'hot topics in thyroid pathology'

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- 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 bubble of microadenomas is really too small to count.

A practical algorithmic approach

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

Multinucleated thyroid hyperplasia
Follicular thyroid carcinoma: histology

- Triangular or solid pattern of follicles (small, normal sized or large - microfollicular, macrofollicular or nevoid follicles, 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. Neoangiogenesis 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 noninvasive 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 renowned 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 microscopically focal by National Comprehensive Cancer Network-NCCN, and at least 4 for American Thyroid Association-ATA guidelines) are associated with a lower risk of recurrence (<1% vs >10%) 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) carcinomas. It is 35% a marker of whether vascular invasion is an independent predictor of poor outcome in PTC.

Collins H, Santinami M, Mark E. Heparinase [204]:415-20
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.
- PT 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 as direct extension into subcutaneous tissue, adjacent viscera (e.g., larynx, trachea, and esophagus), or recurrent laryngeal nerve.


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 in the perithyroidal soft tissue.
- Not surprisingly, 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.


RFS according to ETE status

- Gross ETE
- Minimal ETE
- No ETE

>32% solid/lobular/insular growth NOT compatible with a diagnosis of NFTP

Capsular and vascular invasion are NOT compatible with diagnosis of NFTP!!
Necrosis and increased mitotic activity are NOT compatible with diagnosis of NIFTP

Inclusion criteria:
- Encapsulated
- Clear demarcation
- Follicular growth pattern
- Nuclear features of PTC

Exclusion criteria:
- Invasion
- Papillary >1%
- Plasma membrane bodies
- >30% STR growth
- Increased mitoses
- Tumor necrosis

Low-power image of follicular lesion of undetermined significance (FLUS) and Trabecular Nickerson et al. JAMA Otolaryngol 2018, STR: solid trabecular tissue.
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

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 NiFTF, 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 relabelling 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 metastases 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.

Zhu H, Chen C, Zhang et al. Thyroid 16:1309–1317
Ro J, Goffredo F, Storni L, et al. Thyroid 23:1702–1709

Papillary thyroid microcarcinoma (PTMC)

- BRAF V600E gene mutation has been reported in PTMC in the range of 40% to 50%, similar to FTC greater than 1 cm.
- BRAF V600E-mutated PTMCs have distinct morphologic features when compared with BRAF V600E wild-type PTMCs.
- Majority tumors are more likely to have infiltrative interface with microcystic fibroepithelial and Hurthle cell adenoma reaction mimicking tumors and/or desmoplastic reaction.
- Shimazaki et al. proposed a scoring system based on histologic and molecular features for risk stratification (PTMCCS: papillary tumor cell carcinoma, papillary tumor, and Hurthle cell adenoma with desmoplastic reaction).
- While the association between BRAF V600E mutation and aggressive histopathologic features such as microstomal extrathyroidal extension and lymph node metastasis is speculative, prospective randomized studies are needed to establish an association with poor outcomes.

Figure 2. Superficial tumor location as a biological feature contributing to the infiltrative-pollution score. Include tumor location immediately in the net of the figure, with extrathyroidal extension (A) or without extrathyroidal extension (B).


Table 3

<table>
<thead>
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<tr>
<td>Intermediate (0-5)</td>
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<tr>
<td>High (0)</td>
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Oncocytic ('Hurthle') cell neoplasms

What is a 'Hurthle cell'?

- Hurthle cells are cells that have undergone oncotic change
- Oncotic 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
- Oncotic 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,...)

Hurthle 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 oncotic cells [1898]
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
Follicular epithelial cell neoplasms

Benign

- Hurthle cell adenoma
- Papillary thyroid carcinoma with oncocytic changes
- Follicular thyroid carcinoma

Malignant

- Hurthle cell papillary carcinoma
- Hurthle cell follicular carcinoma
- "Solid" Hurthle cell carcinoma
- Hurthle cell insular (poorly differentiated) carcinoma
- Oncocytic medullary carcinoma
- Medullary thyroid carcinoma with oncocytic changes

Figure 13: The classification of oncocytic thyroid neoplasms.

The WHO classifies Hurthle cell carcinoma of the thyroid as follicular carcinoma, "oncocytic cell type"
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
Poorly differentiated thyroid carcinoma

The story of poorly differentiated thyroid carcinoma: from Longhara's description to the Tunis proposal via Lund Rosen.
Poorly differentiated thyroid carcinoma

- Since the original description in 1983, a long debate has occurred on the way nature of this tumor, on its morphological diagnostic features, on its molecular profile and on its clinical significance.
- Was defined as "anaplastic, non-follicular, non-glandular thyroid carcinoma, having an intermediate behaviour between well-differentiated and anaplastic carcinoma".
- In the 2004 WHO classification, PTC 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 heterogeneous applied in diagnostic practice covering with tumor categories, including the solid and the tall cell variant of PTC on the one side and PTC 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 K.L. Jangalé and a typical case of "small" thyroid carcinomas.

"poorly differentiated 'small' thyroid carcinomas"

of papillary carcinoma. The subsequent discussion eventually brought to a consensus that was summarized by Dr. Renki on behalf of the whole group ([132, 3]) in the proposed diagnostic algorithm, currently termed the "Yusim proposed." The entity PTC was, therefore, defined by the following diagnostic criteria: 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). Lack of the conventional papillary carcinoma nuclear features, which keeps PTC apart from the solid variant of papillary carcinomas; and presence of at least one of these features—mitotic activity >3 x 10 HPF or tumor necrosis or convolutional nuclei. These latter are defined as nuclei smaller and darker than those in papillary carcinomas, round and hyperchromatic with convolutions of the nuclear membrane ("onion-like" contours). Later on, it popu-
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 behavior intermediate between well-differentiated thyroid cancer and undifferentiated (anaplastic) thyroid carcinoma (concept of intermediate prognosis follicular cell-derived thyroid carcinoma).
- Clinically, PDTc is 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 bone, 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 (40%).
MAMMARY ANALOG SECRETORY CARCINOMA
OF THE THYROID GLAND: A PRIMARY THYROID
ADENOCARCINOMA HARBORING ETV6-NTRK3
FUSION

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 vacuolated nuclei and eosinophilic
vacuolated cytoplasm, arranged in tubular,
retrocystic, cribiform, papillary and
solid growth patterns often interdigitated with
filamentous septa, and with a variable TTF-1-positive
calbindin-like secretory material. MASC is typically
positive for S-100 protein, (focal) PAX8,
nontumoral, vimentin, and cytokeratins, namely
CK7 and CK19, and can be focally positive for
p63. Negative for TFE3 and Thyroglobulin.
Similar to its breast and salivary counterpart,
MASC harbors a recurrent balanced chromosomal
translocation (12;15)(p13;q25) leading to ETV6-
NTRK3 gene fusion. The reported cases show the
behavior of a low-grade adenocarcinoma.

IGG4-RELATED DISEASE (IGG4-RD)

- Recently recognized syndrome characterized by mass forming lesions with
  lymphoid/plasmacytic 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 usually has a favorable clinical response to steroid therapy
- The earliest description of this syndrome was as a subtype of autoimmune
  panadenitis, although it is now recognized as a multisystem disorder

IGG4-RELATED THYROID DISEASE

- Thyroid disease characterized by an inflammatory process involving the
  thyroid gland, resulting in a mass-forming lesion with dense lymphoid/plasmacytic
  infiltration and increased IgG4+ cells. It is often associated with systemic
  involvement and may respond well to steroid therapy.
IgG4-related disease (IgG4-RD)

- IgG4-RD can affect virtually any organ system including exocrine glands, lacrimal glands, parotid glands, thyroid gland, breast, bile duct, kidneys (sclerosing cholangitis, glomerulonephritis), retroperitoneum (retroperitoneal fibrosis), lungs (inflammatory pseudotumor), mesotuberculosis, aorta, meninges and pharynx gland

- In most patients with IgG4-RD, 2 or more sites in various combinations are involved

- The mechanisms responsible for the disease remain unclear

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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 multinodular, that show a mild 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 the disease

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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/IgG ratio greater than 40%

- In isolation, elevated numbers of IgG4-positive plasma cells represents a nonspecific feature, detected in a variety of other inflammatory or neoplastic diseases

- Attention to the clinical context, histological features, as well as elevated IgG4 to IgG ratio is critical to avoid 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 as 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: making malignancy for IgG4-related disease represents the most significant pitfall (lymphoma-like-appears). 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 superimposed below-microscopic aggregates, affected by IgG4-related disease, such as in the pancreas, bile, salivary glands, pulmonary, gastrointestinal, lung, and thyroid glands among others.
2. Involvement of multiple organ (head, neck, chest, abdomen).
3. Ultrasound is a direct rapid test of architectural changes.
5. Histopathological levels (≥100).
6. NK/T cell response in immunopathologic therapy. However, it should be emphasized that a variety of other inflammatory diseases can cause similar changes, albeit temporarily and not necessarily in similar.

Deshpande V. Head Neck Pathol 2015;9:4–22
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-rythroiditis with increased numbers of IgG4-positive plasma cells and non-IgG4-rythroiditis (no or few IgG4-positive 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

Hashimoto thyroiditis

Hashimoto thyroiditis

Hashimoto thyroiditis

Hashimoto thyroiditis
The role of ancillary studies in thyroid pathology

Immunohistochemistry

Molecular diagnostics and molecular carcinogenesis in thyroid cancer
Immunohistochemical markers in thyroid pathology
- CD56
- TP53 (p53 tumor suppressor)
- Cytokeratin 19
- HBME-1 (Hepatoma-derived melanoma marker)
- Galectin 3 (Galactoside-binding lectin soluble 3)
- INPP53 (inhibitor of phosphoinositide 3-kinase-phosphatase and tensin homolog)
- TFF1 (Transeptal Fiber-Rich Factor 1)
- Thyroglobulin
- Cytokeratins
- MUC5 (mucin 5 gene)
- PTH (Parathyroid hormone)
- IgG4 (IgG4-related disease)
- BRAF (BRAF gene)

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, TP5Q, INPP53).
- It should be emphasized that in order to reach a proper diagnosis, morphology should always be correlated with IHC and molecular studies!!
Table 1: Immunohistochemical analysis of TTF-1 in thyroid tissue of patients

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>TTF-1 Positive Staining</th>
<th>TTF-1 Negative Staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>80%</td>
<td>20%</td>
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<tr>
<td>Follicular</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>Medullary</td>
<td>60%</td>
<td>40%</td>
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<tr>
<td>Papillary</td>
<td>85%</td>
<td>15%</td>
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<tr>
<td>Follicular</td>
<td>75%</td>
<td>25%</td>
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<tr>
<td>Medullary</td>
<td>65%</td>
<td>35%</td>
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Table 2: Immunohistochemical analysis of TTF-1 in thyroid tissue of patients

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</tr>
<tr>
<td>Medullary</td>
<td>65%</td>
<td>35%</td>
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</table>


TTF-1 and Thymidin expression in a poorly differentiated clear cell thyroid tumor
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/PPARγ)
- 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 patient survival
- Inversion of chromosome arm 7q with AKAP9/BRaf rearrangement, a rare molecular alteration involving the BRAF gene, has been reported in PTC associated with limiting radiation exposure


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

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 35% of cases)
- RAS gene mutation is found in 12% to 17% of anaplastic thyroid carcinomas

King M. Nat Rev Cancer 2010;10(6):386-399
Fagin JA, Mitsudome N. Best Pract Res Clin Endocrinol Metab 2008;22(4):955-969

BRAF Mutations: Summary

- PC with BRAF are prone to dedifferentiation and transformation to PDC and AC
- Other genetic mutations are required to direct this process

Nikitin YE. Atrial natriuretic USCUP, San Antonio 2017

RAS gene mutations

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

Table 4: Molecular genotyping results of 127 tumors in 127 patients according to invasive growth pattern of follicular variant papillary thyroid carcinoma

<table>
<thead>
<tr>
<th>Genotype/Marker</th>
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Table 6: The frequency and clinical value of RET/PTC1

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Table 6: Neoplastic Activity—Adult study

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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.

PAX8-PPARG gene rearrangements

- **PAX8/PPARG gene rearrangement is prevalent in follicular thyroid carcinomas** (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

Other molecular alterations

- **ETV6-NTRK3 rearrangement** has been shown in pediatric and adolescent PTC, which was associated with radiation exposure and more aggressive disease (Some rearrangement as the early discussed mammary analogue secretory carcinoma of the thyroid but tumour 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


**Specific Genetic Events in Thyroid Tumors: Summary**

<table>
<thead>
<tr>
<th>Gene</th>
<th>PC</th>
<th>FC</th>
<th>PDC</th>
<th>AC</th>
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<tbody>
<tr>
<td>BRAF</td>
<td>35%</td>
<td>0</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>RAS</td>
<td>15%</td>
<td>45%</td>
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</tr>
<tr>
<td>RET/PTC</td>
<td>35%</td>
<td>0</td>
<td>9%</td>
<td>0</td>
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<tr>
<td>PAX8-PPARG</td>
<td>1%</td>
<td>36%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P53</td>
<td>1%</td>
<td>5%</td>
<td>24%</td>
<td>74%</td>
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<td>a-catenin</td>
<td>0</td>
<td>0</td>
<td>16%</td>
<td>66%</td>
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</table>

Nikiforov YE. Annual meeting USCAP San Antonio 2017

Beta-catenin staining in a well-differentiated PTC (negative) and anaplastic thyroid carcinoma (positive)
Molecular Pathways in Thyroid Papillary Carcinogenesis

- BRAF 40%
- RAS 15%
- RET-PTC 20%
- N

Molecular Pathways in Thyroid Follicular Carcinogenesis

- RAS 45%
- PAX8-PPAR
- 35%
- N

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 dedifferentiation, but require additional mutations
- p53 and possibly β-catenin directly guide progression

Molecular Alterations in Thyroid Tumors
**Summary**

- The field of thyroid pathology has evolved dramatically over the past years and several major changes occurred including:
  - Identification of low-grade encapsulated follicular variant of papillary thyroid carcinoma in 2005
  - Introduction of the concept of specific differentiated thyroid carcinoma
  - The introduction of the entity medullary analog carcinoma of the thyroid
  - Introduction of novel biologic/clinical characteristics (e.g., the presence and extent of vascular invasion and extrathyroid extension, BRAFV600E status, etc.)

**Current thyroid disease scenario**

- 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