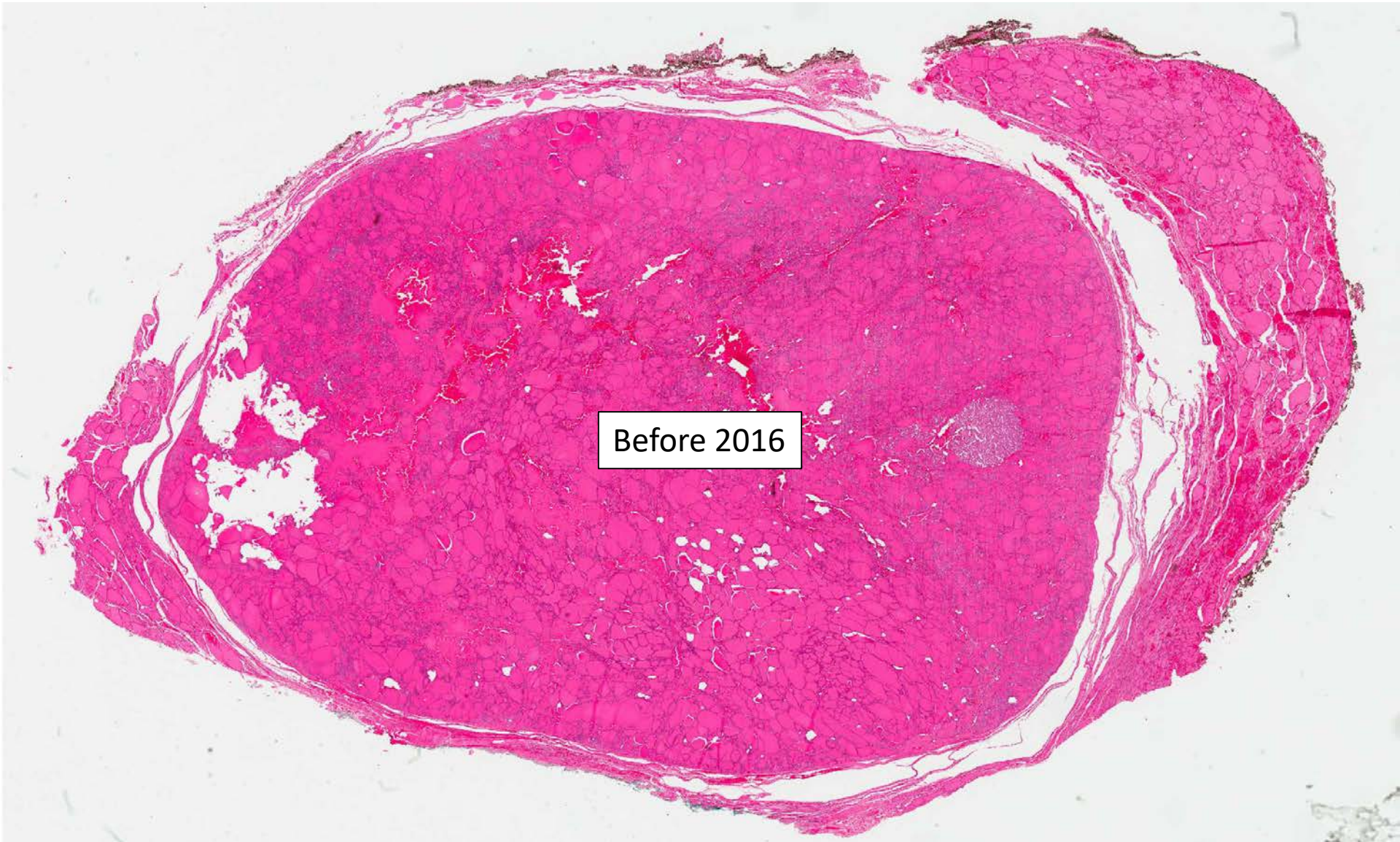
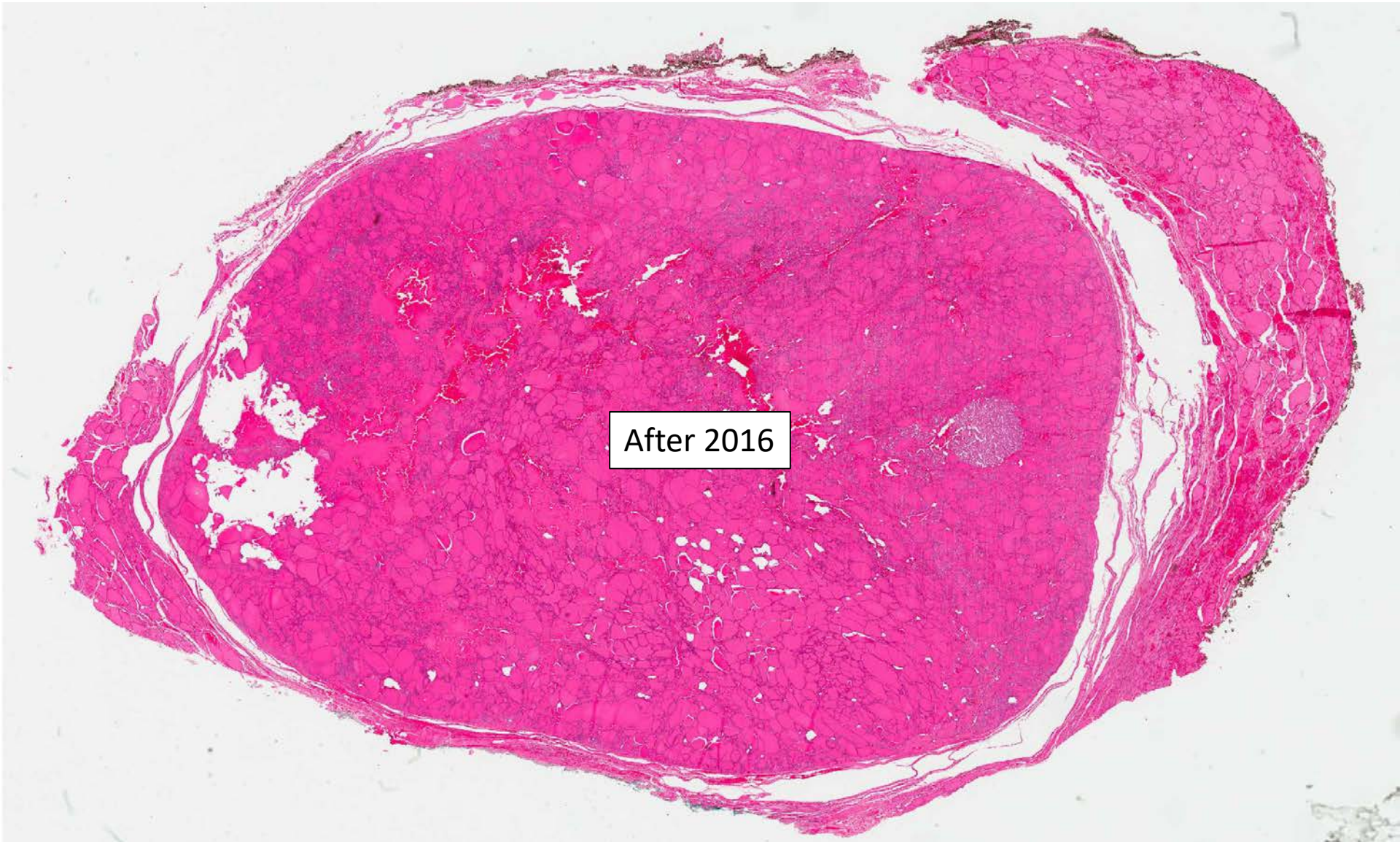
NIFTP: Histopathology of a Cytological Monkey Wrench

B. Wehrli

Non-Invasive Encapsulated Follicular Variant of Papillary Thyroid Carcinoma



Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP)

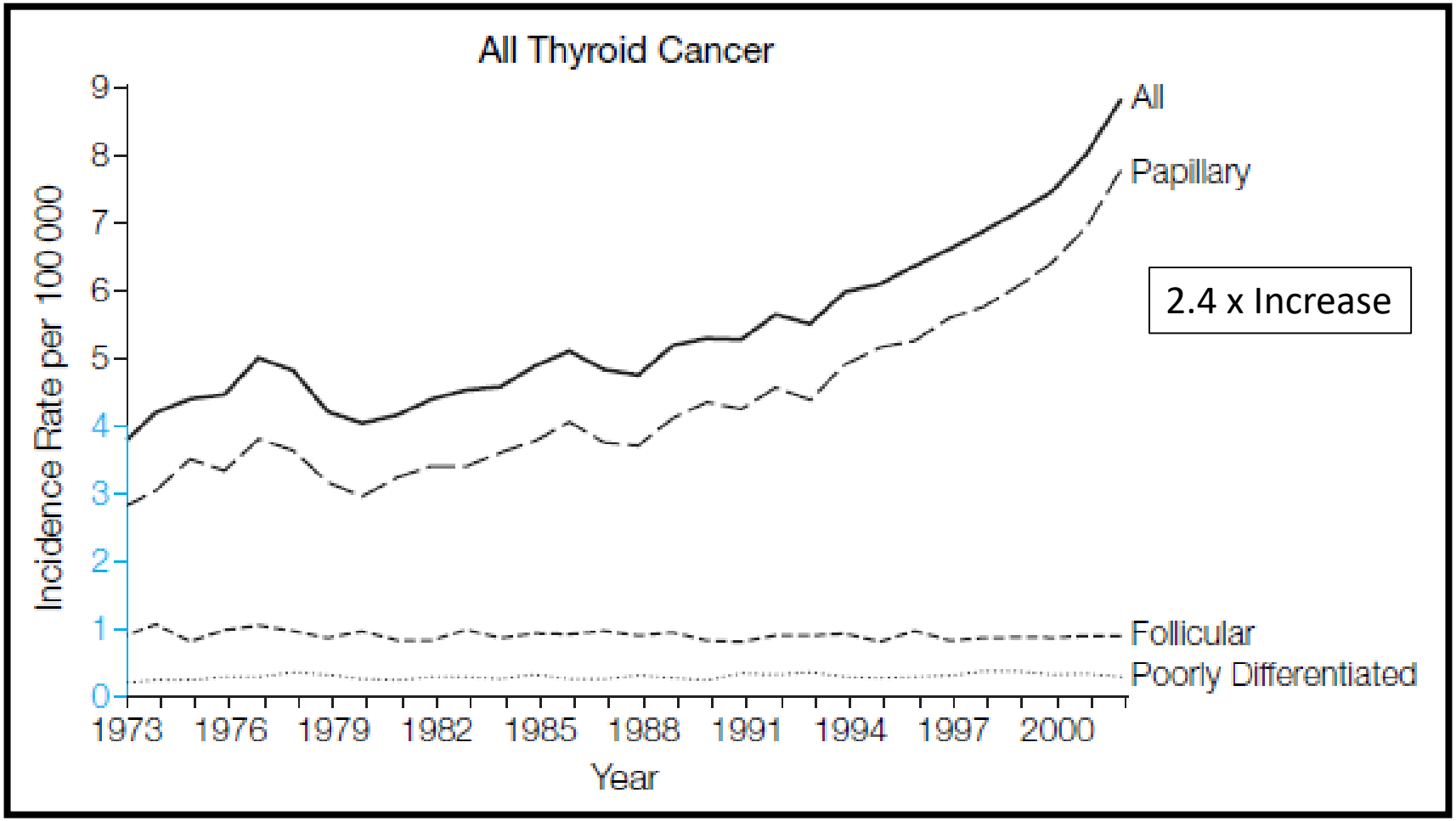


Objectives

- Review development of NIFTP
- Review histological criteria of NIFTP
- Review implications of NIFTP

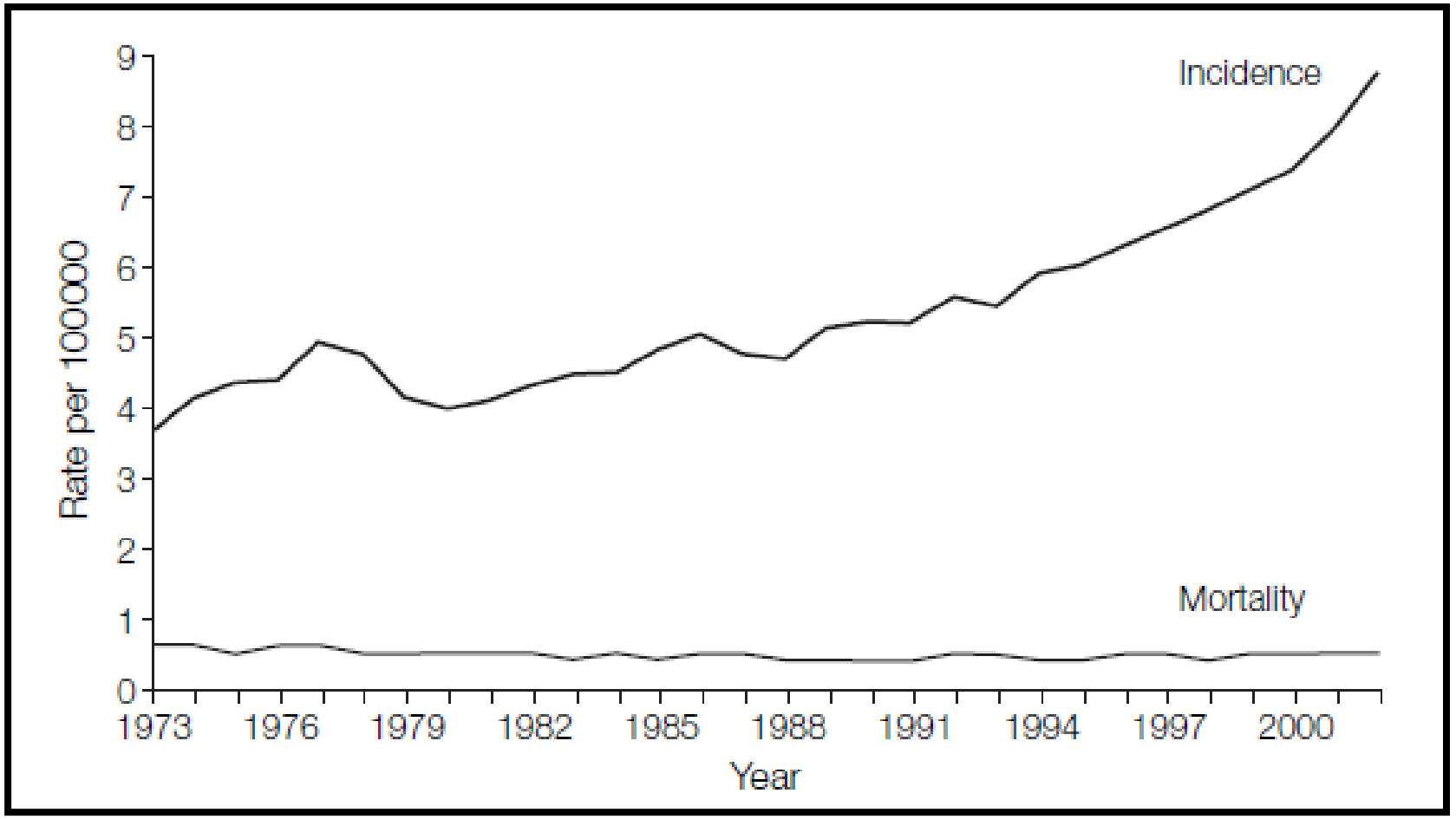
Incidence of Thyroid Cancer (1973-2002)

NCI Surveillance, Epidemiology & End Reporting



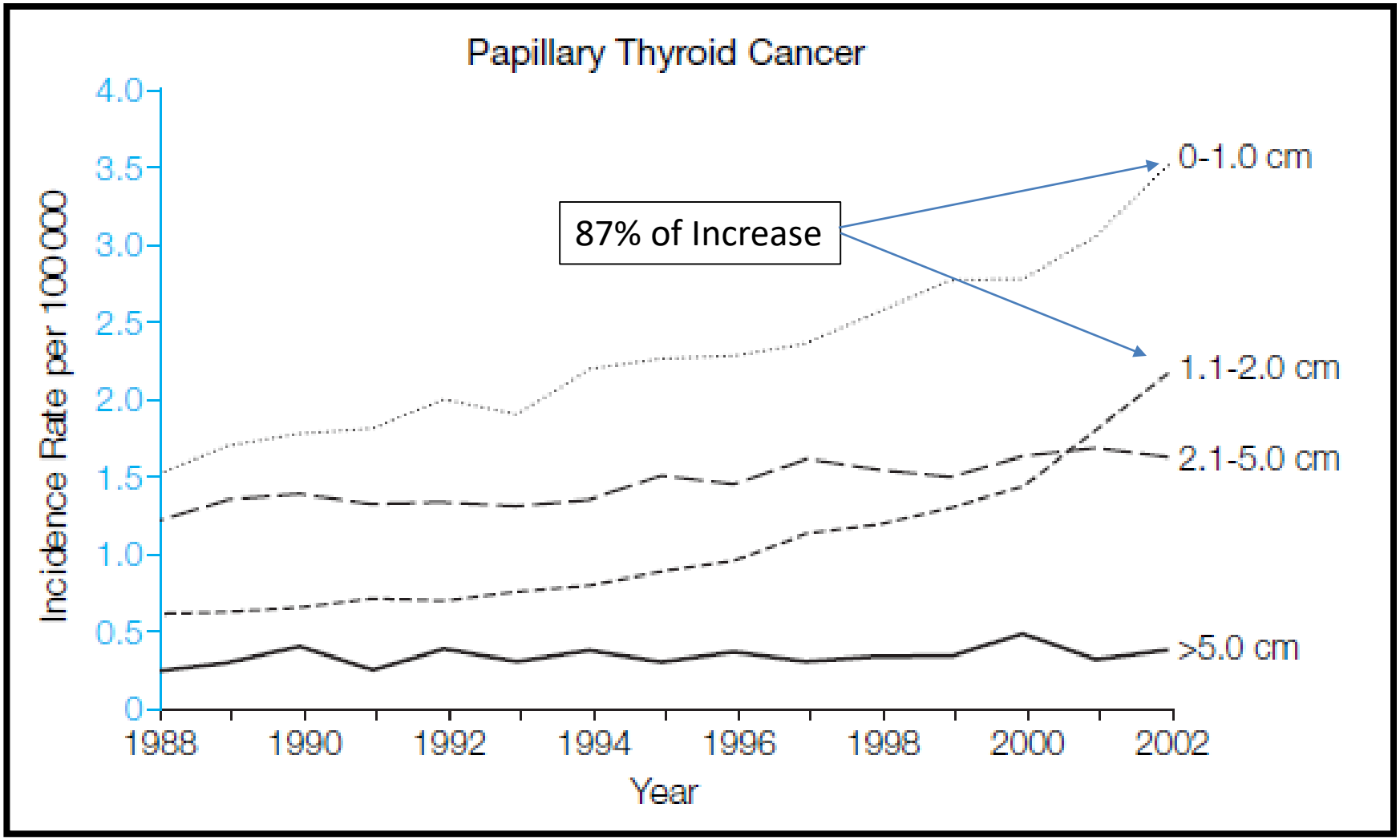
JAMA. 2006;295:2164-2167

Thyroid Cancer Incidence & Mortality (1973-2002)



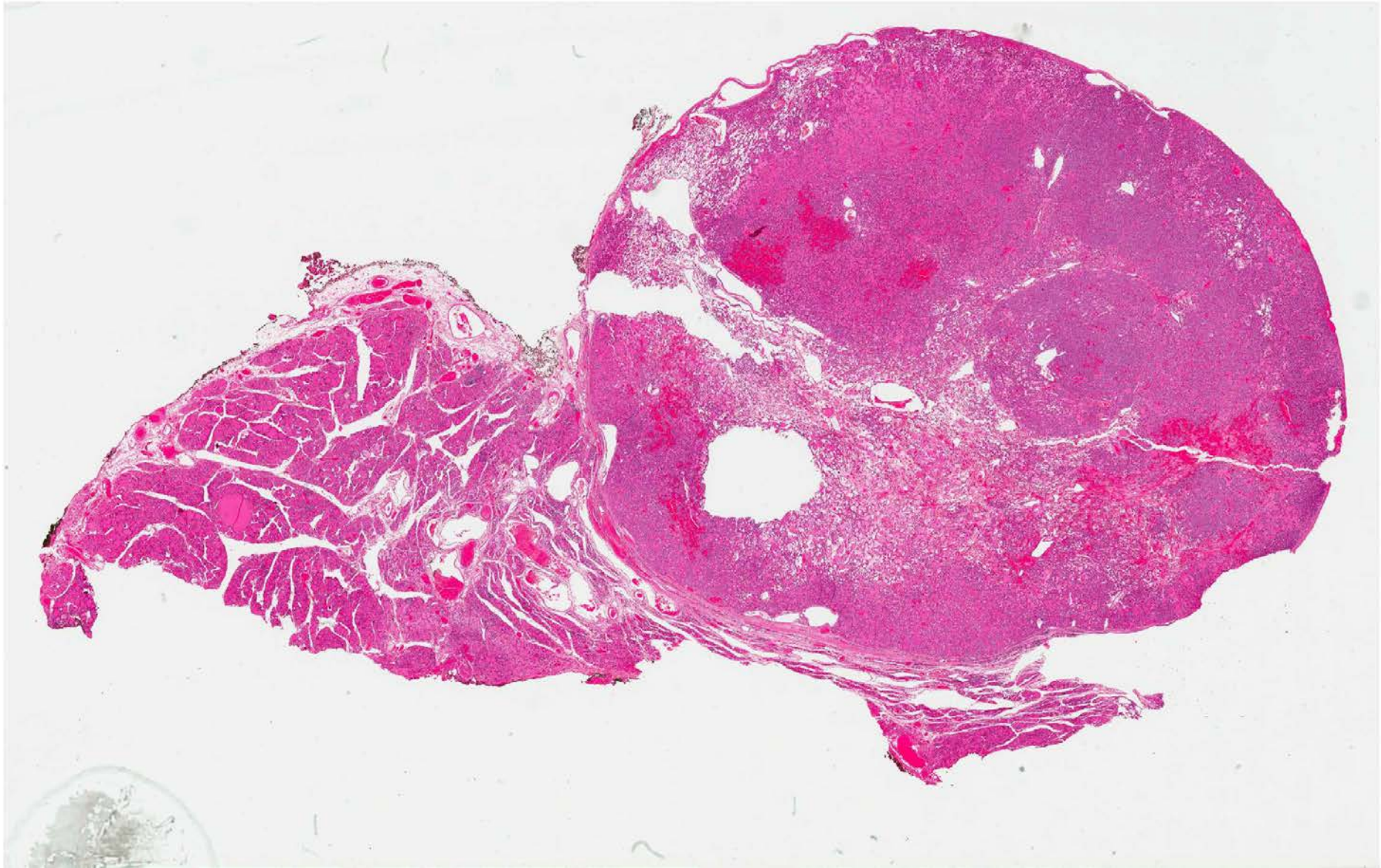
JAMA. 2006;295:2164-2167

Papillary Thyroid Cancer & Size (1988-2002)



JAMA. 2006;295:2164-2167

Papillary Thyroid Carcinoma – Follicular Variant

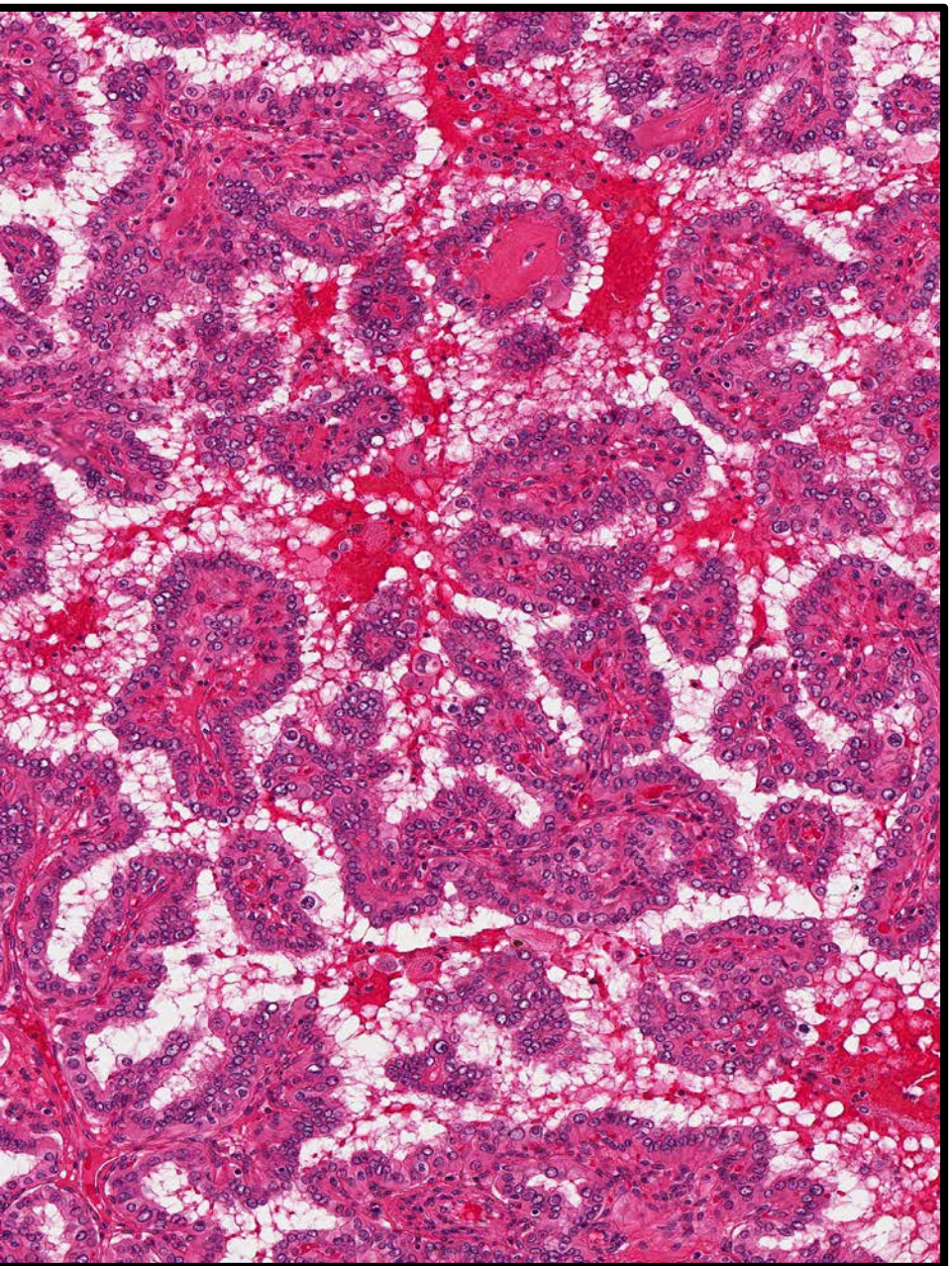


Prevalence of FVPTC at Different Time Intervals

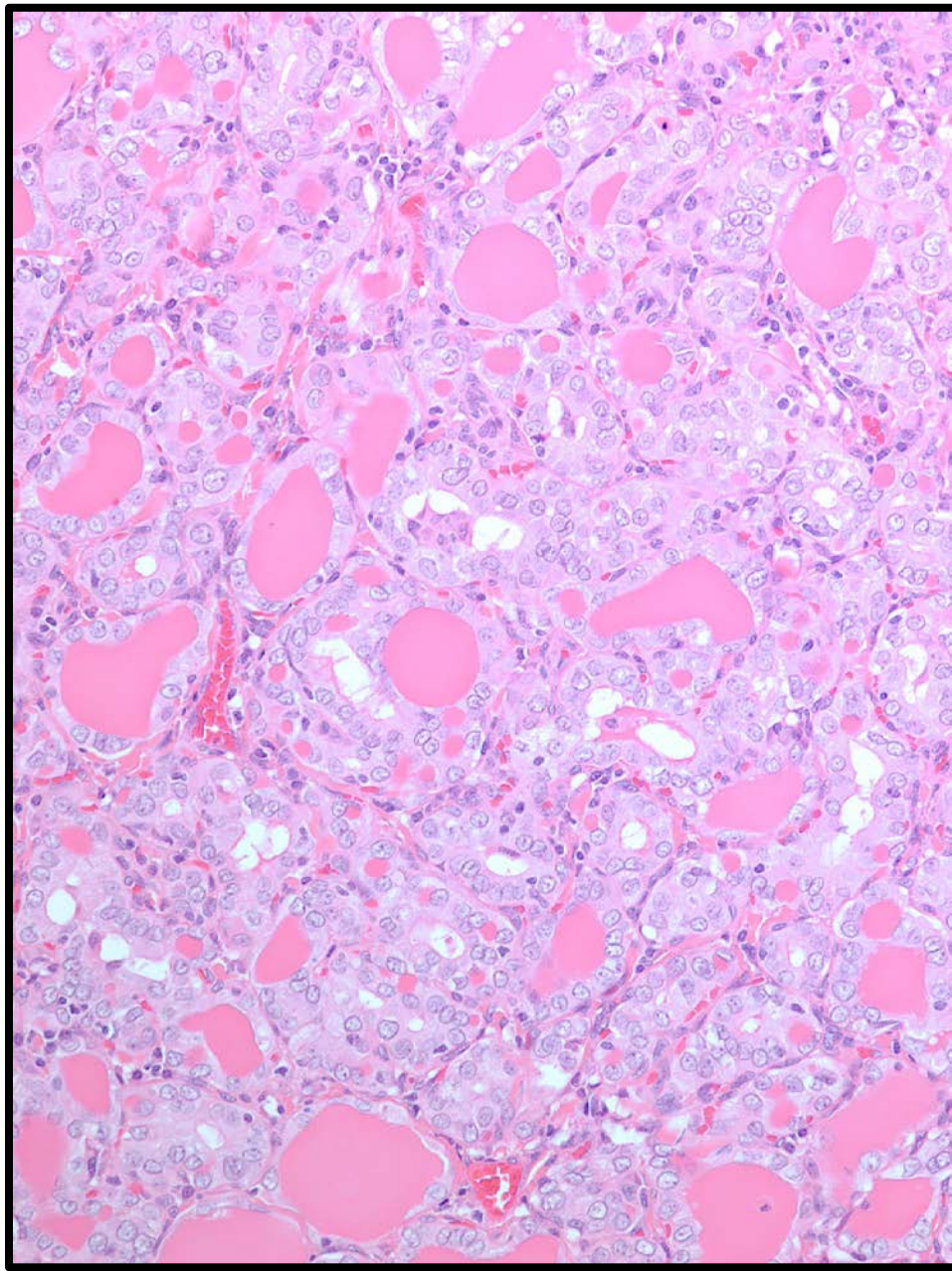
Source	Setting/ Location	Time interval	Total number of PTC	FVPTC (% of all PTC)
Chan KJ et al., *J Clin Endocrinol Metab* 99:E276-E285, 2014	University of Pittsburgh, PA, USA	1974-1992	186	8.1%
		2009	230	25.2%
Lupi et al., *J Clin Endocrinol Metab* 92:4085-4090, 2007	University of Pisa, Pisa, Italy	2006	500	22.8%
R. Ghossein, *unpublished*	MSKCC, New York, USA	1977-1999	615	20.0%
		2000-2003	303	27.7%

JAMA Oncol 2016 Aug 1;2(8):1023-9

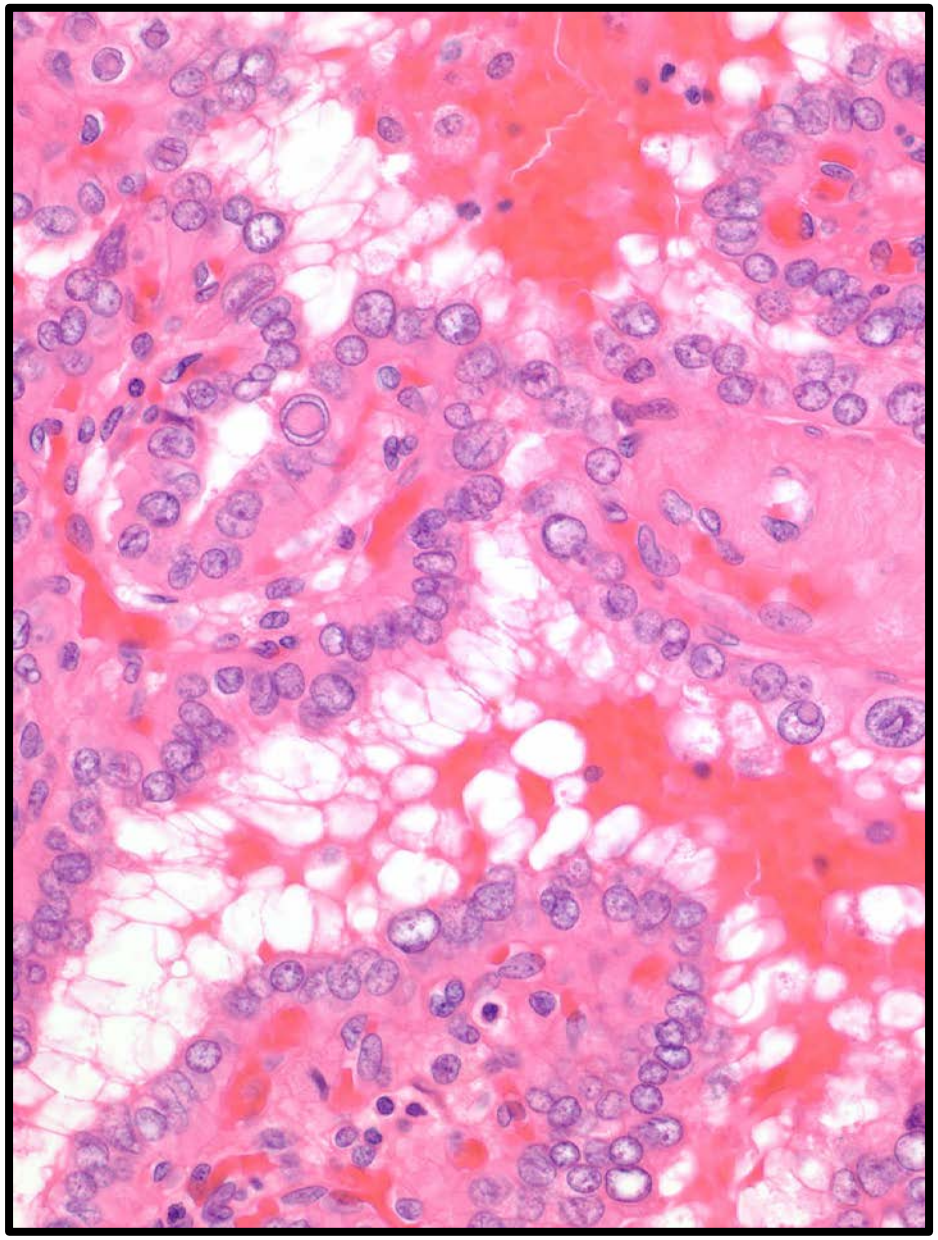
Classic PTC (CPTC)



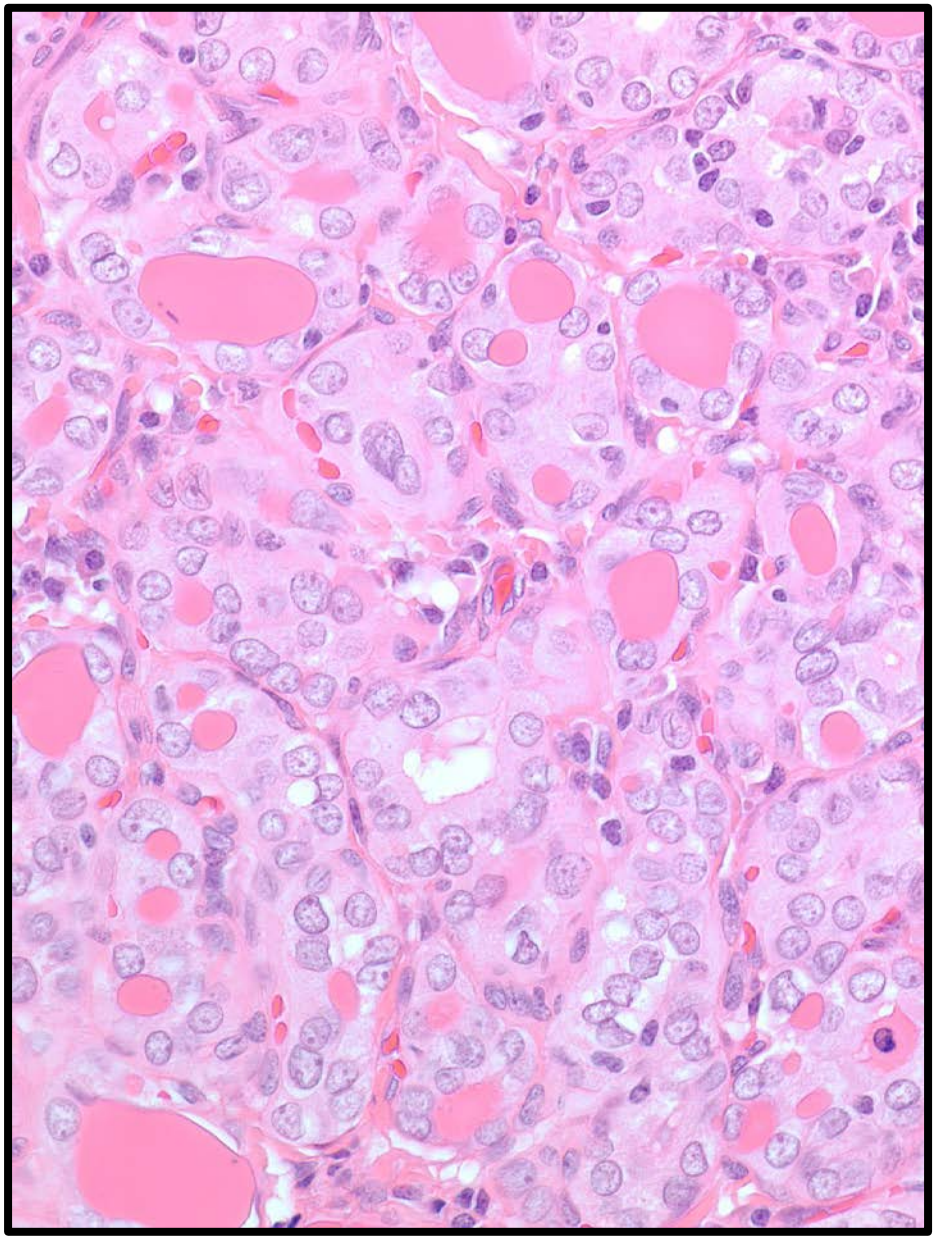
Follicular Variant PTC (FVPTC)



Classic PTC (CPTC)

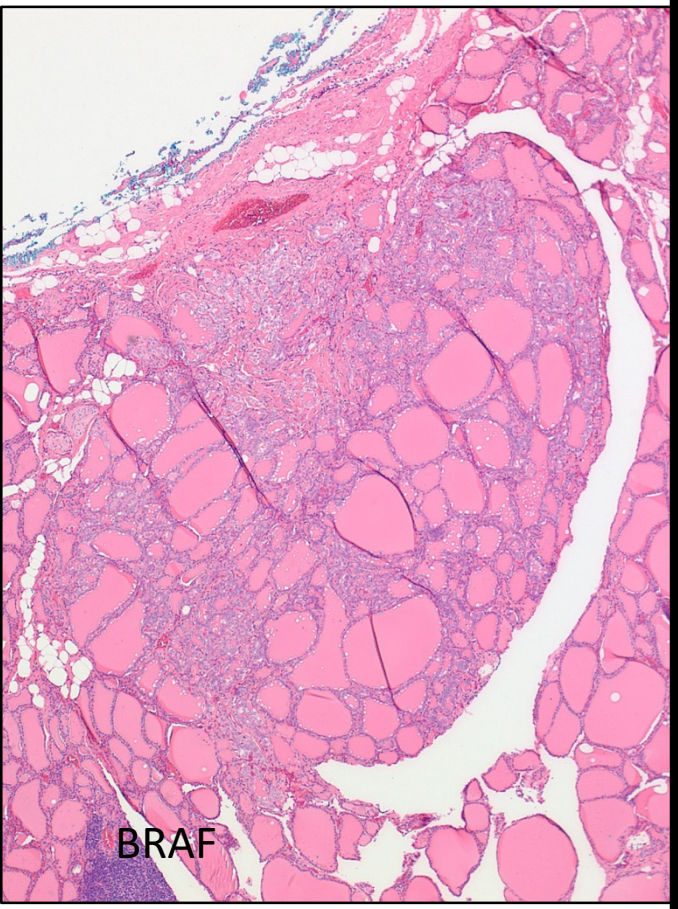


Follicular Variant PTC (FVPTC)

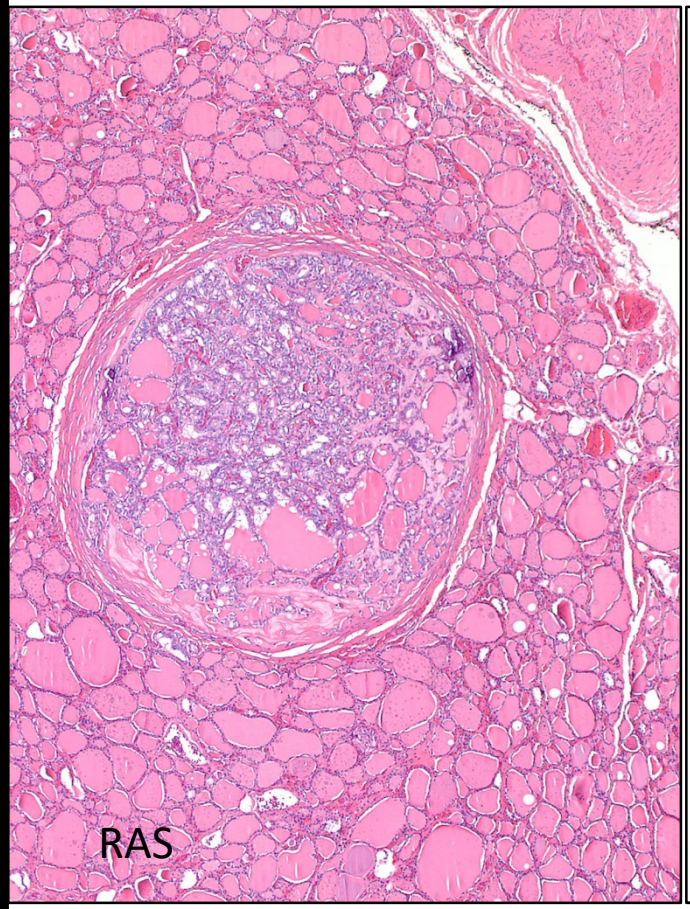


Follicular Variant PTC - Subtypes

Infiltrative/Non-encapsulated

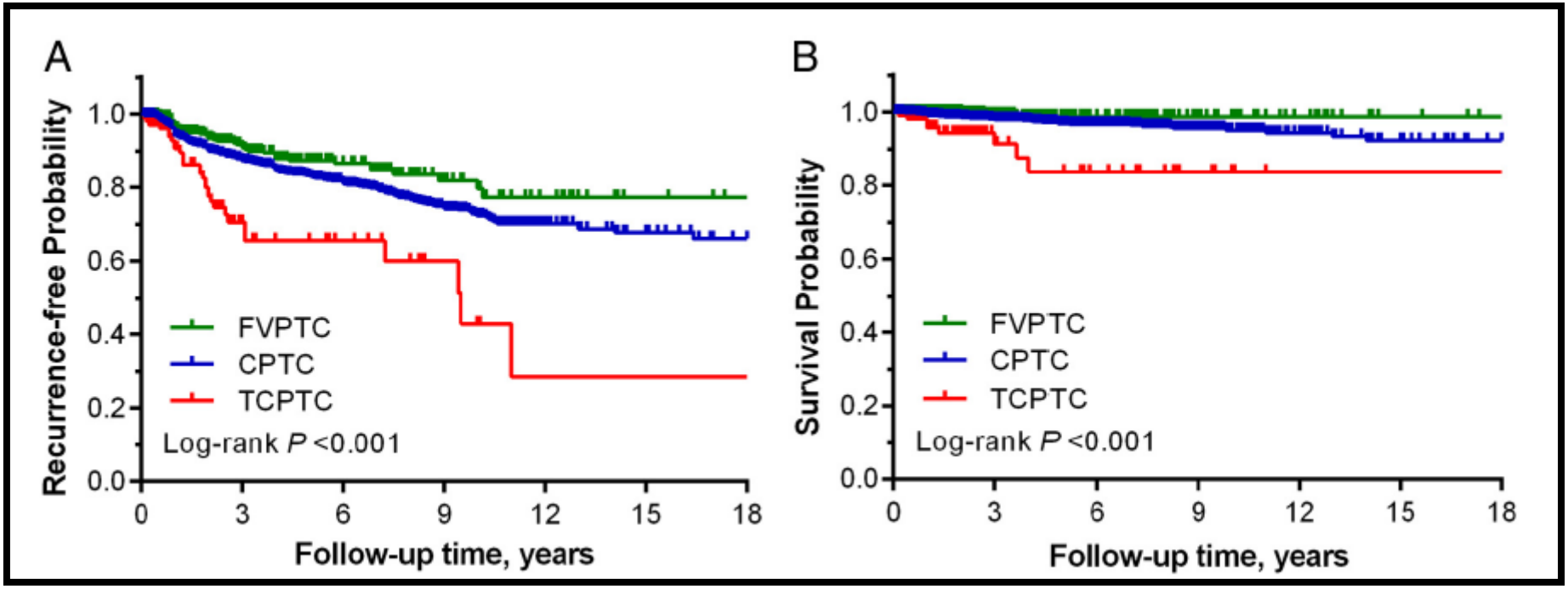


Encapsulated/Well-circumscribed with Capsular and/or Vascular Invasion



Encapsulated/Well-circumscribed without Capsular and Vascular Invasion

Recurrence-Free & Survival Probability of Patients with FVPTC, CPTC, TCPTC



n=6282

J Clin Endocrinol Metab 101:264-274, 2016

Addressing overdiagnosis and overtreatment in cancer: a prescription for change

Laura J Esserman, Ian M Thompson, Brian Reid, Peter Nelson, David F Ransohoff, H Gilbert Welch, Shelley Hwang, Donald A Berry, Kenneth W Kinzler, William C Black, Mina Bissell, Howard Parnes, Sudhir Srivastava

***Panel*: Consensus of the working group recommendations regarding overdiagnosis and overtreatment presented to the National Cancer Institute**

2 Embrace the development of new terminology to replace the word cancer when appropriate, when data or companion diagnostics support the classification of low-risk lesions as indolent lesions of epithelial origin (IDLEs)

3 Create observational registries for IDLEs and disorders with low or uncertain risk of progression to cancer

4 Mitigate overdiagnosis by testing strategies that lower the chance of detecting unimportant lesions

5 Embrace new concepts for how to approach cancer progression and prevention

Lancet Oncol. 2014 May;15(6):e234-42

Question Do clinical outcomes of noninvasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) warrant reclassification of this tumor as nonmalignant?

DESIGN, SETTING, AND PARTICIPANTS International, multidisciplinary, retrospective study of patients with thyroid nodules diagnosed as EFVPTC, including 109 patients with noninvasive EFVPTC observed for 10 to 26 years and 101 patients with invasive EFVPTC observed for 1 to 18 years. Review of digitized histologic slides collected at 13 sites in 5 countries by 24 thyroid pathologists from 7 countries. A series of teleconferences and a face-to-face conference were used to establish consensus diagnostic criteria and develop new nomenclature.

OBJECTIVE To evaluate clinical outcomes, refine diagnostic criteria, and develop a nomenclature that appropriately reflects the biological and clinical characteristics of EFVPTC.

JAMA Oncol 2016 Aug 1;2(8):1023-9

Selection Criteria for Study Cohorts and Case Contribution

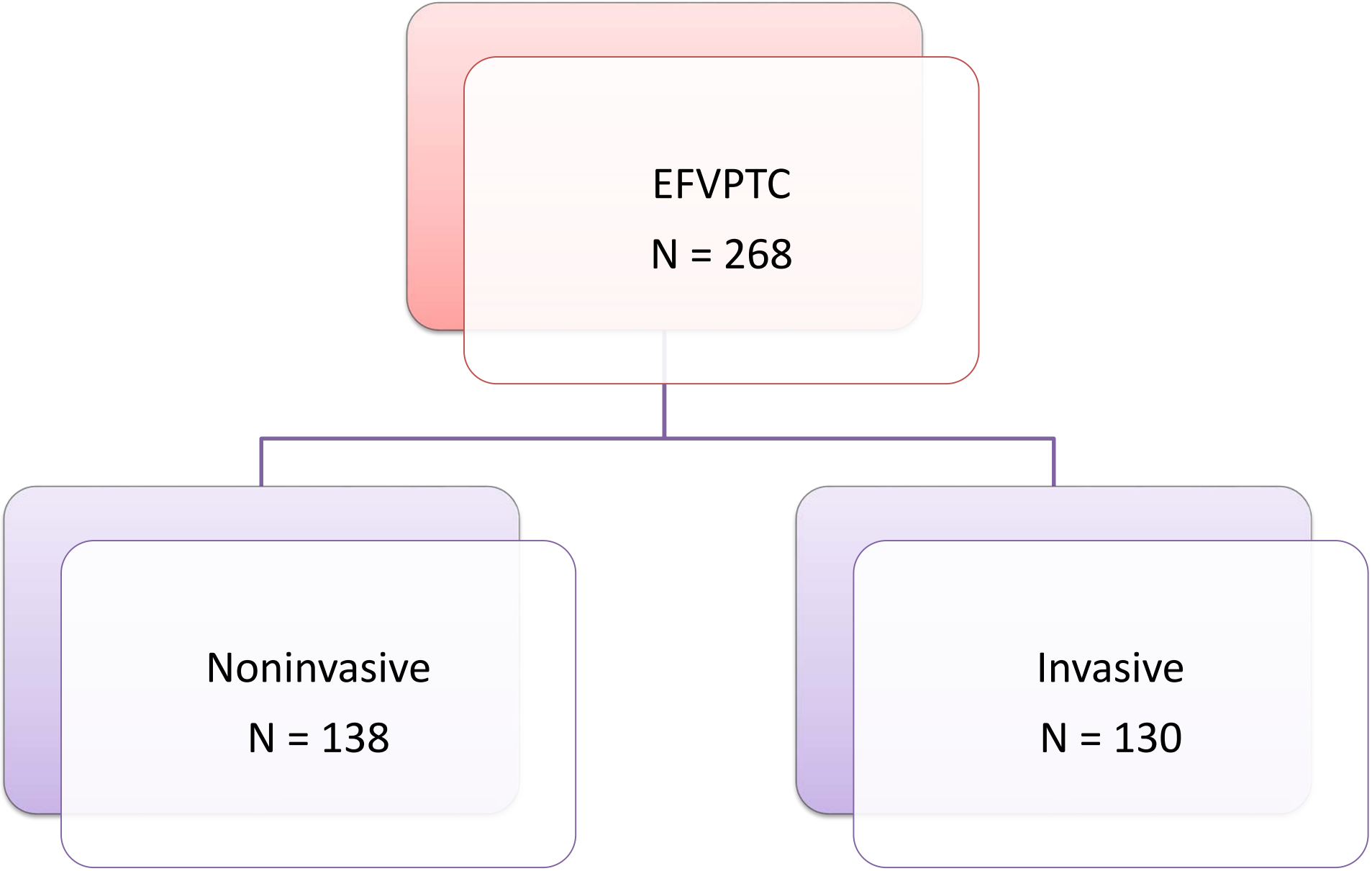
Encapsulated or well-circumscribed nodule

Follicular growth pattern with no papillae

Nuclear features of PTC

- Non-Invasive EFVPTC
  - >1 cm
  - No vascular invasion
  - No capsular invasion
  - Adequate capsule sampling
  - No other invasive tumours in gland except single microcarcinoma
  - No RAI therapy
  - 10 yr F/U minimum

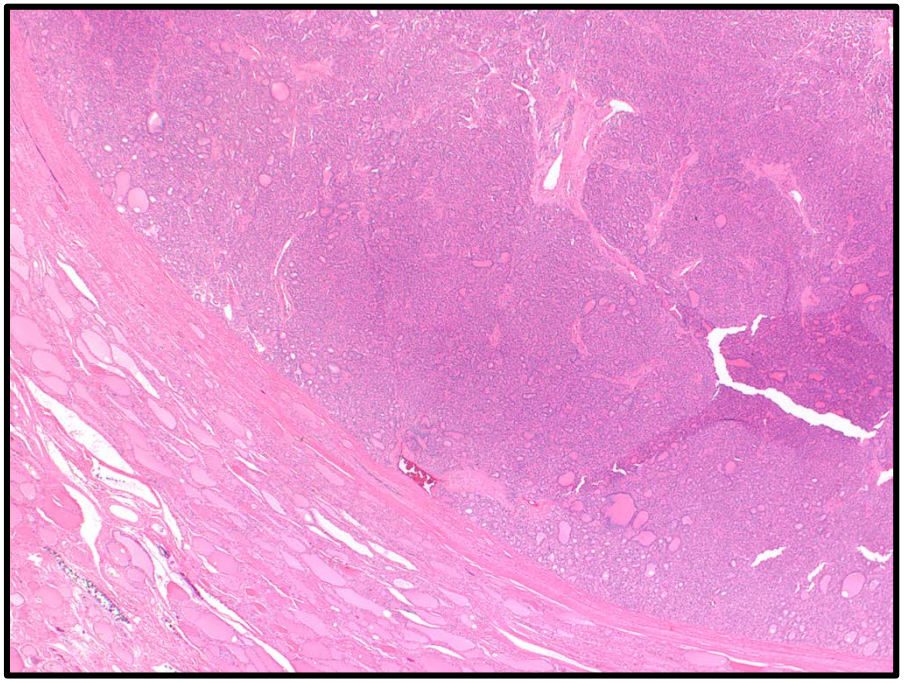
- EFVPTC with Invasion
  - Vascular invasion and/or capsular invasion
  - 1 yr F/U minimum


EFVPTC
N = 268
Noninvasive
N = 138
Invasive
N = 130

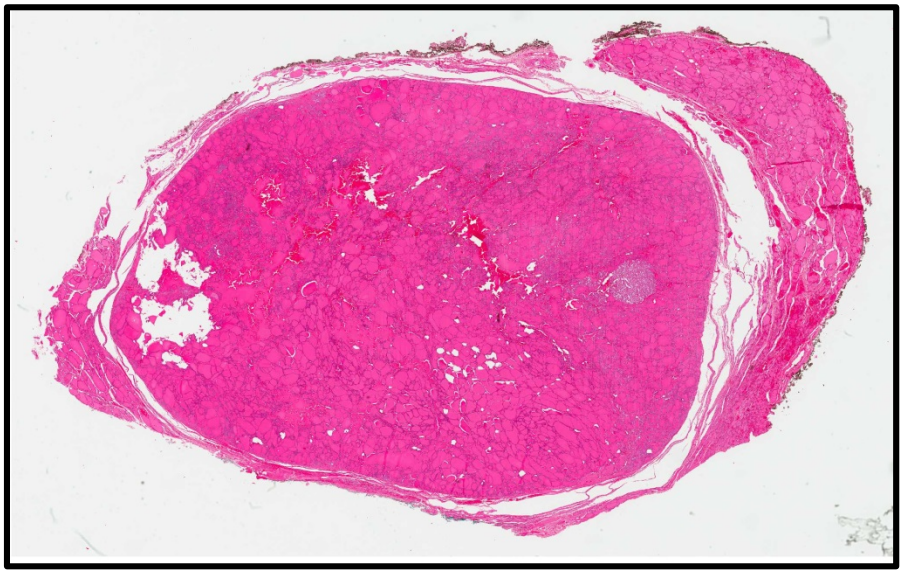
Consensus Diagnostic Criteria for EFVPTC

Major Features

- Encapsulation



- Clear Demarcation



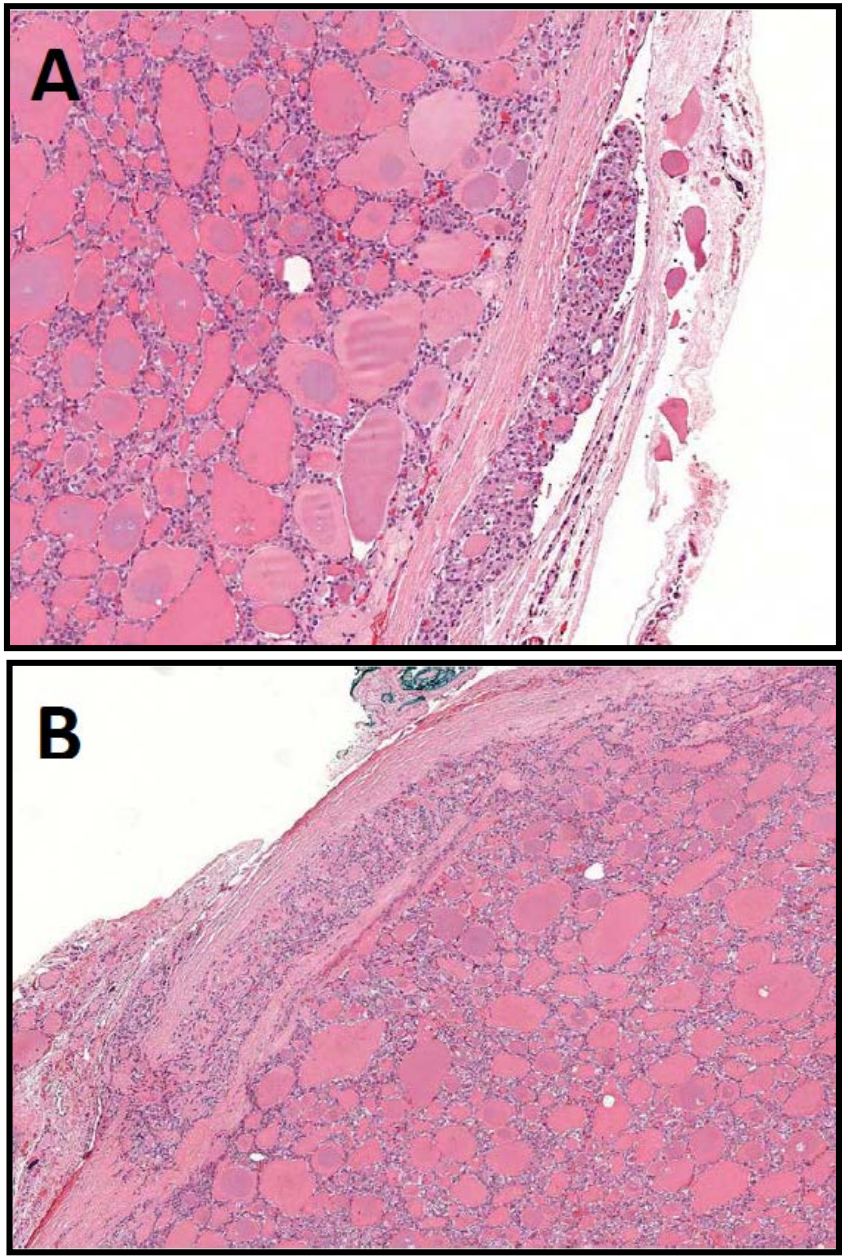
JAMA Oncol 2016 Aug 1;2(8):1023-9

Consensus Diagnostic Criteria for Invasive EFVPTC

Major Features

- Vascular invasion

- Capsular invasion

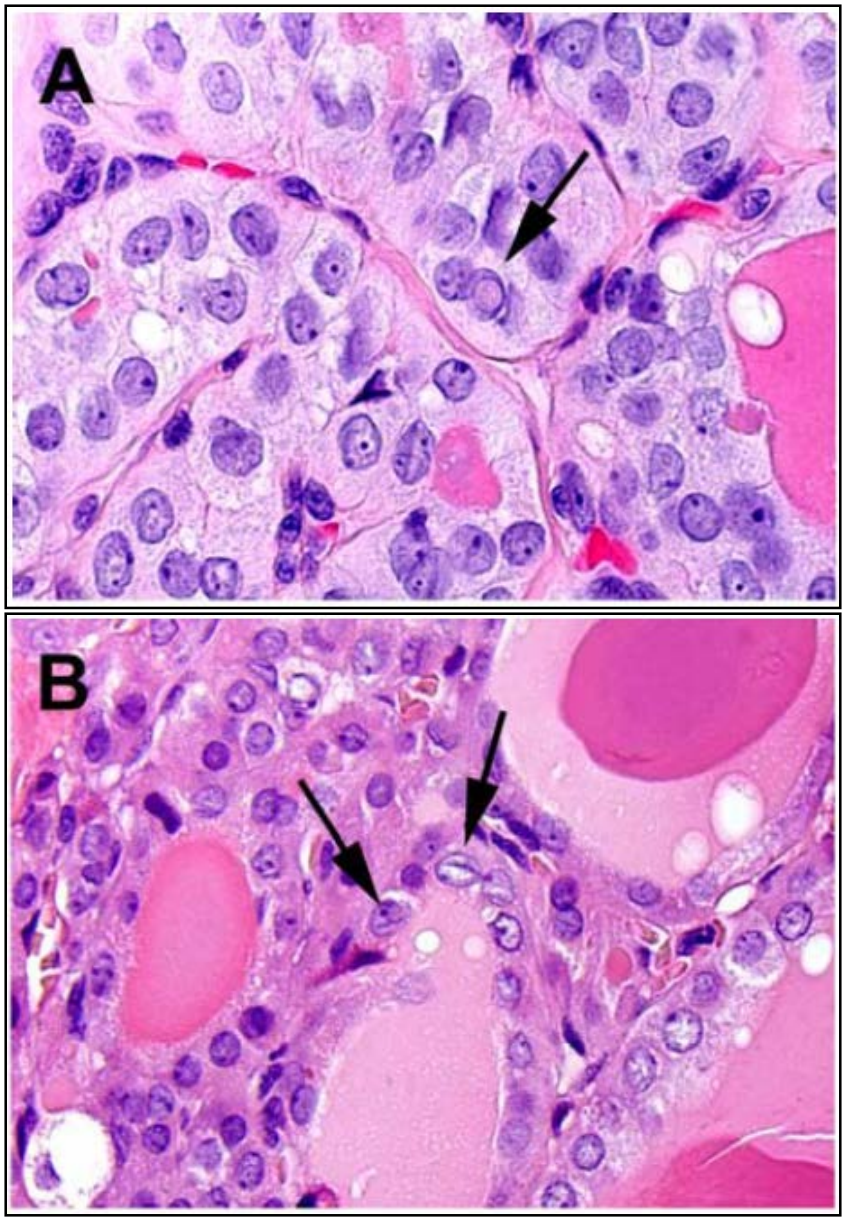


JAMA Oncol 2016 Aug 1;2(8):1023-9

Consensus Diagnostic Criteria for EFVPTC

Major Features

- Nuclear Features of PTC
  - Enlargement
  - Crowding/overlapping
  - Elongation
  - Irregular contours
  - Grooves
  - Pseudoinclusions
  - Chromatin clearing



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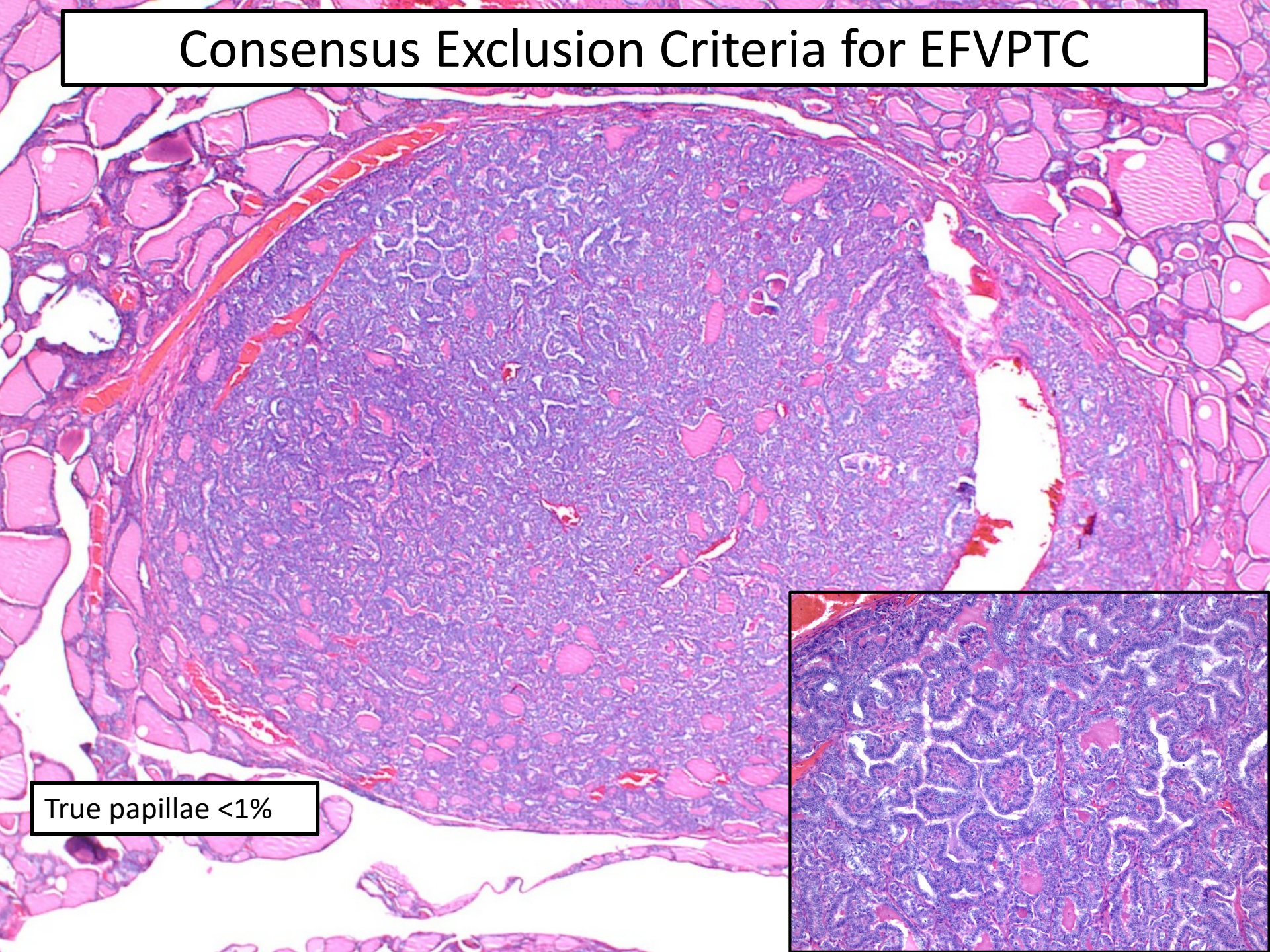
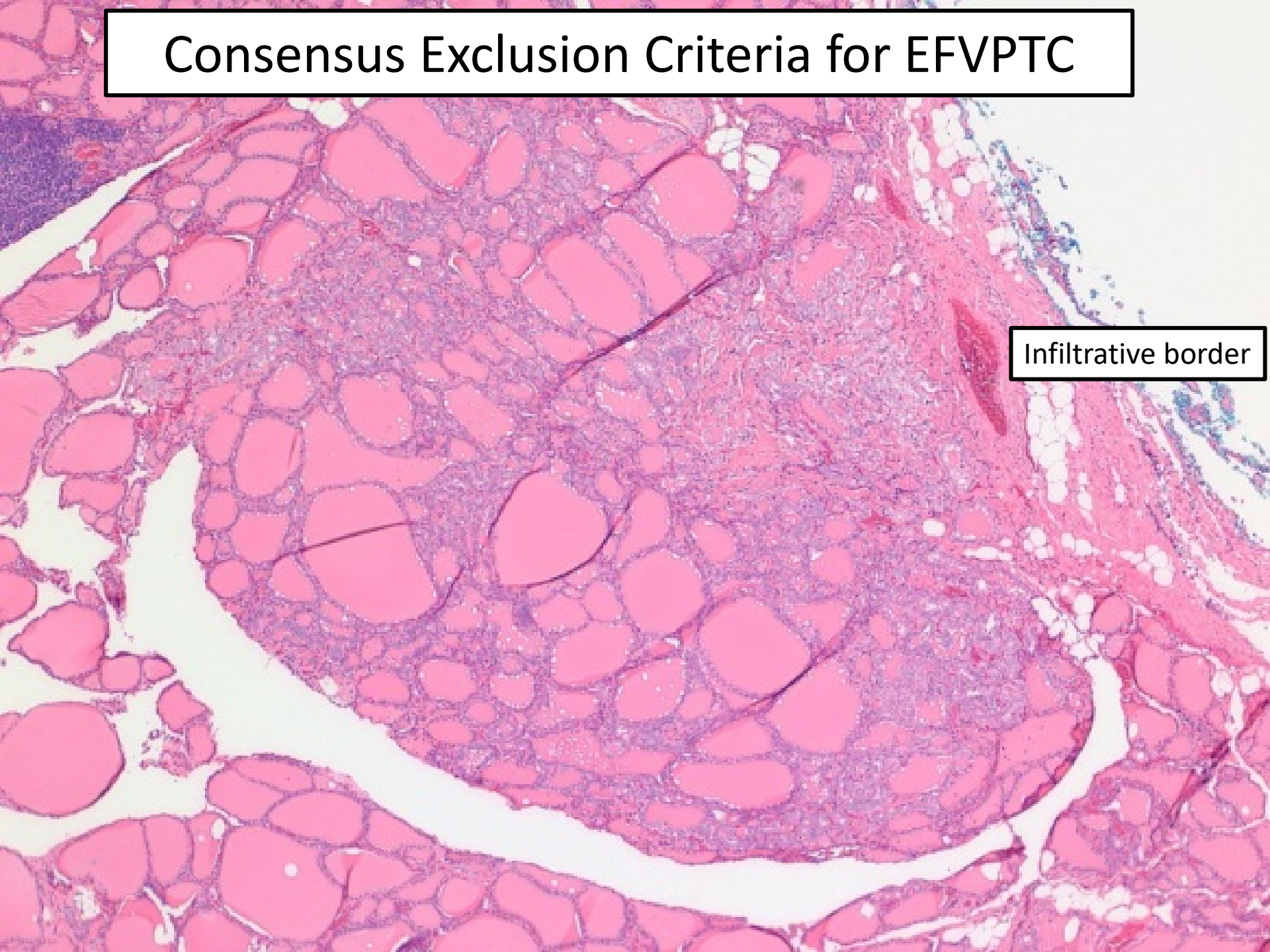
Consensus Exclusion Criteria for EFVPTC

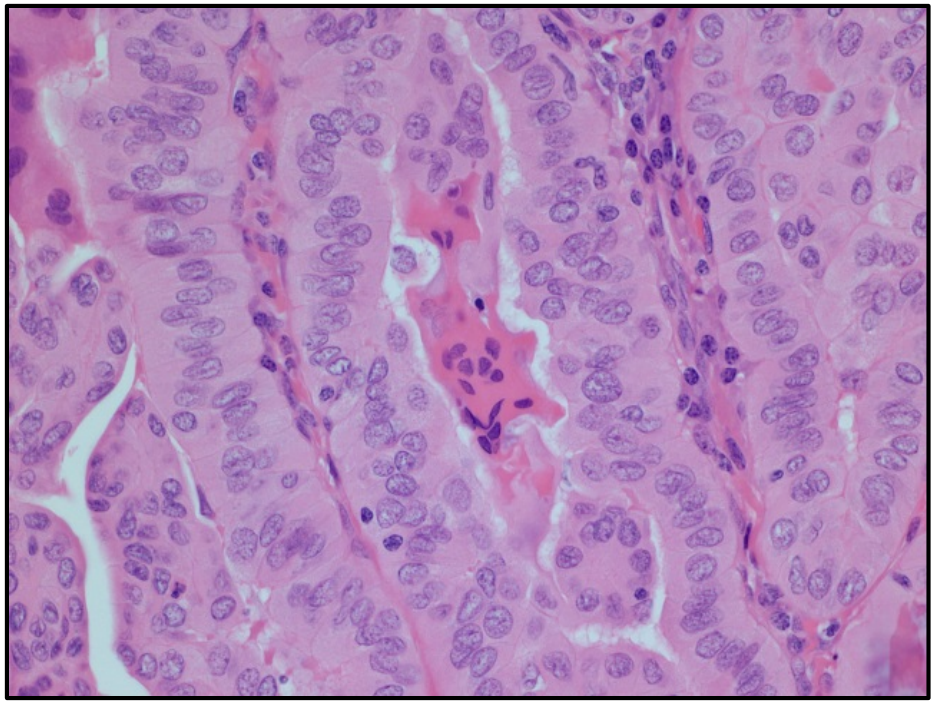


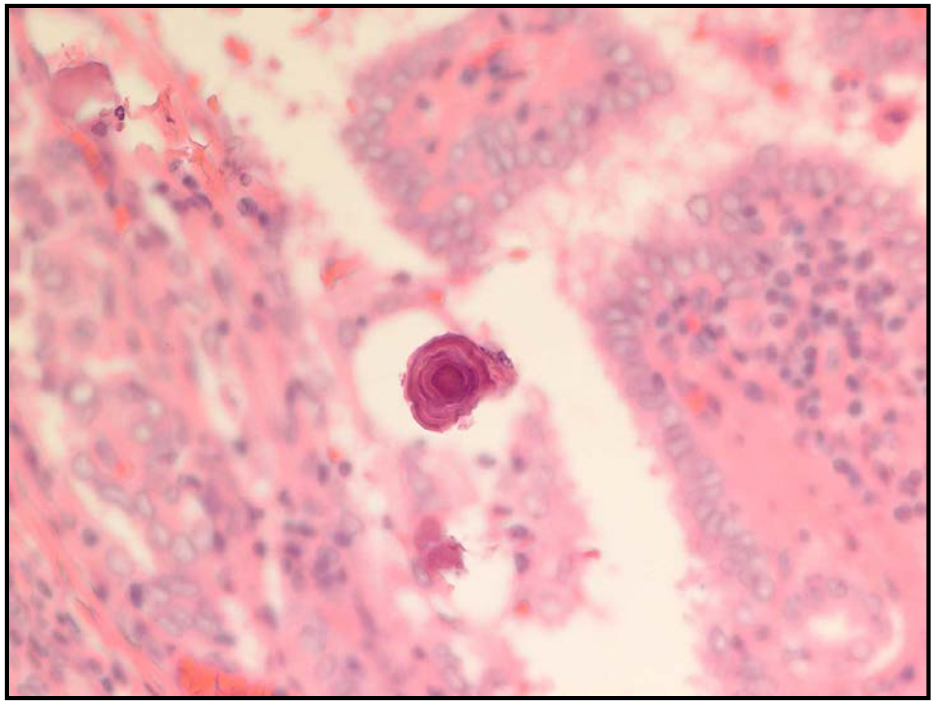
Consensus Exclusion Criteria for EFVPTC

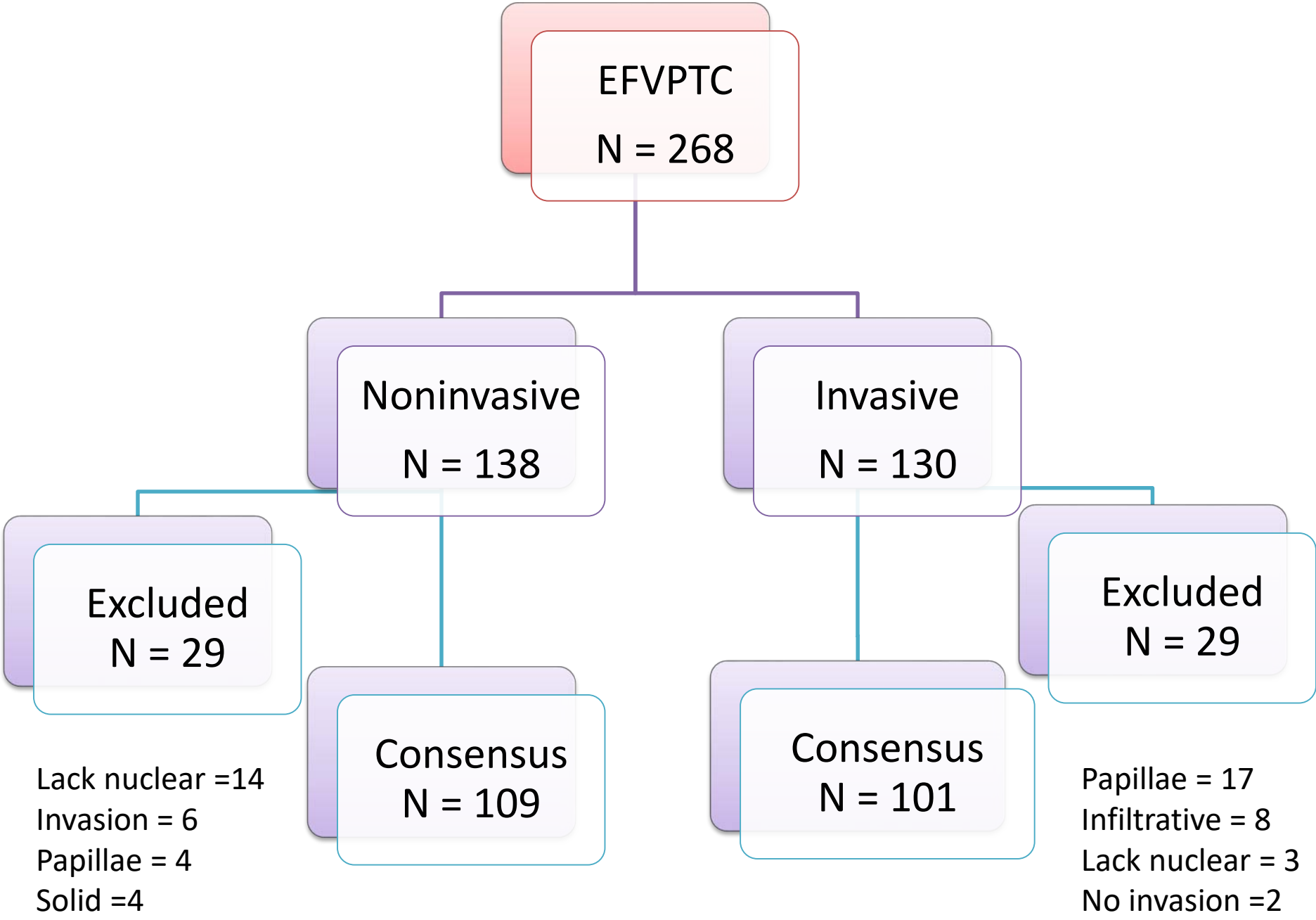


Consensus Exclusion Criteria for EFVPTC

- Psammoma bodies
- Tumour necrosis
- High mitotic activity $\geq$3/10 hpf
- Cell/morphologic characteristics of other PTC variants (tall cell, solid, etc)






EFVPTC
N = 268
Noninvasive
N = 138
Invasive
N = 130
Excluded
N = 29
Consensus
N = 109
Consensus
N = 101
Excluded
N = 29
Lack nuclear =14
Invasion = 6
Papillae = 4
Solid =4
Papillae = 17
Infiltrative = 8
Lack nuclear = 3
No invasion =2

Clinical Information & Outcomes

Characteristic	Group 1 (Noninvasive EFVPTC) (n = 109)	Group 2 (Invasive EFVPTC) (n = 101)
Age, mean (range), y	45.9 (21-81)	42.8 (8-78)
Sex, No. (%)		
Female	91 (83)	71 (70)
Male	18 (17)	30 (30)
Tumor size, mean (range), cm	3.1 (1.1-9.0)	2.5 (0.6-5.5)
Extent of surgery		
Lobectomy	67	15
Total thyroidectomy	42	86
Follow-up, y		
Mean (range)	14.4 (10-26)	5.6 (1-18)
Median	13.0	3.5
Adverse events during follow-up, No. (%)	0	12 (12)

Distant mets: 5

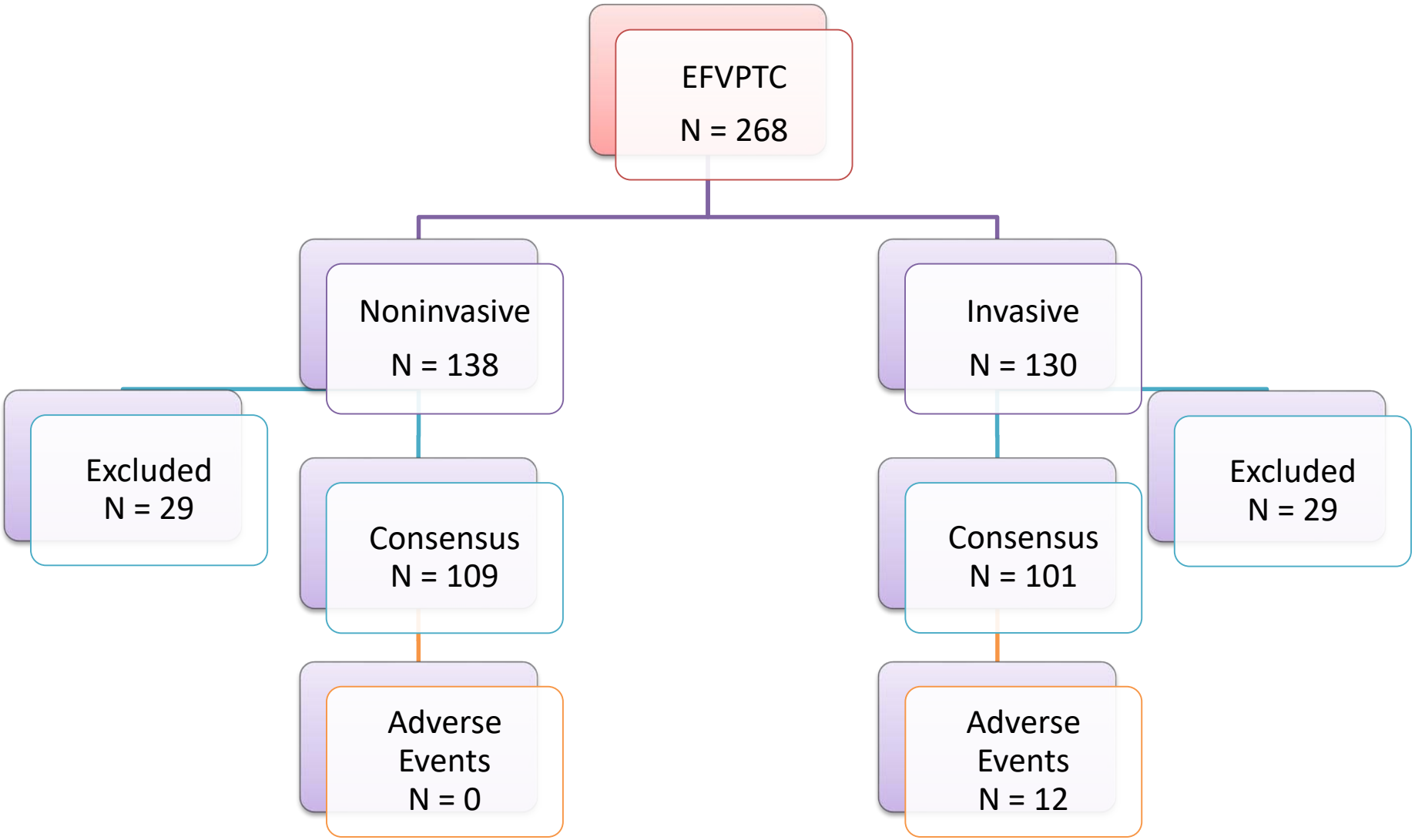
- 2 capsular
- 1 vascular
- 2 caps + vascular

LN recurrence: 1

Local persistence: 1

Biochemical failure: 5

JAMA Oncol 2016 Aug 1;2(3):1023-9



Thyroid tumours classified as noninvasive EFVPTC, using strict criteria, have a very low risk of adverse outcome and should be renamed

Research

Noninvasive

Original Investigation

Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

Yuri E. Nikiforov, MD, PhD; Raja R. Seethala, MD; Giovanni Tallini, MD; Zubair W. Baloch, MD, PhD; Fulvio Basolo, MD; Lester D. R. Thompson, MD; Justine A. Barletta, MD; Bruce M. Wenig, MD; Abir Al Ghuzlan, MD; Kennichi Kakudo, MD, PhD; Thomas J. Giordano, MD, PhD; Venancio A. Alves, MD, PhD; Elham Khanafshar, MD, MS; Sylvia L. Asa, MD, PhD; Adel K. El-Naggar, MD; William E. Gooding, MS; Steven P. Hodak, MD; Ricardo V. Lloyd, MD, PhD; Guy Maytal, MD; Ozgur Mete, MD; Marina N. Nikiforova, MD; Vania Nosé, MD, PhD; Mauro Papotti, MD; David N. Poller, MB, ChB, MD, FRCPath; Peter M. Sadow, MD, PhD; Arthur S. Tischler, MD; R. Michael Tuttle, MD; Kathryn B. Wall; Virginia A. LiVolsi, MD; Gregory W. Randolph, MD; Ronald A. Ghossein, MD

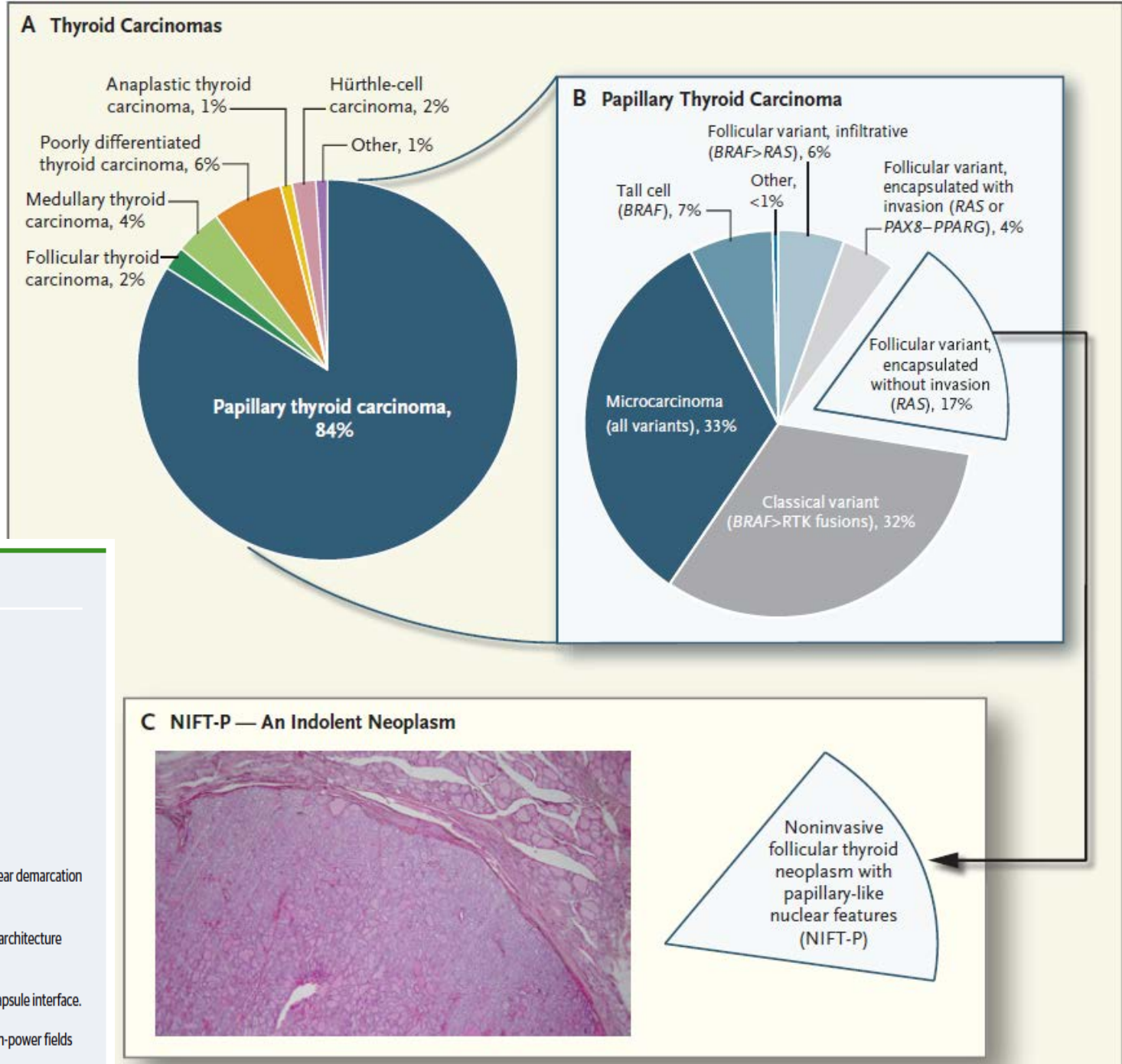
Name to reflect: main morphological features, neoplastic nature, indolent behaviour

JAMA Oncol 2016 Aug 1;2(8):1023-9

Non-Invasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features

(NIFTP)

What are the implications of NIFTP?



Box 2. Diagnostic Criteria for NIFTP

1. Encapsulation or clear demarcation[a]
2. Follicular growth pattern[b] with
   - <1% Papillae
   - No psammoma bodies
   - 30% Solid/trabecular/insular growth pattern
3. Nuclear score 2-3
4. No vascular or capsular invasion[c]
5. No tumor necrosis
6. No high mitotic activity[d]

[a] Thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid tissue.

[b] Including microfollicular, normofollicular, or macrofollicular architecture with abundant colloid.

[c] Requires adequate microscopic examination of the tumor capsule interface.

[d] High mitotic activity defined as at least 3 mitoses per 10 high-power fields (400×).

JAMA Oncol 2016;2(8)

NEJM 2016;375:1054-67

Estimation of Worldwide Incidence of NIFTP

Source	Parameter	Value	Result
Ferlay J. et al (2012)[1]	Total number of new cases of thyroid cancer worldwide	298,000	298,000
Aschebrook-Kilfoy B. et al. (2011)[2]	Percentage of papillary thyroid carcinoma (PTC) among all thyroid carcinomas	84%	250,320
Estimation based on unpublished data[3]	Percentage of encapsulate follicular variant of PTC with no invasion among all PTC	18.6%	**46,560**

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NIFTP Implications - Clinicians

- Estimated 46,000 cases worldwide
- Recurrence rate is likely <1% in the first 15 years
  - De-escalate clinical management
    - No completion thyroidectomy, no RAI therapy
  - Staging not necessary
  - Reduced need for long-term surveillance
  - Reduce risk of secondary disease following RAI

NIFTP Implications – Surgical Pathologist

- As detection of vascular and/or capsular invasion critical to diagnosis, complete capsule sampling important
- Awareness of and application of diagnostic criteria – need to sample entire lesion due to exclusion criteria – psammoma body
- No need to use synoptic report?
- Calculate and compare institutional rates to published rates

Implications - Patients

- Reduce psychological impact – not cancer
- Reduced need for surgery
- Reduced need for RAI therapy
- Reduced need for follow-up surveillance

Thyroid. 2016;26(9):1167-1172

TABLE 1. THYROID CANCER SURVEILLANCE DIRECT AND INDIRECT COSTS FOR THE YEAR AFTER TREATMENT

	Cost per patient	*Cost for all incident patients in 2015 (15,363)*
Direct costs		
Ultrasound (×1)	$123	$1,889,649
Tg test (×2)	$60	$921,780
Tg Ab test (×2)	$58	$891,054
Office visit (×2)	$146	$2,242,998
Total direct costs	$387	$5,945,481
Indirect costs		
Out-of-pocket expenses	$2,400	$36,871,200
Productivity loss	$1,601	$24,596,163
Psychosocial distress	N/A	N/A
Total indirect costs	$4,001	$61,467,363
Total direct and indirect costs	$4,388	$67,412,844

All costs are in US dollars.
Tg, thyroglobulin; Tg Ab, thyroglobulin antibody; TSH, thyrotropin.

TABLE 2. THYROID CANCER SURVEILLANCE DIRECT AND INDIRECT COSTS FOR EACH SUBSEQUENT YEAR AFTER THE FIRST POSTTREATMENT YEAR

Test	*Cost per patient*	*Cost for all prevalent patients in 2015 minus incident cases (132,677)*
Direct costs		
Ultrasound	$123	$16,319,271
Tg test	$30	$3,980,310
Tg Ab test	$29	$3,847,633
Office visit	$73	$9,685,421
Total direct costs	$255	$33,832,635
Indirect costs		
Out-of-pocket expenses	$2,028	$269,068,956
Productivity loss	$1,601	$212,415,877
Psychosocial distress	N/A	N/A
Total indirect costs	$3,629	$481,484,833
Total direct and indirect costs	$3,884	$515,317,468

All costs are in US dollars.

Clinical Safety of Renaming Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: Is NIFTP Truly Benign?

David N. Parente[1] · Wouter P. Kluijfhout[1] · Pim J. Bongers[1] · Raoul Verzijl[1] · Karen M. Devon[1,2] · Lorne E. Rotstein[1] · David P. Goldstein[3] · Sylvia L. Asa[4] · Ozgur Mete[4] · Jesse D. Pasternak[1]

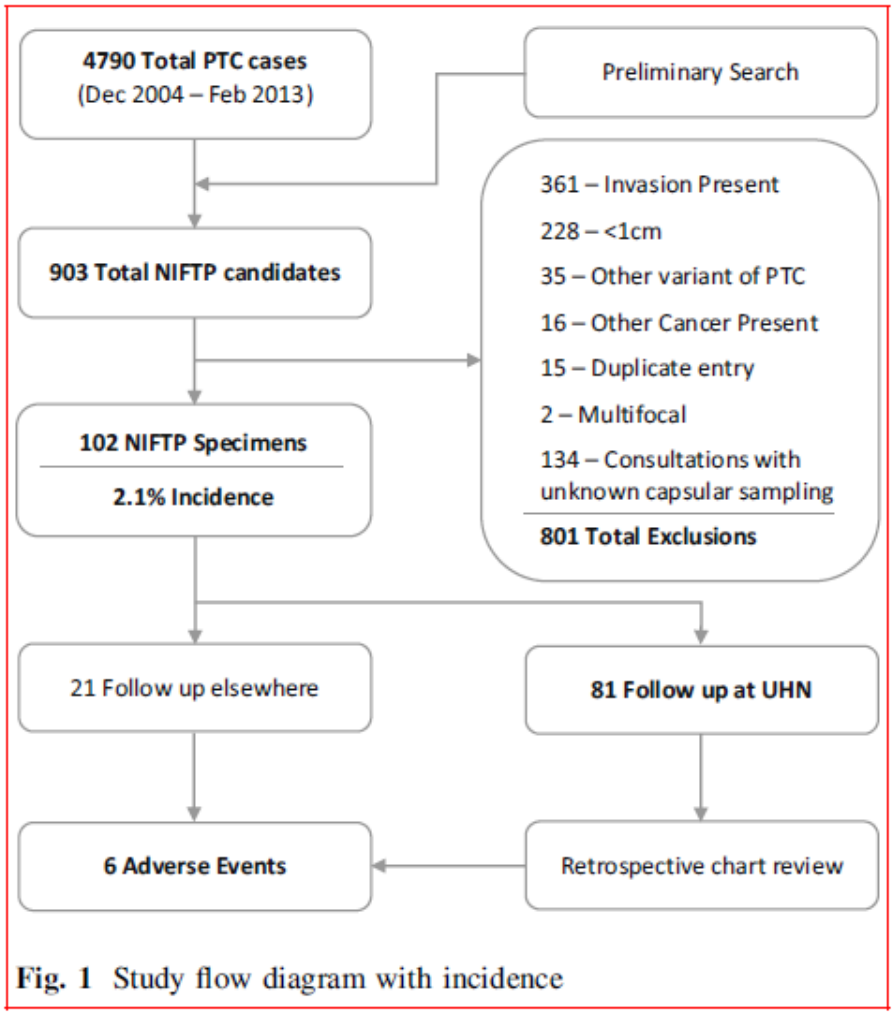

Fig. 1 Study flow diagram with incidence

- Lower incidence – 2.1%
- Adverse outcomes
  - 5 lymph node mets
  - 1 lung mets
- Support de-escalation of treatment
- NIFTP is low-risk cancer, not benign

World J Surg Published online: 21 August 2017

Conclusions

- NIFTP has a very indolent behaviour when strict histologic criteria are met
- Reclassification will affect a large population
- De-escalation of treatment for NIFTP will reduce consequences associated with a diagnosis of cancer