


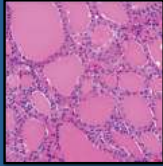
Thyroid Cytopathology



Richard M. DeMay, MD
 Professor of Pathology
 Director of Cytopathology
 The University of Chicago

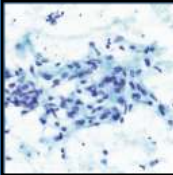
Diseases of the Thyroid

1. Thyroiditis
2. Follicular lesions
 Goiters
 Neoplasms
3. Other thyroid neoplasms
4. Advanced topics

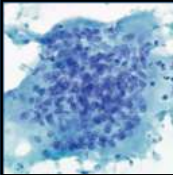


Granulomatous Thyroiditis

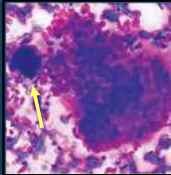
Postviral (cold, flu) syndrome
 Painful thyroid; fever, chills, fatigue



Epithelioid
Histiocytes



Multinucleated
Giant Cells

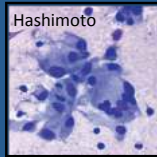


Giant cells munch
on yummy colloid

See giant cells: Think papillary carcinoma!

Granulomatous Reactions

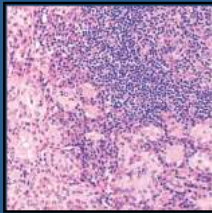
- Nonneoplastic goiter
- Hashimoto thyroiditis
- Granulomatous thyroiditis
- Systemic granulomatous ds,
 eg, sarcoidosis
- Specific infections, eg, TB, fungal
- Palpation thyroiditis
- Previous FNA biopsy
- Foreign body reactions, eg, to Teflon, suture
- Malakoplakia
- Reaction to tumors, eg, papillary CA



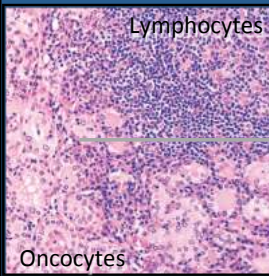
Hashimoto

Hashimoto Thyroiditis

Classic autoimmune disease
 Mid-age, white F (typical)
 Diffuse goiter, hypothyroidism
 + Antithyroid antibodies
 Dx: Lymphocytes + oncocytes
 form spectrum
 DDx: Lymphoma vs Hürthle cell neoplasm

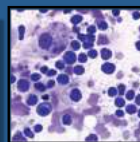
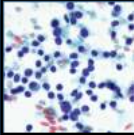
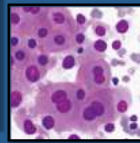
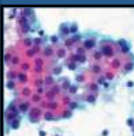


Hashimoto Thyroiditis



Lymphocytes

Oncocytes

Colloid usually scant

4 Clues to Chronic Inflammation

Plasma Cells

Lymphoid Tangles

Lymphoglandular Bodies

Lymphs→Epithelium

Papillary Carcinoma

75-80% of thyroid cancers
 Any age, mean = 45 yrs
 Bimodal 25-30, 55-60
 F > M (2-4 x)
 Prognosis usually excellent
 Except: older age, male, large (>4cm), distant mets, recurrence, aggressive types, eg, tall cell

FNA Bx: Papillary Carcinoma

Architecture	Nucleus
1. 3D papillae w/ cores	7. Grooves
2. 3D "caps" w/o cores	8. INClS
3. Monolayered sheets	9. Fine, pale chromatin
4. "Swirls"	10. Marginated nucleoli
Cytoplasm	Background
5. Squamoid	11. Psammoma bodies
6. Septate vacuoles	12. Epithelioid giant cells
	13. Gummy colloid

Papillary Carcinoma

Architecture

Nuclei

Cytoplasm

Psammoma

Giant Cell

3 Best Clues

1. Papillae
2. Nuclear grooves or inclusions
3. Squamoid cytoplasm

Variants of Papillary Carcinoma

Follicular	Tall cell
Macrofollicular	Columnar cell
Encapsulated	Solid
Hürthle cell (oncocyctic)	Cribriform-morular
Warthin-like	Dedifferentiated
Diffuse sclerosing	Also: microcarcinoma

Some Variants of PTC

Follicular

Hürthle

Tall Cell

"Adenoid Cystic"

Cribriform

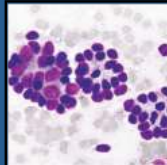
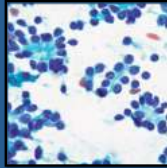
Morular

Poorly Differentiated Carcinoma

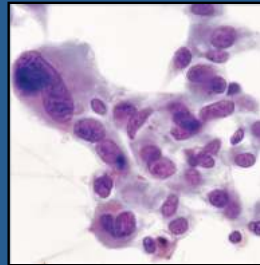
Insular and Non-Insular types

1. Solid/trabecular/insular growth patterns
2. No PTC nuclear features
3. At least one of:
 - a. Convoluted nuclei
 - b. ↑ Mitotic activity
 - c. Necrosis

TG, TTF-1 (+); Calcitonin (-)



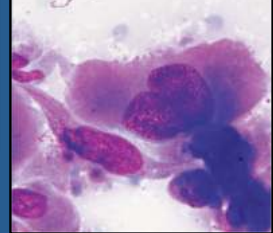
Anaplastic Carcinoma



"Ugly Cells"
Think Anaplastic CA,
exclude metastasis

Recent rapid growth
in long standing nodule
in elderly patient

Spindle, giant, or epithelioid cells

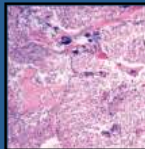


Medullary Carcinoma

Malignant tumor with C cell
neuroendocrine differentiation
Thyroid nodule + ↑ serum calcitonin

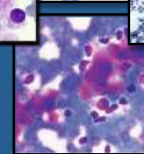
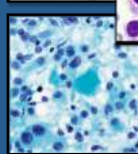
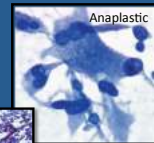
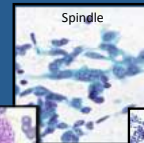
- 75% sporadic: solitary nodule
- 25% familial: bilateral, younger pt

Associated with RET mutations
"The Great Mimicker"
Follicular, Follicular/parafollicular, Oncocytic (Hürthle cell), Clear cell, Papillary, Small cell, Spindle cell, Giant cell (anaplastic) variants



Medullary Carcinoma

Carcinoid + Amyloid



ICC: Calcitonin

When you don't know...
think medullary carcinoma!

Follicular Lesions...



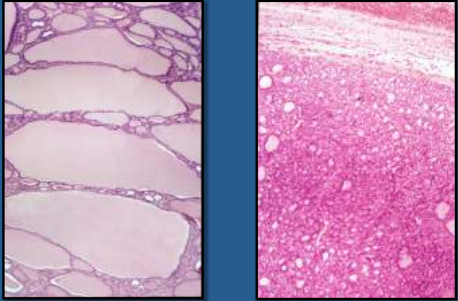
...the *problem diagnosis*

Follicular Lesions

- Goiter
Nonneoplastic
- Follicular Neoplasms
Adenoma
Carcinoma
- Follicular Variant PTC


All more/less encapsulated
nodules of follicles

Goiter vs Neoplasm



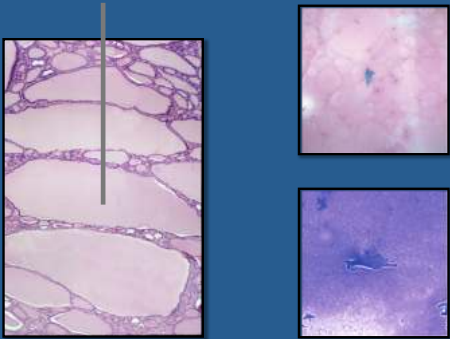
~Never Follicular CA Could be Follicular CA

This is so cool...

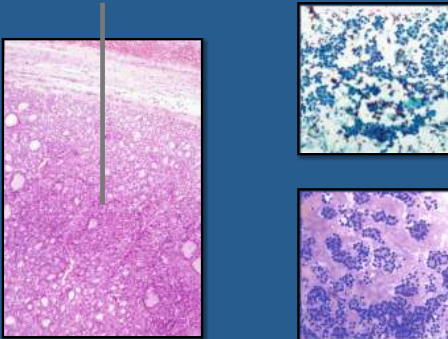


FNA biopsy can predict follicle size!

Macronodules



Micronodules



Clues to Diagnosis

More *colloid*
...more likely *benign*

More *cells*
...more likely *neoplastic*

Colloid vs Cells

	Colloid	Cells
Very low risk of malignancy		15%-30% risk of malignancy
Zone I	Zone II	Zone III
Colloid Nodule (BTN)	Cellular Nodule (FLUS)	Follicular Nodule (SFN)

Benign Thyroid Nodule Follicular Lesion of Undetermined Significance Follicular Neoplasm

3 Steps: Follicular Lesion Dx

1. Colloid vs Cells
2. Refine distinction
3. Exclude Papillary CA

1. Colloid vs Cells*

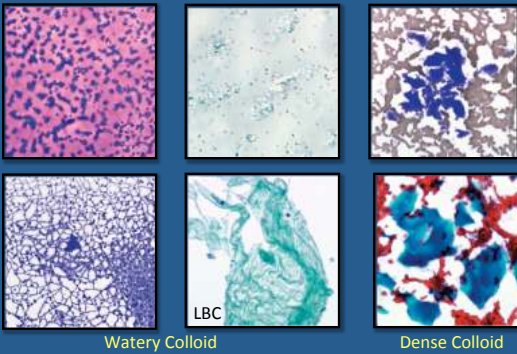
Zone I: Colloid nodule
Colloid \gg Cells

Zone II: Cellular nodule
Colloid \approx Cells

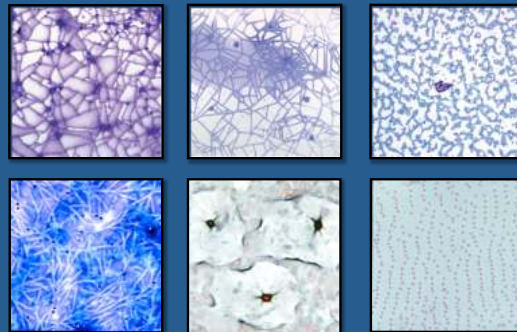
Zone III: Follicular nodule
Cells \gg Colloid

**LBC concentrates cells, loses colloid*

Colloid



Fun with colloid

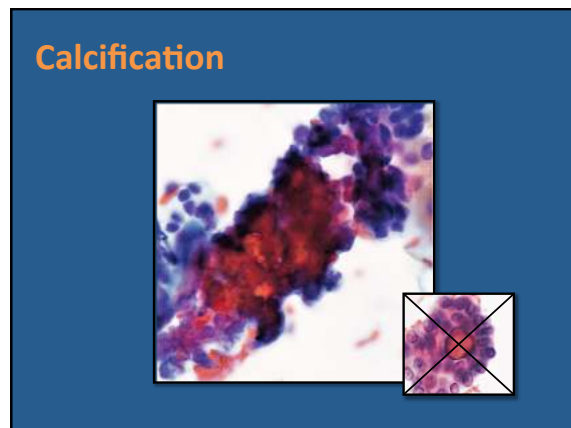
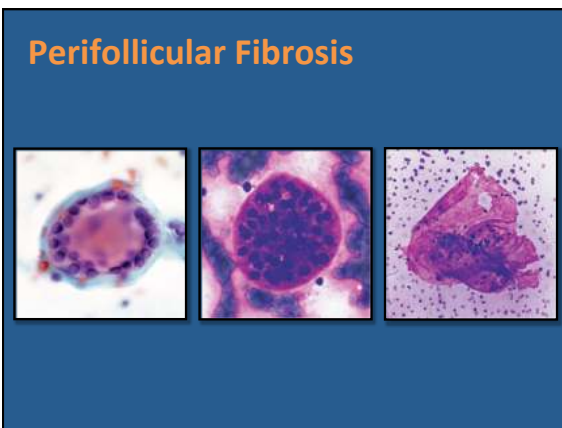
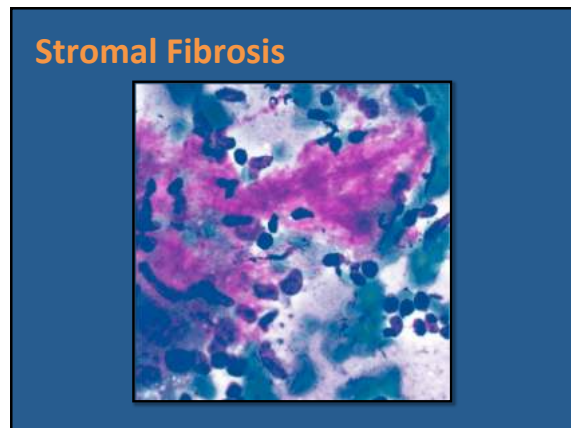
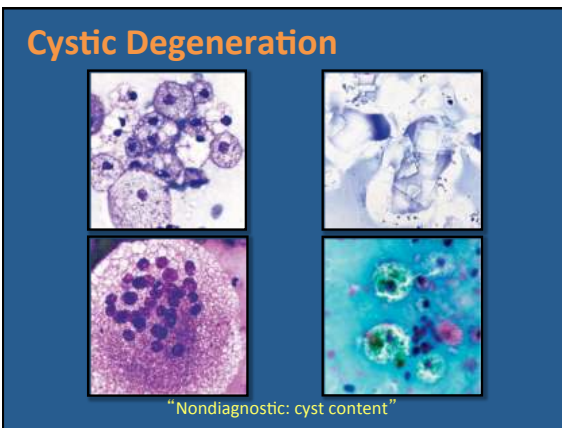
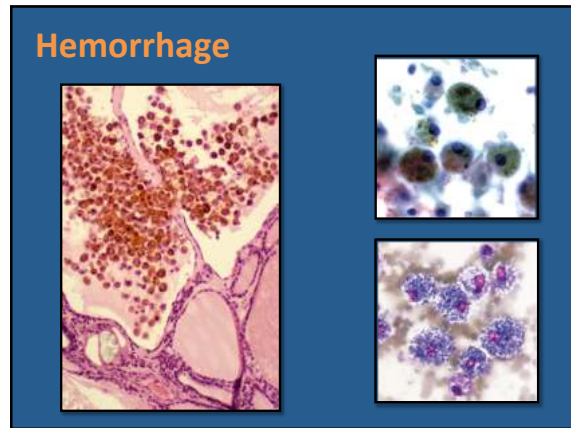
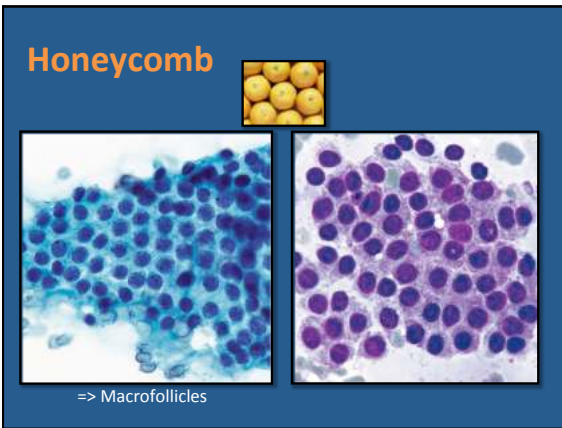


2. Refine distinction

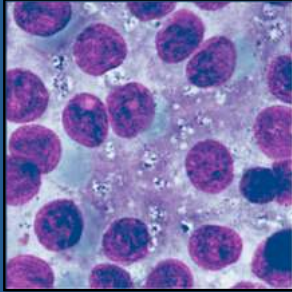
- Clues to goiter
- Clues to neoplasm
- Clues to carcinoma

Clues to Goiter

- Fewer cells, more colloid
- Degeneration, Regeneration
Hemorrhage, Fibrosis, Cysts (foam cells, macrophages, cholesterol), Calcification
Atypical epithelium (WARD cells)
- Variable cells and cell types
- Wide range follicle size
- Honeycomb sheets

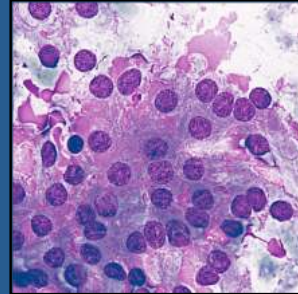


Paravacuolar Granules



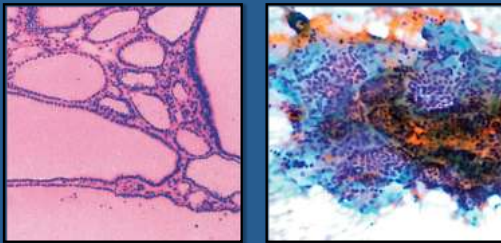
Hemosiderin, Lipofuscin

Flame Cells, Hurthle Cells, etc

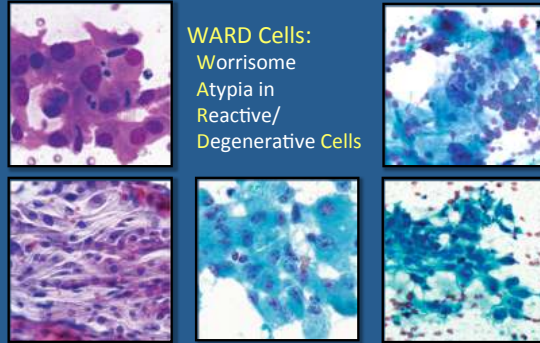


Flame Cells

Range of Follicle Size



WARD Cells: Atypical Epithelium



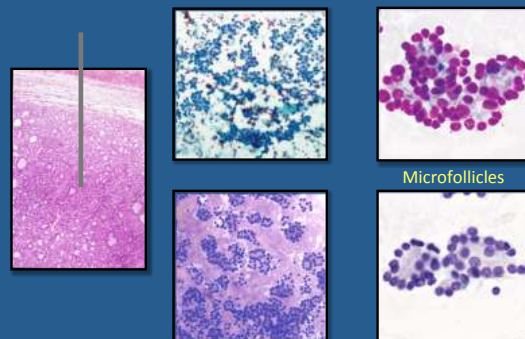
WARD Cells:
Worrisome
Atypia in
Reactive/
Degenerative Cells

Often Line Cysts

Clues to Neoplasm

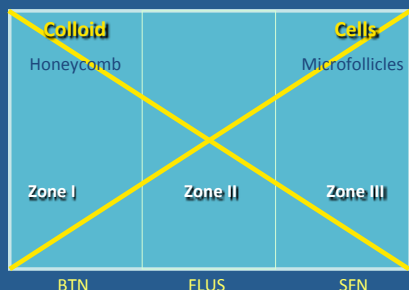
- High cellularity/scant colloid
- Microfollicular pattern
- Nuclei: Uniform, ± enlarged
- Chromatin: May be coarse
- Nucleoli infrequent
- Atypical epithelium (WARD cells)
- usually correlates with goiter!

Clues to Neoplasm



Microfollicles

Follicular Lesions



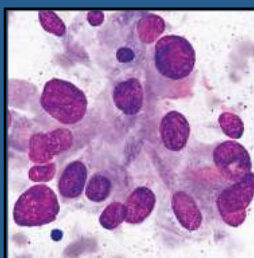
Clues to Follicular CA

Marked...

- **Architectural Abnormality**
 - Crowded, 3D groups
 - Irregular microfollicles
 - Increased single cells
- **Cytologic Atypia**
 - Nuclear Enlargement
 - Pleomorphism
 - Abnormal chromatin
 - Prominent or multiple nucleoli
 - Mitosis (atypical); Necrosis

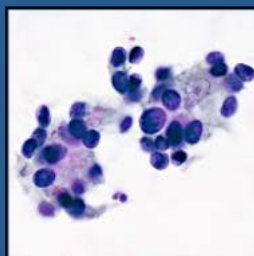
Increases risk of malignancy!

Follicular Carcinoma



Cytologic Atypia

Distorted Follicles

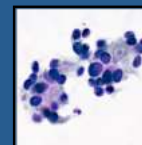
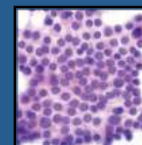


Atypia correlates with invasion!

Follicular Carcinoma

Two Forms...

- **Minimally invasive**
 - Minimally atypical →
 - Minimally malignant
- **Frankly invasive**
 - Frankly atypical →
 - Frankly malignant



3. Exclude Papillary CA

No matter what zone,
look at nuclei to exclude PTC
(colloid is irrelevant!)

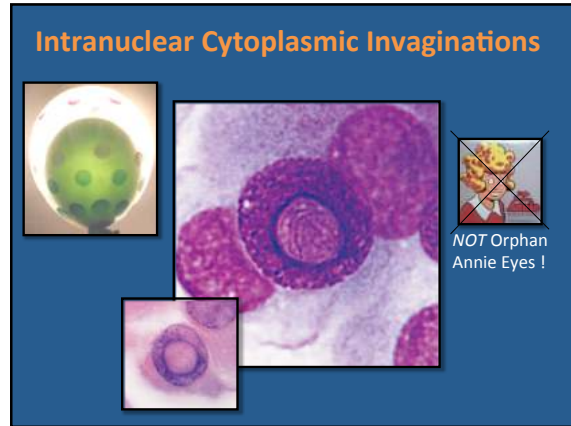
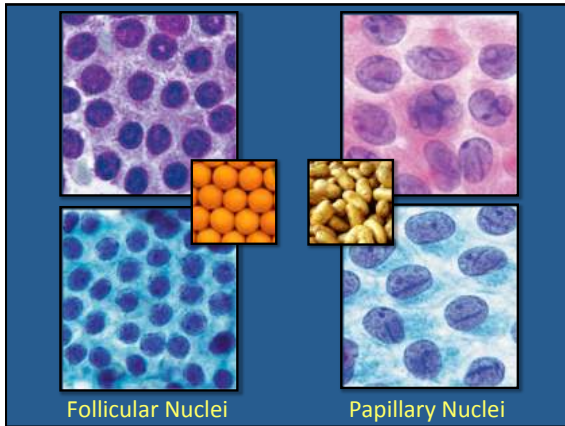
Follicular Variant PTC

Nuclear features key:

- Nuclear grooves (extensive)
- Intranuclear Inclusions (even 1)

Other: Powdery chromatin,
Marginated nucleoli
Papillae, squamoid cytoplasm,
psammoma bodies, etc

Oranges vs Potatoes



Intranuclear Cytoplasmic Invaginations (INCIs)

99/100 Malignant; 9/10 PTC

Fewer INCIs, stricter criteria
 If debatable: *Not* diagnostic
 Often cluster, but if numerous, probably bubble artifact
 Search→epiphany: Zen of Cytology

Advanced Thyroid Cytology

- Hürthle cell lesions
- Riedel thyroiditis
- Poorly differentiated carcinoma
- Hyalinizing trabecular neoplasms
- Hematologic malignancies
- Metastases
- Graves disease
- Therapeutic effects
- Dyshormonogenetic goiter
- Pregnancy

Hürthle Cell Lesions

Mixed Bag of Lesions

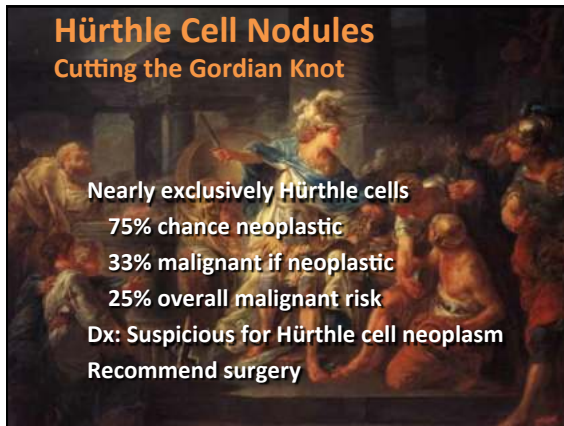
Metaplastic Change

- Normal (↑ age)
- Goiters
- Thyroiditis
- Adenomas
- Carcinomas

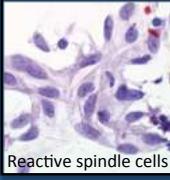
Favors Nonneoplastic: Colloid, Inflammation, Honeycomb Sheets vs Favors Neoplastic: Microfollicles, Diffuse atypia, High N/C, PTC features

Hürthle Cell Nodules Cutting the Gordian Knot

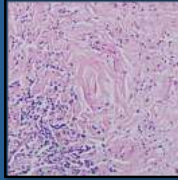
Nearly exclusively Hürthle cells
 75% chance neoplastic
 33% malignant if neoplastic
 25% overall malignant risk
 Dx: Suspicious for Hürthle cell neoplasm
 Recommend surgery




Riedel Thyroiditis



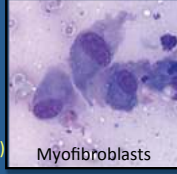
Reactive spindle cells



Myofibroblast



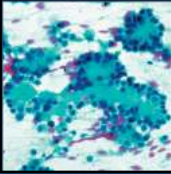
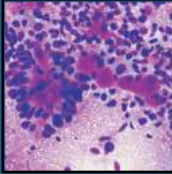
Glassy Fiber



Myofibroblasts

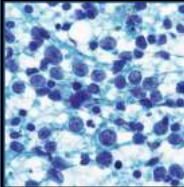
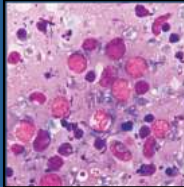
Very rare, F>M
 IgG4 sclerosing dz, EBV?
 Painless, nontender
 Woody hard, infiltrative
 FNA Bx: Scant, unsat?
 DDx: Fibrosing Hashimoto
 (hypothyroid, ↑↑↑ autoAb)

Hyalinizing Trabecular Neoplasms

Unique entity vs PTC vs Others?
 Nuclei: Like PTC, numerous INCIs
 Cytoplasm: Hyaline bodies, no NSGs
 Bkgrnd: Hyaline material, ± Psammomas
 DDx: PTC, Medullary CA
 Thyroglobulin (+), Calcitonin (-)

Hematologic Malignancies

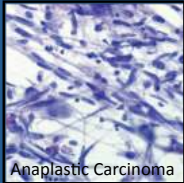
Sudden growth in Hashimoto thyroiditis

- Diffuse large B cell (easier to dx)
- MALTomas (harder to dx)
- Other lymphomas rare

DDx: Florid lymphoid phase Hashimoto
 TGFF: Thank god for flow (cytometry)

Thyroid Sarcomas

Primary sarcomas:
 Extremely rare
 Liposarcoma
 Leiomyosarcoma
 Angiosarcoma



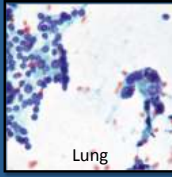
Anaplastic Carcinoma

DDx: Most "sarcomas" = anaplastic CA*


*Both TG and CK can be (-) in anaplastic CA

Metastases

Not rare, but rarely dx in past
 FNA Bx → antemortem dx
 Most pts have known history
 Grave prognostic sign
 Often PD, unlike most 1°'s
 Kidney, lung, breast, GI;
 melanoma; lymphoma
 DDx: Primary thyroid lesion



Lung



Kidney

Graves Disease

Autoimmune disease related to Hashimoto thyroiditis

Dx: Clinical and lab findings

FNA biopsy:

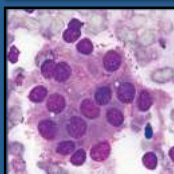
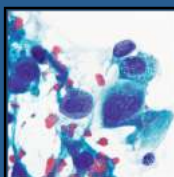
High cellularity

Pale watery colloid

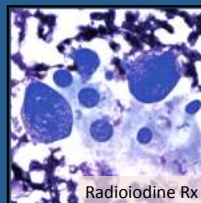
Flame and Hürthle cells

Inflammation, granulomas

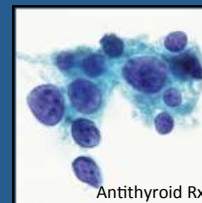
± Therapy atypia



Therapeutic Effects



Radioiodine Rx



Antithyroid Rx

Radiation or antithyroid Rx

→ marked cytologic atypia

Pearl: Random atypia, degeneration

Clinical history crucial in diagnosis!

Dyshormonogenetic Goiter

Congenital hypothyroidism

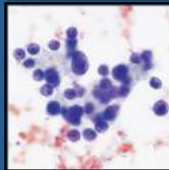
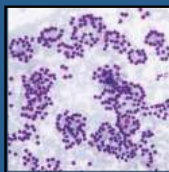
Autosomal recessive

Enzyme defects in hormone synthesis → goiter

FNA: High cellularity, atypia, microfollicles, scant colloid

Mimics neoplasm, may favor CA

Actual malignant change rare!



Pregnancy

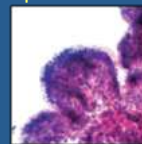
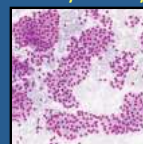
Iodine lost in urine → thyroid hyperplasia

FNA Biopsy:

High cellularity

Watery colloid

Flame cells



Papillary hyperplasia may suggest PTC

Women of childbearing age at risk of PTC

Look for usual features of PTC to dx:

Nuclear grooves, INCI, etc, etc

Molecular Diagnosis

Genetic Alteration	PTC	FTC	PDTC	ATC
RAS	15%	45%	30%	30%
BRAF	50%	0	15%	20%
RET/PTC	33%	0	10%	0
PAX8/PPAR γ	<5% (FVPTC)	50%	0	0
p53	<5%	5%	25%	70%
β -catenin	0	0	25%	65%

Final Thoughts

FNA Bx of a thyroid nodule is benign
...until proven otherwise!

Most thyroid nodules, by far, are benign

Most are benign colloid nodules

Most can be diagnosed by cytology

Most malignant nodules, by far, are PTCs

Most PTCs can be diagnosed by cytology

Therefore:

As a first approximation:
FNA biopsy of thyroid is either
Papillary Carcinoma* or Benign**



*Or other easily recognized cancer

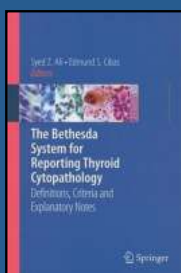
**Most follicular lesions are benign
(goiter, thyroiditis, adenomas: FTC is rare)

A confusion of
tongues...



The Bethesda System

The Bethesda System



Indications for FNA biopsy
Pre-FNA requirements
Training/credentialing
Techniques for FNA biopsy
Specimen adequacy
Diagnostic terminology
Ancillary studies
Post-FNA testing/treatment

Report Format: 6 Tiered System

Diagnosis	Cancer Risk	Management
I. Nondiagnostic	NA	Rpt w/ US
II. Benign	<3%	Follow Clinically
III. AUS ACUS, FLUS	5%-15%	Rpt FNA
IV. Follicular Neoplasm*	20%-30%	Surgery
V. Suspicious	60%-75%	Surgery
VI. Malignant	97%-99%	Surgery

*Specify if Hürthle Cell type

I. Non-Diagnostic

Sparse or degenerated cells
Cyst content (no epithelial cells)
Other (eg, obscured, clotted)

Adequacy

6 groups of ≥ 10 well prepared,
well visualized follicular cells

Exceptions:
Thick colloid (Benign)
Thyroiditis (Benign)
Any atypia

II. Benign

Colloid nodular disease

- Colloid nodule
- Hyperplastic/adenomatoid nodule
- Macrofollicular adenoma

Thyroiditis

- Acute thyroiditis
- Hashimoto thyroiditis

III. Atypia of Undetermined Significance (AUS)

Atypical Cells of Undetermined Significance (ACUS) Cytologic atypia

Follicular Lesion of Undetermined Significance (FLUS) Architectural atypia

Not convincingly benign, but not sufficient for more definitive diagnosis

Risk malignancy: 5% to 15%

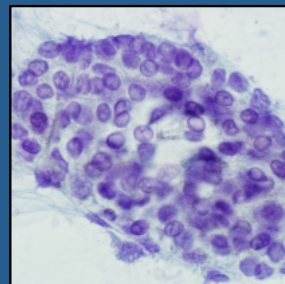
AUS: Diagnostic Uncertainty

Microfollicles, Hürthle cells, cyst lining cells, Rx atypia, or focal features of PTC

Eg, prominent microfollicles or Hürthle cells, but low overall cellularity

Compromised specimens common eg, low cellularity, poor fixation, obscuring blood, excessive clotting

AUS due to poor fixation



R/O Papillary Carcinoma

IV. (Suspicious for) Follicular Neoplasm*

*Specify if Hürthle cell type

Follicular patterned lesions *lacking* nuclear features of PTC

Risk malignancy: 15% to 30%

Notes:

1. Up to 35% non-neoplastic
2. Of malignancies, up to 68% = PTC

V. Suspicious for Malignancy

Suspicious for specific cancer, eg, PTC

Patchy/incomplete nuclear features

Suspicious due to lesion necrosis, eg, ATC

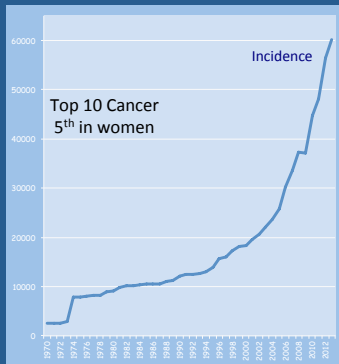
Risk malignancy: 60% to 75%

VI. Malignant

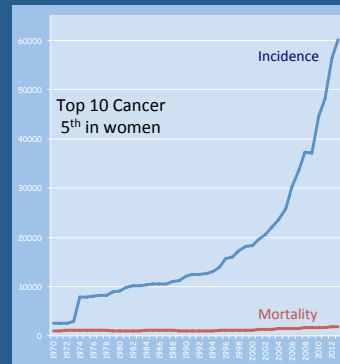
Diagnostic of malignancy
Specify type if possible
Risk malignancy: 97%-99%

You've got cancer !!!

Thyroid Cancer Epidemic



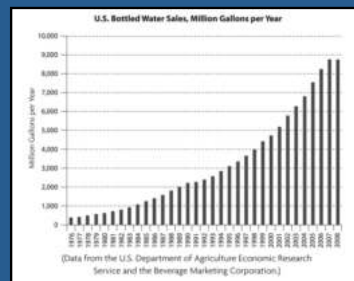
Thyroid Cancer Epidemic



True increase?

1. Environmental carcinogens
2. Environmental radiation
3. Other factors, eg, obesity

Bottled Water Consumption



Plastics have estrogen-like compounds;
may disrupt thyroid endocrine function

Or something else?

1. Advances in diagnostic imaging
 - Detects more abnormalities
2. Increased histologic sectioning
 - Detects incidental micro PTCs
 - Detects more invasion (FAd→FCA)
3. More liberal diagnostic criteria
 - Increased diagnosis of cancer

You' ve got cancer!!!

Up to 100% of adults have thyroid "cancer"

Harach HR et al:
Occult Papillary Carcinoma of the Thyroid

Cancer 56: 531-538, 1985

You' ve got cancer!!!

Up to 100% of adults have thyroid "cancer"

Harach HR et al:
Occult Papillary Carcinoma of the Thyroid:
A 'Normal' Finding in Finland.
Cancer 56: 531-538, 1985

Thank you

All images copyright ASCP Press