Review

Molecular Biology of Thyroid Cancer and Their Clinical Applications

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Thyroid cancer is the most common endocrine malignancy, with papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) being the predominant subtypes. Recent advancements in molecular biology have significantly improved our understanding of thyroid carcinogenesis, leading to novel diagnostic and therapeutic strategies. Key genetic alterations, including BRAF, RAS, RET/PTC fusions, and PAX8-PPARγ rearrangements, play crucial roles in tumor initiation and progression. BRAF mutations, particularly BRAFV600E, are strongly associated with aggressive PTC phenotypes, whereas RAS mutations are prevalent in follicular-patterned thyroid tumors. Poorly differentiated and anaplastic thyroid carcinomas harbor mutations in TP53, TERT promoter, and components of the MAPK and PI3K pathways, contributing to their aggressive behavior. Advances in molecular diagnostics, such as next-generation sequencing and gene expression classifiers, have enhanced the accuracy of thyroid nodule evaluation, reducing unnecessary surgeries. This review provides an in-depth analysis of the molecular mechanisms underlying thyroid cancer and their clinical applications, emphasizing the role of molecular testing in risk stratification, prognostication, and personalized treatment approaches.
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PAPILLARY THYROID CARCINOMA (PTC)

Papillary thyroid carcinoma (PTC) (**Figure 1**) comprises over 80% of all thyroid malignancies, making it the most prevalent form.1 While generally associated with a favorable prognosis compared to other thyroid carcinoma types, PTC carries a substantial risk of recurrence, approaching 28%.[1,2] This underscores the importance of early detection and appropriate treatment strategies to optimize patient outcomes. Microscopically, PTC is characterized by distinct cytological features, including enlarged, crowded nuclei with irregular contours, intranuclear cytoplasmic pseudo-inclusions, nuclear grooving, and a fine, pale chromatin pattern.[3] Beyond its diagnostic role, molecular pathology is increasingly crucial for elucidating the underlying mechanisms of PTC and contributing to the development of novel targeted therapies

Molecular Genetics of Papillary Thyroid Carcinoma

Advancements in molecular genetics over the past two decades have greatly improved the understanding of PTC development. Approximately 70% of PTC cases harbor mutations in the BRAF, RAS, or RET genes, emphasizing their significance in tumorigenesis.[4] These genetic alterations converge on the activation of the mitogen-activated protein kinase (MAPK) pathway, driving cancer progression.[4] Upon binding of an external stimulus, such as a hormone, to its receptor on the cell membrane, RAS is activated, subsequently initiating the activation of RAF. This process triggers a signaling cascade, resulting in the phosphorylationand activation of MEK (MAPK kinase), which in turn activates extracellular signal-regulated kinase (ERK). Once phosphorylated, ERK translocates to the nucleus, where it regulates various cellular processes, including proliferation and differentiation.[5] Mutations in genes encoding key components of the MAPK pathway are implicated in approximately 30% of all human cancers.[6] The distinction between BRAF-like and RAS-like PTCs is increasingly also influencing clinical practice, with BRAF-like PTCs - typically classic or tall cell variants (**Figure 2** - showing infiltrative growth, early lymph node spread, and resistance to radioactive iodine, while RAS-like PTCs, usually follicular variants, are encapsulated, spread through blood vessels rather than lymph nodes, and are more responsive to radioactive iodine.[7]

PTC development is strongly influenced by interactions between genetic mutations and environmental factors, such as exposure to ionizing radiation. The molecular landscape of PTC highlights the complexity of its pathogenesis, where oncogenic drivers not only initiate tumorigenesis but also impact prognosis and therapeutic response. Understanding these genetic alterations is essential for guiding precision medicine approaches and tailoring treatment to individual patient risk profiles.

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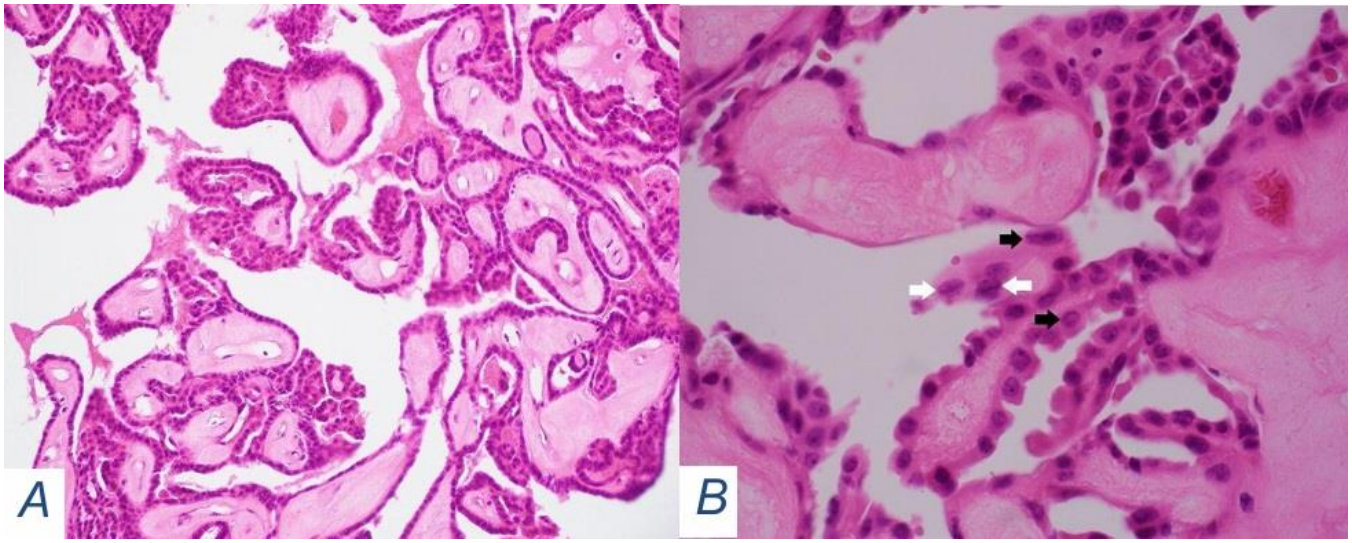

Figure 1. Papillary thyroid carcinoma. (**A**) Low-power view showing complex, branching papillae with delicate fibrovascular cores lined by neoplastic follicular cells (H&E, 200×). (**B**) High-power view highlighting characteristic nuclear features, including enlargement, overlapping, irregular contours, nuclear grooves (white arrows), and occasional intranuclear pseudoinclusions (black arrows) (H&E, 600×).

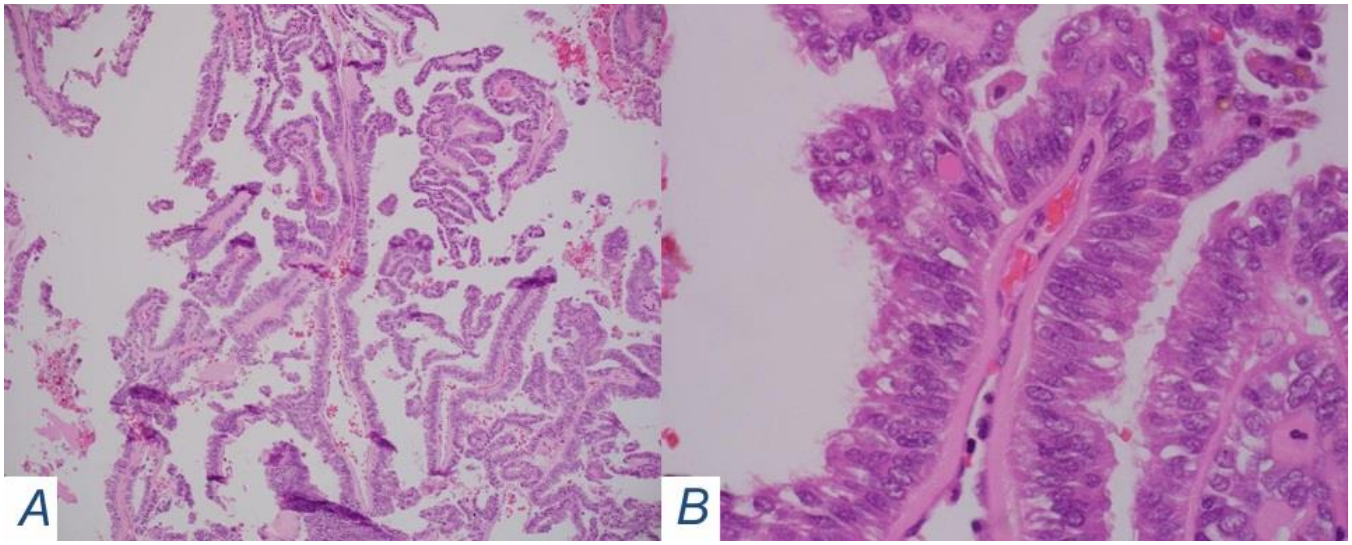

Figure 2. PTC tall cell variant (**A**) Low-power view showing complex, branching papillae lined by elongated tumor cells with abundant eosinophilic cytoplasm and delicate fibrovascular cores (H&E, 100×). (**B**) High-power view demonstrating tall columnar cells whose height is at least three times their width, with basally oriented nuclei exhibiting the typical papillary thyroid carcinoma nuclear features (H&E, 600×).

The RET Fusion Oncogenes (RET/PTC Rearrangements)

RET fusions are the most common chromosomal rearrangements implicated in the development of papillary thyroid carcinoma.[8] The RET gene encodes a receptor for growth factors belonging to the glial cell line-derived neurotrophic factor (GDNF) family, which interacts with a ligand-coreceptor complex to initiate activation and downstream signaling.[9] Under normal physiological conditions, RET expression in thyroid follicular cells is minimal.[10] However, carcinogenesis associated with RET/PTC rearrangements occurs through chromosomal translocations that fuse the C-terminal kinase domain of RET with the promoter and N-terminal domains of other genes.[9] This genetic recombination places RET under the transcriptional control of the fusion partner's promoter, leading to aberrant expression of chimeric RET/PTC proteins in thyroid follicular cells.[9] These fusion proteins retain an intact tyrosine kinase domain, resulting in constitutive activation of the MAPK signaling cascade and uncontrolled cellular proliferation.[11]

Compared to other molecular alterations in PTC, RET/PTC rearrangements are more frequently observed in younger patients, are associated with classic papillary morphology, and exhibit a higher propensity for lymph node metastasis.[4] Among the identified RET/PTC rearrangements, RET/PTC1

and RET/PTC3 are the most prevalent, collectively accounting for over 90% of cases (**Table 1**) compared to RET/PTC2, which is a far less common gene alteration. RET/PTC1 results from fusion with the CCDC6 (H4) gene, whereas RET/PTC3 arises from fusion with NCOA4 (ELE1 or RFG).[12,13] RET/PTC1 is more commonly associated with the classic papillary histological subtype and is linked to a more favorable prognosis, whereas RET/PTC3 is predominantly observed in the solid variant of PTC.[14] A high prevalence of RET/PTC rearrangements has been reported in radiation-associated papillary thyroid carcinomas, particularly in cases following nuclear accidents or exposure to external beam radiation therapy.[12,13] These rearrangements are also frequently identified in childhood PTC and papillary microcarcinomas, supporting their role as an early genetic event in thyroid carcinogenesis.[12,13]

Table 1. Main Genetic Alterations in Papillary Thyroid Carcinoma (PTC).

Mutation	Subtype	Frequency
RET	RET/PTC1 & RET/PTC3	> 90% of RET rearrangement cases
RAS	NRAS codon 61	~ 95% of RAS mutations
	KRAS codon 12	66% of KRAS mutations
BRAF	All BRAF mutations	74.6%
	$BRAF^{V600E}$ mutation	29-83% of PTC cases

Table 2. RAS Mutation Frequencies in Various Thyroid Tumors.

Tumor Type	RAS Mutation Frequency
Follicular thyroid adenomas	26%
Follicular thyroid carcinomas	30-50%
Follicular variant of PTC	30-45%
Poorly differentiated thyroid carcinoma	33%
Anaplastic thyroid carcinoma	20-40%

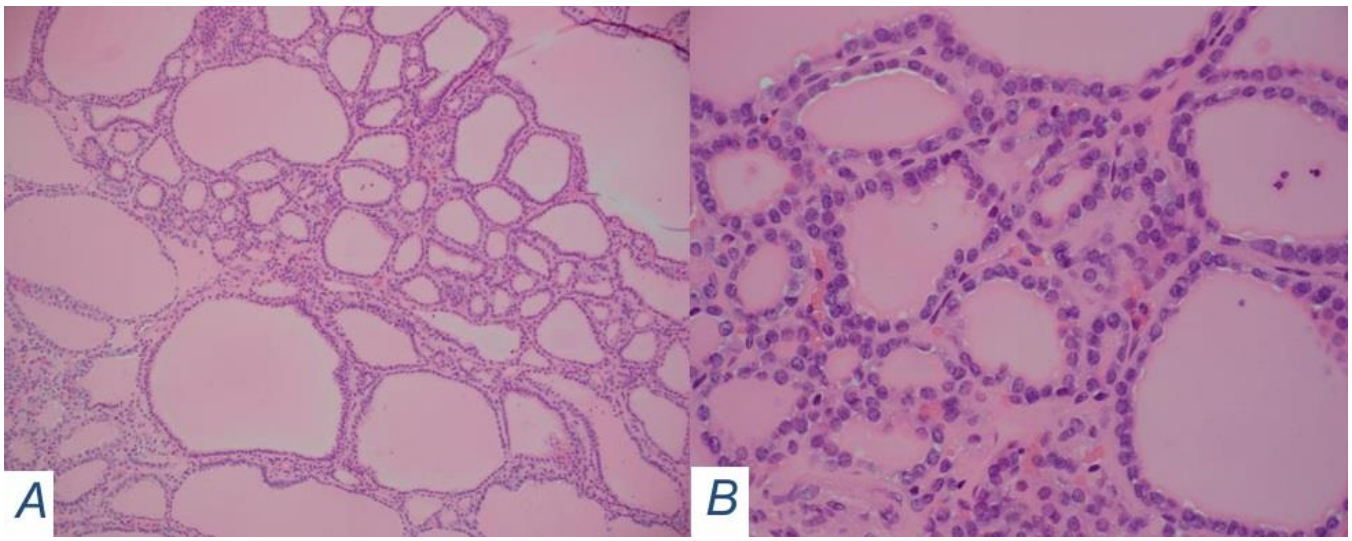

Figure 3. Follicular thyroid adenoma. (**A**) Low-power view of the nodule showing closely packed follicles of varying size, filled with colloid and lined by uniform follicular cells (H&E, 200×). (**B**) High-power view demonstrating small to medium-sized follicles lined by cuboidal epithelial cells with round, evenly spaced nuclei and scant cytologic atypia (H&E, 400×).

RAS Oncogenes in PTC

The RAS gene family encodes intracellular proteins that play a critical role in transmitting signals from activated cell surface receptors to downstream kinases within the MAPK and PI3K-AKT pathway, thereby influencing cell proliferation, differentiation, and survival.[15] These genes produce structurally related G proteins that are anchored to the inner surface of the plasma membrane, where they mediate signal transduction from the extracellular environment.[5] Mutations in RAS genes lead to persistent activation of downstream signaling pathways, ultimately driving abnormal cell proliferation and differentiation.[16] RAS mutations are frequently detected in both benign and malignant thyroid tumors, with a higher prevalence in follicular-patterned lesions, including follicular thyroid adenomas (**Figure 3**)(26%), follicular thyroid carcinomas (30-50%), and follicular variant papillary thyroid carcinomas (**Figure 4**) (30-45%) (**Table 2**).[5] The three main RAS isoform - HRAS,

NRAS, and KRAS - are implicated in thyroid carcinoma through activating mutations.[16] These mutations commonly occur at codons 12, 13, and 61. While NRAS codon 61 alterations are the most prevalent (approximately 95%) (**Table 1**), followed by HRAS mutations at the same site, KRAS mutations predominantly affect codon 12 (66%) (**Table 1**), with the remainder occurring at codon 61.[5] However, subsequent findings reveal that RAS mutations are more commonly associated with poorly differentiated thyroid carcinomas (33%) (**Table 2**, **Figure 5**) and anaplastic thyroid cancers (20-40%) (**Table 2**) than with PTC, suggesting that RAS plays a greater role in tumor progression rather than initiation.[5,16] RAS genetic alterations occur independently of BRAF mutations, indicating that RAS mutations, like BRAF mutations, can independently influence the development of PTC.[5]

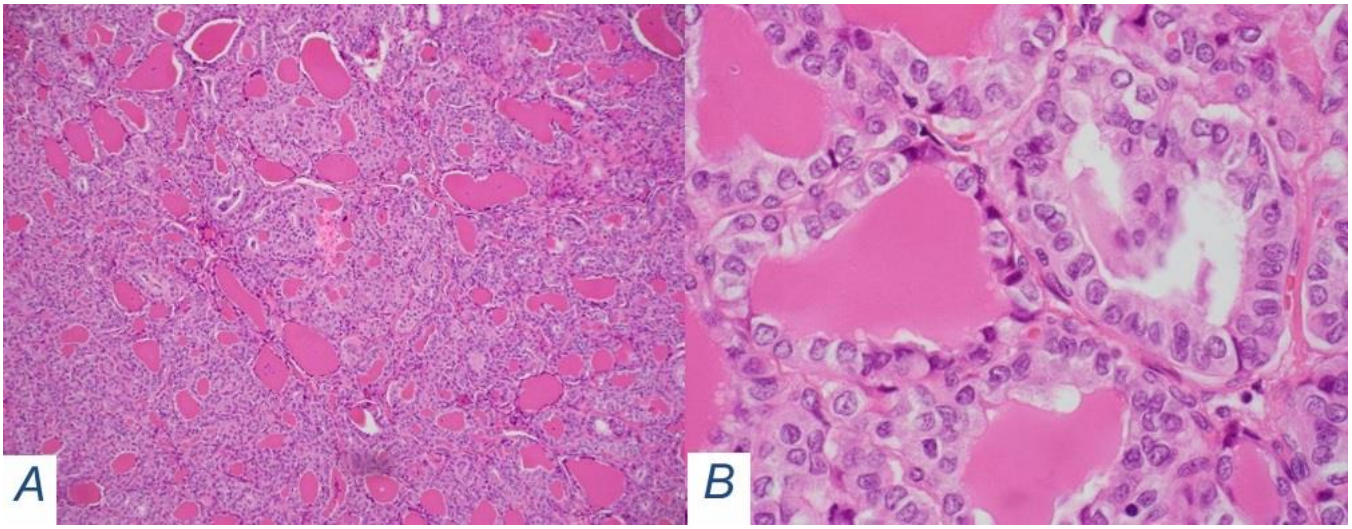

Figure 4. Follicular variant of papillary thyroid carcinoma. (**A**) Low-power view showing a lesion composed predominantly of follicular structures with intervening fibrous septa and minimal papillary architecture (H&E, 100×). (**B**) High-power view revealing follicular cells with characteristic nuclear features of papillary thyroid carcinoma, including nuclear enlargement, overlapping, irregular contours, and chromatin clearing, along with occasional nuclear grooves and pseudoinclusions (H&E, 600×).

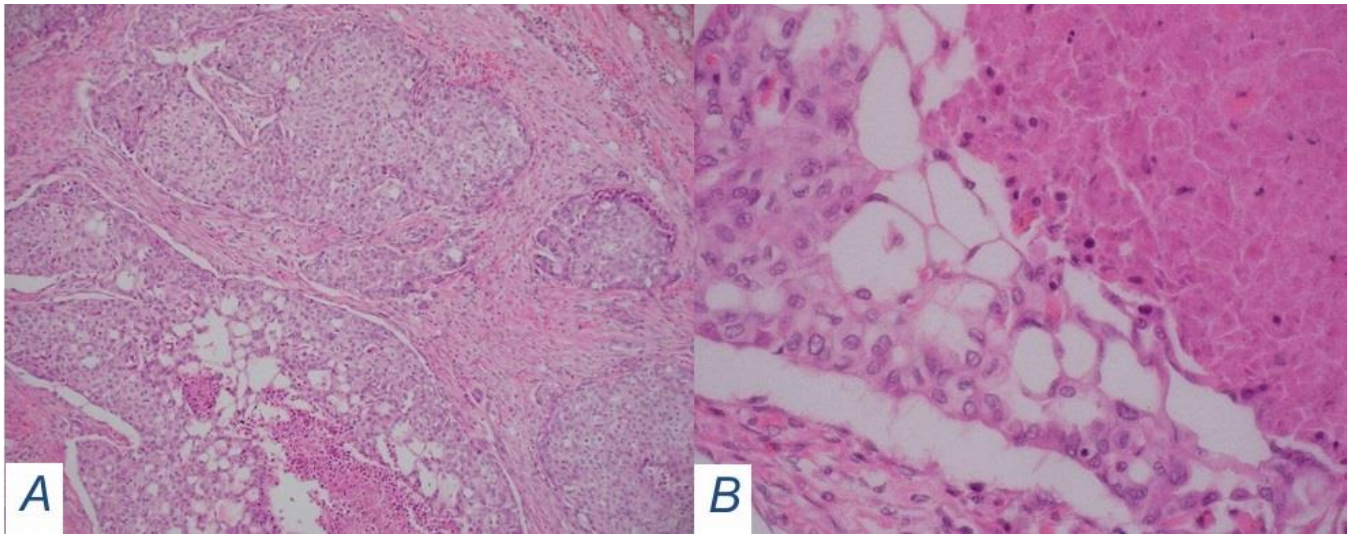

Figure 5. Poorly differentiated thyroid carcinomas. (**A**) Low-power view demonstrating loss of normal thyroid follicular architecture with sheets and nests of tumor cells separated by fibrous stroma. The neoplastic cells are arranged in solid patterns with minimal follicle formation and central necrosis, showing increased cellularity and disorganized growth pattern compared to well-differentiated thyroid tissue (H&E, 100×). (**B**) High-power view revealing densely packed tumor cells with uniform morphology and increased nuclear-to-cytoplasmic ratio. The cells show loss of typical follicular cell polarity and organization, with solid growth pattern and absence of colloid-containing follicles. Nuclear features include moderate pleomorphism and increased mitotic activity (not shown), characteristics of poorly differentiated carcinoma (H&E, 400×).

BRAF Oncogene and its Role in Thyroid Cancer

BRAF, a member of the RAF family (A, B, and C) of serine/threonine kinases, acts as an intracellular effector in the MAPK signaling pathway. This cascade transmits signals downstream, regulating genes involved in cell proliferation, differentiation, and apoptosis.[12] BRAF mutations are found in various tumors, including melanoma (40-70%), thyroid cancer (45%), and colorectal cancer (10%).[5]

BRAF mutations are commonly found in papillary thyroid carcinoma (PTC), with the Tumor Genome Atlas reporting a prevalence of 74.6% (**Table 1**). These mutations can occur through point mutations, chromosomal rearrangements, or small in-frame insertions or deletions, which activate the BRAF gene.[17] BRAF mutations are almost exclusively associated with PTC in thyroid lesions, making it a reliable biomarker for this tumor type.[12] While most PTCs with BRAF mutations have a classical histological appearance, the tall-cell variant of PTC, which is more aggressive, has a particularly high prevalence of BRAF mutations.[18] Additionally, BRAF mutations can progress to poorly differentiated thyroid cancers contributing to a poorer prognosis compared to sporadic thyroid tumors without the mutation.[16] Numerous studies, including meta-analyses, have recognized a link between the BRAFV600E mutation in PTC and high-risk characteristics such as lymph node metastasis, extrathyroidal invasion, recurrence, and advanced clinical stage.[16] However, a large multicenter retrospective study raised doubts about its prognostic significance, as the results became insignificant after adjusting for clinical and clinicopathologic variables.[16] Nevertheless, even after controlling for these factors, a later study by Xing et al., which analyzed data from over 2,000 patients across eight countries, emphasized the potential prognostic value of the BRAFV600E mutation with its association with PTC recurrence remaining significant.[19]

In papillary thyroid carcinoma (PTC), BRAF mutations are the most prevalent genetic alteration and can emerge early in tumor progression, as they present in microscopic PTCs.[6] The most common mutation is a point mutation at nucleotide 1799, where thymine is replaced by adenine, resulting in a substitution of valine by glutamic acid at position 600 in exon 15 (Val600Glu).[20] This mutation accounts for 95% of all BRAF mutations in PTC, with the BRAFV600E mutation being the most frequently observed, found in 29-83% of PTC cases (**Table 1**).[21]

Besides point mutations, BRAF can also be activated through genetic rearrangements, such as the paracentric inversion of chromosome 7q. This inversion causes an in-frame fusion of exons 1-8 of the AKAP9 gene with exons 9-18 of BRAF, producing a fusion protein that includes the kinase domain of BRAF but lacks its autoinhibitory amino-terminal region. The AKAP9-BRAF fusion protein exhibits increased kinase and transforming activity, similar to the BRAFV600E oncoprotein.[13] This fusion is present in 11% of PTCs that developed 5-6 years after ionizing radiation exposure, but it is found in only 0-1% of tumors without a history of radiation or those that developed 9-12 years after exposure.[22] Childhood exposure to ionizing radiation significantly raises the risk of developing PTC with RET rearrangements, and NTRK or BRAF intrachromosomal inversions.

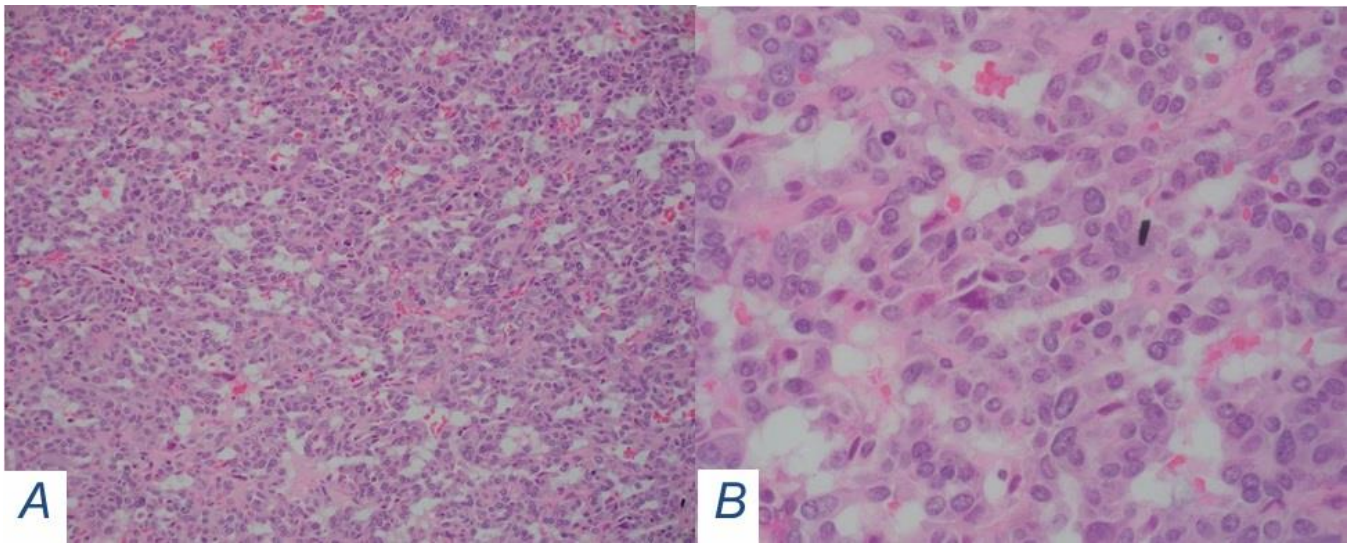

Figure 6. Medullary thyroid carcinoma. (**A**) Low-power view showing solid nests and trabeculae of tumor cells separated by delicate fibrovascular stroma, with areas of amyloid-like eosinophilic material in the background (H&E, 200×). (**B**) High-power view demonstrating polygonal to spindle-shaped tumor cells with granular eosinophilic cytoplasm, eccentric nuclei with finely stippled "salt-and-pepper" chromatin, and interspersed deposits of amyloid (H&E, 600×).

Papillary thyroid cancers with BRAF mutations show a notable decrease in the expression of genes essential for thyroid hormone production, including thyroid peroxidase, thyroglobulin, and the sodium iodide symporter (NIS).[23] There is also evidence that in tumors with oncogenic BRAF, NIS may be mislocalized, moving away from the plasma membrane.[23] This mislocalization suggests that BRAF-mutant tumors may be more prone to becoming resistant to radioactive iodine treatment, which has been observed in clinical cases.[23] Preclinical research has demonstrated that selective MEK inhibitors can inhibit the growth of thyroid cancer cell lines harboring BRAF mutations.[24] However, it is still uncertain whether these inhibitors can effectively reverse the iodine transport dysfunction in a manner that would have clinical relevance.

FOLLICULAR THYROID CARCINOMA (FTC)

The 5th World Health Organization guidelines have categorized FTC into three subtypes - minimally invasive (miFTC), encapsulated angioinvasive (eaFTC), and widely invasive (wiFTC - based on clinical and biological characteristics.[25] Minimally invasive FTC is characterized by microscopic capsular invasion with little to no vascular involvement, whereas tumors with multiple foci, extensive extracapsular extension, or widespread invasion are classified as widely invasive. Although FTC represents only 14% of thyroid cancers, it is considered one of the more aggressive types, with a higher prevalence in adult females and a greater incidence than PTC in iodine-deficient regions.[26]

Molecular Genetics of Follicular Thyroid Carcinomas

The distinguishing feature of FTC is its follicular growth pattern, which can make it challenging to differentiate from follicular adenoma, a benign thyroid lesion exhibiting an overlapping morphological appearance. The crucial step in the diagnosis lies in the identification of vascular or capsular invasion, which serves as the defining characteristic that separates it from the benign counterpart. The advent of molecular diagnostic techniques has revolutionized the approach to thyroid cancer diagnosis, particularly in the context of FTC.

PAX8-PPARγ Rearrangements

The PAX8-PPARγ fusion gene has been identified in approximately one-third of follicular thyroid carcinoma (FTC) cases, with reported frequencies ranging from 12% to 53%.[25] PAX8, a member of the paired box family of transcription factors, is essential for normal thyroid development by supporting thyroid progenitor cell survival and regulating the expression of thyroid-specific genes, whereas PPARγ, a nuclear receptor transcription factor, primarily functions as a key regulator of adipogenesis while also acting as a tumor suppressor.[25] A chromosomal translocation fusing the PAX8 promoter with the PPARγ gene results in the formation of the PAX8/PPARγ fusion protein (PPFP), which either disrupts PPARγ tumor suppressor activity or acts as a novel transcription factor with proto-oncogenic properties.[12] These translocations occur most frequently in FTC but are also detected at lower frequencies in follicular thyroid adenomas (FTA) and papillary thyroid carcinomas (PTC), with prevalence rates of 10–40% in FTCs and 5-20% in benign follicular lesions.[5] The PAX8/PPARγ fusion is associated with diagnosis at an early stage and increased vascular invasion, suggesting a more prominent role in malignant transformation compared to benign or pre-malignant follicular tumors.[12] Therefore, the presence of PAX8/PPARγ fusion increases the likelihood that a lesion is, or may progress to FTC, even though its impact on prognosis remains uncertain.[27]

RAS Mutations in FTC

As previously mentioned, RAS mutations are frequently observed in both benign and malignant thyroid tumors, with a higher incidence in follicular-patterned lesions, including follicular thyroid adenomas (26%) and follicular thyroid carcinomas (30-50%) (**Table 2**).[5] In FTC, NRAS mutations are the most prevalent, followed by HRAS and KRAS.[25] Although RAS mutations are known to drive genomic instability in various cancers, their link to aneuploidy in FTC remains uncertain.[13] A recent study by Ricco et al in 2024 found that 29% of thyroid nodules with indeterminate cytology harbored RAS mutations, of which 58% (95% CI, 47-69%) were malignant, corresponding to a 1.68-fold increased risk.[28] These findings highlight the potential utility of RAS mutation analysis as a diagnostic adjunct to improve the evaluation and management of cytologically indeterminate thyroid nodules.

MOLECULAR GENETICS OF HURTHLE CELL CARCINOMA/ ONCOCYTIC THYROID CARCINOMA

In the 2022 WHO classification, Hürthle cell carcinoma has been reclassified as oncocytic thyroid carcinoma (OCA) rather than a previous variant of follicular thyroid carcinoma (FTC) due to their distinct morphological features and unique genetic profile.[29,30] Additionally, both OCA and oncocytic adenoma (OA) exhibit greater resistance to radioactive iodine therapy compared to follicular-patterned neoplasms.[31] OCAs consist of more than 75% oncocytic cells (specialized type of follicular cell), which are large, with deeply eosinophilic, finely granular cytoplasm and enlarged nuclei containing prominent nucleoli.[32] The histopathological criteria for diagnosing OCAs also allow their classification into minimally invasive, angioinvasive, and widely invasive subtypes, depending on the extent of tumor invasion.[32] OCA is more aggressive than differentiated thyroid carcinomas (DTCs), with higher metastatic rates and rapid disease progression, but this aggressive behavior is primarily observed in widely invasive cases, whereas minimally invasive OCAs have excellent prognoses similar to FTC.[29]

OA and OCA frequently harbor mutations in genes involved in mitochondrial biogenesis, particularly ESRRA and PPARGC1A, and are distinguished by a near-haploid (or monoploid) chromosomal structure.[30] Interestingly, several key driver mutations commonly observed in thyroid cancer, such as RAS, TSHR, EIF1AX, TP53, PTEN, BRAF, PAX8-PPARγ, and MEN1, occur at remarkably low frequencies in OCA, indicating a unique molecular signature and suggesting

a distinct oncogenic mechanism underlying their development.[29]

One of the defining histopathological features of OCA is the marked accumulation of structurally abnormal mitochondria, which is significantly more prevalent in these tumors than in other thyroid malignancies.[29] The mitochondrial genome (mtDNA) encodes 37 genes, including 13 essential components of the mitochondrial electron transport chain (ETC).[29] A study analyzing 45 oncocytic neoplasms revealed that frameshift and missense mutations in mtDNA-encoded complex I subunits were present in 48% (12/25) of cases, with a predominance in OCA.[33] Moreover, 83.3% of oncocytic follicular thyroid nodule (FTN) (five out of six cases) clustered within the ESRRA-overexpressing group.[33]

Chromosomal instability plays a pivotal role in the tumorigenesis and progression of oncocytic carcinomas in which, notably, chromosomal deletions are more prevalent than amplifications.[34] Specifically, most recurrent losses involve chromosomes 8, 22, and 2, while gains are primarily observed in chromosomes 7, 12, and 17.35 In minimally invasive OCA, tumors are typically diploid or harbor a limited number of chromosomal alterations, whereas widely invasive OCA frequently exhibits chromosomal amplifications, consistently affecting chromosome 7.[36] Widespread chromosomal loss, a hallmark of OCA, is uncommon in other malignancies, with chromosomes 5, 7, 12, and 20 rarely affected.[29]

POORLY DIFFERENTIATED CARCINOMA (PDTC) AND ANAPLASTIC CARCINOMA (ATC)

PDTC and ATC are rare but clinically significant thyroid cancers due to their association with poor outcomes. PDTC is mostly diagnosed based on two primary criteria: the Turin and MSKCC criteria. The Turin criteria require a trabecular or nested or solid growth pattern without the nuclear features of PTC and at least one of the following characteristics: convoluted nuclei, a high mitotic rate (≥ 3 mitoses per 10 high-power fields [HPF]), or tumor necrosis.[32] The MSKCC criteria, in contrast, define PDTC by a higher mitotic rate (≥ 5 mitoses per 10 HPF) and the presence of necrosis, irrespective of the growth pattern.[32] ATC is the most aggressive thyroid malignancy, characterized by a complete loss of differentiation and histologically, predominantly epithelioid and spindle cells.[32]

Molecular Genetics of PDTC and ATC

The MAPK and PI3K signaling pathways, along with TP53 mutations, are frequently altered in PDCT and ATC.[7] A key distinction from PTC, which has a largely diploid genome, is that PDTC and ATC exhibit widespread chromosome copy number alterations, particularly in tumors lacking a driver gene mutation.[25]

Mutations of Genes Encoding Effectors in the MAP Kinase Pathway

The MAPK pathway plays a critical role in the development of thyroid carcinoma. Although BRAF and RAS mutations are most frequently observed in PTC and FTC, these mutations also occur at considerable frequencies in PDTC, ranging from 19% to 33% and 5% to 28%, respectively, as well as in ATC, with reported frequencies of 19%-45% and 9.5%-27%, respectively.[25]

BRAF and RAS mutations, which do not coexist in the same tumor, are linked to distinct clinical outcomes in PDTC. Thyroid-specific genes associated with radioiodine uptake remain consistently expressed in RAS-mutated PDTCs but show significantly reduced expression in PDTCs harboring BRAF mutations, leading to radioiodine-resistant tumors. Interestingly, tumors with BRAF mutations are more likely to metastasize to regional lymph nodes, compared to those with RAS mutations with a higher tendency for distant spread.[25]

Mutations of Genes Encoding Effectors in the Phosphatidyl inositol-3′-kinase (PI3K) Pathway

The MAPK (Mitogen-Activated Protein Kinase) pathway and the PI3K (Phosphoinositide 3-Kinase) pathway are two fundamental intracellular signaling cascades that regulate cell growth, proliferation, survival, and metabolism. Similar to the MAPK pathway, the PI3K pathway plays a critical role in thyroid carcinogenesis, primarily through genetic alterations affecting PTEN, PIK3CA, and AKT1.

PTEN (Phosphatase and Tensin Homolog) is a tumor suppressor gene that encodes a dual-specificity phosphatase responsible for converting phosphatidylinositol-3,4,5-trisphosphate (PIP3) back to phosphatidylinositol-4,5-bisphosphate (PIP2). This enzymatic activity serves as a negative regulator of the PI3K-AKT-mTOR signaling pathway. Consequently, PTEN inactivation or deletion results in the loss of negative regulation, leading to persistent activation of this oncogenic pathway.

PIK3CA (Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) encodes the p110α catalytic subunit of PI3K, a key oncogene involved in thyroid tumorigenesis. Copy number gain (CNG) of PIK3CA, resulting from chromosomal amplification, leads to increased PIK3CA expression and subsequent hyperactivation of PI3K signaling, contributing to tumor progression.[13]

AKT1, a central effector of the PI3K pathway, plays a crucial role in promoting cell survival and proliferation by phosphorylating and inactivating pro-apoptotic proteins. In addition, AKT1 activation stimulates mTOR, a downstream effector that facilitates cell growth and metabolic regulation. Activating mutations in AKT1 itself, or alterations in upstream regulators such as PIK3CA and PTEN, can lead to constitutive AKT1 activation, resulting in uncontrolled cell proliferation and tumorigenesis.[7]

These genetic mutations can coexist with BRAF and RAS mutations and appear to be enriched in advanced differentiated thyroid carcinoma. Although RAS activation influences both the MAPK and PI3K pathways, RAS mutations exhibit distinct functional roles. Specifically, KRAS mutations

predominantly activate the MAPK pathway, whereas NRAS mutations preferentially activate the PI3K-AKT pathway.[16]

While alterations in the PI3K/AKT pathway, particularly PTEN, are thought to occur early in thyroid cancer development, they are more commonly detected in advanced thyroid malignancies, including dedifferentiated high-grade thyroid carcinoma (DHGTC), PDTC (0-20%), and ATC (5-25%).[37] Additionally, the absence of PTEN expression on immunohistochemistry in both benign and malignant thyroid tumors is a characteristic finding in Cowden syndrome.[37]

p53 Mutations in PDTC and ATC

Beyond the involvement of MAPK pathway alterations across the full spectrum of thyroid malignancies, TP53 mutations occur at a higher frequency in ATC (43-78%) as thyroid cancer progression and dedifferentiation, compared to PDTC (0-8%) and other DHGTC.[25] The association between TP53 mutations and anaplastic thyroid cancer was first documented in the early 1990s and mutations that impair TP53 function have been detected in nearly half of all human cancers, making it the most prevalent genetic alteration associated with malignancy.[12]

The TP53 gene encodes the p53 tumor suppressor protein, which is essential for preserving genomic stability by regulating cell cycle progression from G1 to S and apoptosis to prevent transformation into malignant cells. The strikingly high frequency of TP53 mutations in anaplastic thyroid carcinoma, combined with their rarity in other thyroid malignancies, suggests that these mutations serve as a distinguishing feature of the disease and contribute to its aggressive behavior; however, despite their diagnostic significance, the low sensitivity of TP53 mutations limits their utility as an independent clinical biomarker.[12]

BETA-CATENIN AND THE APC PATHWAY IN THYROID CARCINOMA

The Wnt signaling pathway is a crucial cellular network essential for embryogenesis, tissue homeostasis, and cancer development, with the canonical Wnt/β-catenin pathway being the most relevant to cancer. This pathway primarily regulates gene expression by stabilizing β-catenin through the APC complex.[38] The β-catenin protein, encoded by CTNNB1, plays a critical role in cell adhesion by binding to cadherins at adherent junctions.[38] Additionally, β-catenin can translocate into the nucleus, where it activates the transcription of key target genes, including cyclin D1 and c-myc. Under normal conditions, β-catenin levels are tightly controlled through degradation by a destruction complex composed of APC, Axin, and GSK-3β.[38] However, Wnt signaling inhibits GSK-3β, preventing β-catenin degradation and leading to its accumulation in the cytoplasm and nucleus. Consequently, mutations that disrupt β-catenin regulation - such as an overactive Wnt pathway, loss of function in the destruction complex, or mutations in CTNNB1 - can result in uncontrolled cell proliferation and aggressive tumor development.[13]

A recent study investigating β-catenin expression in papillary thyroid carcinoma (PTC) found that the loss of membranous and cytoplasmic β-catenin immunoreactivity was significantly associated with an increased number of recurrences, multiple surgical interventions, and a higher cumulative dose of radioiodine therapy. Additionally, reduced membranous and cytoplasmic β-catenin staining correlated with adverse histopathologic features, including lymphovascular invasion, lymph node involvement, distant metastasis, and tumor dedifferentiation.[39] These findings suggest that the early component of the Wnt signaling pathway, particularly the E-cadherin-bound fraction of β-catenin, plays a crucial role in PTC progression. Furthermore, in a broader study examining β-catenin alterations across various thyroid malignancies, mutations in CTNNB1 were identified predominantly in the most aggressive subtypes, including poorly differentiated and anaplastic thyroid carcinomas.[40]

The interaction between β-catenin and E-cadherin is fundamental to cell adhesion and epithelial tissue integrity. Research indicates that E-cadherin associates with cytoplasmic β-catenin to form a complex with α-catenin, which plays a crucial role in maintaining epithelial structure and function. The loss or downregulation of adhesion molecules such as E-cadherin can disrupt cell morphology, enhance cellular motility, and facilitate tumor metastasis. In contrast, excessive E-cadherin expression can suppress β-catenin-mediated transcription, effectively downregulating target gene expression and thereby limiting cell proliferation and migration.[38]

TERT Promoter Mutations

TERT promoter (TERTp) mutations have emerged as significant molecular alterations in thyroid cancer, particularly in aggressive and undifferentiated subtypes (7.5% of PTCs, 17.1% of FTCs, 29% of PDTCs, and 33.3% of ATCs). These mutations, primarily the C228T and C250T hotspot variants, enhance telomerase expression, enabling cancer cells to maintain telomere length and achieve cellular immortality.[25] TERTp mutations have been identified across various thyroid cancer types, with increasing prevalence in PDTC and ATC, where they are associated with worse pathological features, including larger tumor size, extrathyroidal extension, vascular invasion, and distant metastases.[5] Additionally, these mutations correlate with advanced disease stage, poor prognosis, and resistance to radioactive iodine therapy, making them a crucial factor in treatment planning.[41] Furthermore, TERTp mutations exhibit a synergistic effect with BRAF mutations, contributing to tumor dedifferentiation and increased metastatic potential, particularly in older patients.[37] Given their prognostic and predictive value, TERTp mutation testing is increasingly recognized as an important tool for risk stratification and clinical management of thyroid cancer.[42]

NEW ENTITY: NON-INVASIVE FOLLICULAR THYROID NEOPLASM WITH PAPILLARY-LIKE NUCLEAR FEATURES

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is defined as a follicular cell–derived tumor that is encapsulated or clearly demarcated, exhibits a

follicular growth pattern, and shows nuclear changes reminiscent of PTC.[56] These nuclear alterations are typically assessed across three domains: (1) nuclear size and contour, (2) membrane irregularities, and (3) chromatin characteristics. Clinically, NIFTP behaves indolently, with an excellent prognosis and long-term survival, and it represents roughly 9% of papillary thyroid carcinomas worldwide.[57]

On a genetic level, NIFTP tends to cluster with follicular-patterned thyroid tumors rather than with classical papillary thyroid carcinoma. Most cases carry RAS mutations, most often involving NRAS, with reported rates close to 40%.[58] A subset of tumors with the BRAFK601E variant has also been described, and transcriptomic analyses demonstrate that these behave more like RAS-mutated lesions than like those with the aggressive BRAFV600E mutation. In addition to these driver mutations, alterations such as PTEN, DICER1, and EIF1AX can occasionally be detected. Interestingly, these mutations occur with frequencies similar to those seen in follicular adenomas, reinforcing the molecular distinction of NIFTP from classical PTC.[59]

MOLECULAR TESTS/PLATFORMS IN THYROID FNA

Molecular testing in thyroid fine-needle aspiration (FNA) has advanced significantly, transitioning from single-gene mutation analysis, such as BRAF, to small gene panels and, more recently, to comprehensive molecular classifiers that leverage next-generation sequencing (NGS).[43] These advanced assays allow for the simultaneous detection of multiple mutations, gene fusions, and gene expression alterations, including microRNA (miRNA) profiling, enhancing the accuracy of thyroid nodule risk stratification and reducing the need for diagnostic thyroid surgery.[44]

In recent years, there have been several commercially available molecular tests for assessing thyroid nodules with indeterminate cytology (Bethesda III: atypia of undetermined significance [AUS] / follicular lesion of undetermined significance [FLUS], or Bethesda IV: suspicious for follicular neoplasm [SFN] / follicular neoplasm [FN]).[45] These include ThyroSeq v3, Afirma Genomic Expression/Sequencing Classifier, ThyGenX/ThyraMIR, and RosettaGX Reveal. Each assay employs distinct methodologies and algorithms to evaluate the molecular profile of thyroid nodules, with varying clinical utility and unique strengths and limitations.[46]

ThyroSeq v3 (UPMC)

ThyroSeq v3, also known as ThyroSeq Genomic Classifier (GC), is a commercially available molecular assay developed by the University of Pittsburgh Medical Center (UPMC). The sample collection process involves obtaining residual aspirated material from routine FNA and placing it in a nucleic acid preservative solution, which is the optimal approach.[47] The test can also be performed on fixed FNA cells derived from a cytology cell block and formalin-fixed, paraffin-embedded (FFPE) tissue samples.[48]

ThyroSeq v3 employs a DNA- and RNA-based NGS assay to detect a broad spectrum of genetic alterations, including point mutations, insertions and deletions, gene fusions, copy number alterations, and abnormal gene expression.48 The GC score is calculated by summing the individual values of detected genomic alterations within a given sample, thereby distinguishing malignant from benign lesions.[48] The validation study demonstrated that ThyroSeq v3 achieved a sensitivity of 98.0%, a specificity of 81.8%, and an overall accuracy of 90.9% in an FNA validation set.48 However, its accuracy is dependent on adequate sample quality, requiring a minimum of 12% tumor cells in a background of non-neoplastic thyroid cells. Additionally, the test remains viable even with up to 88% blood contamination in the sample.[48]

Afirma Genomic Expression/Sequencing Classifier

The Afirma Genomic Expression Classifier (GEC) by Veracyte, Inc. employs proprietary RNA expression molecular profiling to classify thyroid nodules. Sample collection involves two needle passes to obtain material for molecular testing in addition to the standard FNA sample for cytology.[49] Performance metrics indicate a sensitivity of 92% and specificity of 52% for classifying nodules as suspicious. The negative predictive value (NPV) is 95% for Bethesda III category lesions and 94% for Bethesda IV category lesions.[50] A key limitation of the Afirma GEC is that it classifies nodules as either benign or suspicious without providing details on specific genetic alterations. While a benign result has a high NPV, a suspicious result has a poor positive predictive value (PPV), which varies widely (16-61%) across different reports.[51]

The improved second version, Genomic Sequencing Classifier (GSC), incorporates a broader set of classifiers utilizing thousands of genes. This enhancement allows for better differentiation between oncocytic (Hürthle cell) neoplasms and non-neoplastic oncocytic lesions, while also identifying medullary thyroid cancer (**Figure 6**), parathyroid lesions, BRAFV600E mutations, and RET/PTC fusions. Thus, it improves diagnostic accuracy and PPV while maintaining high NPV.[49] In a "real-world" study of 834 indeterminate thyroid nodules (74% Bethesda III) across three academic centers, the Genomic Sequencing Classifier demonstrated sensitivity, specificity, PPV, and NPV of 95%, 81%, 50%, and 99% for Bethesda III nodules, and 94%, 82%, 65%, and 98% for Bethesda IV nodules, respectively.[52]

ThyGeNEXT and ThyraMIR v2

ThyGeNEXT and ThyraMIR v2 utilize both DNA/RNA mutational markers and microRNA (miRNA) analysis, evaluating the expression levels of 11 microRNAs associated with growth promotion and suppression, along with RNA fusions and mutational analysis of 10 genes.[53,54] These tests can be performed on fresh FNA samples, direct smears, or ThinPrep slides, with no special shipping or refrigeration requirements.[53] The test demonstrates high performance with a reported sensitivity of 98%, specificity of 98%, NPV of 99%, and PPV of 96%.[53] Additionally, ThyGeNEXT and ThyraMIR v2 offer a medullary thyroid carcinoma profile that utilizes

pairwise microRNA expression to detect medullary thyroid carcinoma, which is particularly beneficial in cases lacking identifiable mutations. However, clinical experience with this platform remains limited, and long-term follow-up data are scarce.[53]

RosettaGX® Reveal™ Thyroid miRNA

RosettaGX® Reveal™ is another molecular platform that utilizes miRNA analysis for thyroid FNA samples.[53] The test is compatible with ThinPrep-prepared slides or direct smears.[53] In a retrospective study, RosettaGX Reveal demonstrated an overall accuracy rate of 64.2% with a specificity of 60.3% for benign/noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) cases.[53] In malignant cases, the test achieved a correct classification rate of 77.8%.[53]

Validation studies for these molecular testing methods are based on limited samples of malignant nodules.[55] Given the high cost of these tests, clinicians should also consider sonographic characteristics, nodule size, patient concerns, availability of follow-up imaging, and surgical candidacy before deciding on their use.

SUMMARY

Thyroid cancer is the most common endocrine malignancy, primarily presenting as papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). Significant progress in molecular biology has enhanced our understanding of thyroid carcinogenesis and led to novel diagnostic and therapeutic strategies. Key genetic alterations, including mutations in BRAF, RAS, RET/PTC fusions, and PAX8-PPARγ rearrangements, are central to tumor development and progression. For instance, BRAF mutations, particularly BRAFV600E, are often associated with aggressive PTC, while RAS mutations are common in follicular-patterned tumors like follicular thyroid adenomas and carcinomas. More aggressive forms, such as poorly differentiated and anaplastic thyroid carcinomas, frequently harbor mutations in TP53, TERT promoter, and components of the MAPK and PI3K pathways. Advances in molecular diagnostics, including next-generation sequencing (NGS) and gene expression classifiers, have significantly improved the accuracy of thyroid nodule evaluation, reducing the need for unnecessary surgeries. Commercial platforms like ThyroSeq v3, Afirma Genomic Expression/Sequencing Classifier, ThyGeNEXT/ThyraMIR, and RosettaGX Reveal utilize various methodologies to assess the molecular profile of thyroid nodules, helping to distinguish between benign and malignant lesions and inform clinical management.

CONFLICT OF INTEREST DISCLOSURES

The authors have no conflict of interest to disclose.

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