'hot topics in thyroid pathology'

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'hot topics in thyroid pathology'

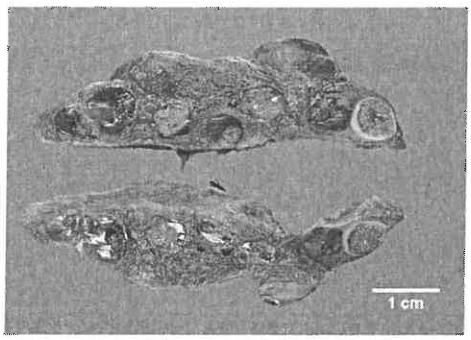
- **Well-differentiated thyroid lesions with follicular pattern** (including noninvasive follicular thyroid neoplasm with papillary-like nuclear features, NIFTP)
- **Papillary thyroid microcarcinoma**
- **Hurthle cell (oncocytic) neoplasms** (Hurthle cell adenoma vs Hurthle cell carcinoma)
- **Poorly differentiated thyroid carcinoma**
- **Mammary analogue secretory carcinoma of the thyroid**
- **IgG4-related thyroid disease**
- The role of ancillary studies (**immunohistochemistry and molecular diagnostics**) in thyroid pathology

Follicular-patterned tumors of the thyroid

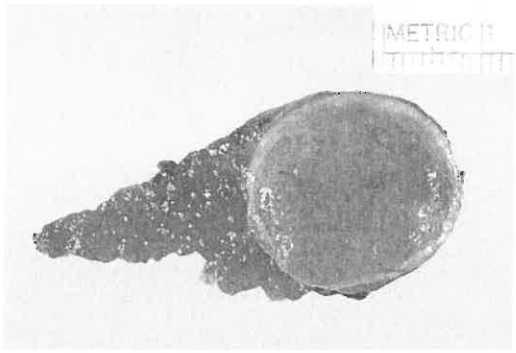
The battle of benign vs malignant vs so-called uncertain

A practical algorithmic approach

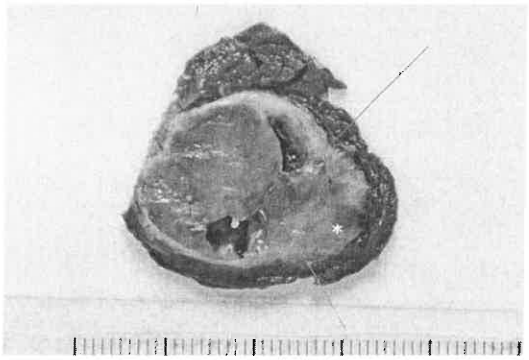
Evolution of the histologic classification of well-differentiated thyroid carcinoma: NIFTP



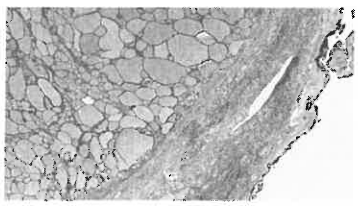
Multinodular thyroid hyperplasia



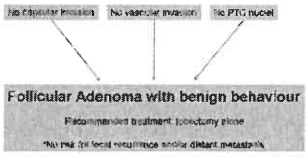
Follicular thyroid adenoma

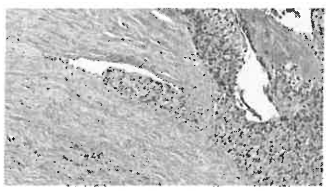


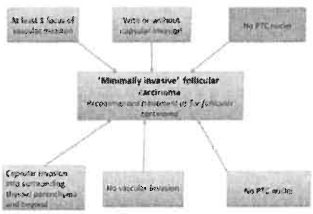
Follicular thyroid carcinoma

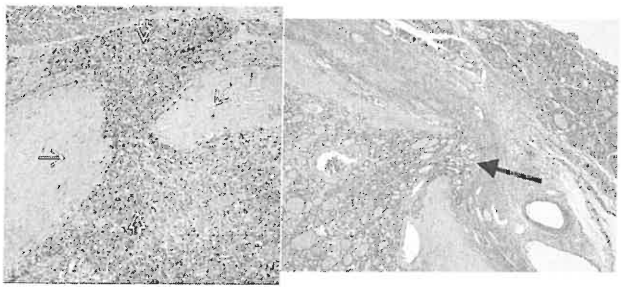


Multinodular follicular hyperplasia

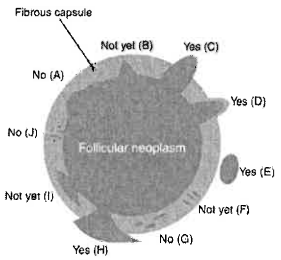






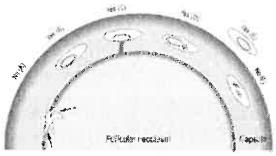


Classical 'mushroom' sign of capsular invasion



Capsular invasion (CI): Schematic drawing for the interpretation of the presence or absence of CI. The diagram depicts a follicular neoplasm (orange) surrounded by a fibrous capsule (green). **a** Installation on the inner aspect of the capsule does not represent CI, **b** sharp tumor bud invades into but not through the capsule suggesting invasion requiring deeper sections to exclude, **c** tumor totally transgresses the capsule invading beyond the outer contour of the capsule qualifying as CI; **d** tumor clothed by thin (probably new) fibrous capsule but already extending beyond an imaginary (dotted) line drawn through the outer contour of the capsule qualifying as CI; **e** satellite tumor nodule with similar features (architecture, cytomorphology) to the main tumor lying outside the capsule qualifying as CI; **f** Follicles aligned perpendicular to the capsule suggesting invasion requiring deeper sections to exclude **g** follicles aligned parallel to the capsule do not represent CI; **h** mushroom-shaped tumor with total transgression of the capsule qualifies as CI, **i** mushroom-shaped tumor within but not through the capsule suggests invasion requiring deeper sections to exclude, **j** neoplastic follicles in the fibrous capsule with a degenerated appearance accompanied by lymphocytes and siderophages does not represent CI but rather capsular rupture related to prior fine needle aspiration.

Ghossein R. Head Neck Pathol 2009;3(1):86-93



Vascular invasion (VI): Schematic drawing for the interpretation of the presence or absence of VI. The diagram depicts a follicular neoplasm (green) surrounded by a fibrous capsule (blue). **a** Bulging of tumor into vessels within the tumor proper does not constitute VI. **b** Tumor thrombus covered by endothelial cells in intracapsular vessel qualifies as VI. **c** Tumor thrombus in intracapsular vessel considered as VI since it is attached to the vessel wall. **d**Although not endothelialized, this tumor thrombus qualifies for VI because it is accompanied by a fibrin thrombus. **e** Endothelialized tumor thrombus in vessel outside the tumor capsule represents VI. **f** Artefactual dislodgement of tumor manifesting as irregular tumor fragments into vascular lumen unaccompanied by endothelial covering or fibrin thrombus.

Ghossein R. Head Neck Pathol 2009;3(1):86-93

Follicular thyroid carcinoma: histology

- **Trabecular or solid pattern of follicles** (small, normal sized or large - microfollicular, normofollicular or macrofollicular respectively)
- **No nuclear features of papillary thyroid carcinoma**
- Invasion of adjacent thyroid parenchyma, capsule (complete penetration) or blood vessels (in or beyond the capsule): **extensive sampling of capsule is recommended**
- **Capsular invasion**: **capsule is typically thickened and irregular**, needs penetration through the capsule (full thickness), may have reactive pseudocapsule around the invasion edge, exclude FNA site
- **Vascular invasion**: vessel within or beyond capsule, tumor covered with endothelium, attached to the wall or with thrombus
- May have nuclear atypia, focal spindled areas, mitotic figures (< 3/10HPF)
- **No necrosis**
- Usually no squamous metaplasia, **no psammoma bodies, no / rare lymphatic invasion**
- Metastatic follicular carcinoma can mimic normal thyroid tissue

WHO classification of Endocrine Organs, 2017

- Three types follicular thyroid carcinoma:
  - *Minimally invasive follicular carcinoma*
    - With capsular invasion only
  - *Encapsulated angioinvasive follicular carcinoma:*
    - Tumors with limited vascular invasion (< 4) have a better prognosis than those with extensive vascular invasion
  - *Widely invasive follicular carcinoma:*
    - Extensive invasion of thyroid and extrathyroidal soft tissue

Armed Force Institute of Pathology (AFIP) classification Tumors of the thyroid and parathyroid glands, 2016

- Two types follicular carcinoma:
  - *Minimally invasive follicular carcinoma*
    - With capsular invasion (not obvious, need to search)
    - With limited (fewer than 4 vessels) vascular invasion
    - With extensive (4+ vessels) vascular
  - *Widely invasive follicular carcinoma*

Extent of vascular invasion and extra-thyroid extension

- In addition to tumor type and size, other features such as the morphological variant of papillary thyroid carcinoma (e.g. tall and columnar cell variants), the **presence** of and **extent of vascular invasion and extrathyroidal extension**, have been shown to provide additional predictive value and are routinely included in a standardized histopathology report

Extent of vascular invasion

- The extent of vascular invasion is one criterion being adopted by several renowed clinical guidelines for initial **risk stratification**
- **The extent** (rather than the existence) of vascular invasion in tumors **a prognostic factor in low grade (well-differentiated) thyroid carcinomas**
- With minimal vascular invasion (defined as a few microscopic foci by National Comprehensive Cancer Network-NCCN, and as less than 4 foci by American Thyroid Association-ATA guidelines) are associated with a low risk of recurrence (0-5%) with an overall similar outcome to those without vascular invasion in low grade (well-differentiated) thyroid carcinoma
- While **the prognostic value of vascular invasion in universally accepted in follicular (and Hurthle cell) carcinoma**, it is still a matter of debate whether vascular invasion is an independent predictor of poor outcome in *PTC?*

Collini P, Samprieto G, Pilotti S. Histopathology 2004;44:35-39
Ito Y, Hirokawa M, Masuoka H, et al. Endocr J 2013;60:637-642
Lang W, Choritz H, Hundeshagen H. Am J Surg Pathol 1986;10:246-255
Wreesmann VB, Nixon IJ, Rivera M, et al. Thyroid Off J Am Thyroid Assoc 2015;25:503-508

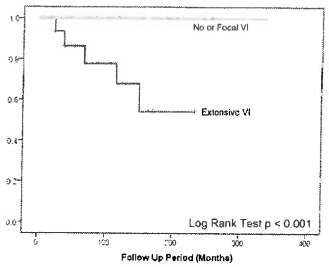


Figure 4. Extensive vascular invasion (VI) is correlated with decreased recurrence free survival in 267 patients with encapsulated low grade follicular cell derived carcinoma (log-rank test, $p < 0.001$). In contrast patients with no or focal VI (<4 vessels) have a very good outcome. Modified from reference[17] with permission.

Xu B, Wang L, Tuttle RM, et al. Hum Pathol 2015;46:1789-1798

Extrathyroidal extension (ETE)

- ETE, defined as **tumor extension beyond the thyroid capsule into the adjacent tissues**, is a common pathologic finding in **papillary thyroid carcinomas**
- ET has long been considered as an adverse prognostic factor and is associated with an increased risk of recurrence and mortality
- ETE can be further divided into two categories: **minimal ETE** and **extensive (gross) ETE**
- *Minimal ETE* is invasion into the immediate perithyroidal soft tissue or sternothyroid muscle, detected typically **at microscopic level** only
- *Extensive ETE* is **usually established clinically** during the operation and is defined a direct extension into subcutaneous tissue, adjacent viscera (e.g. larynx, trachea, and esophagus), or recurrent laryngeal nerve

Xu B, Ghossein R. Eur J Surg Oncol 2017. Ahead of print

Minimal (microscopic) extrathyroidal extension

- **The definition of minimal ETE is problematic and subjective as universal pathologic criteria are lacking**, and the thyroid is devoid of a well-defined capsule and often intermingled with adipose tissue or even skeletal muscle at its periphery
- Not suprisingly, the **interobserver agreement for minimal ETE is poor** among expert endocrine pathologists
- From a practical point of view, this is however not a problem since recent studies have shown that **minimal ETE alone does not significantly impact recurrence free survival.**
- Rather, it is gross ETE that is a strong predictor for recurrence and disease specific death

Su HK, Wenig BM, Haser GC, et al. Thyroid Off J Am Thyroid Assoc 2016;26:512-517

Ito Y, Tomoda C, Uruno T, et al. Surg Today 2006;36:12-18

Shin JH, Ha TK, Park HK, et al. Int J Surg 2013;11:944-947

Ito Y, Tomoda C, Uruno T, et al. World J Surg 2006;30:780-786

Xu B, Ghossein R. Eur J Surg Oncol 2017. Ahead of print

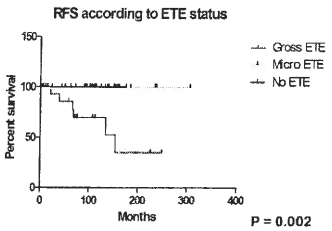
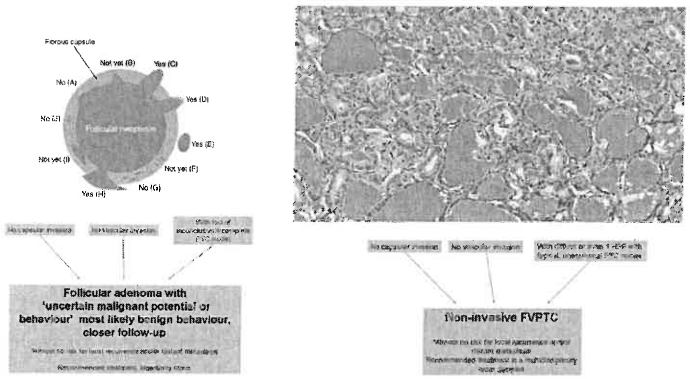
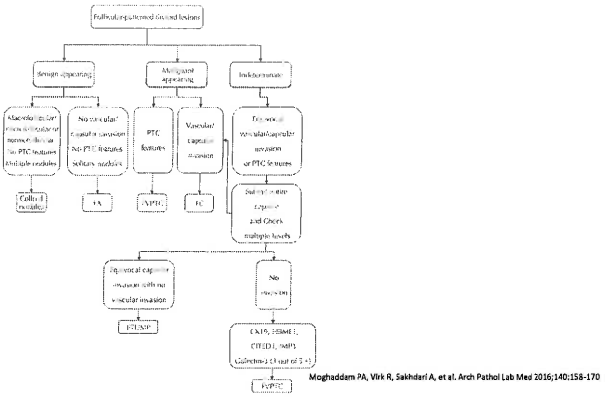


Figure 5. Adverse outcome (defined as the presence of disease at last follow-up) according to degree of extra-thyroid extension (ETE) in papillary thyroid carcinoma cases with adequate follow-up. Only patients with gross ETE (15 cases) had an adverse outcome. There was no survival difference between patients without ETE (11 cases) and those with microscopic (micro) ETE (31 cases). Reprinted with permission from reference.[12]

Rivera M, Ricarte-Filho J, Tuttle RM, et al. Thyroid Off J Am Thyroid Assoc 2010;20:1085-1093





Moghaddam PA, Virk R, Sakhdari A, et al. Arch Pathol Lab Med 2016;140:158-170

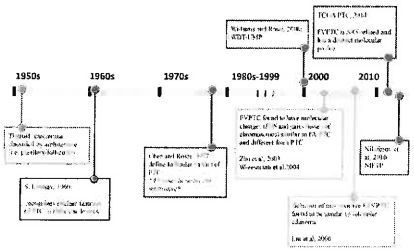


Figure 1. Timeline depicting the changes in the histologic definitions and classification of well differentiated thyroid carcinoma. The references pertaining to the above time points are as follows: Lindsay S,[4] Chen and Rosai,[6] Williams ED et al.,[7] Zhu et al.,[8] Wreesmann et al.,[9] Liu J et al.,[10] the Cancer Genome Atlas Research Network,[11] Nikiforov Y et al.[12] PTC: papillary thyroid carcinoma; FA: Follicular adenoma; FC, follicular carcinoma; WDT-UMP, well differentiated tumor of uncertain malignant potential"; FVPTC, follicular variant of papillary thyroid carcinoma; EFVPTC, encapsulated follicular variant of papillary thyroid carcinoma; TCGA, the cancer genome atlas research network, NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features

Xu B, Ghossein R. Eur J Surg Oncol 2017. Epub ahead of print

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Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma:

A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

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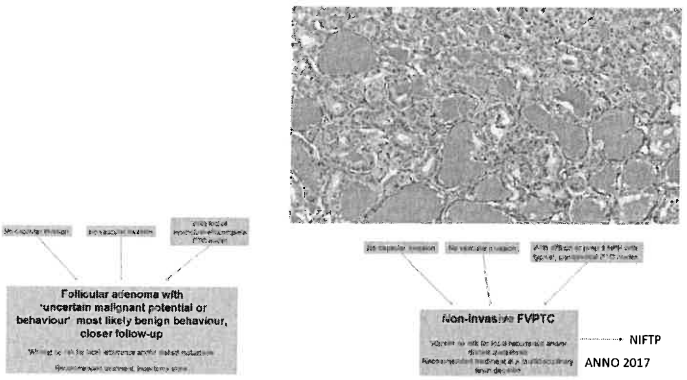
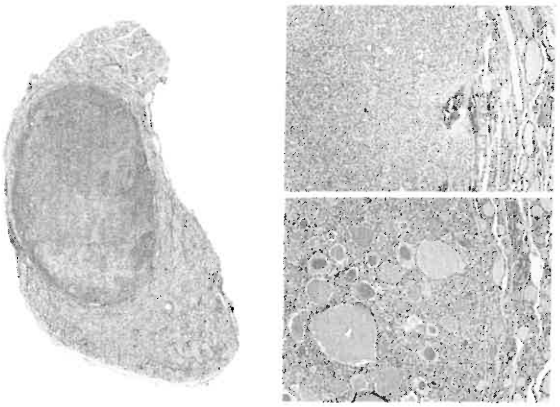
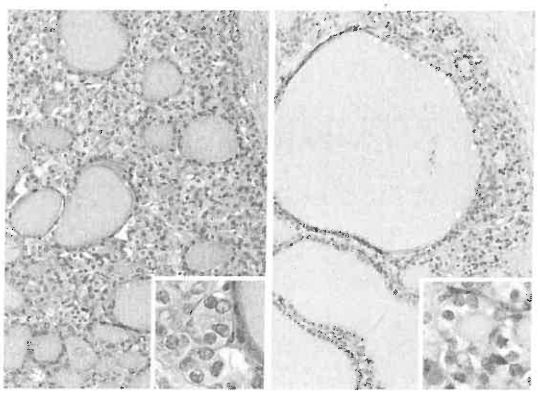
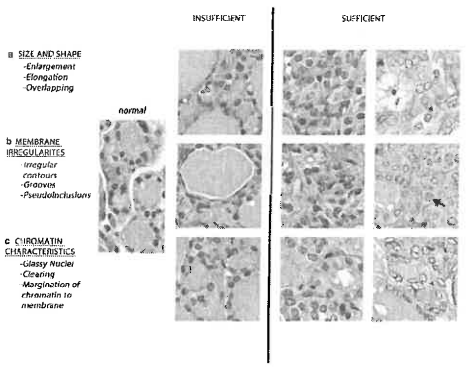
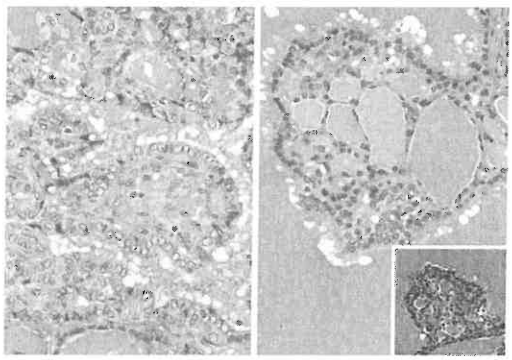
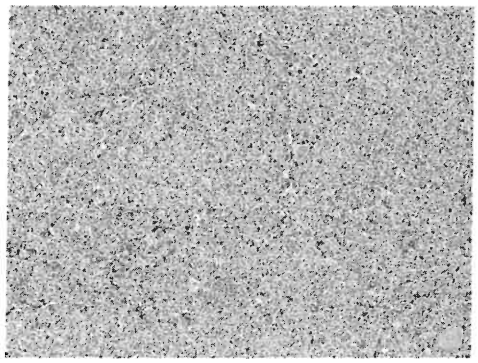

Follicular adenoma with 'uncertain malignant potential or behaviour' most likely benign behaviour, closer follow-up
Non-invasive FVPTC
NIFTP
ANNO 2017



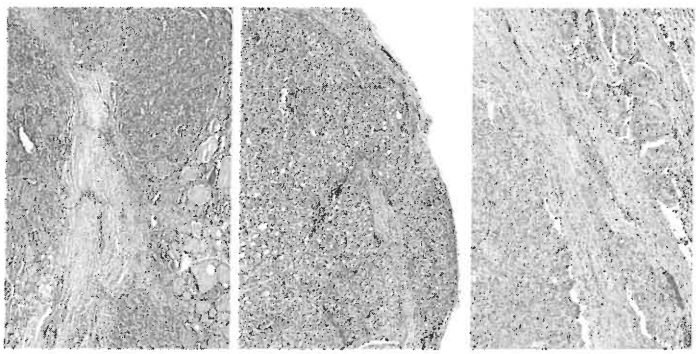



INSUFFICIENT
SUFFICIENT
a SIZE AND SHAPE
-Enlargement
-Elongation
-Overlapping
normal
b MEMBRANE IRREGULARITES
-Irregular contours
-Grooves
-Pseudoinclusions
c CHROMATIN CHARACTERISTICS
-Glassy Nuclei
-Clearing
-Margination of chromatin to membrane

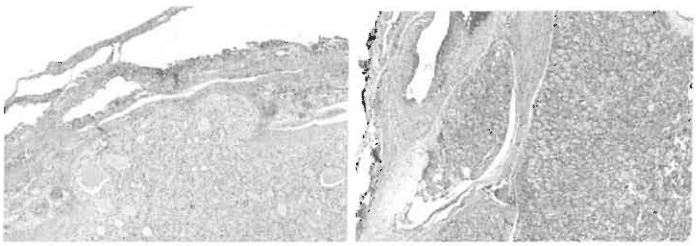




>30% solid/trabecular/insular growth NOT compatible with a diagnosis of NIFTP



Capsular and vascular invasion are NOT compatible with diagnosis of NIFTP!!



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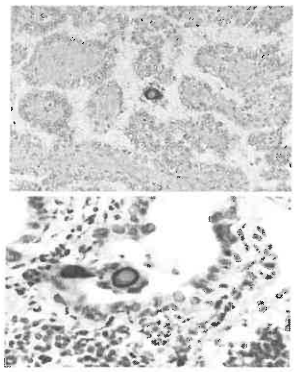
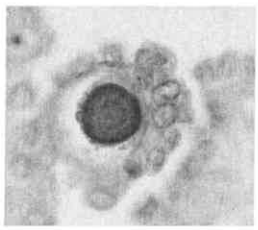
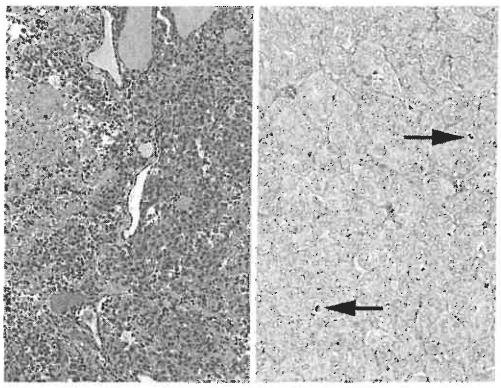
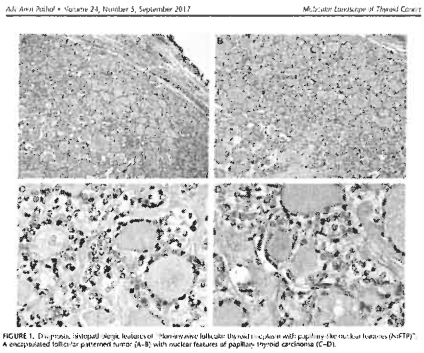


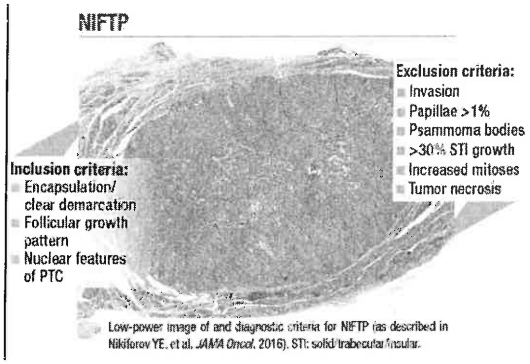




Necrosis and increased mitotic activity are NOT compatible wit diagnosis of NIFTP!!

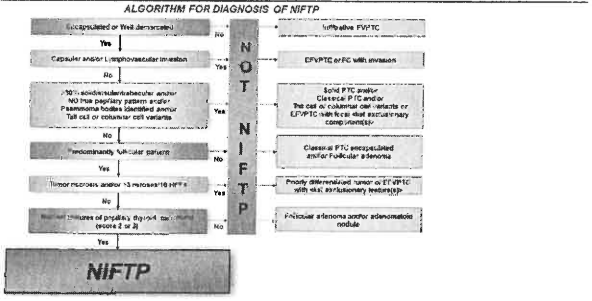


Basolo F, Macerola E, Ugolini C, et al. Adv Anat Pathol 2017;24:252-258



Low-power image of and diagnostic criteria for NIFTP as described in Nikiforov YE, et al. *JAMA Oncol*. 2016). STI: solid/trabecular/insular.

Table 1 An algorithm for the diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclei (NIFTP)



Seethala RJ, Baloch ZW, Barletta JA, et al. Mod Pathol 2017;1-17

Table 3 Summary of grossing and reporting guidelines

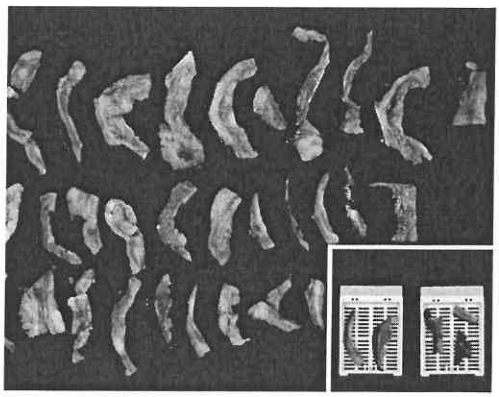
Grossing recommendations

- The entire tumor capsule or tumor–normal interface is submitted for histologic evaluation
- For large lesions, stepwise submission of sections for a limited number (if any) until invasion is found or the luminal border is entirely submitted is acceptable
- Multiple sections can be submitted per block, including the tumor periphery and its junction to the parenchyma
- In the setting of multinodular disease given identification of a fine needle tract may be beneficial to capture the lesion of interest
- For lesions with excessively overcooked nuclear features of papillary carcinoma but without exclusion criteria on initial sectioning, additional sections of the central portion should be submitted to exclude the presence of papillary thyroid carcinoma component

Reporting parameters

- NIFTP does not require a formal staging (i.e. no AJCC or UICC stage)
- Certain oncologic parameters are redundant (i.e. the absence of vascular invasion)
- A limited data set consisting of tumor size, laterality and margin status may be useful
- Ancillary immunohistochemical markers such as HBME-1 and Galectin-3 should be applied with caution.
- During this current period of transition, a comment linking NIFTP to its prior designation as non-invasive encapsulated well-demarcated papillary thyroid carcinoma is recommended.

Seethala RJ, Baloch ZW, Barletta JA, et al. Mod Pathol 2017;1-17



Papillary thyroid microcarcinoma

Incidence and epidemiology

Pathologic features

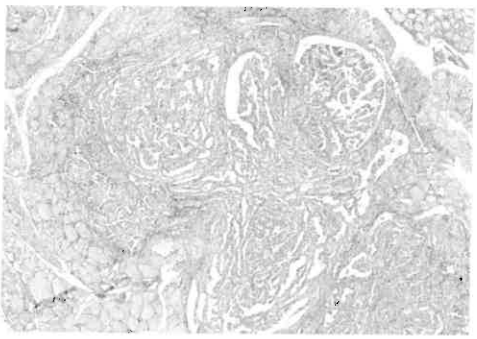
Should all papillary thyroid microcarcinomas be aggressively treated????

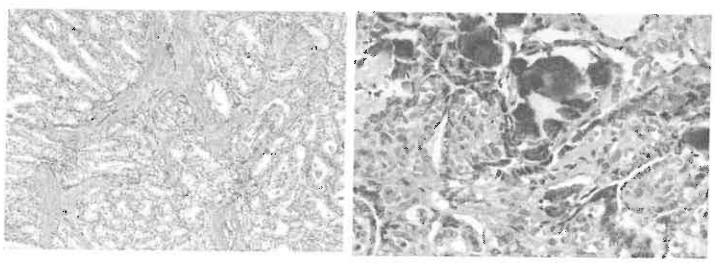
Papillary thyroid microcarcinoma (PTMC)

- PTMC is defined by **size of 1 cm or less in greatest diameter**
- According to a recent study, PTMC constitutes **approximately half of the papillary thyroid carcinomas in patients older than 45 years** *
- The increase in incidence has been partly attributed to the increased detection by widespread use of ultrasonography and FNA to diagnose and monitor thyroid nodules
- In autopsy studies, incidental PTMC incidence has been reported to be in the range of 6% to 36% **

*Hughes DT, Haymart MR, Miller BS, et al. Thyroid 2011;21(3):231-236

**Lang W, Borrusch H, Bauer L. Am J Clin Pathol 1988;90(1):72-76





Papillary thyroid microcarcinoma (PTMC)

- *An entity requiring consideration for reclassification???*
- Subcentimeter PTMCs are **extremely indolent but often overtreated as well**
- Some have suggested in 2003 renaming the incidental PTMCs as *'papillary microtumor'*
- This new nomenclature was however never adapted since, in contrast to NIFTP, **some PMTC give rise to lymph node and distant metastasis**
- **?Histological risk stratification**
- If a molecular marker can help separate the rare 'bad actors' from the vast majority of extremely indolent PTMCs, the relabeling of the indolent tumors will be feasible, and would greatly impact upon treatment deescalation!!

Papillary thyroid microcarcinoma (PTMC)

- **Several studies have tried to identify high-risk features and improved risk stratification in PTMC for optimal management**
- Traditionally, older age, male sex, tumor size, tumor multifocality, vascular invasion, and lymph node metastasis have been linked to the high-risk behavior
- **Extrathyroidal extension** and **lymph node metastasis** have been shown to be important predictors of locoregional recurrence in PTMC
- **Peripheral location of PTMC** has been identified as one of the aggressive features
- Another **unfavorable histologic feature** is the **presence of aggressive variants** (e.g. tall cell and columnar cell variant of microcarcinoma)
- Using the size of PTMC to predict biologic behavior has produced variable results

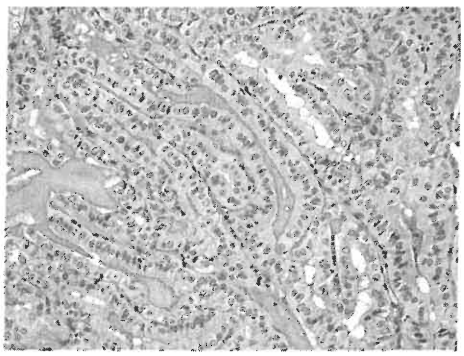
Zhou YL, Gao EL, Zhang W, et al. World J Surg Oncol 2012;10:67

Kuo EJ, Goffredo P, Sosa JA, et al. Thyroid 2013;23(10):1305-1311

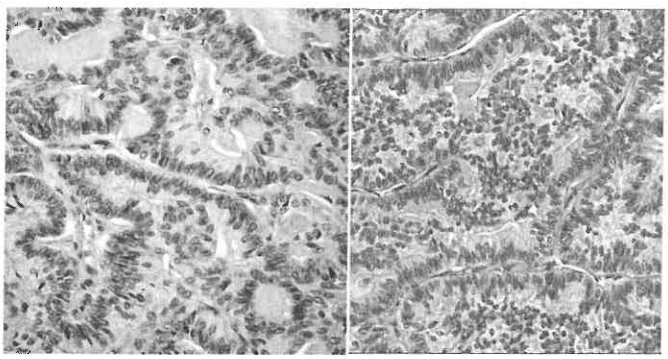
Niemeier LA, Kuffner AH, Song C, et al. Cancer 2012;118(8):2069-2077

Piana S, Ragazzi M, Tallini G, et al. Hum Pathol 2013;44(4):556-565

Bernstein J, Virk RH, Hui P, et al. Thyroid 2013;23(12):1525-1531



Tall cell variant



Columnar cell variant

Papillary thyroid microcarcinoma (PTMC)

- **BRAF V600E gene mutation** has been reported in PTMC in the range of 40% to 70%, similar to PTC greater than 1 cm.
- **BRAF V600E-mutated PTMCs have distinct morphologic features** when compared with BRAF V600E wild-type PTMCs
- Mutated tumors are more likely to have infiltrative interface with nonneoplastic thyroid parenchyma and tumor-associated stroma reaction including fibrosis and/or desmoplastic reaction
- **Niemeier et al proposed a scoring system based on histologic and molecular features for risk stratification** PTMC that included **superficial tumor location*, **intraglandular spread*, and **tumor fibrosis* with **BRAF V600E status*
- While the association between BRAF V600E mutation and aggressive histopathologic features such as microscopic extrathyroidal extension and lymph node metastasis is appreciable, **prospective randomized studies are needed to establish an association with poor outcome**

Virk RK, Van Dyke AL, Finkelstein A, et al. Mod Pathol 2013;26(1):62-70

Finkelstein A, Levy GH, Hui P, et al. Histopathology 2012;60(7):1052-1059

Gouveia C, Can NT, Bostrom A, et al. JAMA Otolaryngol Head Neck Surg 2013;139(11):1164-1170

Niemeijer LA, Kuffner AH, Song C, et al. Cancer 2012;118(8):2069-2077

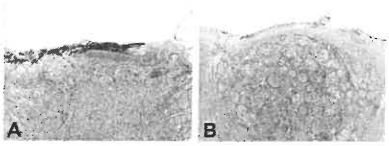


Figure 2.
Superficial tumor location as a histological feature contributing to the molecular-pathological score included tumor location immediately at the surface of the thyroid, with extrathyroidal extension (**A**) or without extrathyroidal extension (**B**).

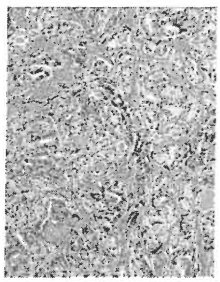


Figure 3.
Significant (2+) sclerosing-type tumor fibrosis that contributed to the molecular-pathological score.

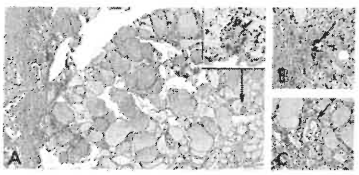
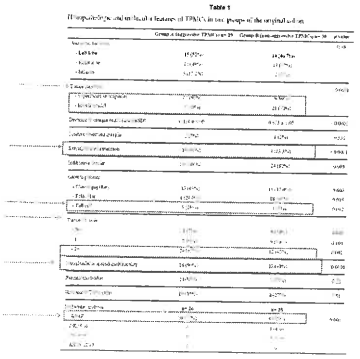


Figure 4.
Criteria for intraglandular tumor spread (IGS) included (**A**) small tumor focus separated from the main tumor mass by a layer of benign thyroid parenchyma (arrow and inset), (**B**) isolated psammoma bodies in the thyroid stroma (arrow), or (**C**) tumor aggregates within the lymphatic channels(arrow).

Table 3

MP scores in the validation cohort of TPMCs and risk of more aggressive tumor behavior

MP_C score	0–2	3	4
MP_N score	0–7	8–10	12
TPMCs with aggressive behavior (n=5)	0	2	3
TPMCs with no evidence of aggressive behavior (n=55)	25	8	2
Risk category (Probability of extrathyroidal spread or recurrence)	LOW (0)	INTERMEDIATE (20%)	HIGH (60%)



Oncocytic ('Hurthle') cell neoplasms

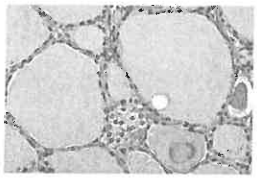
What is a 'Hurthle cell'?

- Hurthle cells are cells that have undergone **oncocytic change**
- Oncocytic change pertains to the cellular change characterized by an **abundant eosinophilic granular cytoplasm due to accumulation of altered mitochondria**
- This change **occurs in inflammatory diseases and when a cell is subjected to similar stress**, these cells are found in irradiated thyroids, ageing thyroids, nodular goiter, chronic lymphocytic thyroiditis/Hashimoto thyroiditis and longstanding Graves' disease
- Oncocytic change can occur in any type of cell and Hurthle cells are **not exclusively seen in the thyroid gland** (e.g. parathyroid, pituitary, adrenal cortex, pancreas, gut, lungs, parotid gland, kidney, breast,...)

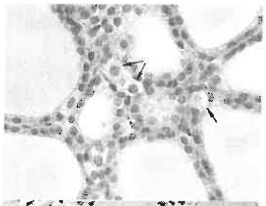
Hurthe cell

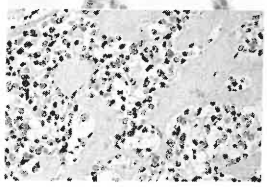
- It is actually wrong to ascribe the Hurthle cell to the German histologist Karl W Hurthle because what he described initially were the parafollicular or C cells
- It was Askenazy who initially described these oncocytic cells (1898)

Karl W Hurthle



Parafollicular cells or C cells



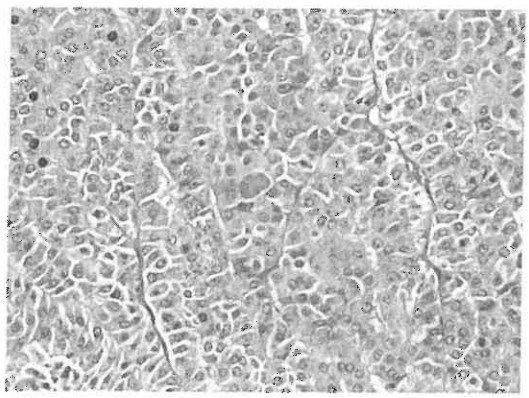


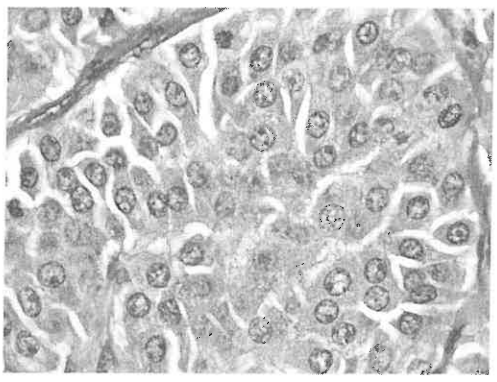
Medullary thyroid carcinoma

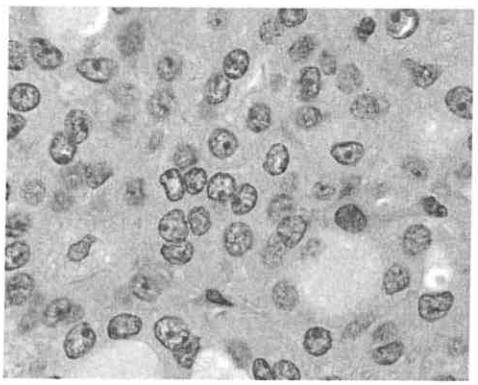
Unfortunately Ewing, in 1919,[28] introduced the misnomer of Hürthle cell for the human thyroid oxyphil cell when in reality Hürthle had described the canine C cell (Fig. 1). This error led Hamperl to lodge a vigorous appeal[44,45] against the term "Hürthle cell" and proffered the term

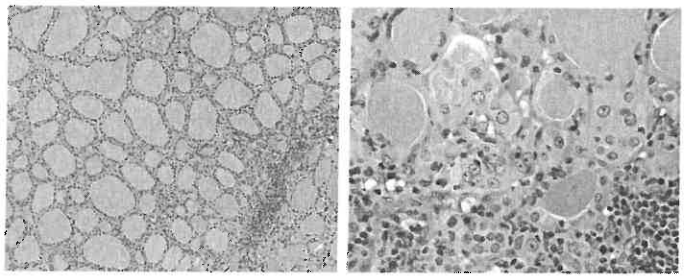
Hurthle cell: histology

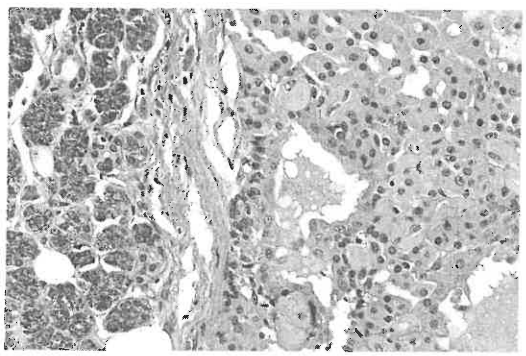
• Cellular features on light microscopy using H&E staining
-large cell size
-polygonal to square
-distinct cell borders
-voluminous granular and eosinophilic cytoplasm
-large nucleus with enlarged nucleolus



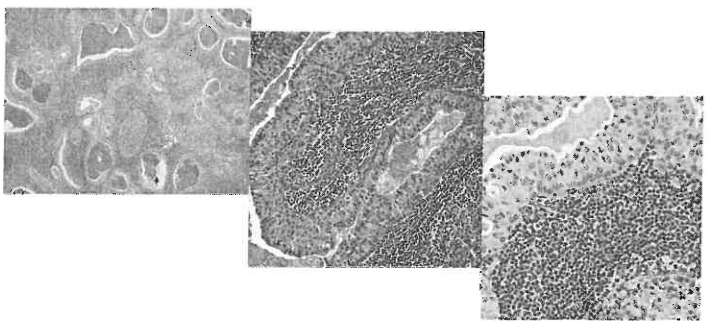




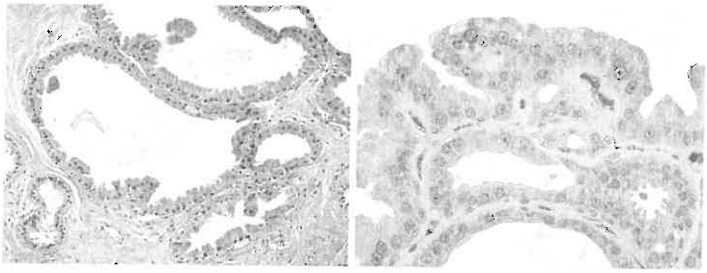




Oncocytic change in parotid gland



Oncocytic changes in a Whartin Tumor (parotid gland)



Apocrine metaplasia in breast

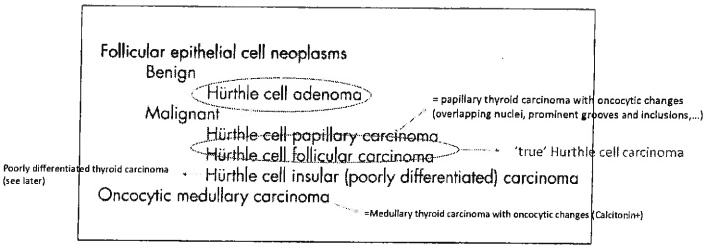
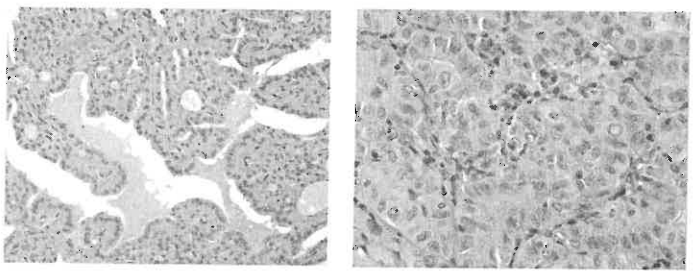


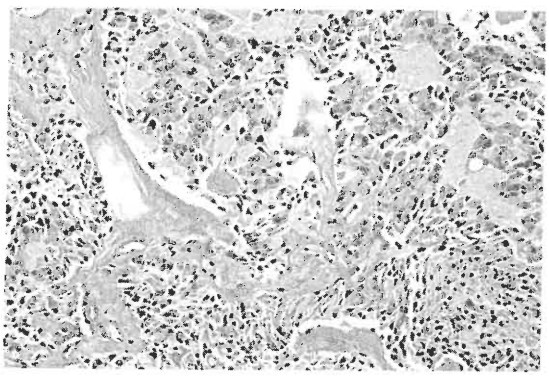
Figure 13 The classification of oncocytic thyroid neoplasms.

Asa SL. J Clin Pathol 2004;57:225-232

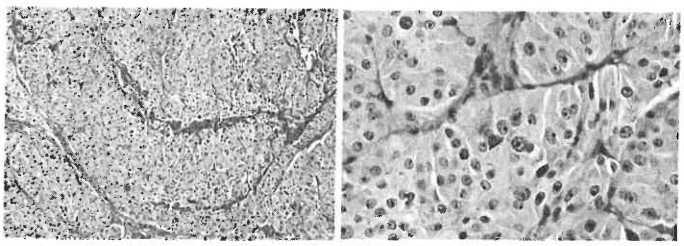
The WHO classifies Hurthle cell carcinoma of the thyroid as follicular carcinoma, 'oxyphilic cell type'



Papillary thyroid carcinoma with oncocytic changes



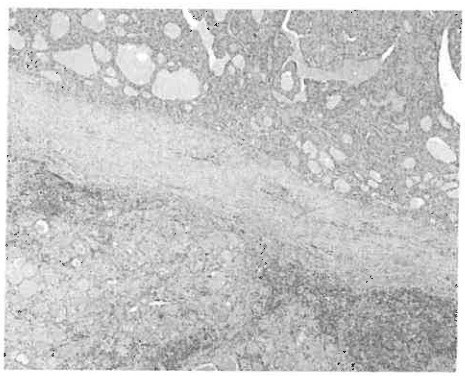
Medullary thyroid carcinoma with oncocytic changes



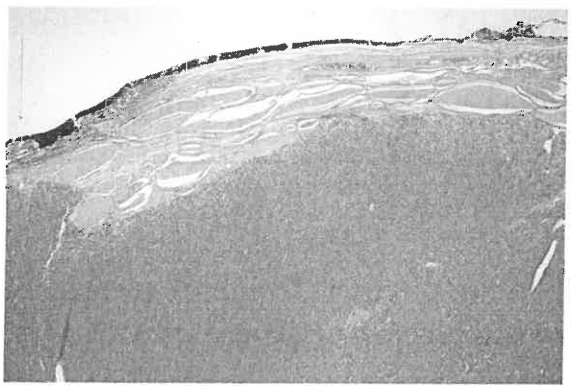
Poorly differentiated oncocytic (Hurthle cell) thyroid carcinoma

Hurthle cell adenoma vs Hurthle cell carcinoma

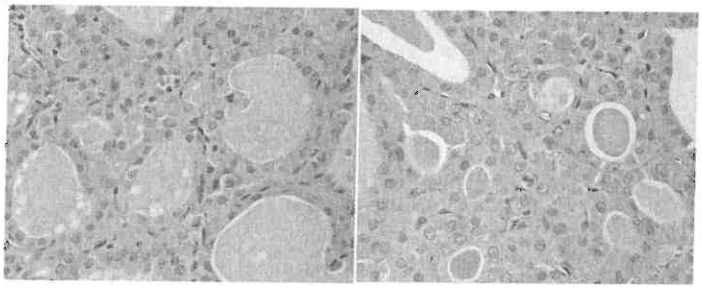
- Hurthle cell nodules are so-called if **>75% of a lesion is composed of this cell type**
- **The criterion for follicular tumors is applied in determining whether a Hurthle cell nodule is benign or malignant**
- Hurthle cell adenoma lacks capsular or vascular invasion
- Hurthle cell carcinoma: presence of capsular and/or vascular invasion
- Hurthle cell carcinoma are further subtyped into minimally invasive and widely invasive tumors



Hurthle cell adenoma

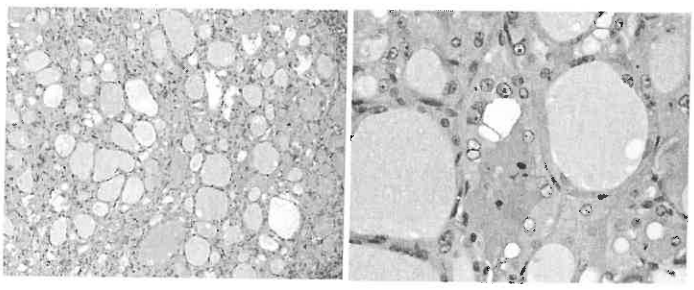


Hurthle cell carcinoma



Hurthle cell carcinoma

CHALLENGING CASES.....



invasive tumor of thyroid with follicular growth pattern and striking Hurthle cell morphology: Hurthle cell (follicular) carcinoma of papillary thyroid carcinoma?

Poorly differentiated thyroid carcinoma

The story of poorly differentiated thyroid carcinoma: from Langhans' description to the Turin proposal via Juan Rosai

Poorly differentiated thyroid carcinoma

- Since the **original description in 1983**, a long debate has occurred on the very nature of this tumor, on its morphological diagnostic features, on its molecular profile and on its clinical significance
- Was defined as **' a thyroglobulin-producing non-follicular non-papillary thyroid carcinoma, having an intermediate behaviour between well-differentiated and anaplastic carcinomas'**
- In the **2004 WHO classification**, PDTC was introduced as **a separate'entity** and its recognition was based on both architectural (non-follicular/non-papillary growth pattern) and high-grade features (invasive growth, high mitotic index and necrosis)
- The **proposed WHO criteria were still controversial** and heterogeneously applied in diagnostic practice (overlap with tumor categories, including the solid and the tall cell variant of PTC on the one side and FTC with predominant solid/trabecular growth pattern on the other)
- As a result of discussions in Turin in 2006 diagnostic criteria were made more specific by a consensus of expert thyroid pathologists with a proposed diagnostic algorithm (**'Turin proposal', 'Turin criteria'**)

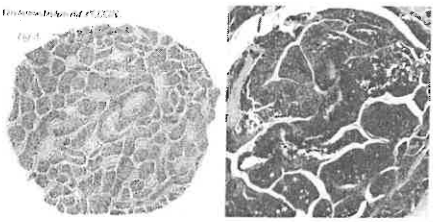


Fig. 1 – Comparison between the original drawing in the article by Dr. Langhans[5] and a typical case of "insular" thyroid carcinoma.

'poorly differentiated 'insular' thyroid carcinoma

Volanti M, Bussolati G, Papotti M. Sem Diagn Pathol 2016;33:277-283

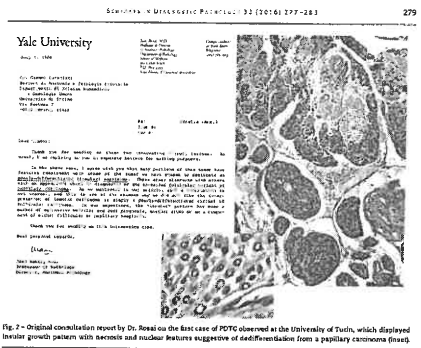


Fig. 2 – Original consultation report by Dr. Rosai on the first case of PDTC observed at the University of Turin, which displayed insular growth pattern with necrosis and nuclear features suggestive of dedifferentiation from a papillary carcinoma (inset).

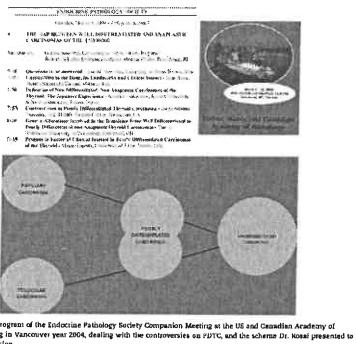


Fig. 3 – Original program of the Endocrine Pathology Society Companion Meeting at the US and Canadian Academy of Pathology meeting in Vancouver year 2004, dealing with the controversies on PDTC, and the scheme Dr. Rosai presented to introduce the session.

Fig. 5 – Dr. Rosai handwriting the first scheme of the proposed PDTC diagnostic algorithm.

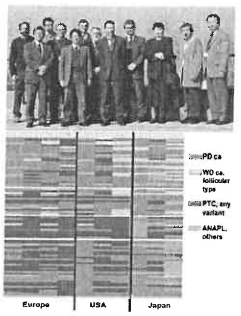
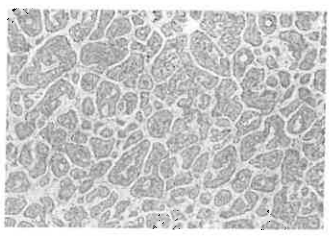
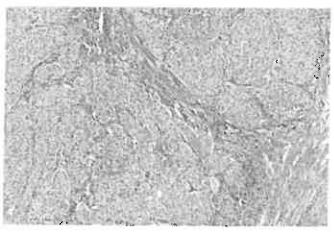
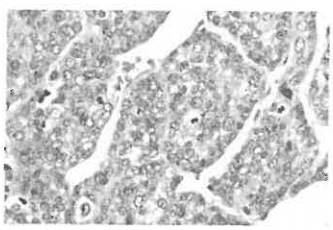


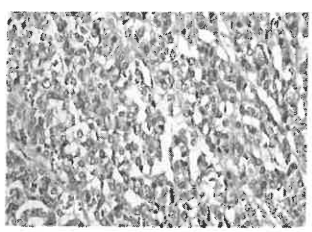
Fig. 4 – Consensus meeting on PDTC in Turin, March 3rd–4th 2006—picture of the participants and a scheme illustrating the disagreements prior to the meeting on PDTC diagnosis (PD ca, green color).

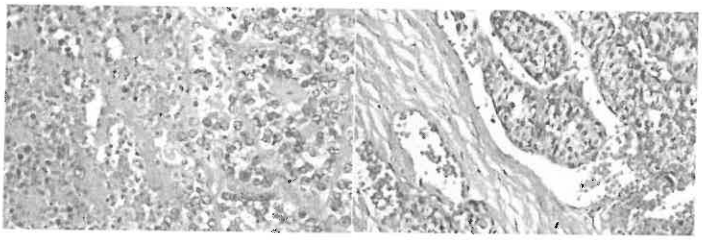
of papillary carcinoma. The subsequent discussion eventually brought to a consensus that was summarized by Dr. Rosai on behalf of the whole group (Fig. 4) in the proposed diagnostic algorithm, currently termed the "Turin proposal." The entity PDTC was, therefore, defined by the following diagnostic criteria: (i) presence of a solid/trabecular/insular pattern of growth in a malignant (invasive) thyroid lesion of follicular derivation (the extent was originally not clearly indicated. In the WHO book, "the majority of the tumor" is mentioned as a requirement [4]; (ii) lack of the conventional papillary carcinoma nuclear features, which keeps PDTC apart from the solid variant of papillary carcinoma; and (iii) presence of at least one of these features—mitotic activity $>3 \times 10$ HPF or tumor necrosis or convoluted nuclei. These latter are defined as nuclei smaller and darker than those in papillary carcinoma, round and hyperchromatic with convolutions of the nuclear membrane ("raisin-like" contours). Later on, a Japa-

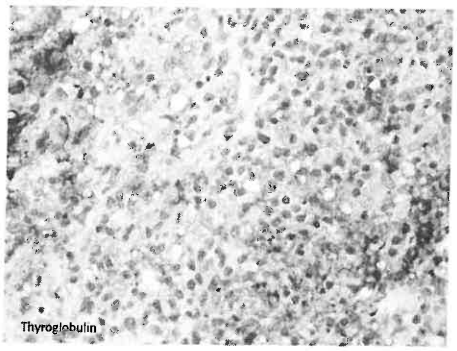


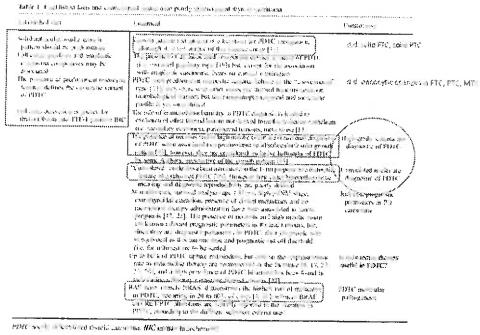


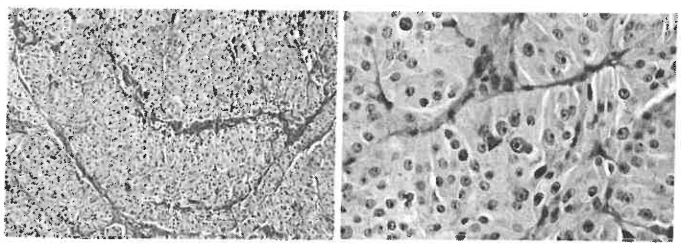




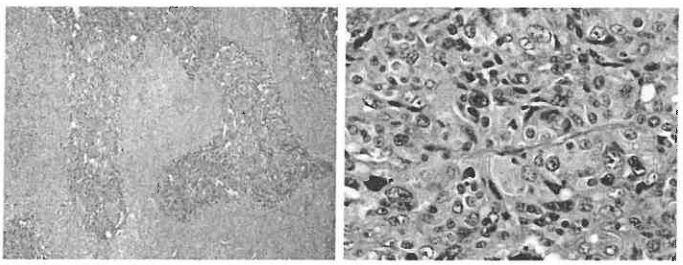




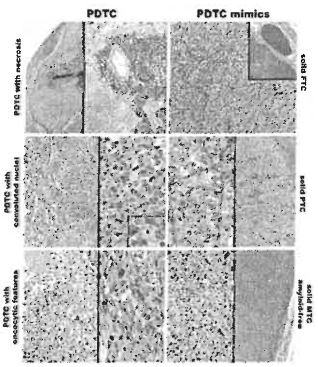




Poorly differentiated oncocytic (Hurthle cell) thyroid carcinoma



Poorly differentiated oncocytic (Hurthle cell) thyroid carcinoma



Volanti M, Bussolati G, Papotti M. Sem Diagn Pathol 2016;33:277-283

Poorly differentiated thyroid carcinoma (PDTC)

- PDTC accounts for **4% to 7% of all thyroid cancers** but the overall prevalence is difficult to establish due to regional variations
- PDTC seems to be **more frequent in iodine deficient areas such as northern Italy or the alpine European region** and less frequently in North America
- PDTC usually occurs in **older individuals**, with a mean age of 55 years and a slight female predominance
- Cases of PDTC in the pediatric population are rare
- PDTC has an **aggressive clinical behaviour intermediate between of well-differentiated thyroid cancer and undifferentiated (anaplastic) thyroid carcinoma** ('concept of intermediate prognosis follicular cell derived thyroid carcinoma')
- Clinically, PDTCs **often present at an advanced stage** with extrathyroidal extension and a propensity for **local recurrence** and frequent relapse
- These tumors **tend to metastasize to regional lymph nodes, lung and bones**, but other sites such as liver and brain have also been observed
- The current mean 5-years survival of patients with PDTC is approximately 50%
- On the molecular level, **RAS mutations (42%) are the most common finding**. Additional molecular alterations: BRAF V600E mutations, high mutation burden, increased chromosomal complexity, frequent **TERT promoter mutation (30%)**

Volanti M, Bussolati G, Papotti M. Sem Diagn Pathol 2016;33:277-283

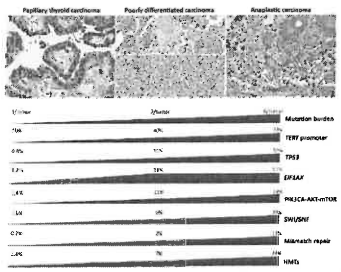


Figure 6 Stepwise molecular pathogenesis of thyroid carcinomas. Genetic profiles of papillary thyroid carcinoma (PTC), poorly differentiated thyroid carcinoma (PDTC), and anaplastic carcinoma (ATC) reveal a stepwise progression of thyroid carcinoma characterized by increased mutation burden and greater frequency of mutations in *TERT* promoter, *TP53*, *EIF1AX*, PIK3CA-AKT-mTOR pathway, SWI/SNF complex, mismatch repair genes, and histone methyltransferase-DNMTs. Microscopic pictures of RAS+ lesions from PTC (top left), ATC (top right), and PDTC (bottom center) with upper picture representing PDTC diagnosed by the MSKCC criteria only and lower picture showing PDTC fulfilling both MSKCC and Turin proposal. Below are the rates of genetic alterations in each histotype. Reprinted with permission from reference [7]

Xu B, Ghossein R. Eur J Surg Oncol 2017. Ahead of print

Mammary analog secretory carcinoma of the thyroid gland: A primary thyroid adenocarcinoma harboring *ETV6–NTRK3* fusion

Sitharthan Degett[1], Lu Wang[1], Ryan N Pradhan[1], Robert R Benson[2], Jatin P Shah[1], Eric J Sherman[3], R Michael Tuttle[1], Ivana A Fagin[4], David S Klimstra[1], Nora Katabi[1] and Ronald A Ghossein[1]

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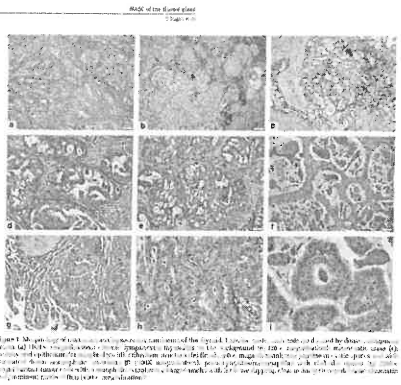
ETV6–NTRK3 fusion was identified in several cancers including the recently described mammary analog secretory carcinoma (MASC) of the salivary glands and a minority of papillary thyroid carcinomas. We describe three cases of primary MASC of the thyroid gland and provide a detailed clinical and pathological characterization of the tumor morphology, immunoprofile, and genetic background. Immunohistochemistry for PAX8, TTF-1, thyroglobulin, mammaglobin, GCDFP-15, S-100 protein, and p63 was used to define the tumor immunophenotype. Fluorescence in situ hybridization for *ETV6* rearrangement was performed in slides, and the next-generation sequencing assay MSK-IMPACT (Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets) was performed in two cases. Primary MASC of the thyroid occurred in two women and one man, age 47–72 years. All patients presented with high T stage, infiltrative, locally aggressive tumors with extrathyroidal extension. Two cases were associated with well-differentiated papillary thyroid carcinoma. Histologically, they appeared as low-grade tumors, resembling MASC of the salivary glands and labeled positive for mammaglobin, GCDFP-15, S-100 protein, p63, weakly positive for PAX8, and negative for TTF-1 and thyroglobulin. Fluorescence in situ hybridization revealed *ETV6* rearrangement in all cases. In two tested cases MSK-IMPACT confirmed the presence of *ETV6–NTRK3* gene fusion. Two patients had at least two local recurrences, one was alive with disease, and one was alive and free of disease after 18 and 17 years, respectively. The third patient was alive and free of disease after 2 years. MASC of the thyroid is histologically, immunophenotypically, and genetically similar to its salivary gland counterpart. Thyroid MASC can be associated with a well-differentiated papillary thyroid carcinoma component, supporting follicular cell origin. Clinically, these carcinomas may show frequent recurrences but are associated with long-term survival. Patients with MASC of the thyroid may potentially benefit from its molecular-targeted therapy.

Laboratory Investigation (2016) 96, 1064–1075; doi:10.1038/labinvest.2016.82; published online 15 August 2016

MASC of thyroid

MASC of the thyroid, comparable with recently described cases in the salivary glands and the breast, is histologically characterized by **uniform cells with vesicular nuclei and eosinophilic vacuolated cytoplasm**, arranged in **tubular, microcystic, cribriform, (pseudo)papillary and solid growth patterns** often divided by **dense fibrous septa**, and with abundant PAS-positive colloid-like secretory material. MASC is typically positive for **S-100 protein, (focal) PAX8**, mammaglobin, vimentin, and cytokeratins, namely **CK7** and **CK19**, and can be focally positive for **p63**. **Negative for TTF1 and Thyroglobulin.** Similar to its breast and salivary counterpart, MASC harbors a recurrent balanced chromosomal translocation t(12;15)(p13;q25) leading to ***ETV6–NTRK3* gene fusion.** The reported cases showed the behavior of **a low-grade adenocarcinoma**.



IgG4-related thyroid disease

IgG4-related disease (IgG4-RD)

- Recently recognized syndrome characterized by **mass-forming lesions with lymphoplasmacytic infiltration, an increased number of IgG4+ cells in the affected tissues, and elevated serum IgG4 levels**
- It is usually found in middle-aged and older patients, with men predominantly affected, and normally has a **favorable clinical response to steroid therapy**
- The earliest description of this syndrome was a subtype of autoimmune pancreatitis, although it is now recognized as a **multisystem disorder**

IgG4-related disease (IgG4-RD)

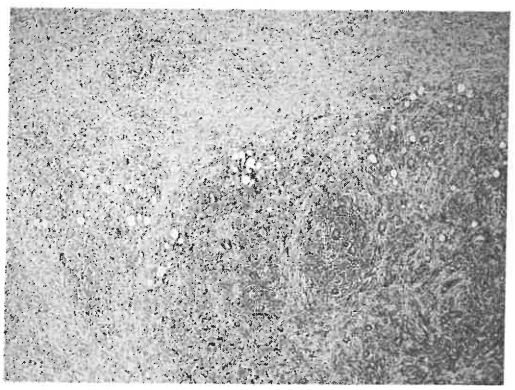
- IgG4-RD can **affect virtually any organ system** including salivary glands, lacrimal glands, periorbital tissues, **thyroid gland**, liver, biliary tract, **kidneys** (tubulointerstitial nephritis, glomerulonephritis), retroperitoneum (retroperitoneal fibrosis), lungs (inflammatory pseudotumor), mediastinum, aorta, meninges and pituitary gland
- In most patients with IgG4-RD, **2 or more sites in various combinations are involved**
- The **mechanisms** responsible for this disease remain **unclear**

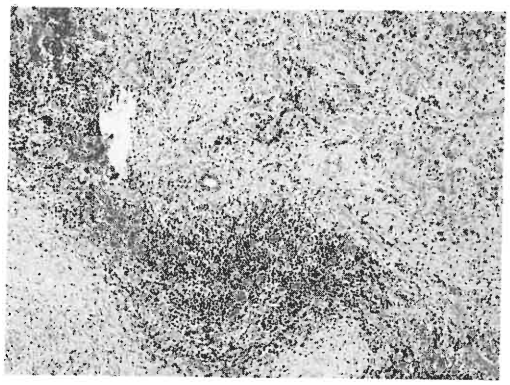
IgG4-related disease (IgG4-RD)

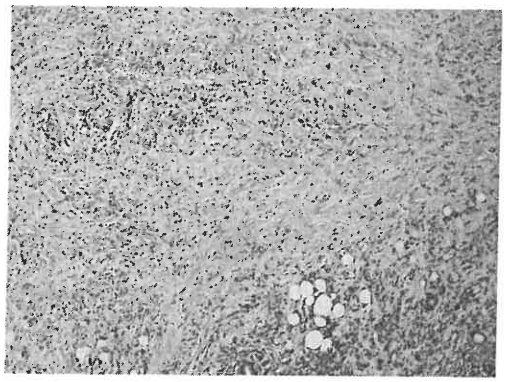
- The disease generally presents with **enlargement of one or more organs**
- **The involvement of multiple organs**, and **a disease that evolves over many years (occasionally decades)**, is a particularly characteristic feature of IgG4-RD
- **Clinically**, the disease is characterized by **tumefactive lesions, often multicentric, that show a swift response to immunosuppressive therapy**
- **An elevated serum IgG4** represents the only validated blood based biomarker. However, elevated serum IgG4 is detected **in only half** the patients with this disease

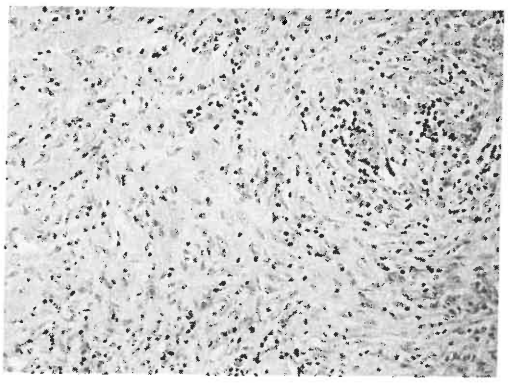
IgG4-related disease (IgG4-RD)

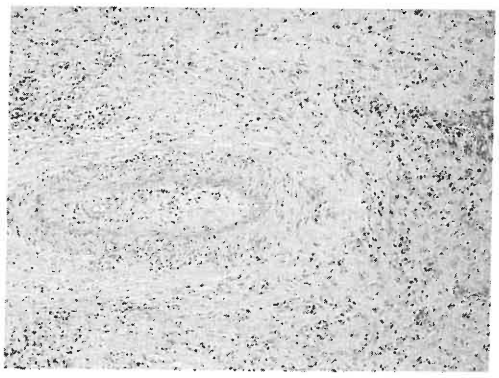
- **Histology** is the **gold standard for the diagnosis of IgG4-RD**: storiform-type fibrosis, obliterative phlebitis, elevated numbers of IgG4 positive plasma cells and an IgG4 to IgG ratio greater than 40%
- In isolation, elevated numbers of IgG4 positive plasma cells represents a non-specific feature, detected in a variety of other inflammatory as well neoplastic diseases
- Attention to the clinical context, histological features, as well an elevated IgG4 to IgG ratio is critical to avoiding overdiagnosis of IgG4-RD

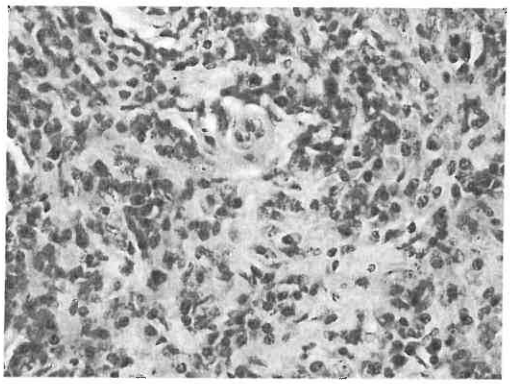


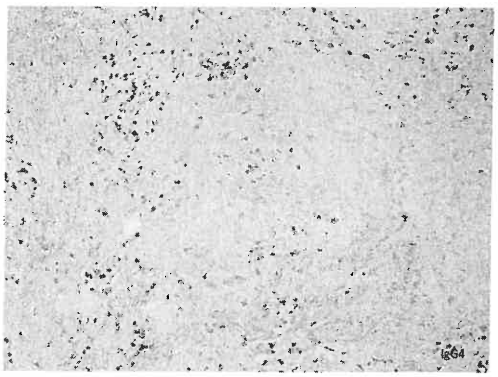












IgG4-related disease (IgG4-RD)

- **IgG4-RD mimics a variety of inflammatory and neoplastic diseases**, and in an individual case the diagnostic possibilities depend significantly on the site of disease as well the clinical presentation

- In my experience, many of these patients are subjected to multiple biopsies, often prompted by a clinical appearance that mimics a malignancy

- **More recently, overdiagnosis of IgG4-RD has emerged**-driven primarily by an over reliance on the IgG4 stain: **mistaking malignancy for IgG4 related disease represents the most significant pitfall** (lymphoma-sarcoma) ! (elevated serum IgG4 levels in some patients with malignancy, and/or a peritumoral lymphoid infiltrate that is rich in IgG4 positive plasma cells)

- The key is to avoid relying solely on serum and tissue IgG4 levels

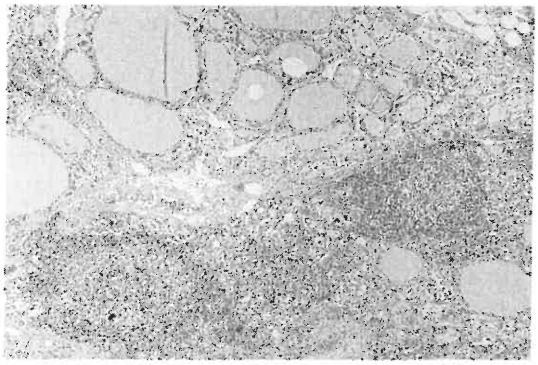
1. Presence of tumefactive lesions involving organs commonly affected by IgG4 related disease such as the pancreas, liver, salivary glands, pachymeninges, retroperitoneum, lung, and lymph nodes, among others.
2. Involvement of multiple organs (listed above), either synchronously or metachronously.
3. Subacute onset without rapid onset of constitutional features.
4. Presence of elevated serum IgG4.
5. Elevated plasmablast levels [9, 16].
6. Swift response to immunosuppressive therapy. However, it should be recognized that a variety of other inflammatory diseases (and some neoplastic diseases, albeit temporarily) could also respond to steroids.

Deshpande V. Head Neck Pathol 2015;9:24-31

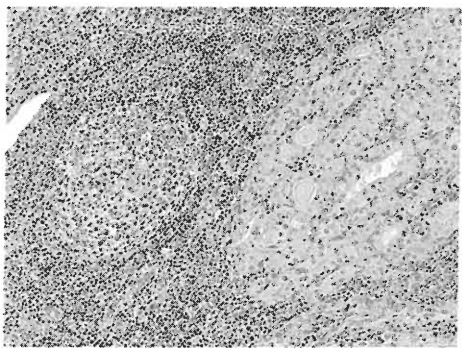
IgG4-related thyroid disease

- **Thyroid gland is one of the organs frequently involved in IgG4-RD**
- Thyroid involvement in IgG4-RD can be in the form of **Hashimoto thyroiditis (HT)** and **Riedel thyroiditis (RT)** (less commonly in this setting compared to HT)
- HT is subclassified to IgG4-thyroiditis (with increased numbers of IgG4-positive plasma cells) and non-IgG4-thyroiditis (no or few IgG4-plasma cells)
- **Histology**: *intense lymphoplasmacytic infiltration (HT>RT), *fibrosis with storiform or a perivascular onion skin pattern (RT>HT), *obliterative phlebitis (RT) and *increased numbers of polyclonal IgG4-producing plasma cells
- It has also been suggested that RT is more commonly seen in systemic pattern of IgG4-RD, while HT is more of an organ-specific type of this disease

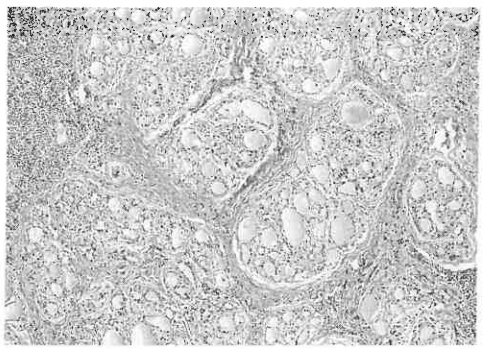
Deshpande V. Semin Diagn Pathol 2012;29(4):191-196
Pusztaszeri M, Triponez F, Pache JC, Bongiovanni M. Thyroid 2012;22(9):964-968
Stone JH. Semin Diagn Pathol 2012;29(4):177-190



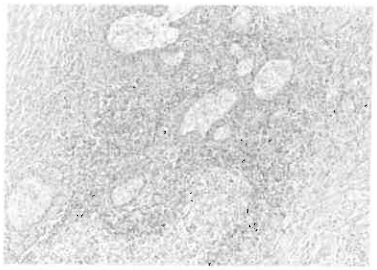
Hashimoto thyroiditis



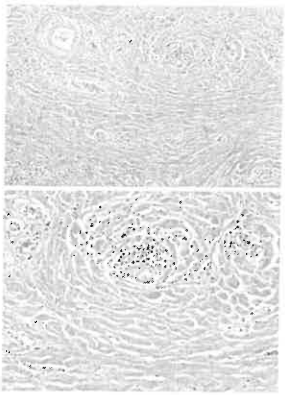
Hashimoto thyroiditis

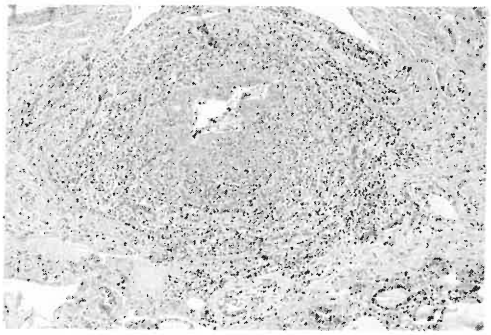


Hashimoto thyroiditis

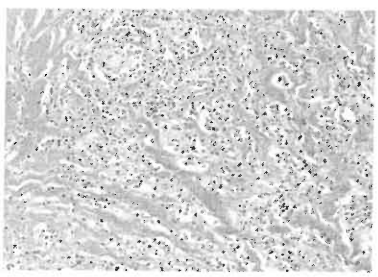


Riedel thyroiditis

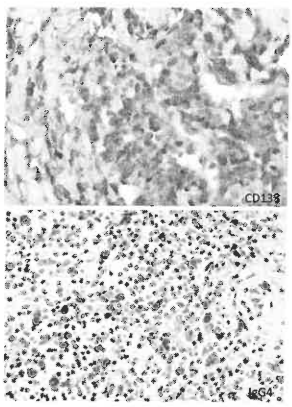




Riedel thyroiditis



Riedel thyroiditis



The role of ancillary studies in thyroid pathology

Immunohistochemistry

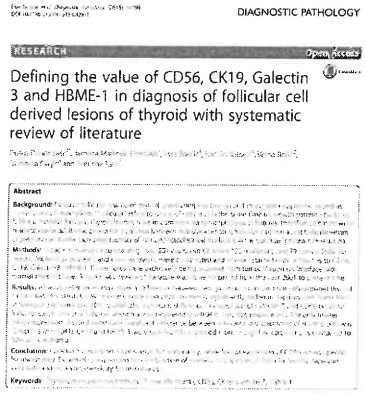
Molecular diagnostics and molecular carcinogenesis in thyroid cancer

Immunohistochemical markers in thyroid pathology

- CD56
- TPO (Thyroperoxidase)
- Cytokeratin 19
- HBME-1 (Hector Battifora mesothelial 1)
- Galectin 3 (Galactoside-binding lectin soluble 3)
- IMP3 (insulin-like growth factor messenger RNA-binding protein-3)
- TTF1 (thyroid Transcription Factor)
- Thyroglobulin
- Calcitonin
- PAX8 (paired box gene 8)
- PTH (Parathyroid hormone)
- IgG4 (see IgG4-related disease)
- BRAF (see molecular tests)

Ancillary IHC and molecular testing in follicular-patterned thyroid lesions

- The role of ancillary studies, such as IHC and molecular diagnostics, in the classification of follicular pattern thyroid lesion into benign and malignant categories is **debatable**
- There is **no single "magic marker" with high degree of sensitivity and specificity** that may aid in the differential diagnosis
- Therefore, **an approach using a panel of antibodies** has been suggested and found to be useful (CD56, Cytokeratin 19, HBME1, Galectin 3, TPO, IMP3)
- It should be emphasized that in order to reach a proper diagnosis, **morphology should always be correlated with IHC and molecular studies** !!



DIAGNOSTIC PATHOLOGY

RESEARCH Open Access

Defining the value of CD56, CK19, Galectin 3 and HBME-1 in diagnosis of follicular cell derived lesions of thyroid with systematic review of literature

Dunderovic D, Lipkovski JM, Boricic I, et al. Diagn Pathol 2015;10:196.

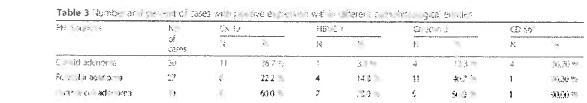


Table 3 Number and percent of cases with positive expression with different immunohistological markers

FH-Neoplasia	No. of cases	CK-19		HBME-1		Galectin-3		CD-56	
		N	%	N	%	N	%	N	%
Cystic adenoma	30	11	36.7 %	1	3.3 %	4	13.3 %	4	30.76 %
Follicular adenoma	27	6	22.2 %	4	14.8 %	11	40.7 %	1	09.09 %
Hürthle cell adenoma	10	6	60.0 %	2	20.0 %	5	50.0 %	1	9.09 %
IgG4-related sclerosing thyroiditis	12	0	0.0 %	0	0.0 %	8	66.7 %	0	0.0 %
Follicular carcinoma	15	5	33.3 %	4	26.7 %	11	73.3 %	3	75.00 %
Hürthle cell carcinoma	25	15	60.0 %	17	68.0 %	17	68.0 %	2	20.00 %
Papillary carcinoma	37	28	75.7 %	28	75.7 %	30	81.0 %	6	28.57 %

*Immunopositivity in >10 % follicular cells

Moghaddam PA, Virk R, Sakhdari A, et al. Arch Pathol Lab Med 2016;140:158-170

Our Institutional Immunohistochemistry Panel and Its Utility in Differentiation Between Follicular-Patterned Thyroid Lesions

Immunostain	Follicular Adenoma	Follicular Carcinoma	FVPTC
CK19	Usually −	Usually +	Usually +
HBME1	Usually −	Usually +	Usually +
Galectin 3	Usually −	Usually +	Usually +
IMP3	−	Usually +	Usually +
sTPO1	−	Usually +	Usually +
TTF	+	Usually +	Usually +
Ki-protein	+	−	−

Abbreviations: sTPO1, 1 HBME, Hector Battifora mesothelial 1; IMP3, insulin-like growth factor 2 mRNA-binding protein 3; PTC, papillary thyroid carcinoma; TTF1, thyroid transcription factor 1.

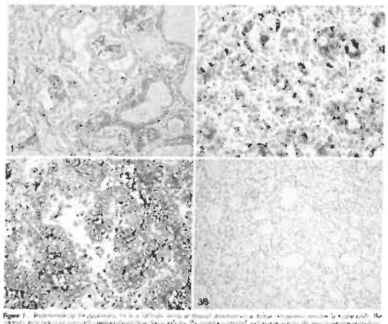
Table 1. Immunohistochemical Detection of Galectin-3 in Thyroid Surgical Specimens*	Fernandez et al	Herrmann et al	Kovacs et al	Weber et al	Prasad et al	Oestreicher-Kedem et al	Cvejic et al	Bartolazzi et al	Saggiorato et al
Normal	0 (0)	...	...	...	0 (0)	...	...	[illegible]	...
CLT	...	...	7/7 (100)	...	...	...	...	3/4 [illegible]	...
NH	0 (0)	0 (0)	...	...	16/29 [illegible]	...	...	[illegible]	...
FA	[illegible]	[illegible]	4/19 (21)	[illegible]	[illegible]	7/15 (47)	...	[illegible]	[illegible]
PTC	[illegible]	22/34 (64)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
FTC	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	7/13 [illegible]	...	54/57 [illegible]	16/19 [illegible]
OVPFTC	...	[illegible]	...	...	...	...	...	33/13 [illegible]	16/17 [illegible]
PDTC	2/3 (67)	...	...	...	...	...	...	13/20 [illegible]	...
ATC	3/3 (100)	...	...	...	[illegible]	...	...	[illegible]	...

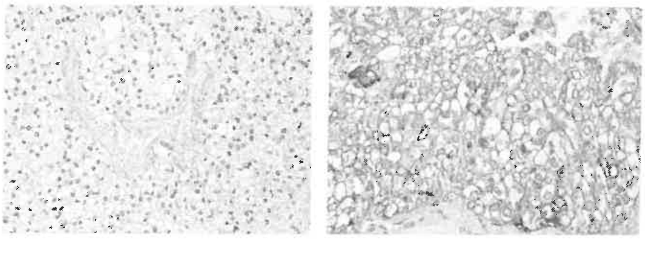
* Values are number/total number (percent). Ellipses indicate not addressed in this article; CLT, chronic lymphocytic thyroiditis; NH, nodular hyperplasia; FA, follicular adenoma; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; OVPFTC, oncocytic variant of papillary and follicular thyroid carcinoma; PDTC, poorly differentiated thyroid carcinoma; and ATC, anaplastic thyroid carcinoma.

Table 2. Immunohistochemical Detection of Hector Battifora Mesothelial (Cell) 1 (HBME-1) in Thyroid Surgical Specimens*	Cheung et al	Mase et al	Prasad et al	Choi et al	Papotti et al	Saggiorato et al	Nikiforova et al
Normal	...	...	[illegible]	...	...	...	...
NH	[illegible]	4/32 (13)	1/29 [illegible]	...	...	...	...
FA	[illegible]	17/62 (27)	2/23 [illegible]	...	3/15 (6.6)	2/30 [illegible]	3/23 (13)
PTC	[illegible]	35/36 (97.2)	[illegible]	[illegible]	14/14 [illegible]	[illegible] (94.6)	...
FTC	2/4 (50)	[illegible] (64.6)	[illegible]	[illegible]	...	[illegible] (89.5)	11/33 (34)
OVPFTC	2/7 (29)	...	1/3 [illegible]	4/6 [illegible]	...	6/17 (39)	...
PDTC	[illegible]	...	...	11/12 [illegible]	...	...	...
ATC	1/2 (50)	0/2 [illegible]	...	2/10 [illegible]	...	...	...

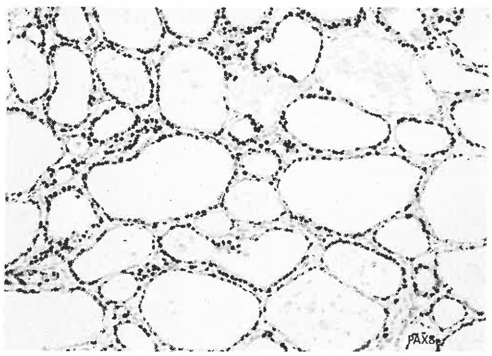
* Values are number/total number (percent). Ellipses indicate not addressed in this article; NH, nodular hyperplasia; FA, follicular adenoma; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; OVPFTC, oncocytic variant of papillary and follicular thyroid carcinoma; PDTC, poorly differentiated thyroid carcinoma; and ATC, anaplastic thyroid carcinoma.

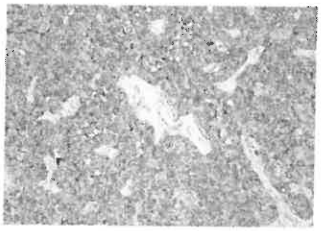
Fischer S, Asa SL. Arch Pathol Lab Med 2008;132:359-372



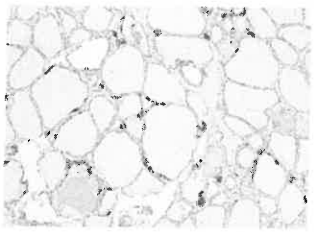


TTF-1 and Thyroglobulin expression in ' a poorly differentiated clear cell thyroid tumor'





Medullary carcinoma



C-cells in normal thyroid

Calcitonin staining

Molecular tests in thyroid lesions

- **Several molecular pathways are involved in the tumorigenesis of different types of thyroid neoplasms**
- Molecular analysis can provide useful information for both *diagnostic and prognostic purposes*
- Molecular analysis may also guide **targeted therapy** based on individual tumor characteristics
- Most molecular alterations found in thyroid neoplasms are due to 1 or 2 main mechanisms:
  - **-point mutations** (e.g. BRAF and RAS gene mutations)
  - **-gene rearrangements** (e.g. RET/PTC and PAX8/PPARG)
- **The commonly found mutations in thyroid neoplasms are typically mutually exclusive**

BRAF gene mutations

- BRAF V600E is the **most commonly observed genetic alteration in papillary thyroid carcinoma** (PTC), which is found in almost half of the classic PTC cases
- BRAF gene mutations are more often seen in the tall cell variant of PTC (70-80%)
- BRAF gene mutations are also commonly found in anaplastic thyroid carcinoma
- BRAF gene mutations are **rarely detected in well-differentiated follicular neoplasms**
- **BRAF gene mutations** have shown some correlation with extrathyroidal invasion, cervical lymph node and distant metastases, resistance to radioactive iodine treatment and possibly with **worse prognosis (although this remains controversial)**
- Inversion of chromosome arm 7q with AKAP9/BRAF rearrangement, a rare molecular alteration involving the BRAF gene, has been reported in PTC associated with ionizing radiation exposure

Riesco-Eizaguirre G, Gutierrez-Martinez P, Garcia-Cabezas MA, et al. Endocr Relat Cancer 2006;13(1):257-269

Xing M. Nat Rev Cancer 2013;13(3):184-199

Xing M, Westra WH, Tufano RP, et al. J Clin Endocrinol Metab 2005;90(12):6373-6379

Ciampi R, Knauf JA, Kerler R, et al. J Clin Invest 2005;115(1):94-101

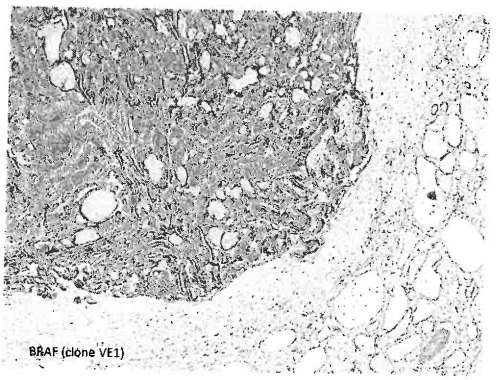
BRAF IHC

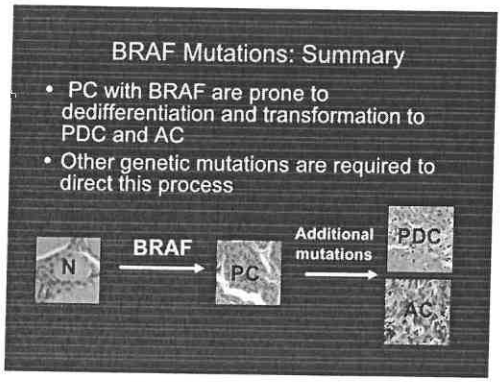
- The clinical utility of **BRAF IHC** has been studied by different groups, which showed that BRAF IHC staining with antibody against mutant BRAF V600E (clone VE1) has both a sensitivity and negative predictive value of 100% and a variable specificity ranging from 61,5 % to 98,7%
- BRAF IHC can be of **additional value in the IHC panel for diagnosis of conventional PTC** in indeterminate thyroid FNA or in difficult surgical cases
- BRAF IHC is a valuable **screening tool** to select patients from confirmatory molecular testing who may benefit from targeted therapy

Fisher KE, Neill SG, Ehsani L, et al. Appl Immunohistochem Mol Morphol 2014;22(8):562-567

Kim YH, Choi SE, Yoon SO, et al. Hum Pathol 2014;45(7):1483-1488

Ilie MI, Lassalle S, Long-Mira E, et al. Thyroid 2014;24(5):858-866





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RAS gene mutations

- RAS gene mutations (NRAS, HRAS, and KRAS) are associated with **follicular-patterned thyroid lesions**
- NRAS is present **in 20% to 50% of follicular thyroid carcinomas and in up to 40% of follicular adenomas**, suggesting an early role for RAS gene mutations in promoting tumorigenesis of follicular neoplasms
- RAS gene mutation is the predominant oncogenic defect in **poorly differentiated thyroid carcinoma** (in 20% to 55% of cases)
- RAS gene mutation is found in 12% to 17% of anaplastic thyroid carcinomas

Xing M. Nat Rev Cancer 2013;13(3):184-199

Esapa CT, Johnson SJ, Kendall-Taylor P, et al. Clin Endocrinol 1999;50(4):529-535

Fagin JA, Mitsiades N. Best Pract Res Clin Endocrinol Metab 2008;22(6):955-969

RAS gene mutations

- RAS mutations are found **more commonly in 'encapsulated follicular variants of papillary thyroid carcinoma'** ('ecapsulated FVPTC') than in other histologic types of PTC, suggesting that 'ecapsulated FVPTC' might be a separate class of thyroid tumors with overlapping features of both PTC and FTC **(--NIFTP!!!!)**

Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell 2014;159(3):676-690

Kim TH, Lee M, Kwon AY, et al. Histopathology 2017, Epub ahead of print.

Basolo F, Macerola E, Ugolini C, et al. Adv Anat Pathol 2017;24:252-258

Table 4. Molecular genotyping results of 177 tumors in 175 patients according to invasive growth pattern of follicular variant papillary thyroid carcinoma

	Encapsulated FVPTC		Infiltrative FVPTC	*P* value	
Genetic abnormalities	Noninvasive, *N* (%)	Invasive, *N* (%)	*N* (%)	Noninvasive vs. invasive	Encapsulated vs. infiltrative
$BRAF^{V600E}$ mutation	9 (12.2)	6 (11.8)	18 (34.6)	1.000	0.001
RET/PTC1 rearrangement	0 (0)	0 (0)	5 (9.6)	1.000	0.002
RET/PTC3 rearrangement	0 (0)	0 (0)	1 (1.9)	1.000	0.294
NRAS mutation	24 (32.4)	20 (39.2)	8 (15.4)	0.452	0.011
HRAS mutation	8 (10.8)	6 (11.8)	0 (0)	1.000	0.011
KRAS mutation	4 (5.4)	8 (15.7)	0 (0)	0.068	0.019
$BRAF^{K601E}$ mutation	2 (2.7)	2 (3.9)	0 (0)	1.000	0.322
Wild type	27 (36.5)	9 (17.6)	20 (38.5)	0.027	0.219

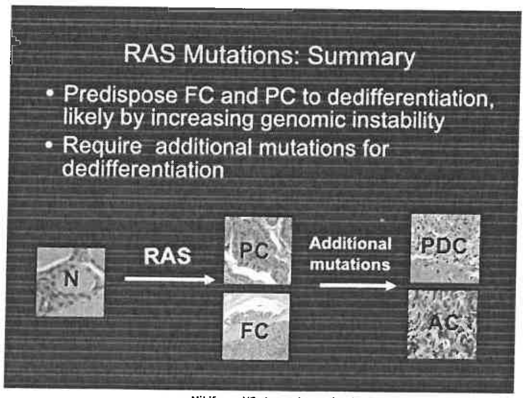
Kim TH, Lee M, Kwon AY, et al. Histopathology 2017, Epub ahead of print.

TABLE 2. Genotype Alterations Found in NIFTP

References	Countries	Techniques	Cases (N)	Genotype	
				Markers	Mutated [n (%)]
Nikiforov et al[13]	USA	NGS	27	$BRAF^{K601E}$	1 (4)
				RAS	8 (30)
				PPARg fusion	6 (22)
				THADA fusion	6 (22)
Lee et al[30]	Korea	PCR/pyrosequencing	21	$BRAF^{K601E}$	1 (5)
				$BRAF^{V600E}$	5 (24)
				RAS	12 (57)
Zhao et al[illegible]	USA	NGS	48	$BRAF^{V600E}$	1 (2)
				RAS	27 (56)
				PPARg fusion	2 (4)
Jiang et al[28]	USA	NGS	4	*RAS*	4 (100)
				TERT promoter*	1 (25)
Borrelli et al[21]	Italy	PCR/Sanger sequencing	19	$BRAF^{K601E}$	2 (11)
				RAS	8 (42)
Howitt et al[illegible]†	USA	PCR/pyrosequencing, real-time PCR	9	*RAS*	3 (33)
				PPARg fusion	1 (11)
Cho et al[illegible]‡	Korea	PCR/Sanger sequencing	102 (cohort 1)	$BRAF^{V600E}$	10 (10)
				$BRAF^{K601E}$	2 (2)
				BRAF deletion	2 (2)
			95 (cohort 2)	$BRAF^{K601E}$	2 (2)
				BRAF deletion	2 (2)
				RAS	42 (47)
Valderrabano et al[33]	USA	NGS	5	*RAS*	1 (20)
				THADA fusion	2 (40)
Bizzarro et al[22]§	Italy	PCR/Sanger sequencing	13	*BRAF*	0 (0)

**TERT* promoter mutation coexisted with *RAS* mutation in 1 case.
†Howitt et al published this study in 2015, before the paper of Nikiforov on diagnostic criteria of NIFTP; however, it seems that authors adopted overlapping histopathologic criteria for selection of their 9 noninvasive encapsulated follicular variant PTCs.
‡Cho et al applied histopathologic criteria for diagnosis of NIFTP and divided their cases into 2 cohorts: (1) papillary structures ≤1% (102 cases) and (2) total absence of papillae (95 cases). In the cohort 1 results of RAS testing were available for 89/95 cases. For the cohort 2 data about *RAS* mutations were not available.
§Bizzarro et al analyzed *BRAF* mutational status only and found a wild-type sequence for all NIFTPs.
NGS indicates next-generation sequencing; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PCR, polymerase chain reaction; PTC, papillary thyroid carcinoma.

Basolo F, Macerola E, Ugolini C, et al. Adv Anat Pathol 2017;24:252-258



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RET/PTC gene rearrangement

- RET/PTC1 and RET/PTC3 are the most common types of the RET/PTC gene rearrangements
- RET/PTC gene rearrangements are found **in 10% to 20% of PTCs**
- They can be **associated with ionizing radiation exposure** and are more commonly seen in the **pediatric population**
- Whether the presence of the RET/PTC rearrangement infers a better prognosis is not clear???
- RET/PTC gene rearrangements are typically **absent in poorly differentiated thyroid carcinoma and anaplastic thyroid carcinoma**

Filie AC, Asa SL, Geisinger KR, et al. Diagn Cytopathol 2008;36(6):438-441
Fagin JA, Mitsiades N. Best Pract Res Clin Endocrinol Metab 2008;22(6):955-969
Moghaddam PA, Virk R, Sakhdari A, et al Arch Pathol Lab Med 2016;140:158-170

PAX8-PPARG gene rearrangements

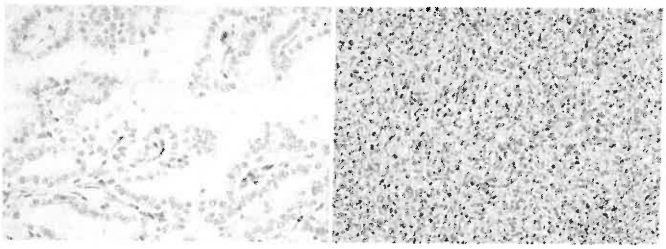
- PAX8/PPARG gene rearrangement is **prevalent in follicular thyroid carcinoma** (variably reported in 36%-63% of cases), as well in 'FVPTC' (**NIFTP**), **follicular adenoma**, and a small proportion of Hürthle cell carcinomas
- It is typically associated with **microfollicular and solid histologic patterns, thick capsule, and capsular and vascular invasion**

Nikiforov YE. Arch Pathol Lab Med 2011;135(5):569-577
Eberhardt NL, Grebe SK, McIver B, et al. Mol Cell Endocrinol 2010;321(1):50-56

Other molecular alterations

- **ETV6-NTRK3 rearrangement** has been shown in pediatric and adolescent PTC, which was associated with radiation exposure and more aggressive disease *(Isame rearrangement as the early discussed mammary analoge secretory carcinoma of the thyroid but tumor with a total different morphology and iHC profile!)*
- **Anaplastic lymphoma kinase (ALK) fusions** have been found in poorly differentiated thyroid carcinoma and anaplastic thyroid carcinoma, which may work as a potential target for therapy with ALK inhibitors (ie. Crizotinib)
- **TP53** and **Beta-catenin gene** (CTNNB1) mutations are more commonly seen in poorly differentiated thyroid carcinoma and anaplastic thyroid carcinoma (but rarely identified in well-differentiated thyroid carcinomas) and are associated with more advanced disease

Leeman-Neill RJ, Kelly LM, Liu P, et al. Cancer 2014;120(6):799-807
Kelly LM, Barila G, Liu P, et al. Proc Natl Acad Sci U S A 2014;111(11):4233-4238
Nishida T, Nakao K, Hamaji M, et al. Surgery 1996;119(5):568-575



Beta-catenin staining in a well-differentiated PTC (negative) and anaplastic thyroid carcinoma (positive)

Specific Genetic Events in Thyroid Tumors: Summary

	PC	FC	PDC	AC
BRAF	39%	0	13%	14%
RAS	15%	45%	24%	55%
RET/PTC	35%	0	9%	0
PAX8-PPARγ	1%	36%	0	0
P53	1%	5%	24%	74%
β-catenin	0	0	16%	66%

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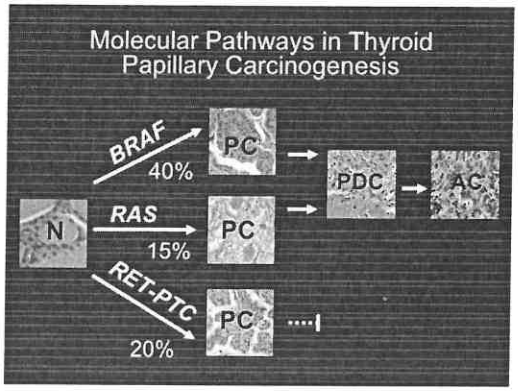

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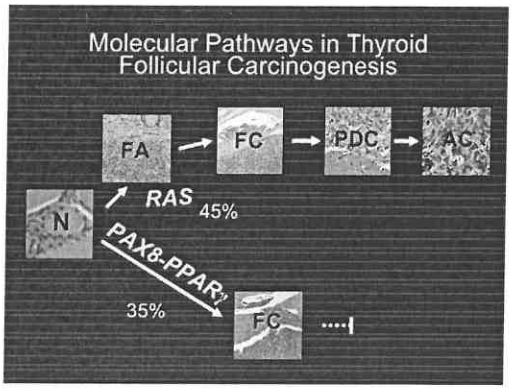

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Molecular Pathways in Progression of Thyroid Carcinomas: Summary

- Studies of gene mutations and LOH supports the following progression:

  WDC ⟶ PDC ⟶ AC
- WD tumors with BRAF and RAS mutations are prone for dedifferntiation, but require additional mutations
- p53 and possibly β-catenin directly guide progression

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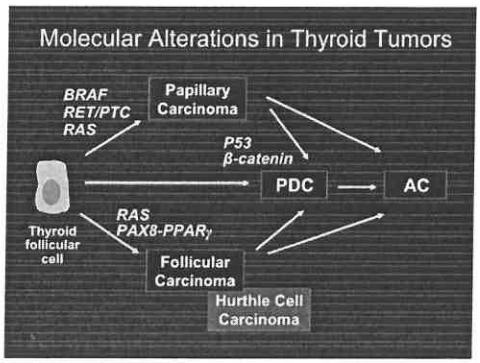

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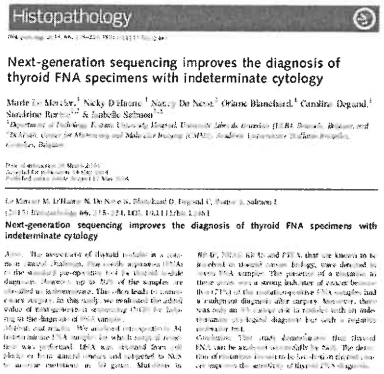

Histopathology

Next-generation sequencing improves the diagnosis of thyroid FNA specimens with indeterminate cytology

Marie Le Mercier,[1] Nicky D'Haene,[1] Nancy De Neve,[2] Orianne Blanchard,[1] Caroline Degand,[1] Sandrine Rorive[1,2] & Isabelle Salmon[1,3]

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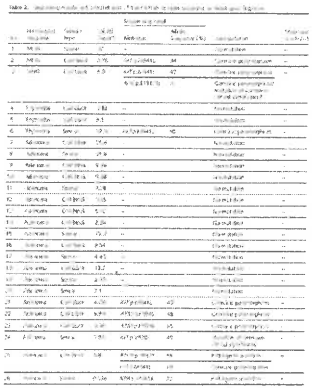
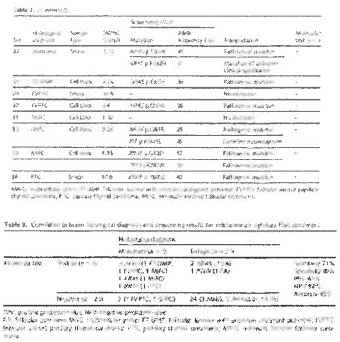
Le Mercier M, D'Haene N, De Neve N, Blanchard O, Degand C, Rorive S, Salmon I

Next-generation sequencing improves the diagnosis of thyroid FNA specimens with indeterminate cytology





Le Mercier M, D'Haene N, De Néve N, et al. Histopathology 2015;66:215-224

summary

- The field of thyroid pathology has evolved dramatically over the past years and several major changes occured including

-reclassifying non-invasive encapsulated follicular variant of papillary thyroid carcinoma as NIFTP

-the introduction of the concept of poorly differentiated thyroid carcinoma

-the introduction of the entity mammary analogue secretory carcinoma of the thyroid

-the invasion requirement to diagnose a Hurthle cell carcinoma

-incorporation of numerous detailed pathologic characteristics (e.g. the presence and extent of vascular invasion and extrathyroidal extension, subtypes of PTC,...)

-IgG4-related thyroid disease

- These shifts in the classification and characterization of thyroid carcinoma have allowed for the de-escalation of therapy in a large number of patients with differentiated thyroid carcinoma
- Papillary thyroid microcarcinoma: an entity requiring consideration for reclassification?
- Role of ancillary tests (IHC and molecular) in thyroid pathology
- Molecular alterations in thyroid tumors