periodic neck ultrasound
- Annual TSH stimulated thyroglobulin
- Annual radioiodine scan if detectable thyroglobulin, distant metastases or soft tissue invasion on initial staging, until no radioiodine uptake tumor is evident
Thank you for your attention