25th Annual Scientific AACE Clinical Congress

Improving the Long Term Management of Benign Thyroid Nodules

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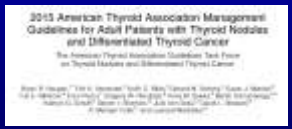
Disclosures

- 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)?

ATA 2015 guidelines


2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

Haugen, et al. Thyroid 2016;26:1

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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

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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)

Bethesda System for Reporting Thyroid Cytopathology (2009) Cibas ES *et al*; AJCP; Gharib Endo Prac 2010;16:468

How Reliable is a Benign Cytology?

Kappa statistic: Measure of interobserver agreement

	TBS-T six-category scheme	
FNA diagnosis	Kappa (95% CI)	Agreement*
Unsatisfactory/nondiagnostic	0.8 (0.66–0.97)	good
Benign	**0.6 (0.43-0.78) fair**	
Follicular neoplasm	0.5 (0.34–0.65)	fair
Suspicious for malignancy	0.2 (0.06–0.37)	poor
Malignant	0.6 (0.46–0.79)	fair

Sources of false negative cytology

- Sampling issues
- Misinterpretation

Walts Diagn Cytopathol 2012 40:E62068; Yang Cancer Cytopathol 2007;111:306; Hall World J Surg 1996;2:848

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

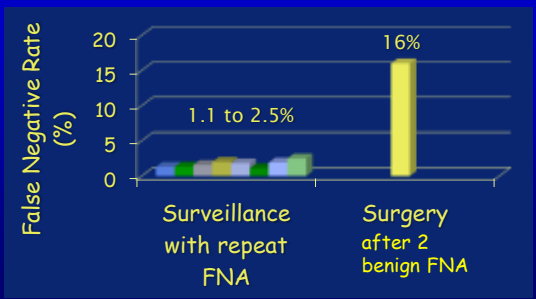
Surgical Series of Benign Cytology

Framework: SURGERY in patients with prior benign FNA cytology

Bias: Selection bias

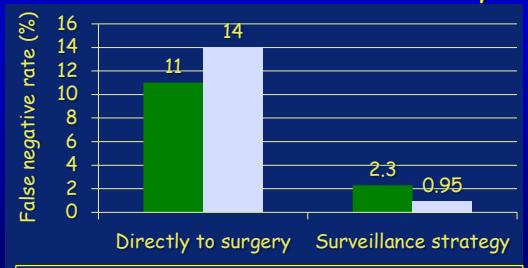
Differences between population with benign cytology for whom surgery is recommended versus those who remain under surveillance

False Negative Benign Cytology:
8 Studies with >250 Patients



Chedade Endocrine Pract 2001; Orlandi Thyroid 2001; Oertel Thyroid 2007; Illouz Eur J Endocrinol 2007; Torre Acta Cytologica 2007; Durante JAMA 2005; Kwak Radiology 2010 Rosario Thyroid 201510:1115; Flanagan Am J Clin Pathol 2006;125:698

False Negative Benign Cytology Varies WITHIN the Same Study



Bias due to non-random assignment to surgery

Chernyavsky Ann Surg Oncol 2012;19:1472
Kwak Radiology 2010;254:292

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"

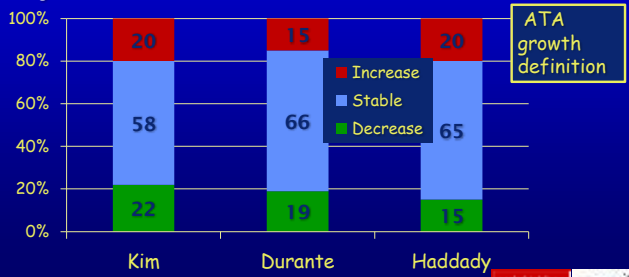
Natural History of Nodules with Benign Cytology

- Ideal study:
  - Nodules with benign cytology with longterm sonographic follow-up and objective definition for size change
  - Mutivariable 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

Alexander Ann Intern Med 2003;138:315; Edrogan Clin Endocrinol 2006;65:767 Kim Radiology 2014;271:272; Puzziello J Endocrinol Invest 2014;37:1181; Durante JAMA 2015;313:926

Growth of Benign Nodules with Benign Cytology

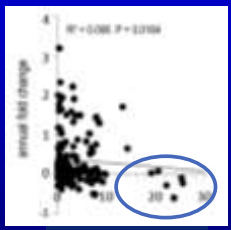
- Kim: 854 cytologically benign nodules, 4 yr mean fu, mean 3 US exams
- Durante: 630 cytologically and 937 sonographically benign nodules in 992 pts, 5 yr fu, annual US exam
- Haddady 1078 cytology benign nodules, minimum 64 mo fu; avg time to growth 52 mo



Kim Radiology 2014;271:272; Durante JAMA 2015;313:926;Hadday 2015 AACE PP 22:3

Conclusions:Nodule More Likely to Grow:

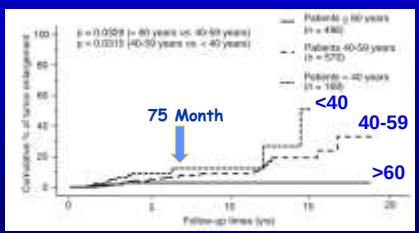
- Younger patients[3,5,6]
- Predominantly solid nodules[2,3]
- Longer fu to detect growth[1,3,4,6]
- Size ? Bimodal distribution
  - Nodules <1cm less likely to grow than nodules >1cm[3,5]
  - Larger nodules >30mL (only small fraction in studies) less likely to grow[4]
- Multinodular glands[5] in lower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



[1]Alexander Ann Intern Med 2003;138:315; [2]Edrogan Clin Endocrinol 2006;65:767; [3]Kim Radiology 2014;271:272; [4]Puzziello J Endocrinol Invest 2014;37:1181; [5]Durante JAMA 2015;313:926, Hadddy AACE 2016

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

Ito Y et al; Thyroid (2014)

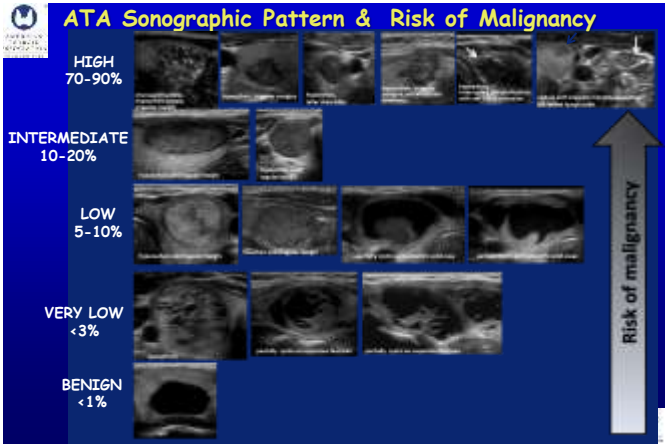
Strategies to Identify Cancer in Nodules with Benign Cytological

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)

Rosario 2015 Thyroid 2015;10:1115

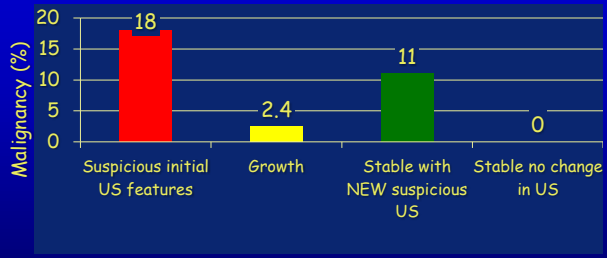


Suspicious US Features

- Marked hypoechogenicity[1,2]
- Microcalcifications[1,2]
- Irregular/microlobulated margin[1,2]
- Shape[1,2]
- Incomplete peripheral calcification[2]
- Abnormal nodes

[1]Kim Radiology 2014;271:272 ; [2]Rosario 2015 Thyroid 2015;10:1115;

Cancer Detection Rates



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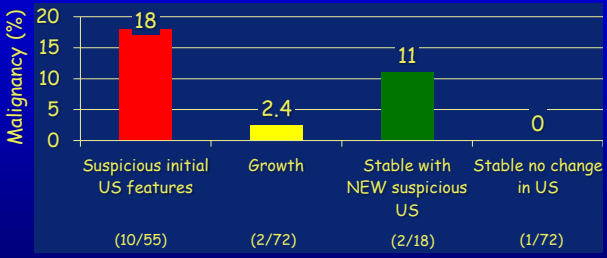
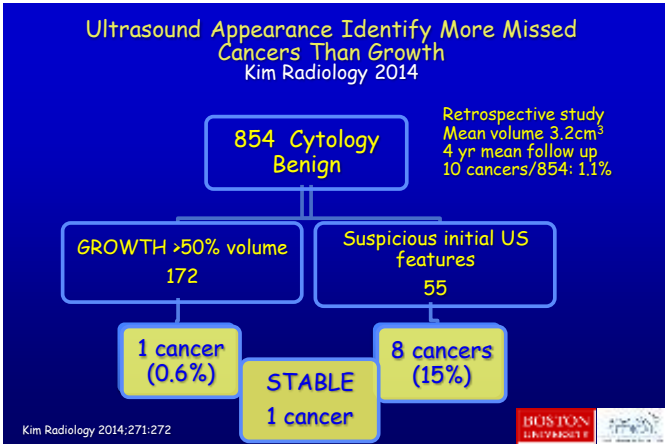
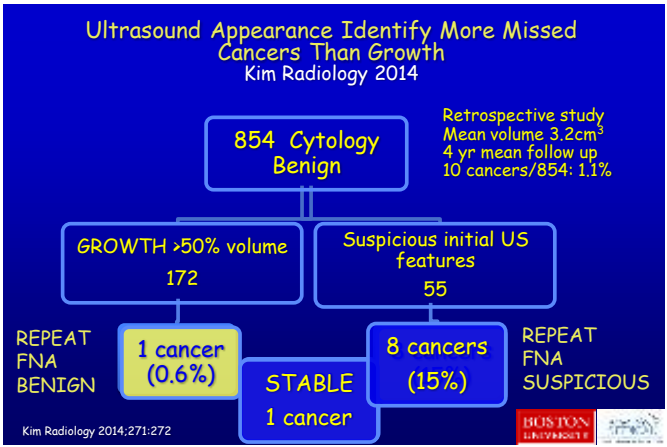


Of the 14 missed cancers, 13 had suspicious US features
(10 on initial US, 1 with growth, 2 new on follow up US)

Rosario 2015 Thyroid 2015;10:1115


Ultrasound Appearance Identify More Missed Cancers Than Growth
Kim Radiology 2014
854 Cytology Benign
Retrospective study
Mean volume 3.2cm3
4 yr mean follow up
10 cancers/854: 1.1%
GROWTH >50% volume
172
Suspicious initial US features
55
1 cancer (0.6%)
STABLE
1 cancer
8 cancers (15%)
Kim Radiology 2014;271:272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Suspicious initial US features
55
REPEAT FNA BENIGN
1 cancer (0.6%)
STABLE
1 cancer
8 cancers (15%)
REPEAT FNA SUSPICIOUS
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

Rosario Thyroid 2015;10:1115; Lim Endocrinol Metab 2013;28:110

Suspicious US features on initial imaging are best indicator of missed malignancy . . .

R23 FU of Nodules with Benign Cytology NEW Recommendation 2015

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**.

R23 FU of Nodules with Benign Cytology NEW Recommendation 2015

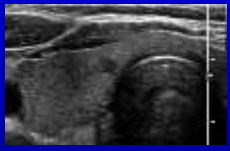
SONOGRAPHIC PATTERN		Strength of Rec	Quality of Evidence
High Suspicion 	Repeat US and US FNA within 12 months	Strong	Moderate
Intermediate/ Low Suspicion 	Repeat US at 12-24months If growth or new suspicious US feature, repeat FNA OR continued observation	Weak	Low
Very Low Suspicion 	Utility of surveillance US and assessment of nodule growth as an indicator for repeat FNA is limited. If repeat US, it should at ≥ 24 months	Weak	Low

R23 FU of Nodules with Benign Cytology NEW Recommendation 2015

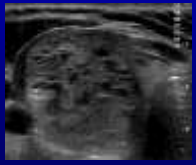
Sonographic Pattern	Strength of rec	Quality of evidence
IF 2nd US FNA done with benign cytology, repeat US for continued risk of malignancy is no longer indicated	Strong	Moderate

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)

1 cancer in 445 (0.2%) spongiform nodules

Moon Radiology 2008;247:262; Bonavita AJR 2009;193; Kim AJNR Am J Neuroradiol 2010;31:1961; Virmani AJR 2011;196:891; Brito J Clin Endocrinol Metab 2014;99:1253

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

SONOGRAPHIC APPEARANCE		Strength of Rec	Quality of Evidence
Very low suspicion: SPONGIFORM PURE CYST	≤1cm: Do not require routine US surveillance	Weak	Low

Observation without FNA is a reasonable option

MOLECULAR MARKER "BENIGN" . . .

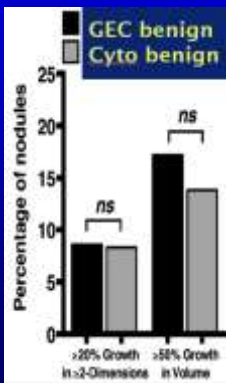
Cytologically indeterminate (AUS/FLUS or follicular neoplasm) with "benign" molecular testing
Do we have any outcome data?

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., >6x3x3 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)

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Thank you for your attention!

QUESTIONS?

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