Management of Thyroid Nodules and Cancer
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Disclosure & Thanks

• Nothing to disclose
• My thanks for the invitation to be with you today
• This presentation includes common thyroid cases developed in a Q&A format
Thyroid Nodule Facts

• 5% prevalence by palpation
• 30-50% prevalence by US (100 million people in U.S.)
• 350,000 new nodules will be diagnosed this year
• More common in women, elderly, with I-def, and after radiation
• 95% are benign

Thyroid Nodule

Case 29-year-old woman is referred for a recently discovered thyroid nodule; she is asymptomatic and has no history of radiation; thyroid palpation shows a solitary, firm 2 cm left lobe nodule

What is the next appropriate test?

A. US exam
B. Serum TSH
C. Radioisotope scan
D. FNA biopsy
29-Year-Old Woman

Recommendation

Measure TSH first; thyroid US should be performed in all pts with known thyroid nodules

Endocr Pract, 2010

Which of the following is not a predictor of malignancy in this patient’s thyroid nodule?

A. History of childhood head-neck radiation
B. Serum TSH level
C. Serum calcitonin (CT) level
D. Nodule size and number
**Serum TSH & Cancer**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>TSH (mIU/L)</th>
<th>Calculated risk of malignancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>0.3</td>
<td>8.1</td>
</tr>
<tr>
<td>40</td>
<td>0.5</td>
<td>8.4</td>
</tr>
<tr>
<td>40</td>
<td>1.0</td>
<td>9.4</td>
</tr>
<tr>
<td>40</td>
<td>3.0</td>
<td>14.6</td>
</tr>
<tr>
<td>40</td>
<td>5.0</td>
<td>21.9</td>
</tr>
<tr>
<td>40</td>
<td>6.0</td>
<td>26.4</td>
</tr>
</tbody>
</table>


**Nodule Size & Cancer**

402 pt Non-palpable nodules

- Nodule 10 mm 9.1%
- Malignant
- Nodule >10 mm 7.0%

Papini et al: JCEM, 2002
Nodule Number & Cancer

<table>
<thead>
<tr>
<th>Study (yr, location)</th>
<th>Individuals (no.)</th>
<th>Definition of nodularity</th>
<th>FNA technique</th>
<th>Cancer rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCall et al (1986 U.S.)</td>
<td>442</td>
<td>Scan/Hx</td>
<td>Palpation</td>
<td>17 13</td>
</tr>
<tr>
<td>Bachmachi et al (2000 U.S.)</td>
<td>443</td>
<td>Scan</td>
<td>Palpation</td>
<td>8 10</td>
</tr>
<tr>
<td>Papini et al (2002 Italy)</td>
<td>484</td>
<td>US</td>
<td>US</td>
<td>8 6</td>
</tr>
<tr>
<td>Deandrea et al (2002 Italy)</td>
<td>420</td>
<td>US</td>
<td>US</td>
<td>6 7</td>
</tr>
</tbody>
</table>

CT Screening Recommendation

- **AACE 2010**: Measurement of nonstimulated serum CT may be considered before thyroid surgery for nodular goiter
- **ATA 2009**: The panel cannot recommend either for or against the routine measurement of serum CT
- **European thyroid Ca Task Force 2006**: Serum CT is recommended in the initial dx evaluation of thyroid nodules
- **Daniels G, 2011**: Routine CT measurements in the U.S. thyroid nodule population to dx cryptic MTC is not indicated at this time
29-Year-Old Woman

Case
Thyroid US confirmed a hypoechoic, solid, solitary 2.0 x 1.5 x 1.5 cm left lobe nodule; US-guided FNA showed a benign, colloid nodule

Q
What is the risk of malignancy in this nodule?
A. 0%
B. 1%
C. 10%
D. 50%

29-Year-Old Woman

Q
What is the recommended follow-up?
A. No follow-up is necessary; dismiss pt
B. Repeat US in 6-18 mo
C. Repeat US & FNA in 6-18 mo
D. Begin T4 suppression therapy and repeat TSH & US in 6-18 mo
Case

50-year-old woman is seen because of a right neck mass discovered on self-exam; there is no prior Hx neck radiation; on exam, a firm 2.0 cm right thyroid nodule is palpable; TSH is 2.0 mIU/L; US showed a predominantly solid, hypervascular 2.0 x 2.0 x 1.8 cm nodule; left OK

FNA showed hypercellularity, no colloid and microfollicles consistent with follicular neoplasm (FN)

What should you order next?
A. Repeat FNA with US guidance
B. Larger Bx
C. Order a thyroid [123I] scan
D. Surgical consultation
Impact of Mutational Testing on the Diagnosis and Management of Patients with Cytologically Indeterminate Thyroid Nodules: A Prospective Analysis of 1056 FNA Samples


Value of molecular markers in suspicious cytology

Cytologic Dx
- AUS/FLUS: Atypia of undetermined significance; FLUS: Follicular lesion of undetermined significance
- SFN: Suspicious for follicular neoplasm; SMC: Suspicious for malignant cells
- JCEM 96:3390, 2011

Cancer risk based on cytology only

Value of molecular markers in suspicious cytology

Testing for panel of mutations (BRAF, RAS, RET/PTC, PAX8/PPARγ)

Mutational status
- Positive
- Negative

Cancer risk
- 88%
- 5.9%
- 87%
- 14%
- 95%
- 28%

Clinical management
- Total thyroidectomy
- Lobectomy
- Lobectomy vs repeat FNA

Probability of Cancer in Thyroid Nodules Depending on the Results of Cytological and Molecular Analysis

<table>
<thead>
<tr>
<th>Results of cytology &amp; molecular analysis</th>
<th>Cancer probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive cytology and positive for mutation</td>
<td>100.0</td>
</tr>
<tr>
<td>Indeterminate cytology alone</td>
<td>40.4</td>
</tr>
<tr>
<td>Indeterminate cytology and positive for mutation</td>
<td>100.0</td>
</tr>
<tr>
<td>Indeterminate cytology and negative for mutation</td>
<td>16.2</td>
</tr>
<tr>
<td>Negative cytology alone</td>
<td>2.1</td>
</tr>
<tr>
<td>Negative cytology and negative for mutation</td>
<td>0.9</td>
</tr>
</tbody>
</table>

JCEM 96: 3390, 2011
Probability of Benign Nodules in Suspicious Cytology

• Afirma assay (Veracyte)
• Test uses gene expression classifier
• Sensitivity was 92% for suspicious cytology
• High NPV for FLUS (95%) and FN (94%)
• GEC is helpful in identifying low risk nodules
• Additional data are necessary

NEJM 2012

50-Year-Old Woman

What is the *optimal* surgical treatment of this pt?

A. Ipsilateral lobectomy
B. Total thyroidectomy
C. Lobectomy followed by completion Tx if cancer found

D. Lobectomy, intraoperative frozen section, and more surgery based on FS report
Pemberton’s Sign

Facial flushing and pain with raised arms in this pt is likely caused by
A. A thymoma
B. Malignant thyroid nodule
C. SVC obstruction due to large goiter
D. Thoracic aortic aneurysm

Thyroid Cancer Facts

- Fastest growing ca in U.S.; increased 3.8% per year 1992-2001
- 8th most common ca in women
- 56,000 new cases with 1,700 deaths in 2012; prevalence 500,000
- PTC is the commonest cause of death (50%) due to thyroid ca
Thyroid Cancer

Relative Frequency

- Medullary: 4%
- Anaplastic: 1%
- Follicular: 9%
- Hürthle: 1%
- Papillary: 85%

National Cancer Database: SEER Registry

Davies L and Welch HJ: JAMA 295:2164, 2006

Thyroid Cancer Incidence and Mortality 1973-2002

Thyroid Cancer Incidence 1973-2002

- Papillary Thyroid Cancer 1988-2002

Incidence

Mortality


Rates/100,000
Papillary Thyroid Cancer (PTC)

- Most common endocrine malignancy
- 80% of new cases worldwide
- F:M 2:1, mean age at Dx 30-40 year

Typical Presentation of PTC & FTC

- Painless mass
- Discovered on routine exam or by pt
- Stable over several mo
- Normal thyroid function
- Diagnosed by FNA (PTC) or suspicious (FTC)
Papillary Thyroid Carcinoma (PTC)

**Case** 28-year-old woman is found to have a 1.5 cm right thyroid nodule on routine pre-pregnancy examination; FNA biopsy showed nuclear changes suspicious for PTC; serum TSH is 0.8 mIU/L

**Q** What additional preop test should you order?

A. Serum thyroglobulin (Tg)
B. Radioisotope scan
C. Thyroid US
D. Neck CT with contrast

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Preoperative Evaluation

- Neck US for contralateral lobe and cervical nodes
- Additional scanning not necessary
- Finding of metastatic disease rarely alters need for Tx
- Routine Tg measurement not recommended
28-Year-Old Woman with PTC

Case
Thyroid US showed a 1.4 x 1.0 x 1.0 cm solid right nodule with microcalcifications; the left lobe appeared normal and no adenopathy was identified.

What is the surgical procedure of choice in the case?

A. Right lobectomy
B. Bilateral subtotal thyroidectomy
C. Near-total or total Tx
D. TTx plus central compartment (level VI) dissection

28-Year-Old Woman with PTC

Initial Surgery
- Lobectomy may be ok for isolated PTC ≤1 cm
- NTTx or TTx if tumor >1 cm
- Therapeutic node dissection (level VI)
- Prophylactic level VI node dissection with T3 or T4
- No node dissection if T1 or FTC
28-Year-Old Woman with PTC

**Case**
Total Tx showed a 1.3 x 1.0 x 0.9 cm FV PTC; no abnormal nodes were identified at surgery

**Appropriate postop care should include**

- A. Radioiodine remnant ablation (RRA) using 100 mCi $^{131}$I
- B. RRA using 30 mCi $^{131}$I
- C. No RRA; start T4 Rx with target TSH <0.01 mIU/L
- D. No RRA; start T4 Rx with target TSH 0.1-1.0 mIU/L

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**Radioiodine Remnant Ablation (RAR)**

- None for PTC ≤1 cm
- May not be necessary for small, minimally invasive FTC
- Recommended for PTC 1-4 cm, node +, or other risk factors
- Recommended for PTC ≥4 cm, M1, or with extrathyroidal extension
PTC

40-year-old man is referred 2 mo after a left thyroid lobectomy for a 2.0 cm follicular lesion; pathologic exam showed the lesion to be a follicular adenoma; in addition, a 0.8 cm PTC was discovered in the resected lobe; no nodes were removed at Tx

Serum TSH is 0.5 mIU/L on T4; Tg 2.2 ng/dL; Tg Ab neg; thyroid US shows a surgically absent L lobe, a normal R lobe, and no adenopathy

Based on current recommendations what do you suggest?

A. Observation with periodic US, TSH & Tg measurement
B. 100 mCi RAI with follow-up
C. Completion Tx, 50 mCi RAI & FU
D. Completion Tx, 100 mCi RAI & FU

40-Year-Old Man with PTMC

Assuming BRAF was demonstrated in surgical tissue, would you recommend completion Tx?

A. No
B. Yes
### Possible Application of BRAF in PTC

<table>
<thead>
<tr>
<th></th>
<th>BRAF V600E</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Pos</td>
</tr>
<tr>
<td>Completion Tx</td>
<td>Yes</td>
</tr>
<tr>
<td>CND</td>
<td>Yes</td>
</tr>
<tr>
<td>Postop RAI Rx</td>
<td>Yes</td>
</tr>
<tr>
<td>Target TSH &lt;0.1</td>
<td>Yes</td>
</tr>
<tr>
<td>TSH-stimulated Tg</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### BRAF V600E Mutation in PTC

A Meta-Analysis

- Occurs only in PTC
- May be present in \( \approx 60\% \) of conventional and 80\% of tall cell PTC
- Associated with higher extrathyroidal extension
- Not associated with age, sex or primary tumor size

Cancer 100:38, 2007
Papillary Thyroid Microcarcinoma

- Accounts for 30-50% of all PTC
- Prevalence 10% (2-30%)
- Nodal metastasis in 20-40%
- Multicentricity in 30-40%

Case

53-year-old woman is evaluated because of a 2.5 cm R lobe nodule and an enlarged R level III node; FNA of both nodule & node shows typical PTC

From your knowledge of TNM staging, her disease is?

A. Stage I
B. Stage II
C. Stage III
D. Stage IV