Thyroid Differentiated Cancer: Does Size Really Count?

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Thyroid Nodules

- Epidemiology and Incidence
- Thyroid cancer procedures for assessment
- FNA readings
- Papillary Carcinoma risk evaluation
- Papillary Carcinoma treatment
- Braf Test
- Case presentation
Nodular Goiter

- Prevalence Rate: 0.08%/yr
- Clinical incidence- Adults: 4-7%
  - Females > Males
- Incidence with ionizing radiation: 20-30%
- Autopsy incidence: 50%
- Occult cancer (Autopsy): 4-28%
Thyroid nodules

• 6-10% adult U.S. population
  – 5% are malignant
• FNA best initial test - 96% PPV
• U/S good to follow or document MNG
• thyroid scan good if symptoms of hyper- or hypothyroidism or if indeterminate cytology/multinodular goiter
• suppression most successful when TSH high
Problems of Thyroid Nodules

Mazzaferri, NEJM 328:553, '93
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Thyroid Cancer - Diagnosis

- Cytology
- Scans
  - Technetium
  - Radioiodine
  - Sestamibi
  - MR/CT/PET
- Ultrasound
- Frozen Sections
- Fixed Sections
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FNA Results of Thyroid Nodule

- Benign --> F/U 6-12 months
- Cyst --> F/U 6-12 months
- Indeterminate --> repeat FNA, $\text{I}^{123}$ scan if same results
- Follicular neoplasm --> $\text{I}^{123}$ scan or surgery
- Suspicious --> surgery
- Carcinoma --> surgery
Thyroid Cancers*

- Papillary: 80%
- Follicular: 11%
- Hürthle: 3%
- Medullary: 4%
- Anaplastic: 2%

*National Cancer Data Base
31,513 patients (1985-1995)
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Thyroid Carcinoma - Nodule Evaluation

Clinically Nonsuspicious
• Nodules < 1 cm in diameter without enlarged cervical lymph nodes and none of the previous criteria

Clinically euthyroid
• TSH measurement
• FNA of nodule
• FNA of clinically suspicious lymph nodes
Increased suspicion if any of the following are present:
- Age < 15 y or > 45 y
- Male sex
- Nodule > 4 cm in diameter
- History of radiation exposure
- Microcalifications
- History of diseases associated with thyroid cancer:
  - Pheochromocytoma
  - Hyperparathyroidism
  - Gardner’s syndrome
  - Familial adenomatous polyposis
  - Carney complex
  - Cowden’s syndrome
Thyroid Carcinoma - Nodule Evaluation

**Highly suspicious**
- 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
Pathology of Thyroid Cancer

• Differentiated thyroid cancer (DTC):
  – papillary - commonly spreads to nodes (40-50%), excellent prognosis
  – mixed - papillary and follicular - acts like papillary, excellent prognosis
  – follicular - slightly worse than papillary, can spread to bone, less to nodes (15%); Hurthle cell Ca is variant

• medullary - sporadic vs. familial (MEN 2A), total thyroidectomy is treatment

• anaplastic - aggressive and fatal, surgical role is biopsy only
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Thyroid Carcinoma - Papillary Carcinoma-FNA High risk

Primary Treatment

Total thyroidectomy if lymph node(s) positive:

• Central neck dissection (level VI), Lateral neck dissection (levels II-V, sparing spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle)
Thyroid Carcinoma - Papillary Carcinoma-FNA Moderate-Low risk

- Total thyroidectomy or completion of thyroidectomy
  OR Lobectomy and isthmusectomy

Followed by:
- TSH and thyroglobulin measurement (4-6 wk postoperatively)
- Total-body I 131 scan
- Positive margins
- Clinically suspicious contralateral lesion
Thyroid Carcinoma - Papillary Carcinoma-FNA Moderate-Low risk

• Aggressive variant
• Multifocal disease

Followed by:
• Total thyroidectomy or completion of thyroidectomy

OR
• Negative margins
• No contralateral lesion

• Consider thyroglobulin measurement and follow up neck ultrasound
Rationale for Total Thyroidectomy for DTC

• improved effectiveness for I131 ablation
• lowers dose needed for I131 ablation
• allows f/u w/ thyroglobulin levels
• decreased recurrence
• improved survival in high risk pts.
• decreased risk of pulmonary mets and dedifferentiated CA
Rationale Against Total Thyroidectomy for DTC

- increased RLN injury and hypoparathyroidism
- contralateral disease not clinically relevant
- survival nearly equivalent for low risk patients
- I131 ablation not necessary for most patients
- thyroglobulin levels not necessary for most patients
Age and Sex
Well Differentiated Thyroid Carcinoma

Percent Survival

Years Survival

Normal Curves – 25 and 58 yrs.

Women <40 yrs.

Men <40 yrs.

Women >39 yrs.

Men >39 yrs.
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RAI-Refractory Disease

• 25-50% of metastatic thyroid cancers lose ability to take up Iodine.
• Iodine Uptake inversely correlates with survival.
• This is attributed to down regulation of the Na+/I- Symporter (NIS).
• Limited treatment options for unrespectable thyroid cancer refractory to RAI.
<table>
<thead>
<tr>
<th>Molecular Changes in Thyroid Cancer</th>
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<tbody>
<tr>
<td>B-RAF V600E</td>
<td>40% of PTC</td>
</tr>
<tr>
<td>RET/PTC</td>
<td>25% of PTC</td>
</tr>
<tr>
<td>RAS</td>
<td>20% of FTC</td>
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<tr>
<td>PAX8-PPARγ</td>
<td>45% of FTC</td>
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<tr>
<td>RET</td>
<td>100% hereditary MTC</td>
</tr>
<tr>
<td>p53</td>
<td>40% sporadic</td>
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<td>ATC</td>
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Targeted Therapy in Thyroid cancer

• Loss of differentiation (inability to trap RAI), unresectable lesion, leads to poor prognosis

• BRAF inhibitors
  – BAY 43-9006 (Sorafenib)
  – Multikinase inhibitor
Sorafenib

- Orally active multikinase inhibitor (study dose 400mg BID).
- Monoclonal antibody with multiple targets including BRAF, VEGFR1, VEGFR2.
- Blocks tumor cell proliferation and angiogenesis.
- FDA approved for treatment of RCC and hepatocellular carcinoma.
Papillary vs. Follicular

Progression-free Survival

P < 0.095

FTC = 19
PTC = 24
BRAFV600E Correlates with worse Survival

Elisei et. al, J Clin Endocrinol Metab, October 2008, 93(10):3943–3949
BRAF (red) x 3
7 centromere (green) x 3
BRAF x4
7 centromere x4
Summary

• Good progression free survival in patients treated with Sorafenib.

• BRAF V600E appears to predict for improved outcome in patients treated with sorafenib.

• BRAF copy number gain may explain improved outcome of patients with FTC over patients with PTC
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Residual Thyroid Cancer

• 25 y/o woman with papillary thyroid cancer
  – Capsular penetration
  – Lymph nodes not sampled

• Dx and Post-Rx (200 mCi) I-131 scans show thyroid remnant only
  – TG off TSH = 110 ng/dL

• Dx I-131 scan 1 year later negative
  – TG off TSH is still 100 ng/dL
Thyroid Cancer
Post therapy (10/98)

Tc-99m markers

I-131 window
Residual Thyroid Cancer: FDG PET Scan 8/99

L Cervical Lymph Nodes

? Central Lymph Nodes
Patient N.A.

- 47 year female evaluated for thyroid nodular disease.
- History of right thyroidectomy 2001 (micropapillary thyroid carcinoma)
- No neck discomfort However, thyroid ultrasound routine obtained
- 1/12 Thyroid ultrasound: right lobectomy, left lobe: solid hypochoic nodules 0.7 x 0.3 x 0.3 cm, 0.7 x 0.6 x 0.4, 0.7 x 0.8 x 0.6
- Followup with thyroid hormone
- 1/13 Thyroid ultrasound right lobectomy left lobe solid hypochoic nodules 0.7 x 0.6 x 0.4 cm, 0.8 x 0.7 x 0.5 cm, 0.8 x 0.9 x .6 cm
- 2/13 TSH 0.21, free T4 1.5, quantitative TG 11.7 ng/dl
Patient P.S.

• 43 year male evaluated for thyroid nodular disease
• Right thyroid nodule, ultrasound solid 2.4x 2.45x2.3 cm no microcalcification
• FNA atypical architecture
P. S.

- 5/13
  - Right thyroid lobectomy isthmusectomy
  - May 2013 Papillary Ca with follicular variant
  - BRAF negative

- 8/13
  - Left thyroidectomy papillary microcarcinoma measuring maximum 0.2 cm
P. S.

• Post op TSH 5.23. free T4 1.4
• Post 2\textsuperscript{nd} surgery TSH 36.11, quantitative TG 1.5
THANK YOU!