Long-term follow-up of patients with benign thyroid nodules

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I declare that I have no potential conflict of interest
How common?

- **Palpation**: 5%*
- **Autopsy**: 50%**
- **Sonography**: up to 67%***

Subclinical nodules are emerging from hiding and demanding our attention

* Tunbridge WM, *Clin Endocrinol (Oxf)*, 1977
** Mortensen JD, *J Clin Endocrinol Metab*, 1955
Evidence increased detection

Neck imaging tests & thyroid cancer incidence

Thyroid-Cancer Incidence and Related Mortality in South Korea, 1993–2011

Evidence increased detection

**Time trend of thyroid surgical procedures**

South Korea, 2001-2015

- Call to stop screening

- 35% reduction in surgical procedures
- 30% reduction in the incidence of thyroid cancer

An epidemic!!

Thyroid Nodules: Is It Time to Turn Off the US Machines?¹
John J. Cronan, MD
Radiology 2008 Jun;247(3):602-4

Editorial: Nonpalpable Thyroid Nodules—Managing an Epidemic
Douglas S. Ross

Thyroid cancer: An epidemic of disease or an epidemic of diagnosis?
Silvia Franceschi¹ and Salvatore Vaccarella
Int J Endocrinol Metab. 2015 October;13(4):e28491.
Published online 2015 October 10.

Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis
Salvatore Vaccarella, Ph.D., Silvia Franceschi, M.D., Freddie Bray, Ph.D., Christopher P. Wild, Ph.D., Martyn Plummer, Ph.D., and Luigino Dal Maso, Ph.D.
Agenda

Long-term follow-up of patients with benign thyroid nodules

1. What does it mean “benign” thyroid nodules?
2. How should we manage these nodules (length and frequency of follow-up, indication for repeat FNA)?
Clinical case #1

- Type 2 diabetes, hypertension.
  A carotid color Doppler ultrasound was performed.

- Detection of thyroid incidentaloma: single isoechoic mixed cystic solid nodule (spongiform), 16.5 mm in maximum diameter.

59 yrs
Clinical case #2

- Thyroid ultrasound screening at routine gynecological visit
- Detection of two thyroid incidentalomas, the larger nodule being hypoechoic, with regular borders, and measuring 11 mm in maximum diameter
Questions

1. Risk of malignancy?

- Single, subclinical nodule, sonographically spongiform
- 62 yrs

- Multiple, subclinical nodules, sonographically hypoechoic
- 33 yrs
Risk of malignancy: paradigm shift

“Yesterday”

FNAC -> US

“Today”

US -> FNAC
2009 ATA guidelines
• **Recommendation 5:**
  FNA is the procedure of choice in the evaluation of thyroid nodules
  *(Rating: A)*

2015 ATA guidelines
• **Recommendation 7:**
  FNA is the procedure of choice in the evaluation of thyroid nodules, *when clinically indicated*
  *(Strong recommendation, High-quality evidence)*

Cooper DS et al, Thyroid, 2009
Haugen BR et al, Thyroid, 2016
Risk of malignancy

“Yesterday”

2010 AACE/AME/ETA guidelines

• Recommendation 4.5.1:
  Clinical management of thyroid nodules should be guided by the combination of US evaluation and FNA biopsy (Grade A; BEL 3)

“Today”

2016 AACE/ACE/AME guidelines

• Recommendation 4.1:
  Combine clinical and US evaluation and, when appropriate, FNA results in the clinical management of thyroid nodules (Grade A; BEL 2)

Gharib H et al, Endocr Pract, 2010

Gharib H et al, Endocr Pract, 2016
Risk of malignancy & US feature

**PPV**

<table>
<thead>
<tr>
<th>US feature</th>
<th>Positive predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoechoic</td>
<td>85</td>
</tr>
<tr>
<td>Present Help</td>
<td>94</td>
</tr>
<tr>
<td>Spongiform nodules</td>
<td>95</td>
</tr>
<tr>
<td>Mainly cystic</td>
<td>95</td>
</tr>
<tr>
<td>Hyperchoic</td>
<td>95</td>
</tr>
<tr>
<td>No central vasculatization</td>
<td>98</td>
</tr>
<tr>
<td>Low stiffness</td>
<td>98</td>
</tr>
<tr>
<td>Simple cyst</td>
<td>100</td>
</tr>
</tbody>
</table>

**NPV**

<table>
<thead>
<tr>
<th>US feature</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild hypoechoogenicity</td>
<td>6</td>
</tr>
<tr>
<td>Macrocalcifications</td>
<td>10</td>
</tr>
<tr>
<td>Central vasularization</td>
<td>16</td>
</tr>
<tr>
<td>Irregular shape</td>
<td>26</td>
</tr>
<tr>
<td>High stillness</td>
<td>38</td>
</tr>
<tr>
<td>Irregular margins</td>
<td>57</td>
</tr>
<tr>
<td>Macrocalcifications</td>
<td>60</td>
</tr>
<tr>
<td>Marked hypoechoogenicity</td>
<td>73</td>
</tr>
</tbody>
</table>

Russ G, Ultrasonography, 2016
ATA US risk categories

**High suspicion**
70-90%

**Intermediate suspicion**
10-20%

**Low suspicion**
5-10%

**Very low suspicion**
<3%

**Benign**
<1%

FNAB: YES if >1 cm
FNAB: YES if >1.5 cm
FNAB: maybe if >2 cm
FNAB: NO

Haugen BR et al, Thyroid, 2016
ATA US risk categories

- **High suspicion**
  - 70-90%

- **Intermediate suspicion**
  - 10-20%
  - 1.1 cm thyroid nodule
  - FNAB: YES

- **Low suspicion**
  - 5-10%

- **Very low suspicion**
  - <3%
  - 1.6 cm thyroid nodule
  - FNAB: NO

- **Benign**
  - <1%

---

FNAB: YES if >1 cm
FNAB: YES if >1.5 cm
FNAB: maybe if >2 cm
FNAB: NO

Haugen BR et al, Thyroid, 2016
AACE/ACE/AME US risk categories

High risk
50-90%

Intermediate risk
5-15%

Low risk
~1%

FNAB: YES if >1 cm

FNAB: YES if >2 cm

FNAB: YES if >2 cm and increasing size or risk history

Gharib H et al, Endocr Pract, 2016
AACE/ACE/AME US risk categories

- **High risk** 50-90%: FNAB YES if >1 cm
- **Intermediate risk** 5-15%: FNAB YES if >2 cm
- **Low risk** ~1%: FNAB NO if >2 cm and increasing size or risk history

Gharib H et al, Endocr Pract, 2016
Questions

1. Risk of malignancy?
2. How should we follow these nodules (length and frequency of follow-up, indication for [repeat] FNA)?
Follow-up of benign nodules

2009 ATA guidelines

**Recommendation 14:**

a) It is recommended that *all benign thyroid nodules* be followed with *serial* US examinations 6-18 months after initial FNA (Rating C)

b) If there is evidence for *nodule growth* … the FNA should be repeated (Rating B)

2010 AACE/ACE/AMET guidelines

**Recommendation 7.6.2.1:**

a) *Cytologically benign nodules* should be followed up ... *repeated* clinical and US examination and TSH in 6 to 18 months (Grade D)

b) Perform repeated UGFNA biopsy in cases of *appearance of clinically or US suspicious features; >50% increase in nodule volume* (Grade B)

Cooper DS et al., Thyroid, 2009

Gharib H et al, Endocr Pract, 2010
Follow-up of benign nodules

Guidelines recommendations: assumptions

a) Benign thyroid nodules are expected to grow
b) Thyroid cancer could be missed by the initial biopsy
c) Growth can reliably identify patients with thyroid cancer
Follow-up of benign nodules

Guidelines recommendations: assumptions

a) Benign thyroid nodules are expected to grow
b) Thyroid cancer could be missed by the initial biopsy
c) Growth can reliably identify patients with thyroid cancer
The study protocol

Design
- Prospective observational study. Multicentric.

Setting
- Thyroid referral centers

Objective
- To determine the natural history of asymptomatic, sonographically and/or cytologically benign thyroid nodules

Durante C et al., JAMA, 2015
Check for eligibility
Enrollment
Thyroid US; TSH, fT4 Clinical data *

* At each site, clinical and ultrasound assessment were performed by the same physician across all study period

Durante C et al., JAMA, 2015
### Results (1)

#### Study cohort (n=992)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age – yrs (mean ±SD)</strong></td>
<td>52.3±13.7</td>
</tr>
<tr>
<td><strong>Female – (n; %)</strong></td>
<td>815 (82.1)</td>
</tr>
<tr>
<td><strong>BMI – Kg/m² (mean ±SD)</strong></td>
<td>26.9±4.8</td>
</tr>
<tr>
<td><strong>TSH – mIU/mL (mean ±SD)</strong></td>
<td>1.46±0.7</td>
</tr>
<tr>
<td><strong>Uninodular goiter – (n; %)</strong></td>
<td>594 (59.8)</td>
</tr>
<tr>
<td><strong>Nodule maximum diameter – mm (mean ±SD)</strong></td>
<td>14.2±8.1</td>
</tr>
<tr>
<td><strong>Solid structure - (n; %)</strong></td>
<td>806 (81.2)</td>
</tr>
</tbody>
</table>

* 630 *cytologically* and 937 *sonographically* benign nodules

Durante C et al., JAMA, 2015
Results (2)

Changes in the size (5 yrs)

Patients: n=992
Nodules: n=1567

66% Remained stable
18.6% Shrank
15.4% Grew

Durante C et al., JAMA, 2015
Mean changes in the largest diameters: +4.9 mm (95% CI 4.2 to 5.5)*
Mean changes in the volumes: +1.9 ml (95% CI 1.4 to 2.5)*

* ANOVA, longitudinal linear model with an unstructured correlation-type matrix

Durante C et al., JAMA, 2015
Results (4)

Patients with growing nodules

Total population

RECPAM analysis for nodule growth

Durante C et al., JAMA, 2015
Results (4)

RECPAM analysis for nodule growth

Durante C et al., JAMA, 2015
Results (4)

RECPAM analysis for nodule growth

Durante C et al., JAMA, 2015
Results (4)

   \textit{HR: 1}

2. Multiple, large, nodules. Younger age.  
   \textit{HR: 20.7}

Durante C et al., JAMA, 2015
Thyroid nodule growth

- Prospective study, control arm of laser ablation trial
- Solid thyroid nodule of 6-17 mL with at least one diameter of 3 cm
- Benin FNAB, negative calcitonin
- Normal thyroid function, no autoimmunity
- Scintigraphically cold nodules

Mean (±SD) nodule volume percentage changes

- Laser ablation group n= 101
- F-up group n= 99

Papini E et al., JCEM, 2014
Follow-up of benign nodules

Guidelines recommendations: assumptions

a) Benign thyroid nodules are expected to grow

b) Thyroid cancer could be missed by the initial biopsy

c) Growth can reliably identify patients with thyroid cancer
Follow-up of benign nodules

Guidelines recommendations: assumptions

a) Benign thyroid nodules are expected to grow
b) Thyroid cancer could be missed by the initial biopsy
c) Growth can reliably identify patients with thyroid cancer
Repeated FNA of thyroid nodules with benign cytologic features

<table>
<thead>
<tr>
<th>Study</th>
<th>Nodules rebiopsied – n (%)</th>
<th>Malignancy – n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajmal S et al., J Am Coll Surg, 2015</td>
<td>89</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Durante C et al., JAMA, 2015</td>
<td>365</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Illouz F et al., Eur J Endocrinol, 2007</td>
<td>298</td>
<td>35 (11.7)</td>
</tr>
<tr>
<td>Alexander EK et al., Ann Intern Med, 2003</td>
<td>74</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Chehade JM et al., Endocr Pract, 2001</td>
<td>254</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Erdogan MF et al., Thyroid, 1998</td>
<td>257</td>
<td>3 (1.2)</td>
</tr>
</tbody>
</table>
FNA: false negative results

Nodules re-biopsied (after 5 yrs)

Cytological findings

- Benign: 361 (98.9%)
- Malignant: 4 (1.1%)

False negative results

Durante C et al., JAMA, 2015
Follow-up of benign nodules

Guidelines recommendations: assumptions

a) Thyroid nodules are expected to grow
b) Thyroid cancer could be missed by the initial biopsy
c) Growth can reliably identify patients with thyroid cancer
# Growth & risk of malignancy

## Systematic review and meta-analysis

### Thyroid nodules with initial benign cytology

<table>
<thead>
<tr>
<th>rFNA</th>
<th>Total number of Nodules</th>
<th>Histology</th>
<th>Total number of nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soo-Yeon Kim</td>
<td>381</td>
<td>Soo-Yeon Kim</td>
<td>77</td>
</tr>
<tr>
<td>Rosario</td>
<td>178</td>
<td>Jung Moon</td>
<td>7</td>
</tr>
<tr>
<td>Jung Moon</td>
<td>45</td>
<td>Chernyavsky</td>
<td>98</td>
</tr>
<tr>
<td>Jun Lim</td>
<td>6</td>
<td>Jun Lim</td>
<td>6</td>
</tr>
<tr>
<td>Durante</td>
<td>365</td>
<td>Total</td>
<td>188</td>
</tr>
<tr>
<td>Yeon Kim</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>978</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ospina NS et al., Clin Endocrinol, 2016
# Growth & risk of malignancy

<table>
<thead>
<tr>
<th>Reference standard</th>
<th>LR (growth)</th>
<th>LR (no growth)</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical histology</td>
<td>0.83</td>
<td>1.2</td>
<td>0.58</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.56–1.2)</td>
<td>(0.82–1.8)</td>
<td>(0.26–1.3)</td>
</tr>
<tr>
<td>I²</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Repeat FNA</td>
<td>1.8</td>
<td>0.53</td>
<td>2.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.48–6.4)</td>
<td>(0.30–0.96)</td>
<td>(0.26–18.0)</td>
</tr>
<tr>
<td>I²</td>
<td>71.8%</td>
<td>5.4%</td>
<td>78%</td>
</tr>
</tbody>
</table>

LR, likelihood ratio; DOR, diagnostic odds ratio; CI, confidence interval.
Follow-up of benign nodules

Guidelines recommendations: assumptions

a) Benign thyroid nodules are expected to grow

b) Thyroid cancer could be missed by the initial biopsy  No (rare!)

c) Growth can reliably identify patients with thyroid cancer  No evidence

Is there any patient who may benefit from repeat FNA in nodules with initial benign cytology?
Criteria for repetition FNA

Nodules re-biopsied: 209.
Cancer detection rate:

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspicious initial US features</td>
<td>18.2%</td>
</tr>
<tr>
<td>Stable with NEW suspicious US</td>
<td>11.1%</td>
</tr>
<tr>
<td>Growth</td>
<td>2.4%</td>
</tr>
<tr>
<td>Stable no change in US</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Suspicious US features are best indicator of missed malignancy

Rosario et al., Thyroid, 2015
ATA guidelines

Follow-up of benign nodules

2009 - Recommendation 14

a) It is recommended that all benign thyroid nodules be followed with serial US examinations 6-18 months after initial FNA

b) If there is evidence for nodule growth ... the FNA should be repeated

2015 - Recommendation 23

The follow up of thyroid nodules with benign cytology diagnoses should be determined by risk stratification based upon ultrasound pattern.

Cooper DS et al., Thyroid, 2009
Haugen BR et al., Thyroid, 2016
F-up benign nodules

- **High suspicion (70-90%)**
  - Micronodules
  - Hypoechoic, irregular margins
  - Hypoechoic, cellular thyroid nodule

- **Intermediate suspicion (10-20%)**
  - Hypoechoic, solid, regular margins
  - Hypoechoic cyst with acoustic shadowing

- **Low suspicion (5-10%)**
  - Hypoechoic solid, irregular margins
  - Partially cystic with vascular areas

- **Very low suspicion (<3%)**
  - Hypoechoic solid, irregular margins
  - Partially cystic with suspicious features

- **Benign (<1%)**
  - Cyst

**Risk of malignancy**

- **US + FNA:** 12 mo.
- **US:** 12-24 mo.
- **FNA:** if new suspicious US
- **US:** >24 mo.

*Haugen BR et al, Thyroid, 2016*
AACE/ACE/AME guidelines

Follow-up of benign nodules

2010 - Recommendation 7.6.2.1

a) Cytologically benign nodules should be followed up ... repeated clinical and US examination and TSH in 6 to 18 months (Grade D)
b) Perform repeated UGFNA biopsy in cases of appearance of clinically or US suspicious features; >50% increase in nodule volume (Grade B)

Gharib H et al, Endocr Pract, 2010

2016 - Recommendation 7.2.1

a) A repeat FNA is recommended in nodules with suspicious US features (BEL 2, GRADE A) and/or with a >50% increase in volume (BEL 3, GRADE B)

Gharib H et al, Endocr Pract, 2016
2015 ATA guidelines

Nodules with 2 benign FNA cytologies

Recommendation 23

If a nodule has undergone repeat US-guided FNA with a second benign cytology result, ultrasound surveillance for this nodule for continued risk of malignancy is no longer indicated

Strong recommendation, Moderate-quality evidence

Haugen BR et al., Thyroid, 2016
Conclusions

- The majority of benign thyroid nodules will never become clinically significant overtime.
- The long-term follow up of these nodules should be determined by risk stratification based upon ultrasound pattern.
Long-term follow-up: algorithm

**Low risk**
- No suspicion US pattern (<5%)
- Benign cytology (if any)

**High risk**
- Suspicion US pattern (>5%)
- Benign cytology

**Frequency**
- Repeat neck US at >24 months
- Repeat neck US at 12-24 months

**Length**
- ???
- ???

**Repeat FNA**
- Yes, if new suspicious US features
- (Yes, in nodule with a >50% increase in volume)
- Yes, in nodules with high suspicious US features and/or if new suspicious US features
- (Yes, in nodule with a >50% increase in volume)