

Thyroid Nodules

Triennial Course
Panel Discussion
October 2012

1

Case 1:

- Currently 70 year old female remote history breast cancer (1987), in remission
- In August 2005 palpable thyroid mass detected at routine physical
- Asymptomatic. Normal thyroid function tests.

2

Exam Date: 08/02/2005
Radiology No: 139897

ULTRASOUND THYROID:

For thyroid mass.

Thyroid sonography was performed. No previous studies were submitted for comparison.

The right lobe of the thyroid gland measures 4.5 x 1.8 x 2.8 cm while the left lobe measures 4.7 x 2.4 x 2.0 cm. There is marked heterogeneity in the thyroid gland. There is a dominant nodule in the mid pole of the right lobe of the thyroid gland measuring 3.0 x 1.7 x 2.9 cm. There is a smaller 1.3 x 1.1 x 1.1 cm solid nodule in the inferior pole of the right lobe of the thyroid gland.

Within the left lobe of the thyroid gland, there is a heterogeneous complex nodule in the mid pole measuring 2.4 x 1.4 x 1.5 cm. In the inferior pole, there is a solid nodule measuring 0.9 x 0.5 x 0.9 cm. In the mid to upper pole, there is a 0.9 x 0.7 cm solid nodule. Superiorly in the left lobe of the thyroid gland, there is a 4 x 2 x 3 mm calcified and shadowing nodule.

The isthmus measures 1.1 cm in thickness and contains a 2.2 x 1.6 cm heterogeneous nodule.

IMPRESSION: MULTIPLE, NONSPECIFIC THYROID NODULES AS DESCRIBED ABOVE. THERE IS A DOMINANT 3.0 CM MASS IN THE MID POLE OF THE RIGHT LOBE OF THE THYROID GLAND. FURTHER EVALUATION WITH A FINE-NEEDLE ASPIRATION IS RECOMMENDED AS CLINICALLY WARRANTED.

RP

Would you make underwriting decision here?

3

EXAM DATE	EXAM#	TYPE/EXAM
12/01/2005	000722046	CCUS/US THYROID

Real-time ultrasonography of the thyroid gland was performed. Comparison is made with the previous exam dated 8/2/2005.

The right lobe measuring 4.2 cm in length x 1.8 cm AP x 2.9 cm in width. A dominant nodule is seen in the mid pole measuring 3.1 x 1.8 x 2.9 cm. This is essentially unchanged. In the lower pole, there is a nodule measuring 1.0 x 1.1 x 1.1 cm. This is also unchanged from the previous examination.

The left lobe measures 4.3 cm in length x 2.3 cm AP x 2.2 cm in width. Again there is a dominant mixed solid and cystic nodule measuring 2.2 x 1.4 x 1.5 cm, not changed from previous exam. In the lower pole, there is a solid nodule measuring 1.0 x 0.8 x 0.9 cm, unchanged from previous exam. In the mid to upper pole, additional nodule measuring 1.0 x 0.6 x 0.9 cm, which is unchanged. Superiorly in the thyroid gland, there is a small nodule with calcification, difficult to delineate now measuring 1.6 x 0.8 x 1.0 cm. Previously this was not as clearly defined, although the overall size does not appear to have significantly changed.

The isthmus measures 6.2 mm with a nodule measuring 1.9 x 0.9 x 1.4 cm. This is unchanged from the previous exam.

IMPRESSION:

1. MULTIPLE NODULES IN BOTH THYROID LOBES AS DESCRIBED ABOVE. NO SIGNIFICANT CHANGE SINCE 8/05.
2. FINDINGS ARE CONSISTENT WITH MULTINODULAR GOITER.

Would you make underwriting decision here?

4

Spec Date: 12/21/05
Received: 12/21/05-1529

SOURCE

FINE NEEDLE ASPIRATION Thyroid (RIGHT)

PATIENT INFORMATION

ACTUAL COLLECTION DATE: 12/21/05
PATIENT HISTORY: RIGHT DOMINANT NODULE

*****DIAGNOSIS*****

Immediate Interpretation: THYROID, RIGHT, ULTRASOUND, FINE NEEDLE ASPIRATION:
FOLLICULAR NEOPLASM
Final Interpretation: FOLLICULAR NEOPLASM. SEE COMMENT.

*****COMMENT*****

The risk of malignancy in this setting is 10-30%. The differential diagnosis of Follicular Neoplasm includes Follicular Adenoma, Well Differentiated Follicular Carcinoma, cellular nodule in hyperplasia and Follicular Variant Papillary Carcinoma.

5

Spec Date: 12/21/05
Received: 12/21/05-1530

SOURCE

FINE NEEDLE ASPIRATION Thyroid (LEFT)

PATIENT INFORMATION

ACTUAL COLLECTION DATE: 12/21/05
PATIENT HISTORY: LEFT THYROID NODULE WITH CALCIFICATIONS.

*****DIAGNOSIS*****

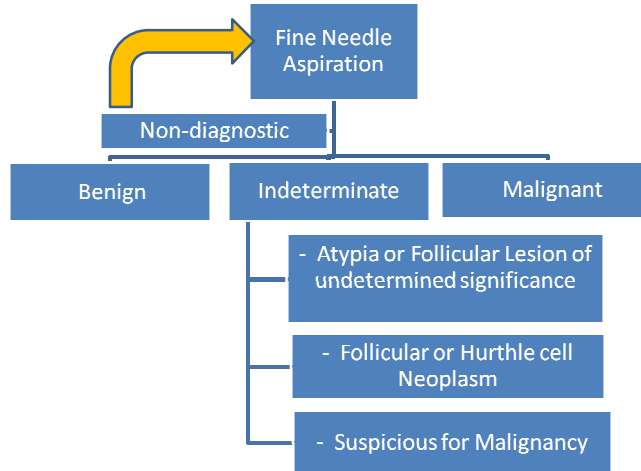
Immediate Interpretation: THYROID, LEFT, ULTRASOUND, FINE NEEDLE ASPIRATION:
BENIGN THYROID NODULE. COLLOID NODULE
Final Interpretation: LESS THAN OPTIMAL. NON-SPECIFIC PATTERN. SEE COMMENT.

*****COMMENT*****

This sample shows low cellularity, demonstrates less than moderate amounts of definite colloid and/or does not fulfill specific criteria for any defined diagnostic category. No atypia nor overt malignancy are identified. Clinical correlation and follow-up warranted. Repeat FNA should be considered as indicated clinically.

6

Thyroid nodules



From: Popoveniuc G and Jonklaas J. Thyroid Nodules. Med Clin N Am 96 (2012) 329-349.

Went to Surgery 2-8-06

Spec Date: 02/08/06
Received: 02/08/06-1056

SPECIMEN

RIGHT THYROID LOBE WITH ISTHMUS

HISTORY

PRE-OP DIAGNOSIS: Right thyroid neoplasm

GROSS DESCRIPTION

The specimen is received in formalin labelled "Right Thyroid Lobe with Isthmus" and consists of a multilobulated 18 gram thyroid lobe without an orienting device. The specimen measures 4.3 by up to 4.0 x 1.3 cm. and has a smooth purple to red external surface. The external surface is inked black and the specimen is serially sectioned revealing multiple cysts varying from purple-red with thin strips of fibrous tissue traversing the cavity to soft and dark purple and hemorrhagic. The entire specimen is submitted in eight blocks labelled A through H.

*******DIAGNOSIS*******

Thyroid, right lobe with isthmus, excision -
 A) Follicular adenoma, microcystic pattern.
 B) Multinodular goiter.
 C) Focal mild chronic thyroiditis.
 D) No malignancy.

Case Discussion

- Breast cancer is one of few cancers that may metastasize to thyroid. Others include kidney, colon, and lung cancers.
- Her age 70 was risk factor.
- The likelihood of malignancy in multi-nodular thyroid gland is same as in single solitary nodule in normal thyroid gland.
- Selection of which nodule(s) for FNA is based on size, ultrasound appearance, growth pattern, or other suspicious characteristics.
- The left FNA was not diagnostic (inadequate specimen) and the right FNA was follicular neoplasm which had 20-30% likelihood of malignancy, which is what prompted surgery.

9

Molecular assays

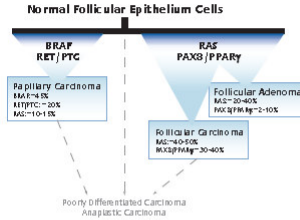
- Performed on Fine Needle Aspirate material
- Two available:
 - Asuragen™, molecular analysis for likely malignant
 - Veracyte™, molecular analysis for likely benign

10

Improving Pre-operative Diagnosis of Thyroid Nodules

- Aids in the resolution of indeterminate cytology and more
- Markers supported by numerous peer-reviewed publications including the ATA Guidelines*
- Run as an adjunct to your current cytopathology testing
- Aids in the characterization of malignancies

*The ATA recommendation bears a "C" rating meaning it is based on expert opinion.



BRAF and Beyond

Malignancy in Thyroid Nodules

Type of Testing	Sensitivity
Cytology alone	44-60%
Cytology plus mutation panel	80-90%



Visit www.Asuragen.com/ClinicalLab to learn more!



Source: Paper Ad as appeared in JCEM Feb 2012 Vol 97 No. 2 www.asuragen.com/ClinicalLab • 877-723-0018 • ClinicalLabSupport@Asuragen.com

Molecular Testing for Mutations in Improving the Fine-Needle Aspiration Diagnosis of Thyroid Nodules

Yuri E. Nikiforov, David L. Steward, Toni M. Robinson-Smith, Bryan R. Haugen, Joshua P. Klopper, Zhaowen Zhu, James A. Fagin, Mercedes Falciglia, Katherine Weber, and Marina N. Nikiforova

J Clin Endocrinol Metab, June 2009, 94(6):2092-2098

Cytology Diagnosis	Molecular Testing (MT)	Histologic Diagnosis	MT Performance
FLUS (21)	Mutation Positive (3) BRAF (1), RAS (2)	Malignant (3) PC (3)	Sensitivity 100% Specificity 100% PPV 100% NPV 100% Accuracy 100%
	Mutation Negative (18)	Benign (18) HN (15), FA (3)	
Follicular or Hurthle cell neoplasm (23)	Mutation Positive (9) BRAF (4), RAS (3), PAX8/PPARY (1), RET/PTC (1)	Malignant (9) PC (7), FC (2)	Sensitivity 75% Specificity 100% PPV 100% NPV 79% Accuracy 87%
	Mutation Negative (18)	Malignant (3) PC (1), FC (2) Benign (11) HN (10), FA (1)	
Suspicious for malignancy (7)	Mutation Positive (3) BRAF (4), RET/PTC (1)	Malignant (3) PC (3)	Sensitivity 60% Specificity 100% PPV 100% NPV 90% Accuracy 71%
	Mutation Negative (4)	Malignant (2) PC (2) Benign (2) HN (2)	

FIG. 4. Performance of molecular testing in specific categories of indeterminate FNA cytology.

Press Releases

Sharing Breaking News and Important Information

Veracyte Announces Study Results Published Online in New England Journal of Medicine Which Suggest that Its Afirma® Gene Expression Classifier Can Reduce Unnecessary Thyroid Surgeries
Findings Also Presented at ENDO 2012: The 94th Annual Meeting & Expo

Jun 25, 2012

From: www.veracyte.com

13

Alexander EK et al. Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate Cytology NEJM 2012, June 25

<http://www.nejm.org/doi/pdf/10.1056/NEJMoa1203208>



Gene expression classifier	Histology at surgery, malignant (N = 85)	Histology at surgery, benign (N = 180)
Suspicious	78	87
Benign	7	93

Prevalence of malignancy was 32%
Negative predictive value = 93%

14

Case 2:

- Currently age 49 year old female
- Family history of thyroid cancer in grandmother
- Moved to USA from Eastern Europe 2001
- Seen 2009 for palpable thyroid nodule
- States had previous thyroid ultrasound in 2001
- Asymptomatic. Normal labs.

15

5-2-09

INDICATION: 46-year-old female with palpable thyroid nodule.

COMPARISON: The report of the thyroid ultrasound of April 30, 2001.

FINDINGS: The right thyroid measures 2.5 x 2.0 x 4.9 cm. The left thyroid measures 1.5 x 1.3 x 4.4 cm. Multiple colloid cysts are identified in the left lobe, the largest of which measures 1.4 x 0.6 x 0.7 cm. A dominant solid nodule is identified in the right lobe measuring 2.1 x 1.3 x 1.8 cm. Additional small spongy nodules measuring less than a centimeter are seen in the right lobe and also several colloid cysts.

IMPRESSION: Multinodular thyroid gland. 2.2 cm dominant solid nodule identified in the right lobe. Based on size criteria an ultrasound-guided biopsy is recommended for this nodule, unless it is stable since the 2001 scan.

Comparison with the prior thyroid ultrasound will be made when the images are available from the film library.

THYROID U.S.
Reason: PALPABLE MASS

FINAL ADDENDUM

ADDENDUM: A review of the images of April 30, 2001, demonstrates the dominant solid nodule in the right lobe. The nodule has doubled in size since the scan of 2001 and based on this size criteria, an ultrasound-guided biopsy is still recommended.

16

FINAL DIAGNOSIS

Microscopic Examination and Diagnosis
STATEMENT OF SPECIMEN ADEQUACY:
Satisfactory for evaluation.

INTERPRETATION(S):
THYROID, RIGHT, FINE NEEDLE ASPIRATION (THIN PREP AND SMEARS):
- **ATYPICAL CELLS PRESENT.**
- **SEE COMMENT.**

COMMENT
The specimen is hypercellular and contains medium and large sized groups of follicular epithelial cells. There are scattered nuclear grooves as well as features suggestive of nuclear pseudoinclusions. Therefore, papillary thyroid carcinoma cannot be entirely ruled out. Clinical and radiologic correlation is recommended.

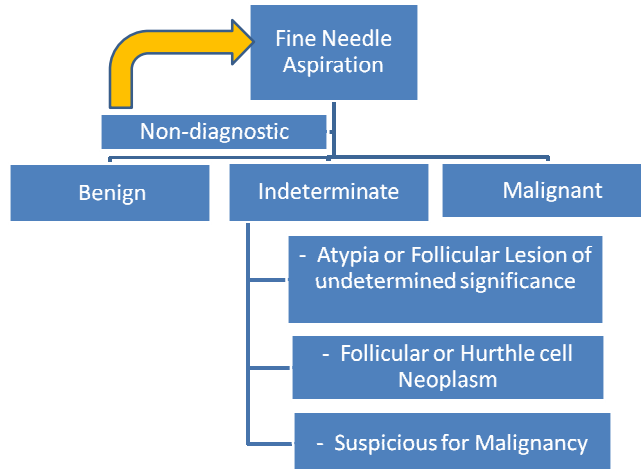
Clinical History

ENLARGED THYROID ON PHYSICAL EXAM MED RIGHT LOBE / ISTHMUS NODULE = 2.3 X 1.7 X 1.8CM

SOURCE OF SPECIMEN(S)
Thyroid, Fine Needle Aspiration, Right

GROSS DESCRIPTION
Specimen: Received is/are 30cc's of light peach cytolyt solution and 4 slides in 95% ethyl alcohol. Also received are 2 air dried slides for Diff stain.(GW,gw)
Prepared:
#Smears:6
Concentration technique, #slides (i.e. Thin Prep):1
Cell Block:Cell block attempted, but not obtained
Additional studies:

Thyroid nodules



From: Popoveniuc G and Jonklaas J. Thyroid Nodules. Med Clin N Am 96 (2012) 329-349.

FINAL DIAGNOSIS

MICROSCOPIC EXAMINATION AND DIAGNOSIS

THYROID, RIGHT LOBE, LOBECTOMY:

- **PAPILLARY THYROID CARCINOMA, FOLLICULAR VARIANT ASSOCIATED WITH SCAR AND CALCIFICATION (0.3 CM).**
- **SEPARATE FOCUS OF MICROPAPILLARY CARCINOMA (0.1 CM) (BLOCK LABELED F)**
- **MULTINODULAR GOITER**
- **MARGINS NEGATIVE FOR TUMOR**

COMMENT

ONCOLOGY TABLE-THYROID

1. Maximum tumor size (cm): 0.3 cm
2. Tumor location: Right lobe
3. Multifocality: Yes
4. Histology: Papillary carcinoma, follicular variant
5. Margins: Negative
6. Capsular invasion: Negative
7. Extrathyroidal extension: Negative
8. Vascular/Lymphatic invasion: Negative
9. Lymph nodes: # examined - 0; # positive - n/a
10. TNM code: pT1, pNX, pMX
11. Non-neoplastic thyroid: Multinodular goiter
12. Comments: The findings are reported to [REDACTED] on 5/22/2009.



In an area adjacent to the frozen section, there is a dominant nodule displaying features of a hyperplastic nodule. The central portion of this nodule shows a 0.7 cm calcified area. Within this calcified nodule there is what appears to be a scar with some hemorrhage which is also seen in the frozen section slide. A 0.3 cm focus of papillary thyroid carcinoma, follicular variant, is noted in this nodule. There is a separate incidentally found focus of micropapillary carcinoma in block F. There are several areas with nodules which have an adenomatous appearance. However, no definite nuclear features of papillary thyroid carcinoma are seen in these nodules (blocks I, H), [REDACTED]

kv

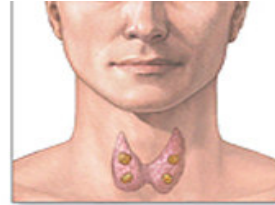
DATE REPORTED: 5/22/2009

Case 2 discussion

- Family history was important.
- Further detail on where Eastern Europe, may have been important.
- FNA was cellular, increasing probability that findings were true positive.
- Molecular assay role? Possibly to plan surgical approach?

Background Statistics, US population

- Prevalence palpable nodule about 4%
- Incidentally detected, 20-60% population
- Thyroid cancer rates:
 - 5.6/ 100,000 male
 - 16.3/ 100,000 female
- death rates
 - thyroid cancer 0.6/100,000 population
- Distinguishing between benign disease and malignant is goal of clinical/ radiographic/ tissue evaluations



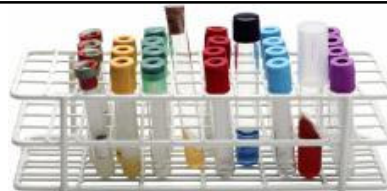
ADAM

Image from
www.nlm.nih.gov/medlineplus/thyroid

From: www.seer.cancer.gov/csr/1975_2009_pops09

21

Evaluation



- Thyroid Stimulating Hormone (TSH)*
- Calcitonin
- Thyroid ultrasound
- Fine needle aspiration
 - ?molecular assays
- Emerging technologies: elastography?

From : Popovenluc G and Jonklaas J. Thyroid Nodules. 2012 Med Clin N Am 96:329-349.

*McLeod DS et al. Thyrotropin and thyroid cancer diagnosis: a systematic review and dose-response meta analysis. JCEM Aug 2012 97(8):2682-2692.

22

Radioactive Iodine Scan



<http://www.endocrineweb.com/conditions/thyroid/thyroid-gland-function>

23

Suspicious radiographic features on ultrasound

- Micro-calcifications
- Hypoechoogenicity
- Irregular margins
- Solid
- Intranodule vascularity
- More tall than wide
- Growth on serial studies

From : Popoveniuc G and Jonklaas J. Thyroid Nodules. 2012 Med Clin N Am 96:329-349.

24

Risk factors for thyroid cancer

- Radiation exposure
- Age < 20 or > 60
- History goiter
- Family history thyroidal disease
- Male gender
- Family history multiple endocrine neoplasia-2, Cowden's syndrome, familial polyposis, Carney complex, Werner's
- Rapid growth, hoarseness, pain, nodule fixation
- Palpable cervical lymph nodes

From : Popoveniuc G and Jonklaas J. Thyroid Nodules. 2012 Med Clin N Am 96:329-349.