25th Annual Scientific AACE Clinical Congress
Improving the Long Term Management of Benign Thyroid Nodules

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Disclosures

• No disclosures
When can we STOP surveillance of a nodule after a
• Benign cytology (One, Two or More)?
• Lack of Growth?
• Benign Molecular Test (High NPV vs. High PPV)?

To Discuss:
Problems of a “benign” cytology
• Natural history nodules with benign cytology
• Strategies to identify missed malignancy
  • US features
  • Growth
• Nodules that are sonographically benign
• Nodules with “benign” molecular signatures
Benign Cytology Has Low Risk of Malignancy

- **Non-diagnostic:** 1-4%
- **Benign:** 0-3%
- **AUS/FLUS:** 5-15%
- **Follicular neoplasm:** 15-30%
- **Suspicious for malignancy:** 60 to 75%
- **Malignant:** 97-99%

Gharib: False negative rate 5% (range 1-11)


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How Reliable is a Benign Cytology?

Kappa statistic: Measure of interobserver agreement

<table>
<thead>
<tr>
<th>FNA diagnosis</th>
<th>Kappa (95% CI)</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsatisfactory/benign</td>
<td>0.8 (0.60-0.97)</td>
<td>strong</td>
</tr>
<tr>
<td>Follicular neoplasm</td>
<td>0.5 (0.34-0.65)</td>
<td>fair</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>0.2 (0.06-0.37)</td>
<td>poor</td>
</tr>
<tr>
<td>Malignant</td>
<td>0.6 (0.46-0.79)</td>
<td>fair</td>
</tr>
</tbody>
</table>

**Benign** 0.6 (0.43-0.78) fair

**Sources of false negative cytology**
- Sampling issues
- Misinterpretation

False Negative Rate of Cytology

- Ideal study: benign cytology and pathology confirmation
- What we have:
  - Observational surveillance series
  - Surgical series
- Growth was defined as:
  - >50% change in volume or
  - >20% increase at least in two dimensions (minimum 2 mm) in a solid nodule or solid portion of a cystic nodule

Observational Surveillance Series

- Framework: FOLLOW UP of patients with benign FNA cytology with varied criteria for repeat FNA
- Biases:
  - Selection bias-differences between those who undergo repeat FNA vs. not
  - Information or misclassification bias-categorization of benign
Surgical Series of Benign Cytology

Framework: SURGERY in patients with prior benign FNA cytology
Bias: Selection bias
Differences between population with benign cytology for whom surgery is recommended versus those who remain under surveillance

False Negative Benign Cytology:
8 Studies with >250 Patients

False Negative Benign Cytology Varies WITHIN the Same Study

Cytology False Negative Rate Influenced By:

- Experience of operator - biopsy sampling error
- Experience of cytopathologist - interpretation error
- Study methodology
- Unclear role of “Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)”
- Probably MUCH closer to 2-3% than 10-15%
  - Uncertainty is the basis for the need for continued “watchful waiting”

Kwak Radiology 2010;254:292
Natural History of Nodules with Benign Cytology

• Ideal study:
  • Nodules with benign cytology with long-term sonographic follow-up and objective definition for size change
  • Multivariable analysis of predictors for nodule size change with appropriate sample size

• Studies for evaluation:
  • 3 retrospective series
    • Database analysis from large thyroid nodule centers
  • 2 prospective studies
    • 1 control arm of LT4 trial
    • 1 multicenter observational cohort study


Growth of Benign Nodules with Benign Cytology

• Kim: 854 cytologically benign nodules, 4 yr mean fu, mean 3 US exams
• Durante: 630 cytologically and 937 sonographically benign nodules in 992 pts, 5 yr fu, annual US exam
• Haddady 1078 cytology benign nodules, minimum 64 mo fu; avg time to growth 52 mo

Conclusions: Nodule More Likely to Grow:

- Younger patients\(^3,5,6\)
- Predominantly solid nodules\(^2,3\)
- Longer fu to detect growth\(^1,3,4,6\)
- Size ? Bimodal distribution
  - Nodules <1cm less likely to grow than nodules >1cm\(^3,5\)
  - Larger nodules >30mL (only small fraction in studies) less likely to grow\(^4\)
- Multinodular glands\(^5\) in lower iodine areas
- **GROWTH NOT ASSOCIATED WITH CANCER** (ALL REFERENCES)


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Small Thyroid Cancers (PTC) Usually Do Not Grow During Average 75 Month FU

1235 patients with low risk PTC who chose observation

More likely to grow, develop nodal metastasis and progression in <40 vs. >60 years

\(\text{Ito Y et al. Thyroid (2014)}\)
Strategies to Identify Cancer in Nodules with Benign Cytological

What is the Indication to Repeat a Thyroid Nodule FNA with a Prior Benign Cytology?
Pedro W. Rosario and Maria R. Calsolan

• Prospective study of 560 cytologically benign nodules <25% cystic
• FU US at 6 and 12 months, then annual US
• 4 groups with repeat FNA
  • Suspicious US features on 1st image, routine repeat FNA in 6 months (n=55)
  • Growth >50% volume (n=82)
  • Stable but developed suspicious US features at fu (n=18)
  • Stable but new suspicious US at fu (n=54)
Suspicious US Features

- Marked hypoechogenicity\textsuperscript{1,2}
- Microcalcifications\textsuperscript{1,2}
- Irregular/microlobulated margin\textsuperscript{1,2}
- Shape\textsuperscript{1,2}
- Incomplete peripheral calcification\textsuperscript{2}
- Abnormal nodes

\textsuperscript{1}Kim Radiology 2014;271:272; \textsuperscript{2}Rosario 2015 Thyroid 2015;10:1115;
Of the 14 missed cancers, 13 had suspicious US features (10 on initial US, 1 with growth, 2 new on follow up US)
Retrospective study
Mean volume 3.2 cm³
4 yr mean follow up
10 cancers/854: 1.1%

854 Cytology
Benign

GROWTH >50% volume
172

1 cancer
(0.6%)

Suspicious initial US features
55

8 cancers
(15%)

STABLE
1 cancer

Kim Radiology 2014;271:272
What Does New Suspicious US Features Predict?

• Development of NEW suspicious US features is NOT common in cytology benign nodules
  • Rosario 2015—5.5%
  • Lim 2013—4%
• If new suspicious US features appear ~11% cancer risk

To find 1 missed cancer, you need to follow 200 cytologically benign US nonsuspicious nodules

Suspicious US features on initial imaging are best indicator of missed malignancy . . .
Given the low false negative rate of US FNA cytology and the higher yield of missed malignancies based upon nodule sonographic features rather than growth, the follow up of thyroid nodules with benign cytology diagnoses should be determined by risk stratification based upon **sonographic pattern**.

<table>
<thead>
<tr>
<th>SONOGRAPHIC PATTERN</th>
<th>Strength of Rec</th>
<th>Quality of Evidence</th>
</tr>
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<tbody>
<tr>
<td>High Suspicion</td>
<td>Repeat US and US FNA within 12 months</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate/ Low Suspicion</td>
<td>Repeat US at 12-24months If growth or new suspicious US feature, repeat FNA OR continued observation</td>
<td>Weak</td>
</tr>
<tr>
<td>Very Low Suspicion</td>
<td>Utility of surveillance US and assessment of nodule growth as an indicator for repeat FNA is limited. If repeat US, it should at &gt; 24 months</td>
<td>Weak</td>
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R23 FU of Nodules with Benign Cytology NEW Recommendation 2015

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<tr>
<td>IF 2\textsuperscript{nd} US FNA done with benign cytology, repeat US \textit{for continued risk of malignancy} is no longer indicated</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
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Sonographically Benign Nodules

- Subcentimeter nodules
- Spongiform pattern
Sonographically Benign Nodules
<1 cm in size without suspicious US features

- Subcentimeter nodules
  - 5 year follow up of 852 nodules <1cm sonographically NONsuspicious (ABSENCE of hypoechogenicity, irregular margins, tall>wide shape, microcalcifications, vascularity)
  - 1 cancer after 5 years diagnosed with new irregular margins and hypoechogenicity on follow up US and no growth

Durante JAMA 2015;313:926;

Spongiform Nodules are BENIGN
(10% of Thyroid Nodules)

- Moon: 1/52 (1.9%) PTC
- Bonavita: 0/210 PTC
- Kim: 0/117 PTC
- Virman 0/66 PTC
- Brito Meta-analysis
  - 13 studies: 18,288 nodules; average size 15 mm
  - Highest diagnostic OR indicating benignity
  - Spongiform 12 (95% CI, 0.61–234.3)

R24 FU of nodules that have not had FNA
NEW recommendation 2015

<table>
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<th>SONOGRAPHIC APPEARANCE</th>
<th>Strength of Rec</th>
<th>Quality of Evidence</th>
</tr>
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<tr>
<td>Very low suspicion:</td>
<td>&lt;1cm: Do not require routine US surveillance</td>
<td>Weak Low</td>
</tr>
<tr>
<td>SPONGIFORM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PURE CYST</td>
<td></td>
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</tr>
</tbody>
</table>

Observation without FNA is a reasonable option.

MOLECULAR MARKER “BENIGN” . . .

Cytologically indeterminate (AUS/FLUS or follicular neoplasm) with “benign” molecular testing
Do we have any outcome data?
Molecular Tests Reporting NPV for Cytologically Indeterminate Nodules

- Afirma® gene expression classifier (GEC) transcriptome microarray analysis, bioinformatics for discriminatory function—Industry funded prospective multicenter
- ThyroSeq® version 2 Next Generation sequencing—Single investigator’s center
- ThyGenX® and ThyraMIR™ (oncogene panel and miRNA)—Retrospective multicenter

GEC Benign Nodules and Cytology Benign Nodules Grow At Same Rate

- US surveillance for nodule growth: 58 GEC benign (cytology AUS/FLUS or follicular neoplasm) vs. 1224 cytology benign
- Mean FU 13 months of GEC
- Surgery in 6/10 GEC benign growing nodules
  - 5 benign
  - 1 minimally invasive follicular cancer

Angell J Clin Endocrinol Metab epub Sept 2015
Molecular “Benign” Nodules
QUESTIONS THAT STILL NEED TO BE ANSWERED

• We need more data
• What is the cancer rate in indeterminate cytologies with negative molecular testing with long term FU
• What is the clinical significance of the pathologies of missed cancers?

SUMMARY

• Risk of cancer in cytologically benign nodules is low 5%
• Growth is NOT a risk for malignancy in cytology benign nodules
• Initial or subsequent development of suspicious US characteristics is the best predictor of cancer in cytology benign nodules
• US BENIGN thyroid nodules
  • Simple cysts
  • <1 cm nodules without suspicious US characteristics
  • SPONGIFORM nodules
SUMMARY

• FU of cytology benign nodules
  • Features do not require FU for CANCER
    • Simple cysts
    • <1 cm nodules without US suspicious features
    • SPONGIFORM nodules
    • Nodules with 2 benign cytologies
  • But we should follow for growth
    • Which nodules grow?
    • Not < 1 cm and > 30 ml (i.e., >6×3×3 cm SAG X AP X TR)
      • <1 cm nodules with benign US features do NOT need to be followed
      • Really big nodules don’t grow BUT should be removed if obstructive sx
      • All other nodules have the risk for growth
        * FU every 1-2 years
    • Not cancers in the first 6 years (in retrospective and small prospective studies)

Thank you for your attention!

QUESTIONS?