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AVANCES EN TIROIDES

Possibilities of molecular diagnosis in the setting of suspected thyroid cancer

Posibilidades del diagnóstico molecular ante la sospecha de cáncer de tiroides

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Abstract

Recent advances in cancer genomics have reshaped our understanding of pediatric thyroid carcinoma, revealing a distinct molecular landscape dominated by oncogenic kinase fusions rather than by point mutations, as seen in adults. Large cohort studies and systematic reviews have defined a pediatric-specific three-tier molecular classification: Tier 1 encompasses RAS-like, DICER1-, and PTEN-driven tumors associated with low-risk, often follicular-pattern differentiated thyroid carcinoma; Tier 2 includes BRAF V600E-mutant tumors, which present with classic papillary histology and high rates of lymph node involvement but relatively preserved radioiodine uptake; and Tier 3 groups RET-, NTRK-, ALK-, and other kinase-fusion-positive tumors, which are enriched in young children, frequently multifocal and invasive, and often associated with reduced radioiodine avidity and higher rates of distant metastases. Germline predisposition syndromes, including DICER1 and PTEN hamartoma tumor syndromes, as well as multiple endocrine neoplasia type 2, explain a substantial minority of pediatric thyroid cancers and necessitate early genetic testing and family-based surveillance.

These genetic insights are increasingly driving risk-adapted clinical algorithms: low-risk, Tier 1 tumors are being considered for lobectomy and de-escalated follow-up, whereas Tier 3 fusion-driven carcinomas warrant extensive surgery, early or reserved radioiodine, and in advanced cases, targeted therapy. The emergence of highly selective RET and TRK inhibitors, validated by trials such as LIBRETTO-121, has established a new paradigm in advanced, radioiodine-refractory or metastatic disease, with the potential for tumor regression and restoration of radioiodine uptake. This talk synthesizes recent literature to outline how refined molecular diagnostics are transforming diagnosis, surgical planning, and systemic therapy in pediatric thyroid carcinoma.

Resumen

Los avances recientes en la genética del cáncer han redefinido nuestra comprensión del carcinoma de tiroides en la infancia, revelando un perfil molecular propio dominado por fusiones de quinasas en lugar de mutaciones puntuales, como ocurre en los adultos. Estudios recientes han permitido definir una clasificación molecular pediátrica en tres niveles: el nivel 1 agrupa tumores de tipo RAS-like, impulsados por DICER1 y PTEN, asociados a carcinoma diferenciado de bajo riesgo, frecuentemente de patrón folicular; el nivel 2 incluye tumores con mutación BRAF V600E, que presentan histología papilar clásica y alta tasa de afectación de ganglios linfáticos, pero con captación

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de yodo radiactivo relativamente preservada; y el nivel 3 agrupa tumores con fusión de RET, NTRK, ALK y otras quinasas, que se concentran en niños pequeños, son frecuentemente multifocales e invasivos, y se asocian con menor captación de yodo radiactivo y mayor tasa de metástasis a distancia. Los síndromes de predisposición germinal, incluidos los síndromes DICER1 y PTEN-related, así como la neoplasia endocrina múltiple tipo 2, explican una proporción significativa de los carcinomas de tiroides en niños y requieren análisis genético precoz y seguimiento familiar.

Estas bases genéticas están remodelando los algoritmos de manejo clínico, ya que los tumores de bajo riesgo del nivel 1 se consideran candidatos a lobectomía y a una desescalada del seguimiento, mientras que los carcinomas de alto riesgo, impulsados por fusiones (nivel 3), exigen cirugía extensa, planes de administración de yodo radiactivo adaptados y, en enfermedad avanzada, terapia dirigida. La irrupción de inhibidores específicos de RET y de NTRK, validados en estudios como LIBRETTO-121, ha establecido un nuevo paradigma en el manejo de la enfermedad avanzada o refractaria al yodo radiactivo, con posibilidad de re-diferenciación tumoral y recuperación de la captación de yodo. Esta ponencia ilustra cómo la incorporación de la genética molecular está transformando el diagnóstico, la estrategia quirúrgica y el tratamiento sistémico del carcinoma de tiroides en la población pediátrica.

Introduction

Thyroid carcinoma is the most common endocrine malignancy in childhood and adolescence and in many high-income countries, ranks among the most frequent solid tumors in adolescents, particularly in girls. Differentiated thyroid carcinoma (DTC), comprising papillary (PTC) and follicular thyroid carcinoma (FTC), accounts for approximately 95% of pediatric thyroid cancers, whereas medullary thyroid carcinoma (MTC) and poorly differentiated or anaplastic histologies are rare in this age group. Compared with adults, children more often present with larger primary tumors, higher rates of cervical lymph node involvement, and an increased prevalence of pulmonary metastases at diagnosis, yet disease-specific survival exceeds 95–98% at long-term follow-up. These clinicopathologic differences have long suggested that pediatric thyroid carcinoma represents a biologically distinct entity rather than simply an early manifestation of the adult disease[1].

Over the past decade, landmark genomic studies in adults, particularly The Cancer Genome Atlas (TCGA), have established a paradigm in which differentiated thyroid carcinomas can be broadly categorized into “BRAF-like” and “RAS-like” molecular subtypes, each associated with distinct transcriptomic signatures and degrees of thyroid differentiation[2]. However, systematic sequencing of pediatric DTC cohorts published since 2020 has revealed a strikingly different distribution of oncogenic drivers in children, with a predominance of oncogenic kinase fusions and a much lower frequency of point mutations when compared with adults. These pediatric series have also clarified strong associations between specific genetic alterations and patterns of invasion, lymphatic and hematogenous spread, radioiodine (RAI) avidity, and response to systemic targeted therapies[3].

Concurrently, substantial progress has been made in understanding germline cancer predisposition syndromes predisposing to non-medullary thyroid carcinoma, including DICER1 syndrome, PTEN hamartoma tumor syndrome, and familial adenomatous polyposis, as well as in refining genotype–phenotype correlations and management recommendations for multiple endocrine neoplasia type 2 (MEN2) and inherited MTC. These insights have coincided with the clinical availability of highly selective tyrosine kinase inhibitors (TKIs) directed against RET and NTRK rearrangements, and with increasing pediatric experience using BRAF and MEK inhibitors in advanced BRAF-mutant disease. Together, these advances are reshaping diagnostic algorithms, surgical decision-making, use of RAI, and the approach to systemic therapy in children with advanced or refractory thyroid carcinoma[4].

The present talk focuses on recent advances in the understanding of genetic alterations in pediatric thyroid cancer and their clinical implications. After summarizing epidemiology and clinicopathologic features, I will discuss the evolving somatic landscape of pediatric DTC, emerging data on germline predisposition to non-medullary thyroid carcinoma, and contemporary insights into the genetics of pediatric MTC. These genetic advances are then integrated into a discussion of their impact on risk stratification, surgical extent, RAI use, and the deployment of precision therapeutics in children and adolescents with thyroid cancer.

Epidemiology and Clinicopathologic Features

Pediatric thyroid carcinoma is rare (≈1.1 per 100,000), but the incidence has risen steadily, and thyroid carcinoma is now one of the most common solid malignancies in adolescents, particularly girls. Differentiated tumors derived from follicular cells (papillary and follicular thyroid carcinoma) account for ≈95% of pediatric thyroid cancers, with papillary thyroid carcinoma (PTC) representing ~80–90% in most series[2,3]. Compared with adults, children present with larger primary tumors, a much higher prevalence of regional lymph node metastasis (often 60–80%), and a higher prevalence of pulmonary metastases, yet long-term disease-specific survival remains >95–98% over 20–30 years[1].

Recent European and Asian consensus documents emphasize that pediatric thyroid cancer cannot simply be managed as "small adult DTC," given age-specific patterns of spread, unique genetic drivers, and different late-effect profiles of surgery and radioiodine. These considerations frame the importance of a pediatric-specific genetic paradigm[5].

Somatic Genetic Landscape of Pediatric DTC

From TCGA to a Pediatric 3-Tier Model

Adult DTC is dominated by point mutations in BRAF and RAS, with a relatively smaller contribution from gene fusions, leading to the widely used "BRAF-like vs RAS-like" classification derived from TCGA data[2]. In contrast, integrated analyses of pediatric DTC cohorts published since 2020 have consistently demonstrated that children exhibit a fusion-enriched profile, with oncogenic fusions accounting for roughly one-third to two-thirds of cases, particularly in younger children and in radiation-associated tumors. Point mutations in BRAF, RAS, and other genes still occur but at lower frequencies than in adults, and their prognostic implications appear to differ by age. Two comprehensive syntheses, one by Yang et al. in Endocrine Reviews and another by Vanderniet et al. in Cancers, proposed a pediatric-specific, three-tier molecular classification that better reflects the distribution of drivers and their clinical associations in children[1,3]. In this framework:

- Tier 1 (low risk for invasive behavior): RAS-like tumors driven by RAS family mutations, DICER1, PTEN, non-V600E BRAF, or PAX8::PPARG.
- Tier 2 (intermediate risk): BRAF V600E–mutant tumors.
- Tier 3 (high risk): Kinase fusion–positive tumors (RET, NTRK, ALK, MET).

Fusions account for roughly one-third to two-thirds of pediatric DTCs, particularly in children under 10 years, compared with ≈15% in adults, whereas point mutations dominate adult tumors but represent <25% of pediatric cases. The 3-tier system correlates with ultrasound patterns, cytology, histology, rates of lymph node and distant metastases, and RAI avidity, and has been explicitly proposed as a framework for integrating somatic testing into preoperative risk stratification (Table 1).

Kinase Fusions: RET, NTRK, ALK, and Others

RET fusions. RET fusions are the single most common driver in pediatric PTC, occurring in ≈25–40% of cases overall and in a higher proportion of radiation-associated and very early-onset tumors. Several recent cohort studies report that RET rearrangements, predominantly CCDC6::RET and NCOA4::RET, are strongly associated with younger age, larger tumors, and frequent nodal and distant metastases[3].

NTRK fusions. Recent multi-institutional series highlight NTRK1/3 fusions in ≈10–20% of pediatric PTCs, most commonly ETV6::NTRK3 and TPR::NTRK1. A 2022–2023 analysis of NTRK-rearranged pediatric PTC confirmed a predominance in children with diffusely infiltrative, multifocal, and metastatic disease[3].

A 2021 JCI study of 106 pediatric PTCs reported 21 RET-fusion and 4 NTRK-fusion tumors and showed that fusion-positive tumors have lower thyroid differentiation scores and reduced expression of the sodium-iodide symporter (SLC5A5) compared with adult fusion-positive PTCs. Two young girls with RAI-refractory metastatic PTC treated with larotrectinib and selpercatinib, respectively, had marked tumor regression and restoration of RAI uptake, enabling effective therapeutic RAI, illustrating the concept of oncogene-directed "redifferentiation."[6]

ALK and other fusions. ALK fusions appear in up to 7% of pediatric PTCs and are also associated with invasive disease and occasional transformation to poorly differentiated thyroid carcinoma. MET and BRAF fusions are less common but fall within the same high-risk "fusion-like" group[3].

BRAF-Mutant Tumors

BRAF V600E remains the dominant driver in adult PTC but is less frequent in children. Contemporary pediatric series since 2020 report BRAF V600E in ≈15–25% of pediatric PTC overall, with higher frequencies in adolescents and in some Asian cohorts, but rarity in prepubertal children[1]. Pediatric BRAF-mutant PTC is associated with:

- Classic papillary architecture and typical cytology,
- High rates of regional nodal metastases,
- Generally low rates of distant metastasis and radioiodine-refractory disease, in contrast to adults.

These differences are partly attributed to the near-absence of TERT-promoter co-mutations in pediatric BRAF-mutant tumors, which in adult PTC drive dedifferentiation and poor outcomes. BRAF fusions are rare but do occur, particularly in radiation-exposed populations, and are usually grouped in the high-risk fusion-like tier 1[3].

Table 1. Possibilities of molecular diagnosis in the setting of suspected pediatric thyroid cancer.

Tier and genetic subgroup	Representative alterations	Approx. frequency in pediatric DTC	Typical histology	Ultrasound pattern	Nodal / distant mets	RAI avidity	Risk tier
Tier 1: RAS-like	NRAS, HRAS, KRAS, non-V600E BRAF, PAX8::PPARG, DICER1, PTEN	<10%	Follicular-pattern, encapsulated	Smooth margins, low-suspicion nodules	Low	High when metastatic	Low
Tier 1: DICER1/ PTEN	DICER1 hotspot, PTEN	~5–10% (FTC-enriched)	Follicular carcinoma, follicular-pattern PTC, NIFTP	Usually well-defined, often multiple nodules	Low (but higher in FTC with DICER1 hotspot)	High	Low
Tier 2: BRAF-mutant	BRAF V600E	~15–25%	Classic PTC, often with psammoma bodies	Irregular, hypo-echoic, microcal-cifications	High nodal mets, lower distant mets than fusions	Moderate to high; low if dedifferenti-ated	Interme-diate
Tier 3: RET fusions	CCDC6::RET, NCOA4::RET, others	~25–40%	Follicular-variant, cribriform-morular, radiation-associated	Lobulated, infiltrative, irregular margins	Very high (often present at diagnosis)	Variable, often low or RAI-refractory when metastatic	High
Tier 3: NTRK fusions	ETV6::NTRK3, TPR::NTRK1, others	~10–20%	Follicular-variant, infiltrative growth	Diffusely infiltrative, often bilateral/ multifocal	Very high, frequent pulmonary mets	Often low, but can be restored by TRK inhibition	High
Tier 3: ALK / other fusions	EML4::ALK, AGK::BRAF, ETV6::BRAF, MET fusions	<5–7% (ALK); rare (others)	Follicular-variant, solid or densely cellular	Infiltrative, often with vascular invasion	High, occasional progression to PDTC/ ATC	Variable, often low in advanced disease	High

FTC: follicular thyroid carcinoma; NIFTP: non-invasive follicular thyroid neoplasm with papillary-like nuclear features; PTC: papillary thyroid carcinoma; RAI: radioiodine; PDTC: poorly differentiated thyroid carcinoma; ATC: anaplastic thyroid carcinoma.

RAS-Like, DICER1, PTEN and Other Low-Risk Drivers

RAS mutations (NRAS, HRAS, KRAS) make up a minority (<10%) of pediatric DTC drivers, much less than in adult FTC and follicular-variant PTC. DICER1 hotspot mutations and PTEN alterations, in contrast, are relatively enriched in pediatric FTC and follicular-patterned PTC, often in the context of germline predisposition syndromes[1].

RAS-like/DICER1/PTEN-driven tumors typically present as encapsulated follicular-pattern lesions with smooth ultrasound margins, indeterminate Bethesda III/IV cytology, low rates of nodal and distant metastasis, and excellent outcomes; they form the molecular basis for considering lobectomy rather than routine total thyroidectomy in carefully selected pediatric patients[1].

Germline Predisposition Syndromes

Updated reviews underscore that ≈5–13% of pediatric DTC arises in the context of germline cancer-predisposition syndromes[7]. Key syndromes and their predominant genetic alterations are:

- DICER1 syndrome (germline DICER1): High lifetime risk of multinodular goiter and DTC; pediatric FTC is particularly enriched for DICER1, with recent series showing germline or somatic DICER1 variants in up to 50% of pediatric FTCs.
- PTEN hamartoma tumor syndrome (PHTS): Elevated risk of multinodular goiter and predominantly follicular-pattern tumors.
- Familial adenomatous polyposis (APC), Carney complex (PRKAR1A), and Werner syndrome (WRN): Lower absolute prevalence in childhood but important for thyroid surveillance.
- Familial non-medullary thyroid carcinoma (FNMTC): A clinically defined entity; exome-level drivers remain elusive, but early pediatric onset and multifocality should prompt family screening.

Vanderniet et al. provide a practical framework for selecting pediatric patients for germline testing based on age at onset, histology (e.g. FTC <10 years), macrocephaly, and family history[3].

Genetic Landscape of Pediatric MTC

1. MTC accounts for approximately 4–5% of pediatric thyroid cancers and is overwhelmingly associated with germline activating RET mutations causing multiple endocrine neoplasia type 2 (MEN2A, MEN2B) or familial MTC[8]. Recent work adds four relevant dimensions:

2. Genotype–phenotype refinements in MEN2. Contemporary MEN2A/MEN2B cohorts refine the risk associated with specific RET codons (e.g. 618, 620, 634, 804, 918) and support a graded approach to prophylactic thyroidectomy, confirmed by multicenter natural-history analyses and large database studies of incidentally discovered RET variants[9].

3. Somatic RET and RAS in sporadic pediatric MTC. Sporadic pediatric MTC remains rare, but modern series show that when present, it is typically driven by somatic RET mutations (often M918T) and less frequently RAS, mirroring adult sporadic disease.

4. Large outcome cohorts integrating somatic profiling. A 2024 tertiary-center cohort of 144 patients diagnosed with MTC at ≤21 years showed that 86% had hereditary MTC, while sporadic cases, though only 14% were more frequently RET-driven at the somatic level and presented with more advanced TNM stage and higher rates of persistent disease; nonetheless, disease-specific survival remained excellent over decades of follow-up[8].

5. RET-targeted therapies in pediatric MTC. Highly selective RET inhibitors have moved rapidly into pediatric practice. The global LIBRETTO-121 trial includes children and adolescents with RET-mutant MTC and RET-fusion thyroid carcinoma[10]; interim data show high objective response rates and durable disease control with selpercatinib, with safety profiles broadly similar to adults.14 In 2024, the FDA extended selpercatinib's indication to children ≥2 years with advanced RET-mutant MTC or RET-fusion thyroid carcinoma, based in part on these data.

Clinical Implications of Recent Genetic Insights

Molecular Testing to Stratify Thyroid Nodules and Guide Surgery

Pediatric-specific data support extending adult concepts of molecularly informed thyroid nodule management to children, while recognizing pediatric-specific risks and performance characteristics. Several large pediatric FNA series using modern NGS panels (e.g. ThyroSeq v3) demonstrate high prevalence of actionable oncogenic drivers in Bethesda III–V nodules and a strong correlation between fusion status and invasive behavior, including extrathyroidal extension, nodal disease, and distant metastases[11–13]. These findings support the integration of somatic testing into preoperative risk stratification.

Recent consensus reviews recommend somatic oncogene testing for pediatric nodules with indeterminate cytology and for widely invasive carcinomas, as a standard component of preoperative planning[1,14].

Surgical Extent and De-escalation

Several reviews and guideline-oriented commentaries argue that in the genomic era, not all pediatric DTC requires total thyroidectomy[5,15,16]. Emerging data suggest that:

- Low-risk, RAS-like/DICER1/PTEN-driven tumors, particularly solitary, intrathyroidal T1–T2 lesions without nodal disease, can often be safely managed with lobectomy, reducing risks of hypoparathyroidism and recurrent laryngeal nerve injury.

- Fusion-positive or BRAF-mutant PTC with multifocality, bilateral disease, or nodal metastases generally warrant total thyroidectomy and central neck dissection.

This shift is reflected in pediatric-specific reviews and in national guideline updates, including the 2024 Korean Thyroid Association pediatric DTC guideline, which explicitly integrates molecular drivers into risk-adapted surgical recommendations[14].

Radioiodine Avidity, Redifferentiation, and Driver-Specific Biology

The 2021 JCI cohort and subsequent mechanistic work highlight that pediatric fusion-positive PTCs—especially RET and NTRK fusions—have lower thyroid differentiation scores and reduced expression of the sodium-iodide symporter compared with BRAF-mutant tumors, explaining a higher propensity for RAI-refractory disease[6]. This same cohort and later case reports showed that TRK and RET inhibitors can partially restore NIS expression and RAI uptake ("redifferentiation") in previously non-avid metastases, and that combining targeted therapy with RAI can induce major tumor responses and occasionally, durable remissions in children.

Targeted Systemic Therapies in Children and Adolescents

The therapeutic landscape has shifted dramatically recently.

- RET inhibitors. Selpercatinib and pralsetinib are highly selective RET-inhibiting TKIs with potent activity in RET-mutant MTC and RET-fusion DTC. LIBRETTO-121 and related pediatric cohorts show objective response rates around 40–60%, with many responses ongoing beyond 12 months, underpinning 2024 regulatory approvals for children ≥2 years with RET-altered MTC or thyroid carcinoma[10].

- TRK inhibitors. Larotrectinib and entrectinib show high response rates (>70–80%) in TRK-fusion solid tumors, including pediatric PTC, and can induce RAI-avid redifferentiation[6,17–19].

- BRAF/MEK inhibition. Dabrafenib plus trametinib has been used in pediatric BRAF V600E-mutant thyroid carcinoma, with emerging—but still limited—experience in advanced or anaplastic transformation[1].

- Multi-targeted TKIs. Lenvatinib, sorafenib, and cabozantinib remain options for children with progressive, RAI-refractory DTC or MTC without targetable fusions/mutations, but toxicity profiles are less favorable than modern oncogene-specific inhibitors[1].

- Neoadjuvant and adjuvant use. Inspired by early data from Kazahaya et al. and subsequent institutional series, multiple groups now advocate for pilot neoadjuvant targeted therapy in children with invasive thyroid carcinomas encasing the trachea, esophagus, or major vessels, aiming to down-stage disease and reduce surgical morbidity. Oncogene-directed therapy is also being evaluated as an adjuvant or consolidation strategy in children with bulky, incompletely resected metastatic disease[1].

Implications for Guidelines and Care Models

Recent position papers and regional reviews emphasize that the genetic breakthroughs mandate re-thinking models of pediatric thyroid cancer care[5,14,16]. Key themes include:

- Embedding high-quality molecular diagnostics (somatic and, when indicated, germline) into standard care pathways for pediatric thyroid nodules and cancers.

- Establishing multidisciplinary “advanced pediatric thyroid cancer” programs that integrate pediatric endocrinology, surgery, oncology, genetics, nuclear medicine, and radiology, particularly for fusion-positive and syndromic cases.

- Adopting harmonized, pediatric-specific guidelines that balance excellent oncologic outcomes with minimization of long-term sequelae from surgery, radioiodine, and systemic therapy.

Concluding remarks and future directions

In conclusion, the integration of contemporary molecular data has fundamentally redefined pediatric thyroid carcinoma as a distinct entity from its adult counterpart, with a fusion-enriched genome and a pediatric-specific three-tier risk stratification model that strongly correlates with clinical behavior and therapeutic response. The delineation of germline predisposition syndromes and the identification of somatic drivers in both differentiated and medullary thyroid carcinomas now provide a robust framework for early diagnosis, tailored surgical extent, and guided use of radioiodine and targeted therapies. The advent of highly selective RET and TRK inhibitors, together with emerging experience with BRAF- and MEK-directed agents, offers unprecedented opportunities to improve outcomes in children with advanced or refractory disease, often by enabling re-differentiation strategies and radioiodine rescue. Moving forward, prospective validation of molecularly informed algorithms, harmonization of pediatric-specific guidelines, and international collaboration to standardize molecular testing and access to targeted therapies will be essential to fully translate these genetic advances into optimized, individualized care for pediatric thyroid cancer patients.

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