

Hôpitaux Universitaires Paris Centre



COCHIN
BROCA
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CLUB THYROÏDE
ILE DE FRANCE

On le disait bénin, puis malin, et retour à la case bénin: le NIFT-P

Le pathologiste a-t-il la solution ?

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Table ronde avec N Chereau et G Rüss

Historique/rappels

WHO histological classification of thyroid and parathyroid

Thyroid carcinomas

| | |
|---|--------|
| Papillary carcinoma | 8260/3 |
| Follicular carcinoma | 8330/3 |
| Poorly differentiated carcinoma | |
| Undifferentiated (anaplastic) carcinoma | 8020/3 |
| Squamous cell carcinoma | 8070/3 |
| Mucoepidermoid carcinoma | 8430/3 |
| Sclerosing mucoepidermoid carcinoma with eosinophilia | 8430/3 |
| Mucinous carcinoma | 8480/3 |
| Medullary carcinoma | 8345/3 |
| Mixed medullary and follicular cell carcinoma | 8346/3 |
| Spindle cell tumour with thymus-like differentiation | 8588/3 |
| Carcinoma showing thymus-like differentiation | 8589/3 |

Thyroid adenoma and related tumours

| | |
|-------------------------------|--------|
| Follicular adenoma | 8330/0 |
| Hyalinizing trabecular tumour | 8336/0 |

Other thyroid tumours

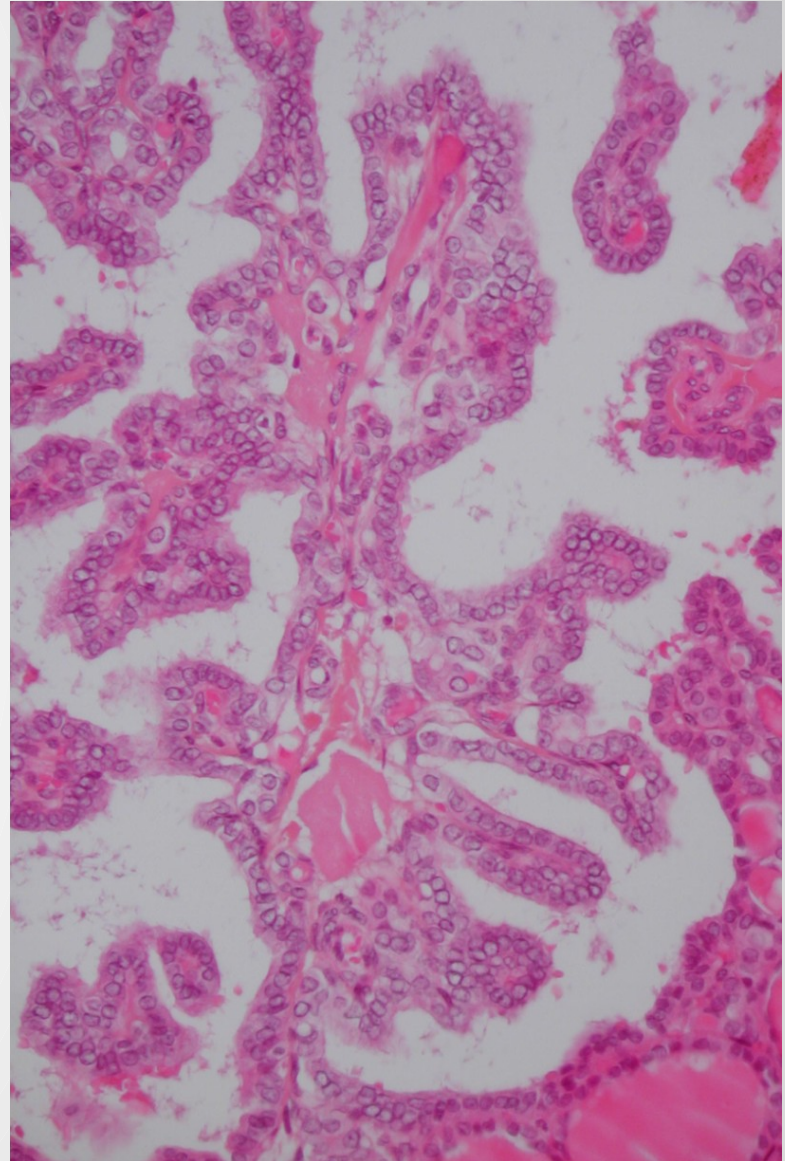
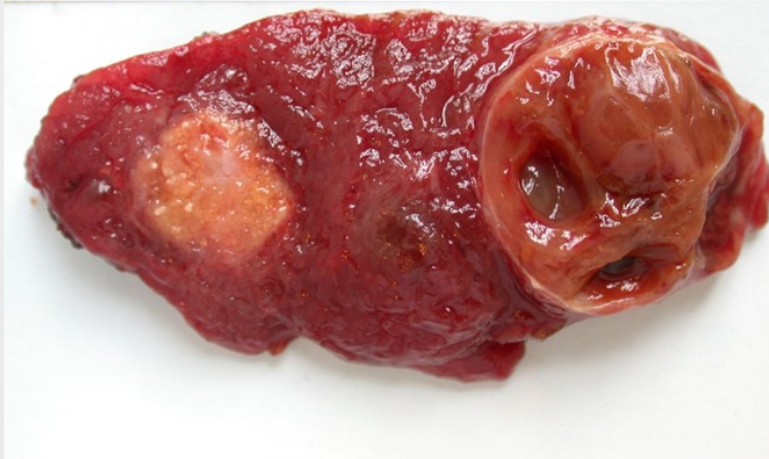
| |
|-----------------------------------|
| Teratoma |
| Primary lymphoma and plasmacytoma |
| Ectopic thymoma |
| Angiosarcoma |
| Smooth muscle tumours |
| Peripheral nerve sheath tumours |
| Paraganglioma |
| Solitary fibrous tumour |
| Follicular dendritic cell tumour |
| Langerhans cell histiocytosis |
| Secondary tumours |

Parathyroid tumours

| |
|-----------------------|
| Parathyroid carcinoma |
| Parathyroid adenoma |
| Secondary tumours |

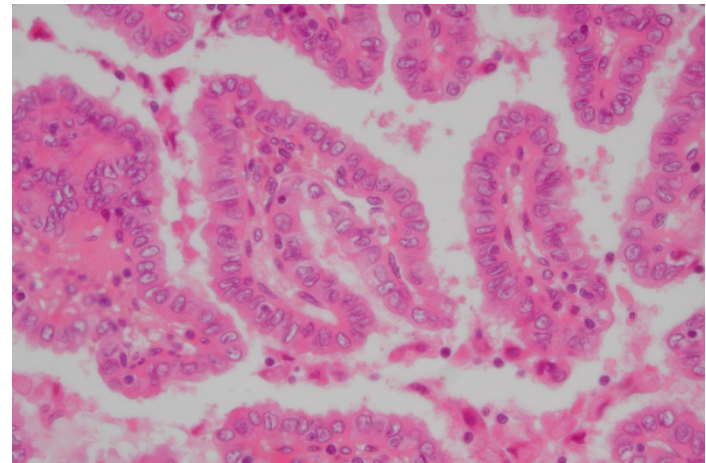
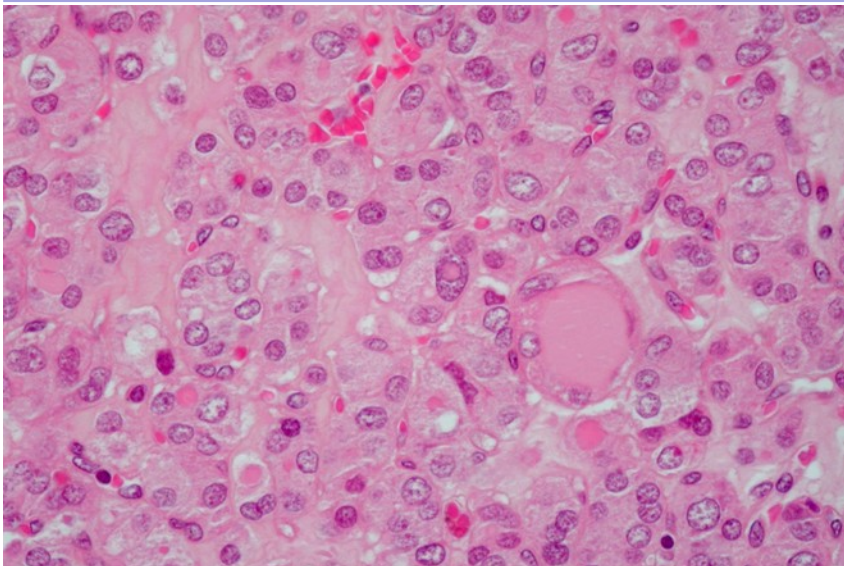
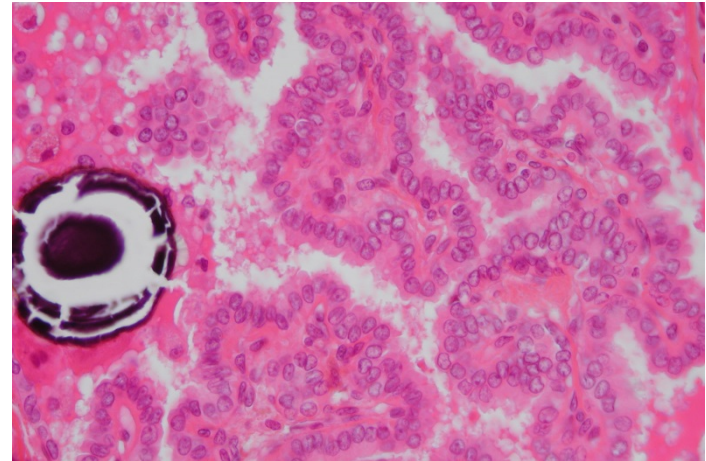
Carcinome papillaire

- Papilles
- Atypies cyto-nucléaires

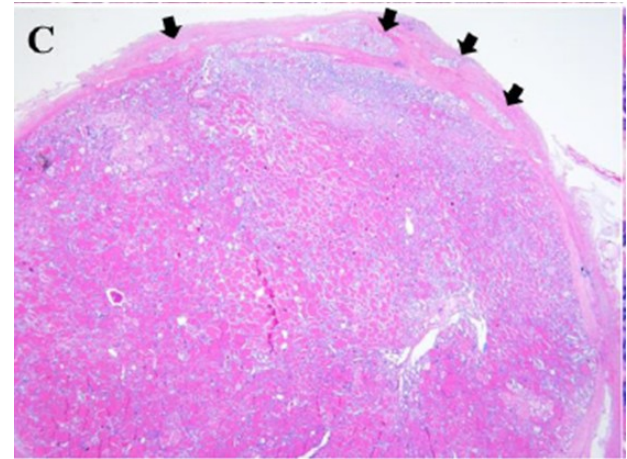
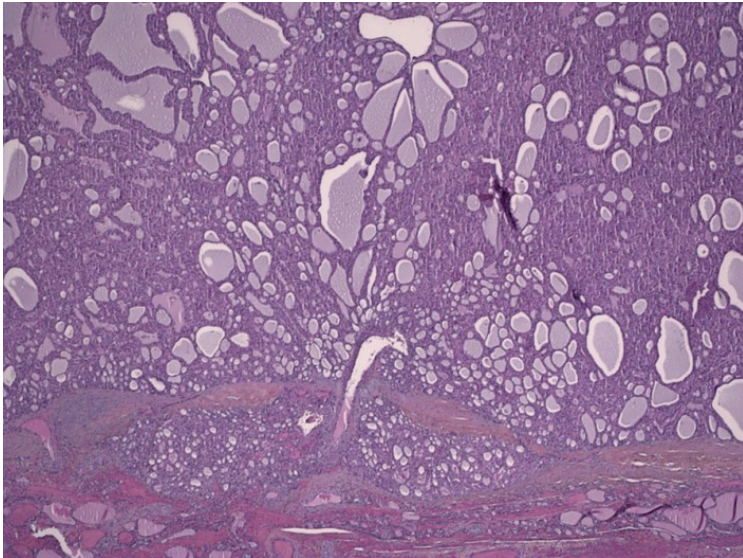


Critères nucléaires

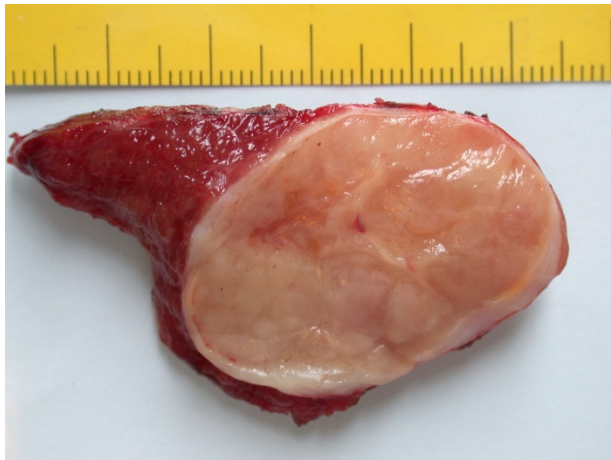
1. Augmentation de la taille du noyau
2. Noyau allongé
3. Chevauchement
4. Contours irréguliers
5. Aspect rainuré
6. Pseudo inclusions
7. Clarification des noyaux
8. Chromatine marginée
9. Aspect en verre dépoli
10. Microcalcifications



Carcinome vésiculaire



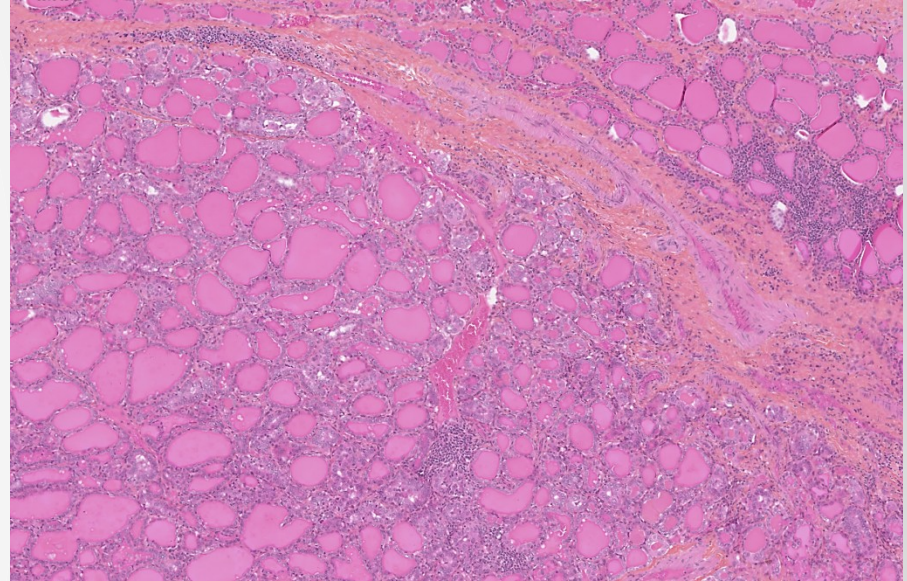
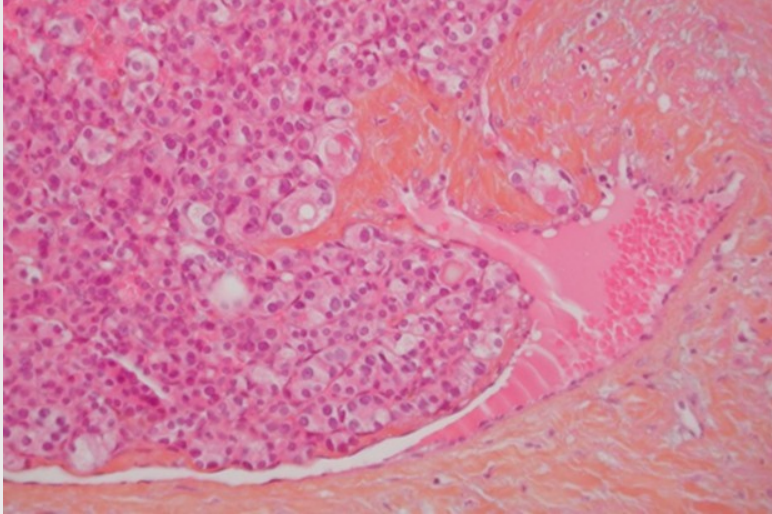
JBCM 2017



- Absence d'ACN de type papillaire
- Invasion/Effraction capsulaire
- Angioinvasion

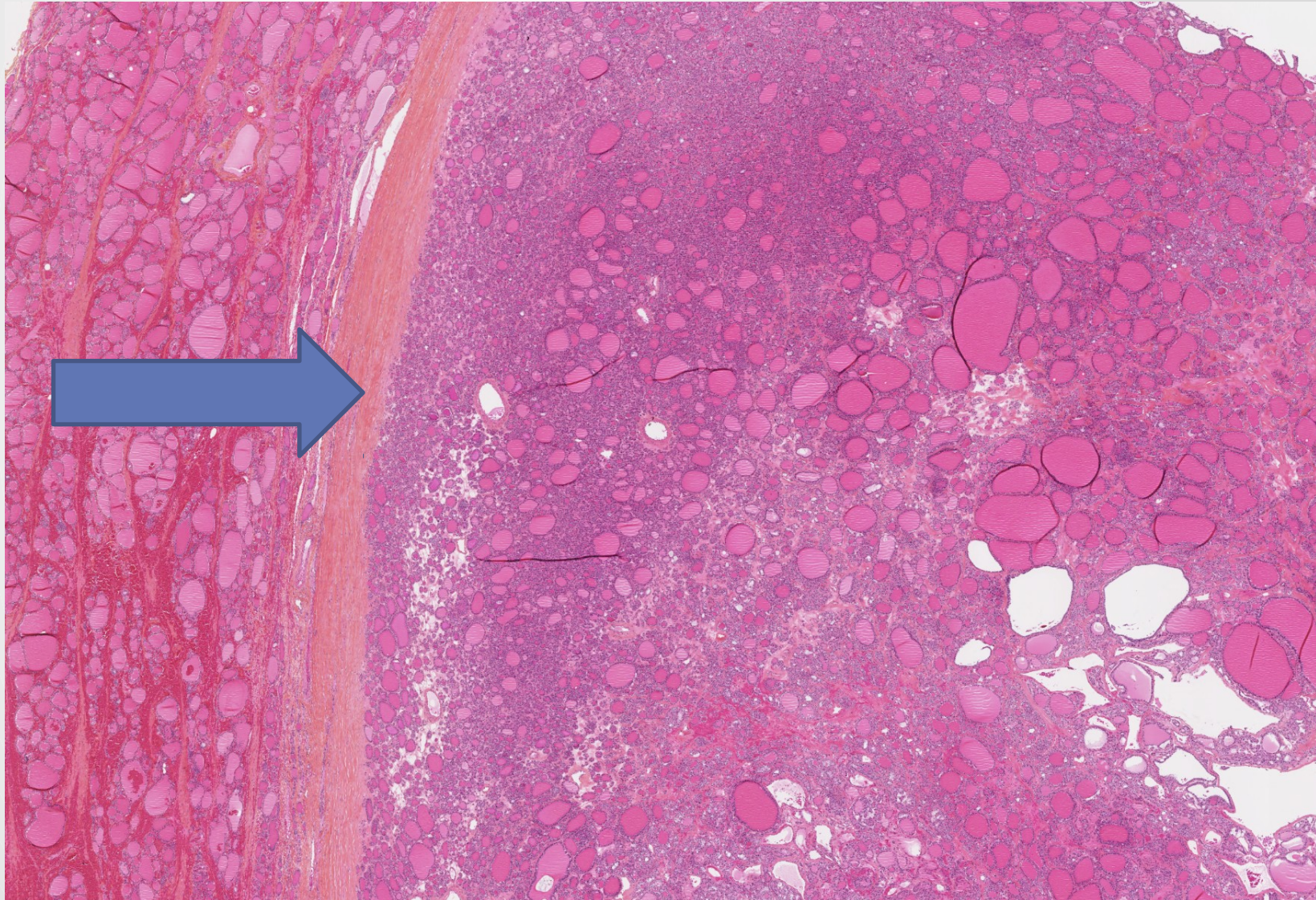
Carcinome vésiculaire invasif

Carcinome vésiculaire



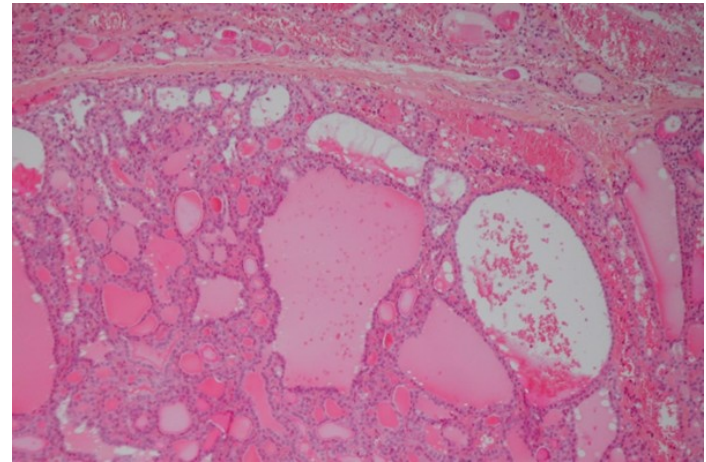
Tumeur vésiculaire de potentiel de malignité incertain
Carcinome vésiculaire minimally invasive

Adénome vésiculaire



Carcinome papillaire d'architecture vésiculaire

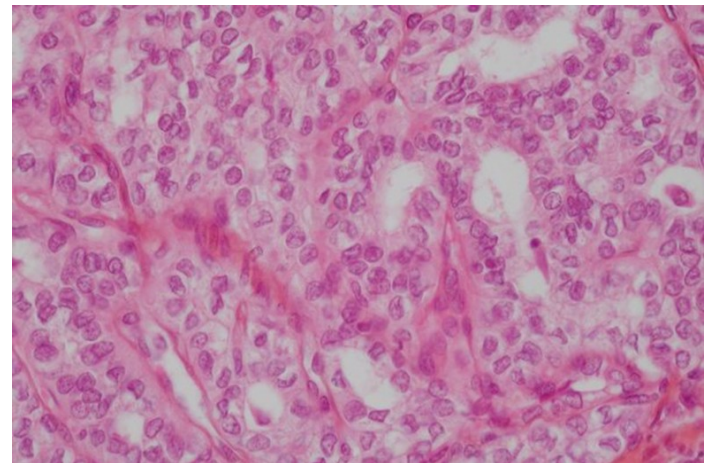
- Entité :1977
- Absence de papilles
- ACN de type papillaire
- Traitement des carcinomes papillaires



2 formes:

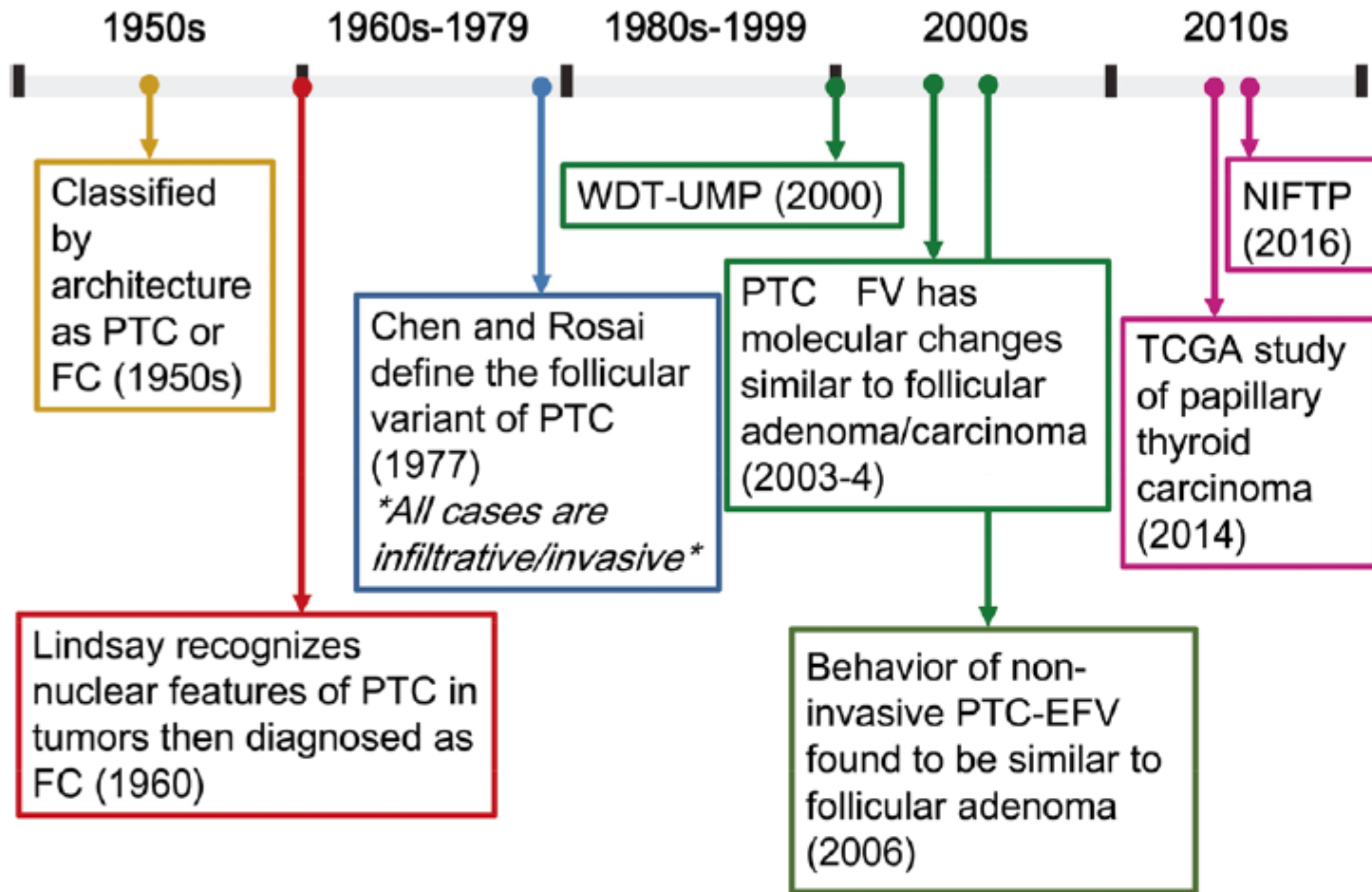
Non encapsulée (FVPTC): carcinome papillaire variante vésiculaire invasif

Encapsulée (EFVPTC): carcinome papillaire variante vésiculaire encapsulé non invasif



Chem KT et Rosai J. Follicular variant of thyroid papillary carcinoma: a clinicopathologic study of six cases. AJSP, 1977: 123-30

Timeline of well differentiated thyroid carcinoma



Endocr Pathol (2017) 28:128–138
DOI 10.1007/s12022-017-9478-3



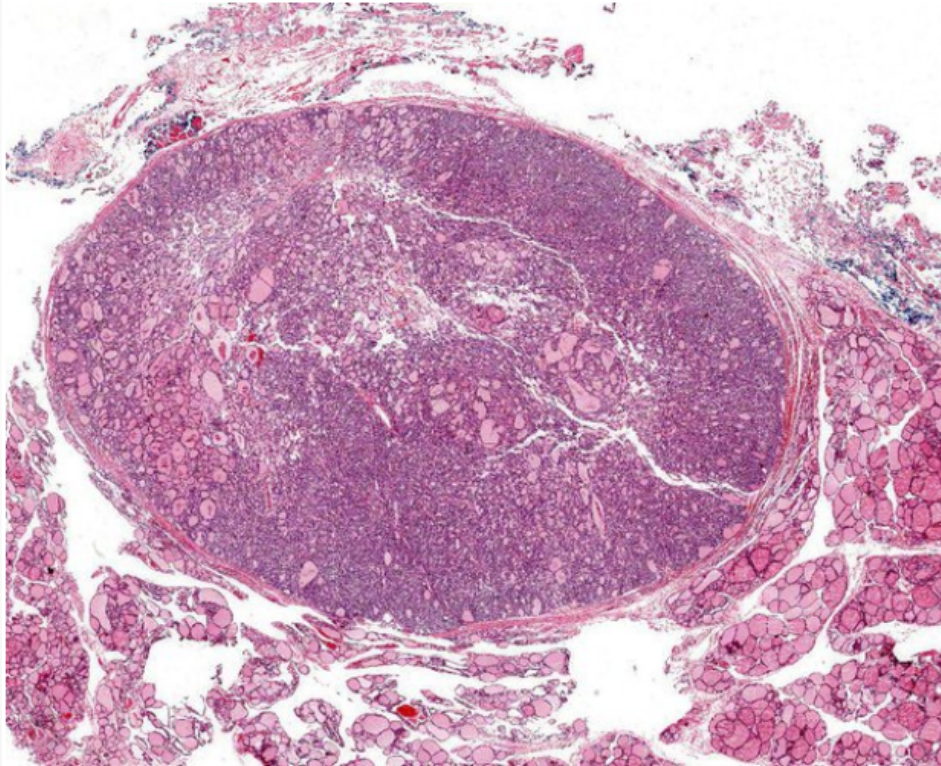
Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features: Historical Context, Diagnosis, and Future Challenges

Bin Xu¹ · Giovanni Tallini² · Ronald A. Gosselin³

TCGA
The Cancer Genome atlas



It's Not Cancer: Doctors Reclassify a Thyroid Tumor



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

By GINA KOLATA

APRIL 14, 2016

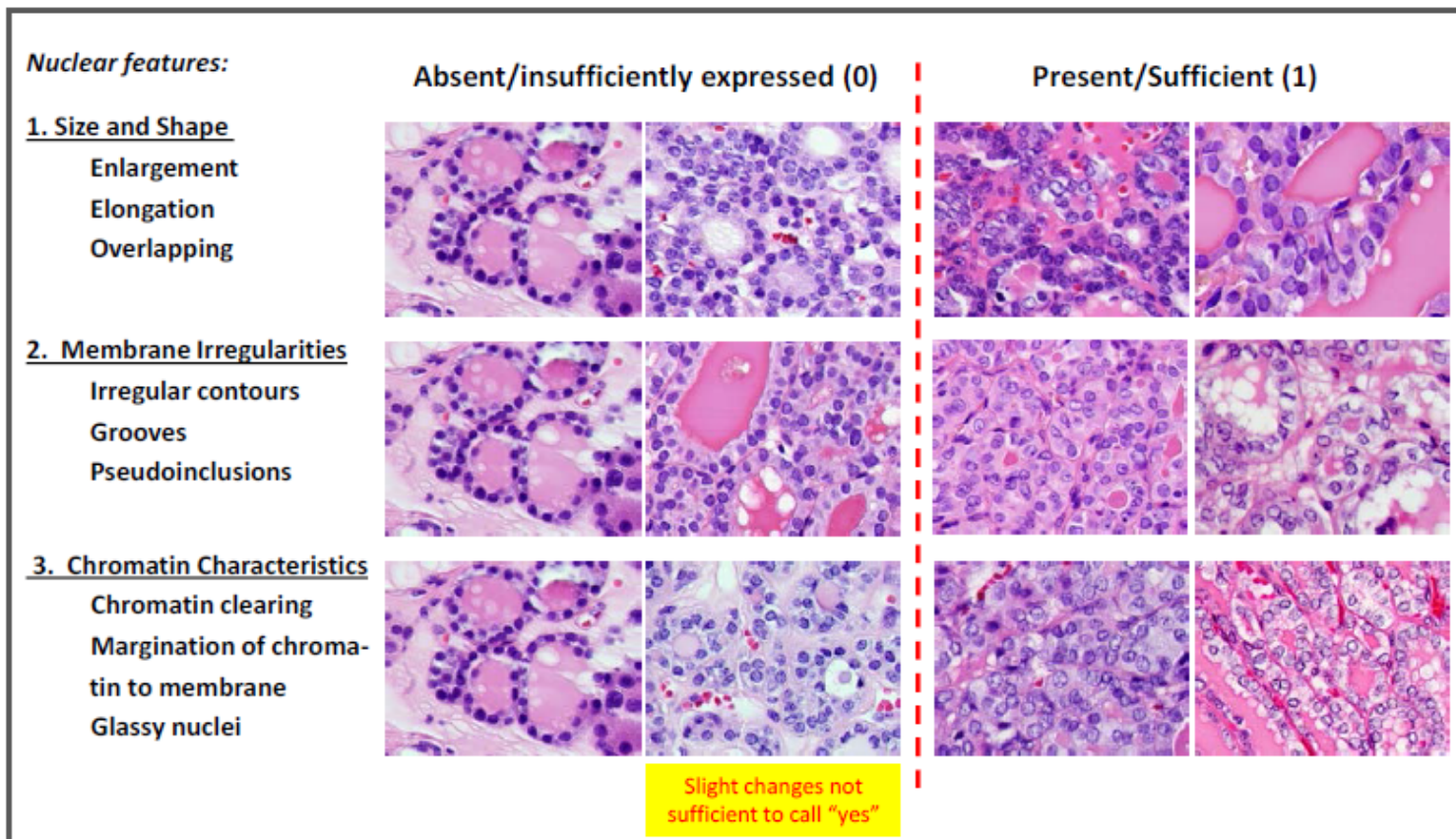
An international panel of doctors has decided that a type of tumor that was classified as a [cancer](#) is not a cancer at all.

Table 3. Diagnostic criteria for NIFTP

Diagnostic criteria

- Encapsulation or clear demarcation¹
- Follicular growth pattern² with:
 - <1% papillae
 - no psammoma bodies
 - <30% solid/trabecular/insular growth pattern
- Nuclear Score 2-3
- No vascular or capsular invasion³
- No tumor necrosis
- No high mitotic activity⁴





eFigure 4. Visual guide for scoring nuclear features using the three-point scoring scale.

Table. Summary of Follow-up Information for Patients in the Study Groups

| 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) |

Constatactions/Pronostic

| Auteurs | | EFVPTC | Suivi | Récidive |
|--|---------------------------------|---------------|--------------|-----------------|
| Liu Z <i>et al</i> Cancer 2006; 107: 1255-64 | MSKCC, USA | 43 cas | 11.1 ans | 0% |
| Piana S <i>et al</i> Am J Surg Pathol 2010;34:868-72 | Université de Bologne, Italie | 45 cas | 11.9 ans | 0% |
| Kakudo <i>et al</i> Pathology Int 2012; 62: 155-60 | Kobe-Tokiwa University Japon | 20 cas | 8 ans | 0% |
| Vivero M <i>et al</i> Thyroid 2013;23:273-9 | | 27 cas | 9.25 ans | 0% |

Le pronostic des EFVPTC : excellent

Traitement : celui du carcinome papillaire

Exérèse chirurgicale : thyroïdectomie partielle si < 1 cm / totale si > 1 cm

+ curage

+/- irathérapie (iode 131) selon le contexte

NIFT-P

Néoplasme vésiculaire non invasif thyroïdien avec des noyaux de type papillaire

Ce n'est pas une nouvelle entité

C'est un nouveau nom pour une tumeur connue d'évolution favorable qui ne doit plus être appelée « Cancer »

Il s'agit d'une tumeur avec un potentiel malin très faible (<1%)

Aucune chirurgie complémentaire après résection complète ni aucune irathérapie n'est nécessaire pour la majorité de ces lésions

Inclusion en totalité de la capsule nécessaire pour porter ce diagnostic

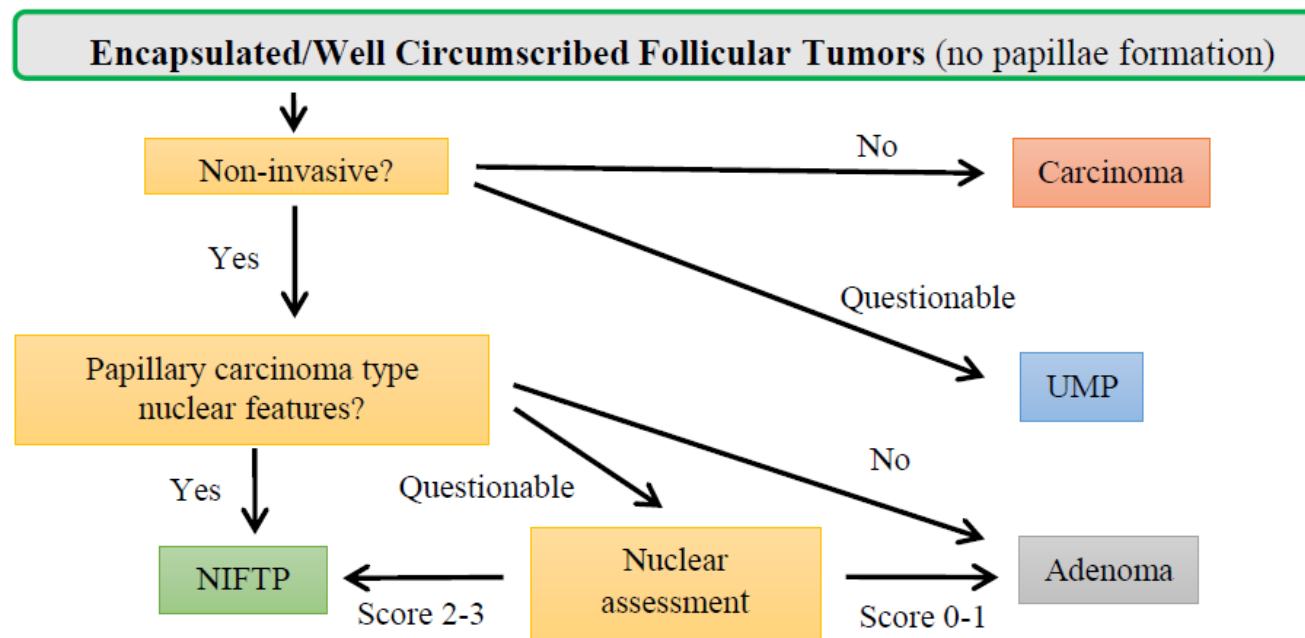


Fig. 2: Diagnostic algorithm of carcinoma, NIFTP, WDT-UMP, FT-UMP and adenoma. NIFTP: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features. UMP: Uncertain malignant potential (WDT-UMP and FT-UMP). Modified from the 4th edition WHO classification of thyroid tumor presented by Tallini G. (reference 3).

OMS 2017

- **Journal of Basic & Clinical Medicine**
2017, 6 (1):1-2

ATA Thyroid 2017;27 (4):481-3

Table 1: WHO classification of thyroid tumors in the 4th edition

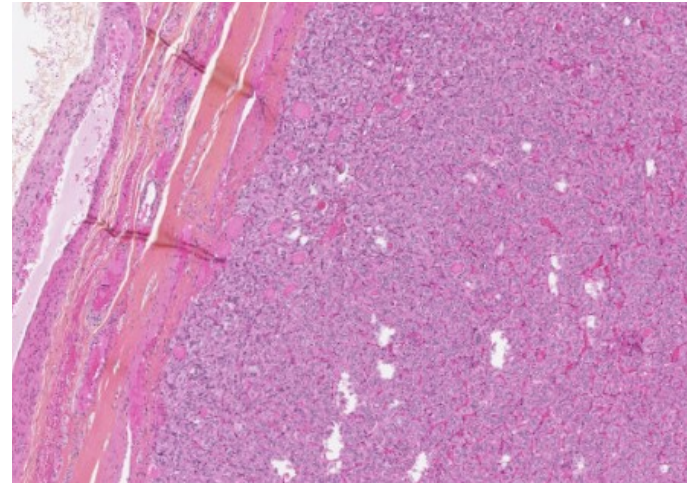
| | |
|------|---|
| 1 | Follicular Adenoma |
| 2 | Hyalinizing Trabecular Adenoma/Tumor |
| 2A | Other Encapsulated Follicular Patterned Thyroid Tumors |
| 2A-1 | Uncertain Malignant Potential (UMP) |
| 2A-2 | Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP) |
| 3 | Papillary Carcinoma |
| 4 | Follicular Carcinoma |
| 4A | Hurthle Cell Tumors |
| 5 | Poorly Differentiated Carcinoma |
| 6 | Undifferentiated Carcinoma |
| 7 | Squamous Cell Carcinoma |
| 8 | Medullary Carcinoma |
| 9 | Mixed Medullary and Follicular Cell Carcinoma |
| 10 | Mucoepidermoid Carcinoma |
| 11 | Sclerosing Mucoepidermoid Carcinoma with Eosinophilia |
| 12 | Mucinous Carcinoma |
| 13 | Ectopic Thymoma |
| 14 | Spindle Epithelial Tumor with Thymus-like Differentiation |
| 15 | Intrathyroid Thymic Carcinoma |
| 16A | Paraganglioma |
| 16B | Peripheral Nerve Sheath Tumors (including Schwannoma) |
| 16C | Benign Vascular Tumors |
| 16D | Angiosarcoma |
| 16E | Smooth Muscle Tumors (including Leiomyoma and Leiomyosarcoma) |
| 16F | Solitary Fibrous Tumor |
| 17A | Langerhans Cell Histiocytosis |
| 17B | Rosai-Dorfman Disease |
| 17C | Follicular Dendritic Cell Tumor |
| 17D | Primary Thyroid Lymphoma |
| 18 | Germ Cell Tumors |
| 19 | Secondary Tumors |

2 questions

- **Le NIFT-P est il vraiment une tumeur bénigne ?**
- **Peut on en faire le diagnostic en amont de la chirurgie ?**



FVPTC



| | Frequency | Mutations RAS | THADA fusion | PAX8-PPAR gamma | RET/PTC | BRAF V600E Mutation |
|--------------------|------------|---------------|--------------|-----------------|-----------|---------------------|
| Encapsulated FVPTC | 50% | 23% | 11.5% | 11.5% | 0% | 0% |

**La plupart des NIFT-P présentent des altérations moléculaires: néoplasmes
Aucune des altérations moléculaires associées au PTC: BRAFV600E/RET
Les mutations les plus fréquentes sont RAS/PPARG/gène de fusion THADA**

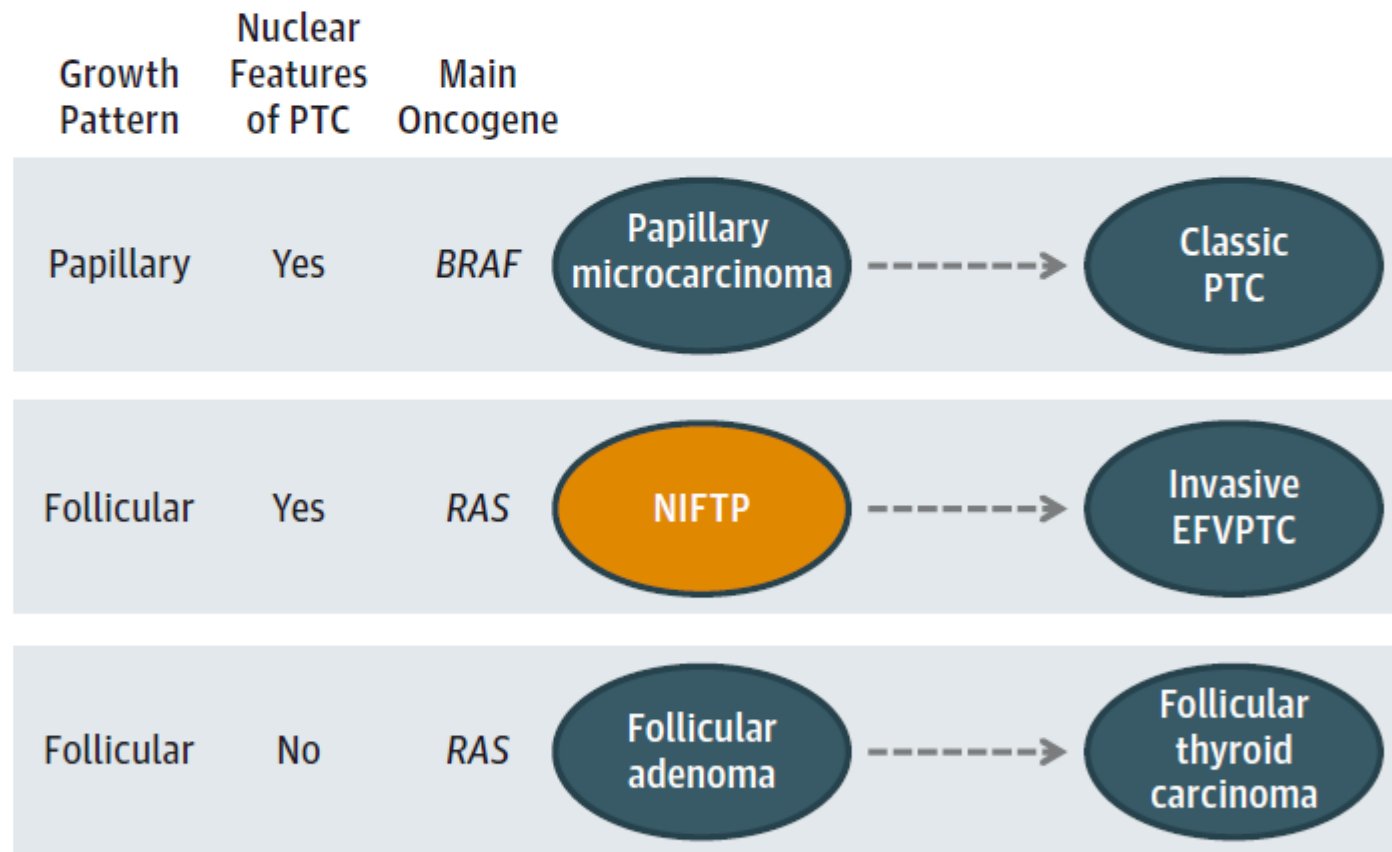
eTable 7. Summary of cases used as a validation set for three-point nuclear scoring scheme

| Case Number | Nuclear Score | | | Total Score (Mean) | Molecular results |
|-------------|-------------------------------|--------------------------------|----------------------------------|--------------------|---------------------|
| | Nuclear size and shape (Mean) | Membrane irregularities (Mean) | Chromatin characteristics (Mean) | | |
| A49 | 0.91 | 1.00 | 0.91 | 2.82 | <i>THADA</i> fusion |
| A157 | 0.14 | 0.09 | 0.05 | 0.27 | NEG |
| A123 | 0.82 | 0.55 | 0.82 | 2.18 | <i>PAX8/PPARG</i> |
| A124 | 1.00 | 0.64 | 0.95 | 2.59 | <i>HRAS</i> |
| A152 | 0.14 | 0.18 | 0.50 | 0.82 | NEG |
| A158 | 0.09 | 0.09 | 0.00 | 0.18 | NEG |
| A145 | 1.00 | 0.86 | 1.00 | 2.86 | <i>NRAS</i> |
| A129 | 0.82 | 0.95 | 0.91 | 2.68 | <i>THADA</i> fusion |
| A153 | 0.77 | 0.14 | 0.00 | 0.91 | NEG |
| A137 | 1.00 | 1.00 | 0.82 | 2.82 | <i>PAX8/PPARG</i> |
| A138 | 1.00 | 0.91 | 1.00 | 2.91 | <i>NRAS</i> |
| A151 | 0.05 | 0.09 | 0.05 | 0.18 | NEG |
| A150 | 0.05 | 0.00 | 0.00 | 0.05 | NEG |
| A140 | 1.00 | 0.73 | 0.77 | 2.50 | <i>PAX8/PPARG</i> |
| A156 | 0.05 | 0.05 | 0.00 | 0.09 | NEG |
| A141 | 0.86 | 0.68 | 0.95 | 2.50 | <i>HRAS</i> |
| A155 | 0.18 | 0.50 | 0.09 | 0.77 | NEG |
| A131 | 0.82 | 1.00 | 1.00 | 2.82 | <i>ALK</i> fusion |
| A149 | 0.50 | 0.09 | 0.32 | 0.91 | NEG |
| A143 | 1.00 | 0.50 | 1.00 | 2.50 | <i>NRAS</i> |
| A154 | 0.23 | 0.23 | 0.09 | 0.55 | NEG |
| A130 | 1.00 | 0.82 | 1.00 | 2.82 | <i>THADA</i> fusion |
| A146 | 0.14 | 0.09 | 0.23 | 0.45 | NEG |
| A147 | 0.45 | 0.27 | 0.27 | 1.00 | NEG |
| A144 | 0.86 | 0.86 | 1.00 | 2.73 | <i>NRAS</i> |
| A148 | 0.32 | 0.18 | 0.23 | 0.73 | NEG |

References

- **Sule Canberk**, Zubair W. Baloch,, Fernando Schmitt Diagnosis of Non-invasive Follicular Tumor with Papillary-like Nuclear Features (NIFTP): A Practice Changer for Thyroid Fine-needle Aspiration Interpretation ***BJCM 2017***
- **Yuri E. Nikiforov**, role of molecular markers in thyroid nodule management: then and now ***Endocrine Practice*** rapid electronic article in press
- **Jen-Fan Hang**, William H. Westra, David S. Cooper, Syed Z. Ali, The Impact of Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features on the Performance of the Afirma Gene Expression Classifier ***Cancer Cytopathology 2017***

Figure 2. Putative Scheme of Thyroid Carcinogenesis



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- **Journal of Basic & Clinical Medicine**
2017, 6 (1):1-2

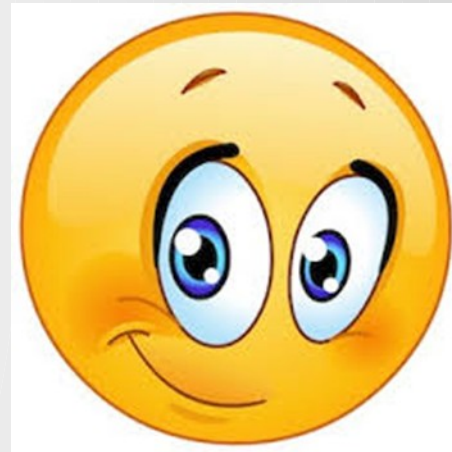
Chapter 2A: Borderline/precursor tumor category

Table 1: WHO classification of thyroid tumors in the 4th edition

| | |
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| 19 | Secondary Tumors |

2 questions

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- **Peut on en faire le diagnostic en amont de la chirurgie ?**



W Faquin, Cancer Cytopathology, 2015

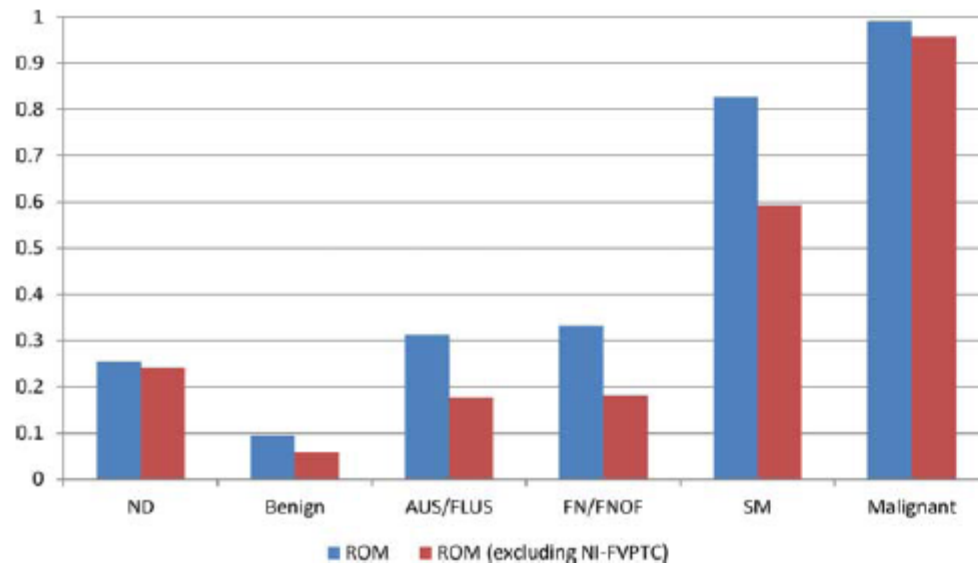


Figure 2. Impact of reclassifying NI-FVPTC on ROM for the categories of The Bethesda System for Reporting Thyroid Cytopathology. AUS/FLUS indicates atypia of undetermined significance/follicular lesion of undetermined significance; FN/FNOF, follicular neoplasm/follicular neoplasm with onco-cytic features; ND, nondiagnostic; NI-FVPTC, noninvasive follicular variant of papillary thyroid carcinoma; ROM, risk of malignancy; SM, suspicious for malignancy.

TABLE 2. FINE-NEEDLE ASPIRATION DIAGNOSTIC CATEGORIES

| <i>FNA diagnosis</i> | <i>Total cases (%)</i> | <i>Benign diagnoses</i> | <i>Malignant diagnoses</i> | <i>NFVPTC diagnoses</i> | <i>% ROM</i> | <i>% ROM if NFVPTCs nonmalignant</i> | <i>% Absolute decrease in ROM</i> | <i>% Relative decrease in ROM</i> |
|-----------------------|------------------------|-------------------------|----------------------------|-------------------------|--------------|--------------------------------------|-----------------------------------|-----------------------------------|
| Nondiagnostic | 53 (8.1) | 43 | 10 | 1 | 18.9 | 17.0 | 1.9 | 10 |
| Benign ^a | 167 (25.5) | 145 | 22 | 13 | 13.2 | 5.4 | 7.8 | 59 |
| AUS/FLUS ^b | 97 (14.8) | 59 | 38 | 17 | 39.2 | 21.6 | 17.6 | 45 |
| SFN | 88 (13.4) | 48 | 40 | 7 | 45.5 | 37.5 | 8.0 | 18 |
| SUS | 94 (14.4) | 12 | 82 | 39 | 87.2 | 45.7 | 41.5 | 48 |
| POS | 156 (23.8) | 2 | 154 | 8 | 98.7 | 93.6 | 5.1 | 5 |
| Total | 655 | 309 | 346 | 85 | 52.8 | 39.8 | 13.0 | 25 |

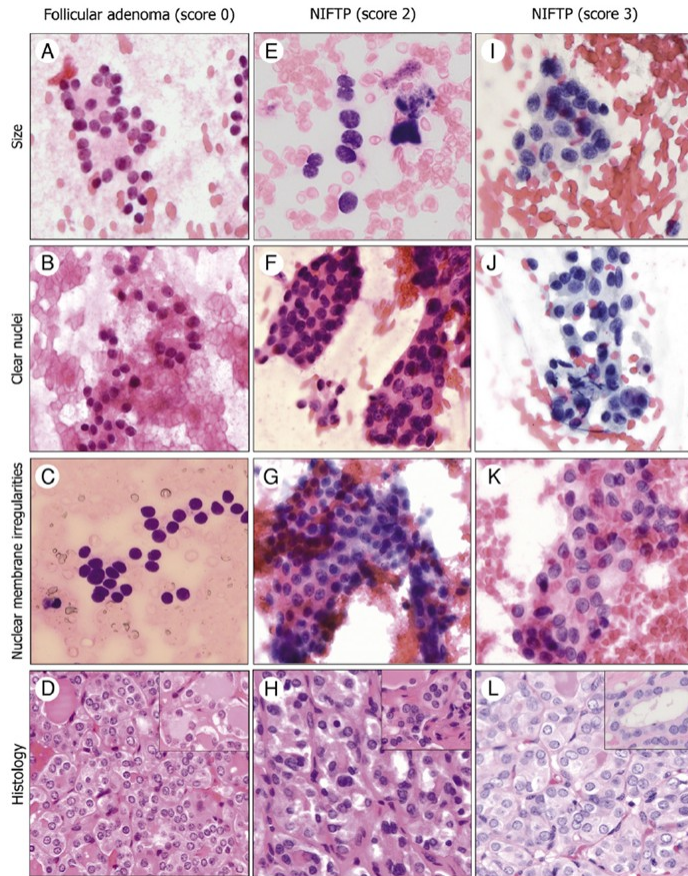
The table includes the number of benign, malignant, and NFVPTC cases in each FNA diagnostic category, the risk of malignancy (ROM) given the current characterization of NFVPTC as carcinoma, the ROM if NFVPTC was not considered carcinoma, the resulting absolute decrease in ROM, and the resulting relative decrease in ROM.

^aReferred for surgery because of large nodule size, compressive symptoms or suspicious clinical or sonographic findings.

^bReferred for surgery because of persistent AUS/FLUS cytology, or suspicious clinical or sonographic findings.

Bethesda et NIFT-P

F. Maletta



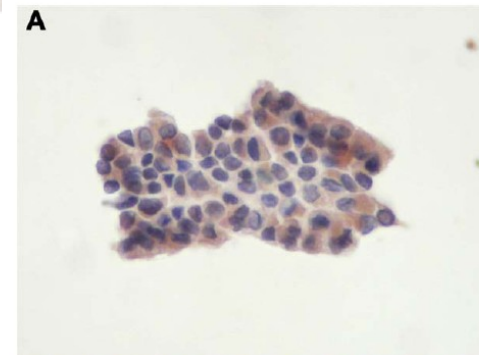
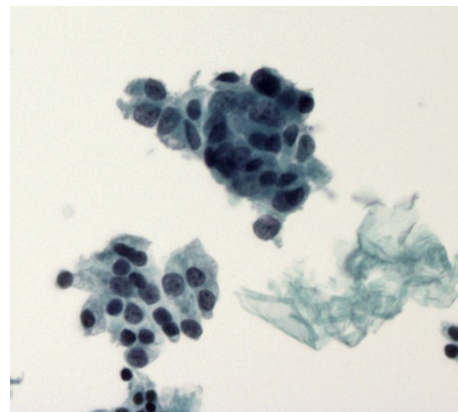
- **NIFT-P se distingue des nodules bénins**

- **56% NF**
- **27% SM**
- **15% ASI**
- **2% malin KP**

- **Malin:**
calcifications/papilles/inclusions

NIFT-P : un challenge pour les cytopathologistes

- Consensus/apprentissage sur l'histologie
- Classer les ACN mineures ou modérées en ASI/LFSI
- Classer les ACN plus marquées sans architecture papillaire en **Néoplasme folliculaire** plutôt qu'en SM (Chirurgie conservatrice-lobectomie):
- Utiliser ICC/BM
- BRAF V600E et PD-L1



- Préciser le profil IHC/ICC de NIFT-P
- Corrélation avec le score radiologique (Tirads/ATA)

Chowdhury, S., Veyhl, J., Jessa, F., et al., 2016. Programmed death-ligand 1 overexpression is a prognostic marker for aggressive papillary thyroid cancer and its variants. Oncotarget 7, 32318–32328.