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Faculty/Presenter Disclosure

Faculty: Blair Walker

Relationship with commercial interest

- No industry ties
- No off label therapeutics
- No management bias

Rapid Update Thyroid Cytopathology/ Pathology for Surgeons (in 20 min!)

- Bethesda update and NIFTP
- AJCC 8th edition

NIFTP = Noninvasive follicular thyroid neoplasm with papillary-like nuclear features

Bethesda revisited
House keeping

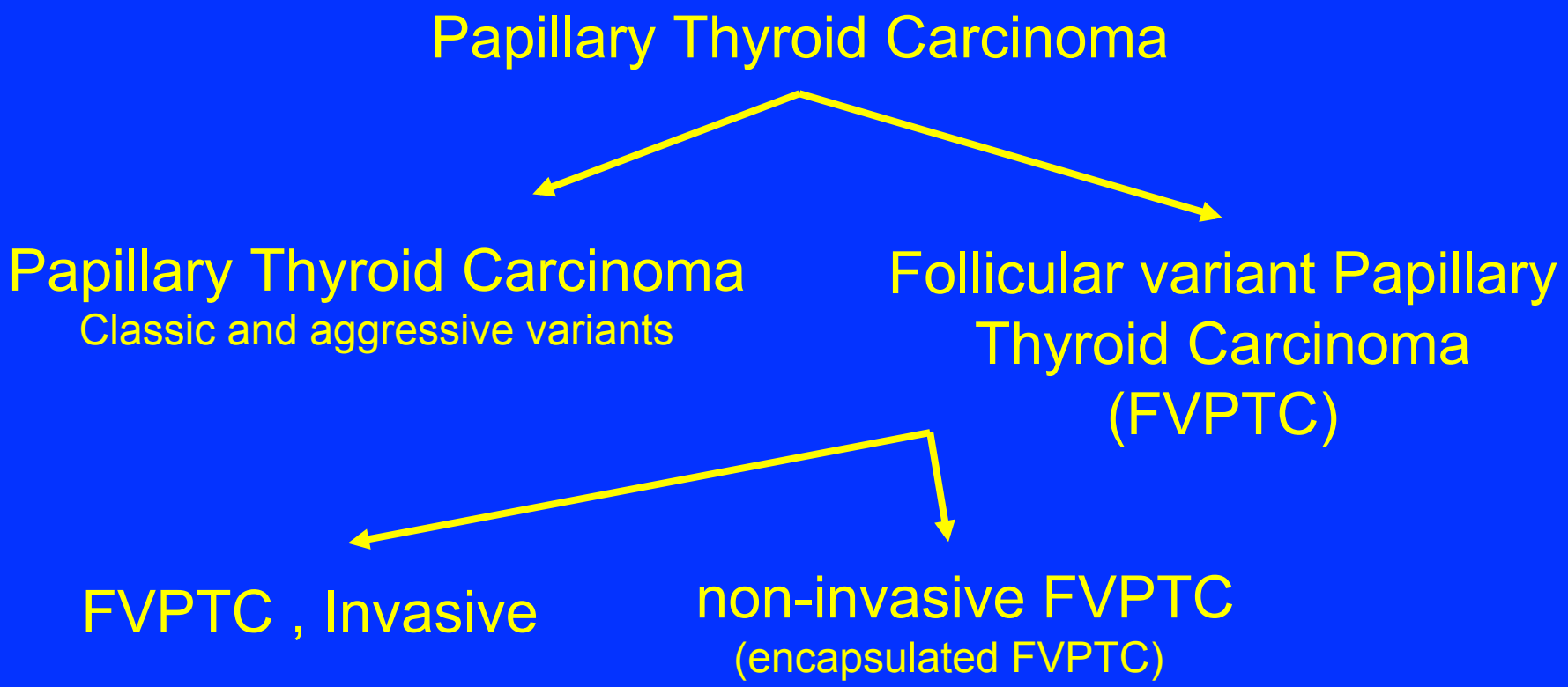
- Number should have names (Bethesda II-benign)
- AUS = FLUS (not different diagnosis)
- Cyst fluid only is unsatisfactory
- Repeat FNA don’t need to wait 3 months

Bethesda update and NIFTP
Bethesda revisited

The 2017 Bethesda System for Reporting Thyroid Cytopathology Edmund S. Cibas1 and Syed Z. Ali
THYROID Volume 27, Number 11, 2017

Bethesda revisited
Diagnostic considerations

- Hurthle cell nodules could be signed out as AUS based on clinical features or Hashimoto's
- Consideration of NIFTP as non-malignant surgical disease
  - Risk of malignancy reduced
  - Recommendation that "malignant" diagnosis is reserved for classic PTC


Papillary Thyroid Carcinoma
Papillary Thyroid Carcinoma
Classic and aggressive variants
Follicular variant Papillary Thyroid Carcinoma (FVPTC)
FVPTC , Invasive
non-invasive FVPTC
(encapsulated FVPTC)

FVPTC , Invasive

non-invasive FVPTC
(encapsulated FVPTC)

encapsulated FVPTC

More aggressive “papillary” features:

- Papillary architecture
- Psammoma bodies
- Infiltrative border
- High mitotic rate
- Aggressive variant subtypes

NIFTP

(noninvasive follicular thyroid neoplasms with papillary-like nuclear features)

Defined tumor with favorable outcome

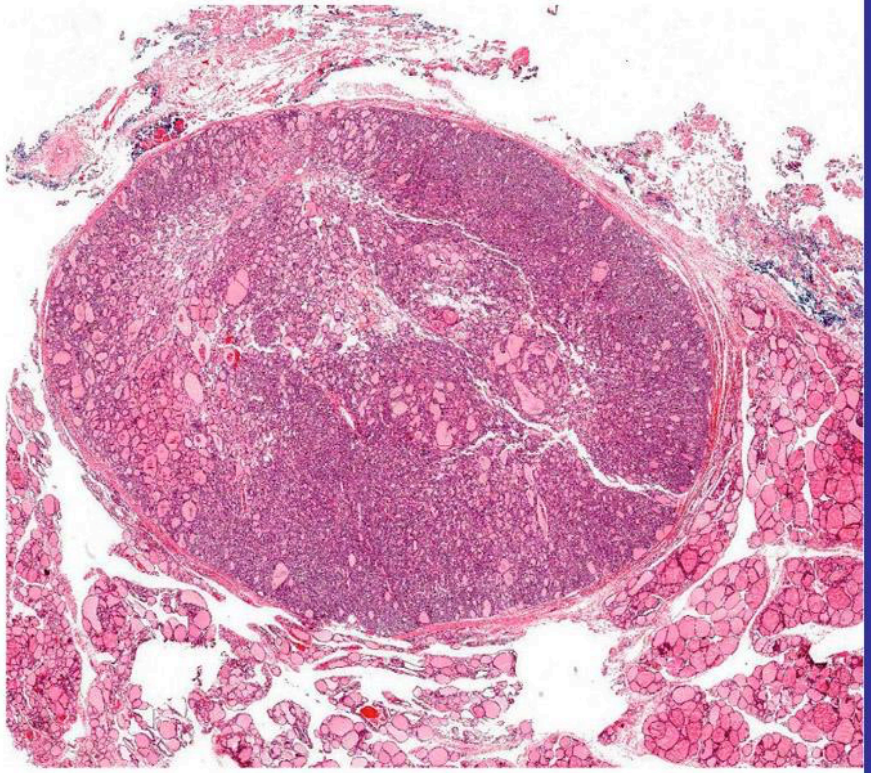
NIFTP

- Diagnosis excludes papillary or aggressive features
- Needs entire lesion submitted

- Defines a tumor with low (not zero) risk of metastasis
- Definition enriches for tumors with RAS mutations (like follicular carcinoma) rather than BRAF mutations (like classic PTC)

It's Not Cancer: Doctors Reclassify a Thyroid Tumor

The New York Times



A noninvasive follicular thyroid neoplasm with papillary-like nuclear features, or Niftp, a type of tumor that was previously considered a kind of cancer, but has been downgraded by a panel of doctors. Yuri Nikiforov

Dr. Gregory W. Randolph, director of the thyroid and parathyroid surgical clinic at Harvard's Massachusetts Eye and Ear Infirmary.

They finally settled on NIFTP, in part because its acronym, which he pronounced "Nift-P," was catchy, he said.

The new name, the reclassification, he added, is "just awesome," because it explicitly defines those small nodules in the thyroid as **nonmalignant**.

Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift

"a very low risk of adverse outcome when the tumor is noninvasive"

"this lesion entails a very low risk of adverse outcome and therefore should not be termed cancer"

"Furthermore, tumors analyzed in this study also recapitulate the FA to FTC sequence of progression with the capacity for invasion, suggesting that NIFTP likely represents the "benign" counterpart or precursor of the invasive EFVPTC"

"Following the conference, a statement from a number of participants emphasized the need to revise terminology, replacing the word "cancer" when data emerge to support a more indolent designation."

NIFTP

Lloyd RV, Asa SL, LiVolsi VA, Sadow PM, Tischler AS, Ghossein RA, Tuttle RM, Nikiforov YE.The evolving diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)? Human Pathology 74, April 2018, Pages 1-4

"Although the Nikiforov publication indicated that a NIFTP diagnosis had a low risk of adverse outcome, this statement has been misinterpreted by some investigators to conclude that they are benign tumors

Parente D et al	2.1% nodal mets (one distant)
Cho U, et al.	3% nodal mets

Parente D, Kluijfhout WP, Bongers PJ, et al. World J Surg 2017;8(42):321-6.
Cho U, Mete O, Kim MH, et al. Mod Pathol 2017;30:810-25.

Take away #1

- NIFTP are low risk but not benign

NIFTP experience at SPH 2010-2015

- Of all cases signed out as PTC (n=175), 7 were likely NIFTP (4%)
- Additional 4 cases in “false positives” in sPTC and PTC cytology group were signed out as “atypical adenomas”
- But 301 nodules not reviewed

Reduction in Risk of malignancy when NIFTP considered benign - SPH

	ROM NIFTP=PTC	ROM NIFTP=benign	Difference pre/post NIFTP
Benign		6%	
AUS	36%	32%	4%
sFN	23%	24%	0%
sPTC	85%	78%	7%
PTC	99%	97%	2%

Bethesda revisited

- Table 2. The 2017 Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management

Diagnostic category	*Risk of malignancy if NIFTP ≠ CA (%)*	*Risk of malignancy if NIFTP = CA (%)*
Nondiagnostic or unsatisfactory	5–10	5–10
Benign	0–3	0–3
Atypia of undetermined significance or follicular lesion of undetermined significance	6–18	~10–30
Follicular neoplasm or suspicious for a follicular neoplasm	10–40	25–40
Suspicious for malignancy	45–60	50–75
Malignant	94–96	97–99

Take away #2

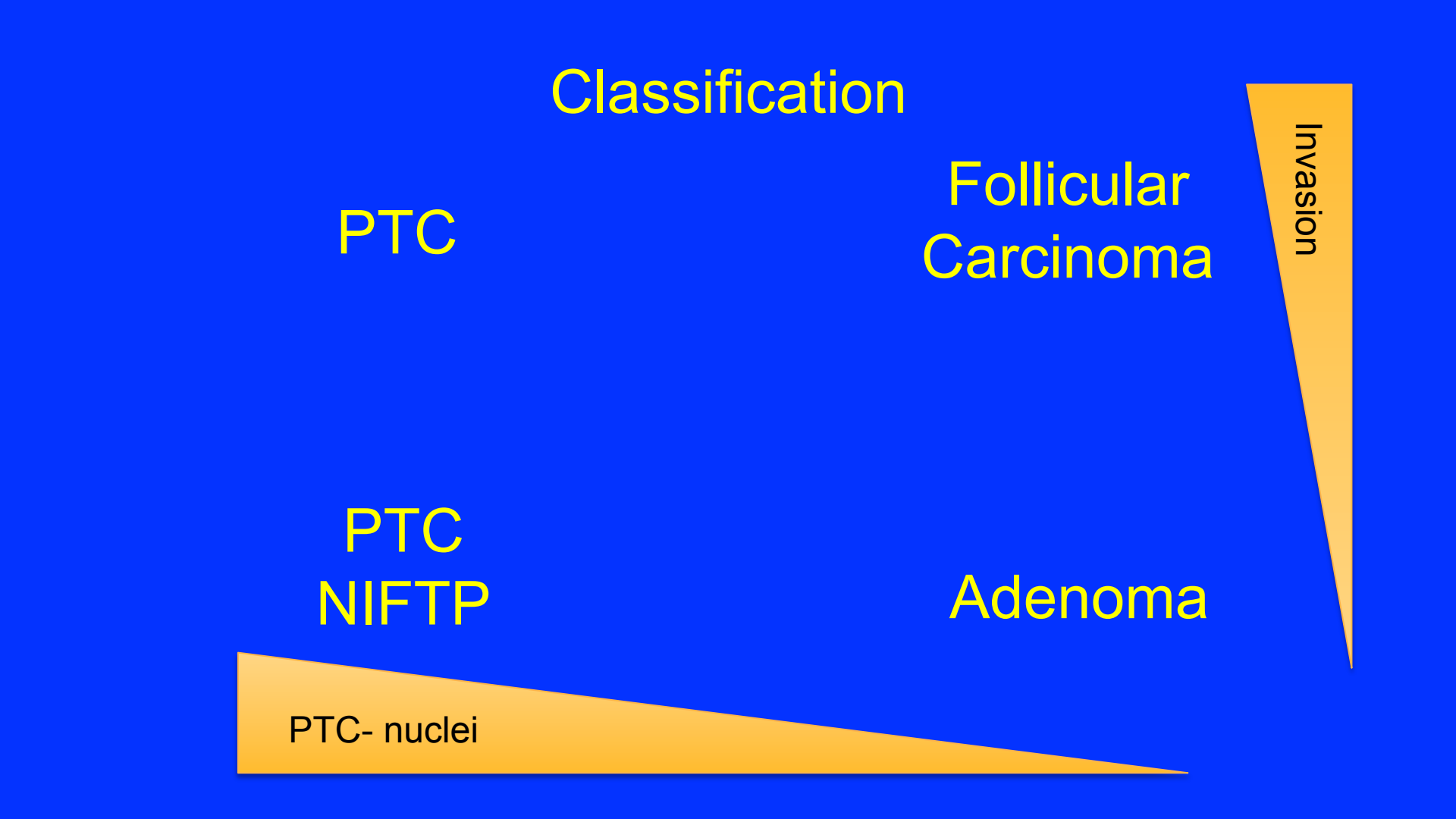
- NIFTP is not a cytologic diagnosis

Bethesda throw aways

Note: Although the architectural features suggest a follicular neoplasm, some nuclear features raise the possibility of an invasive follicular variant of papillary carcinoma or its recently described indolent counterpart, NIFTP; definitive distinction among these entities is not possible on cytologic material.

Note: The cytomorphologic features are suspicious for a follicular variant of papillary thyroid carcinoma or its recently described indolent counterpart NIFTP.

Note: A small proportion of cases (*3–4%) diagnosed as malignant and compatible with papillary thyroid carcinoma may prove to be NIFTP on histopathologic examination.


Classification
PTC
Follicular Carcinoma
PTC NIFTP
Adenoma
Invasion
PTC- nuclei

Reduction in Risk of malignancy when NIFTP considered benign - SPH

	SPH
AUS	4%
sFN	0%
sPTC	7%
PTC	2%

Reduction in Risk of malignancy when NIFTP considered benign

	SPH	Maia & Amendoeira*	Strickland et al. (2015)	Brandler et al. (2017)	Faquin et al. (2016)
AUS	4%	5%	45%	16%	13%
sFN	0%	10%	18%	36%	15%
sPTC	7%	13%	48%	32%	23%
PTC	2%	5%	5%	1%	3%

*From Endocrine-Related Cancer (2018) 25, R247–R258

Risk of malignancy - SPH

	ROM NIFTP=benign
Benign	6%
AUS	32%
sFN	24%
sPTC	78%
PTC	97%

To avoid false-positives due to NIFTP, it suggests limiting use of the malignant category to cases with “classical” features of papillary thyroid carcinoma (true papillae, psammoma bodies, and nuclear pseudoinclusions)

Take away #3 in your institution

- NIFTP reduce the risk of malignancy
- Pathologist will worry more and hedge on malignant diagnosis

Rubber meets the road - NIFTP and Bethesda Cytology

- The cytological features of NIFTP are those of PTC but more subtle
- Liquid based cytology (ThinPrep, filters) will find more than smears
- trying to separate them from PTC will reduce the sensitivity of cytology for PTC
- The real impact of NIFTP at SPH (and BC) is equivalent to noise in the system

Rubber meets the road - NIFTP and Bethesda Histology

- No one is advocating review of all possible NIFTP cases
- A review is only valid if the entire lesion is put through
- In my experience, BC has been very conservative in the recognition of “PTC-like” nuclear features and the past incidents of NIFTP in “PTC” diagnosis will in the order of 4%
- Going forward that incidence will be higher as a bin to put in borderline cases (“atypical adenomas”)

Rubber meets the road - NIFTP and Bethesda Histology

- The entire lesion (center and capsule) needs to go in
- The diagnostic criteria may be in flux and still subject to human frailty
- Because of this I would prefer “low risk of adverse outcome” vs “benign”

AJCC 8th Ed

AJCC 8 th edition

1. The age cutoff used for staging increased from 45 to 55 years of age at diagnosis.

Differentiated thyroid cancer

When age at diagnosis is…	***And T is…***	***And N is…***	***And M is…***	***Then the stage group is…***
< 55 yrs	Any T	Any N	M0	I
	Any T	Any N	M1	II

AJCC 8 th edition

1. N1 disease no longer upstages a patient to stage III.

   If <55 years of age at diagnosis, N1 disease is stage I

   If >55 years of age, N1 disease is stage II.

AJCC 8 th edition

2. Minor extrathyroidal extension detected only on histological examination was removed from the definition of T3 disease.

pT3b: Tumor of any size with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid or omohyoid muscles)

AJCC 8 th edition

2. T3 division

T3a >4 cm confined to the thyroid gland.

T3b gross extrathyroidal extension into strap muscles

AJCC 8th edition

3. Level VII lymph nodes, previously classified as lateral neck lymph nodes (N1b), were reclassified as central neck lymph nodes (N1a) to be more anatomically consistent and because level VII presented significant coding difficulties for tumor registrars, clinicians, and researchers.

4. distant metastases in older patients
is classified as stage IVB disease
rather than stage IVC disease.

The eighth edition downstages a significant number of patients by

(i) raising the age cut off from 45 to 55 years of age at diagnosis and

(ii) removing regional lymph node metastases and microscopic extrathyroidal extension from the definition of T3 disease.

AJCC 8 th edition

The eighth edition also re-emphasizes the critical importance of gross extrathyroidal extension as an unfavorable prognostic factor while minimizing the significance of minor extension through the thyroid capsule, which is identified only on histological examination.

AJCC 8 th edition

Likewise, by removing lymph node metastases and minor extrathyroidal extension from the definition of T3 disease,

A significant number of patients (45–54 years old, N1, M0) will be downstaged to stage I, and

older patients will be downstaged to either stage I (≥55 years old, minor extrathyroidal extension, N0, M0) or stage II (≥55 years old, N1, M0).

AJCC 8 th edition

2. Minor extrathyroidal extension

"Review of the surgeon's operative report is encouraged as it may also describe evident capsular invasion, gross extrathyroidal extension, and/or unresected tumor.

Information on completeness of resection is also important in determining adjuvant therapy and surveillance regimen"

CAP protocol Jan 2016

Take away #4

- To properly stage patients surgeons need to tell pathologists:

1. If there is clinically relevant extrathyroidal extension
2. Which nodes are involved

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NIFTP experience at SPH 2010-2015

If NIFTP or atypical adenoma, what was the cytology?

Bethesda	percentage	number
Benign	0%	0
AUS	36%	8
sFN	0%	0
sPTC	36%	4
PTC	27%	3

Bethesda revisited

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