

Thyroid Cancer: Concise Literature Review

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ABSTRACT

Background: Thyroid cancer is the most common endocrine malignancy and its global incidence has increased substantially over the past decades. While most cases correspond to well-differentiated tumors with excellent prognosis, a subset of patients develops aggressive disease characterized by recurrence, metastasis, and resistance to therapy.

Objective: To provide a concise overview of the current literature regarding the epidemiology, histologic heterogeneity, molecular pathogenesis, diagnostic approaches, and contemporary management strategies for thyroid cancer.

Methods: A narrative review of the literature was conducted focusing on key themes in thyroid cancer research, including incidence trends, molecular drivers of tumorigenesis, subtype-specific characteristics, emerging biomarkers, and advances in systemic therapies.

Results: Thyroid cancer incidence has risen significantly worldwide, largely due to increased detection of small papillary thyroid carcinomas, raising concerns regarding overdiagnosis. Histologically, thyroid cancer comprises several subtypes, including papillary, follicular, Hürthle cell, poorly differentiated, anaplastic, and medullary carcinomas, each with distinct biological behavior and prognosis. Molecular alterations involving the MAPK pathway, particularly BRAF and RAS mutations, play central roles in tumor initiation, while additional alterations such as TERT promoter and TP53 mutations contribute to disease progression and dedifferentiation. Diagnostic evaluation relies on ultrasound-guided fine-needle aspiration and guideline-based risk stratification. Standard treatment includes surgery with selective use of radioactive iodine in differentiated tumors. For advanced or refractory disease, targeted therapies and multikinase inhibitors have expanded treatment options. Emerging research on the tumor immune microenvironment and circulating biomarkers may further refine diagnosis and personalized therapy.

Conclusion: Thyroid cancer represents a heterogeneous group of malignancies with diverse clinical behavior. Advances in molecular biology, targeted therapy, and risk-adapted management strategies are reshaping treatment paradigms. Continued research is needed to address persistent challenges such as overdiagnosis, therapeutic resistance, and the development of reliable biomarkers for disease monitoring.

KEYWORDS: Thyroid cancer; Papillary thyroid carcinoma; Molecular pathogenesis; BRAF mutation; TERT promoter mutation; Thyroid tumor heterogeneity; Targeted therapy; Radioactive iodine; Tumor immune microenvironment; Circulating biomarkers.†

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INTRODUCTION

Thyroid cancer is the most common endocrine malignancy and has shown a marked increase in incidence worldwide over recent decades (1,2). Despite this rise, prognosis is generally excellent for differentiated thyroid cancers (DTCs), with reported 5-year survival rates approaching 98–99% in many series, largely reflecting the predominance of indolent papillary thyroid carcinomas (PTCs) (1). However, thyroid cancer is not a uniform disease. Its biological behavior, prognosis, and therapeutic options vary considerably according to histologic subtype, molecular alterations, and tumor microenvironment (3,4).

Current literature emphasizes a dual reality: on one hand, the widespread detection of small low-risk tumors has led to concerns regarding overdiagnosis and overtreatment; on the other, a subset of patients develops aggressive disease with recurrence, metastasis, dedifferentiation, and resistance to conventional therapy (2,5). This review summarizes the current literature on the epidemiology, histologic heterogeneity, molecular pathogenesis, diagnosis, and management of thyroid cancer, with emphasis on emerging targeted and personalized therapeutic approaches.

LITERATURE REVIEW

Epidemiology and Risk Factors

Thyroid cancer accounts for approximately 2–2.5% of all malignancies and constitutes the vast majority of endocrine cancers (1). The increase in incidence observed globally has been attributed largely to the increased use of ultrasound and cross-sectional imaging, which has facilitated detection of small papillary microcarcinomas that might otherwise have remained clinically silent (2). This pattern has raised substantial concern regarding overdiagnosis, particularly in low-risk PTC (2,5). Still, some authors argue that improved

detection alone does not fully explain the epidemiologic trend, as more advanced and clinically meaningful tumors may also be increasing in frequency (2).

Established risk factors include prior exposure to ionizing radiation and family history, both of which remain clinically relevant in patient risk assessment (1).

Histologic Types and Biological Heterogeneity

Thyroid cancer encompasses several major histologic subtypes, each with distinct biological and clinical features. Papillary thyroid carcinoma is the most common subtype, representing approximately 80–84% of cases, followed by follicular thyroid carcinoma, oncocytic/Hürthle cell carcinoma, poorly differentiated thyroid carcinoma (PDTC), anaplastic thyroid carcinoma (ATC), and medullary thyroid carcinoma (MTC) (1,3,6).

A central concept in recent literature is the marked heterogeneity of thyroid cancer. This heterogeneity exists at histologic, genetic, epigenetic, and microenvironmental levels and is particularly evident among follicular-cell-derived malignancies (4). Such diversity helps explain the wide spectrum of clinical behavior observed across thyroid cancers, ranging from indolent microcarcinomas to rapidly fatal undifferentiated tumors (4,7).

Papillary thyroid carcinoma usually carries an excellent prognosis, but aggressive variants such as tall cell, diffuse sclerosing, columnar cell, hobnail, and solid variants are associated with less favorable outcomes and may justify more aggressive management (8,9). Follicular thyroid carcinoma and Hürthle cell carcinoma remain diagnostically and therapeutically challenging, partly because cytology often cannot reliably distinguish malignant from benign lesions, and because many practice recommendations are extrapolated from papillary thyroid cancer data rather than generated specifically for these entities (6).



Figure 1. Follicular thyroid cancer



Figure 2, Solid lesion measuring 3x2cm in the upper pole of the right thyroid lobe

PDTC and ATC represent the aggressive end of the disease spectrum. PDTC is rare but accounts for a disproportionate number of thyroid cancer–related deaths outside of ATC, while ATC, though uncommon, causes the majority of thyroid cancer mortality because of its highly invasive and rapidly progressive nature (3,10,11).

Molecular Pathogenesis and Progression

The molecular pathogenesis of thyroid cancer has become a central focus of contemporary research. Differentiated thyroid cancers are commonly driven by alterations activating the MAPK pathway, particularly BRAF V600E and RAS mutations (7,12). Disease progression from DTC to PDTC and ATC is associated with the accumulation of additional molecular abnormalities, including alterations in TP53,

PI3K/AKT effectors, EIF1AX, NF2, and chromatin-remodeling genes such as those of the SWI/SNF complex (12).

Among these events, TERT promoter mutations have drawn particular attention because they are uncommon in benign thyroid lesions but enriched in advanced disease, especially PDTC and ATC. These mutations have been strongly associated with recurrence, mortality, and aggressive tumor behavior, particularly when coexisting with BRAF V600E in papillary thyroid carcinoma (13).

This stepwise molecular evolution provides a useful framework for understanding dedifferentiation, disease aggressiveness, and resistance to conventional therapy (10,12,13).

Table 1. Major Histologic Types of Thyroid Cancer: Prevalence, Key Molecular Features, Clinical Behavior, and Management Tumor Immune Microenvironment

Histologic Type	Approximate Frequency	Cell of Origin	Key Molecular Alterations	Clinical Characteristics	Typical Management
Papillary thyroid carcinoma (PTC)	~80–84%	Follicular cells	BRAF V600E, RAS, RET/PTC ± TERT aggressive disease	Most common subtype; generally indolent but prone to lymph node metastasis; aggressive variants (tall cell, hobnail, diffuse sclerosing) have worse prognosis	Surgery (lobectomy or total thyroidectomy based on risk); selective radioactive iodine (RAI); TSH suppression; surveillance
Follicular thyroid carcinoma (FTC)	~4–10%	Follicular cells	RAS mutations, PAX8-PPARγ rearrangements; ± TERT promoter	More likely than PTC to metastasize hematogenously (bone, lung); diagnosis difficult on cytology	Surgical resection (often total thyroidectomy); RAI in selected patients; surveillance with thyroglobulin
Hürthle cell carcinoma (oncocytic carcinoma)	~2–3%	Follicular cells	Mitochondrial alterations; ± RAS, TERT	DNA Often more aggressive than FTC; reduced avidity in some tumors	Surgery; selective RAI; systemic therapy for advanced disease

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Histologic Type	Approximate Frequency	Cell of Origin	Key Molecular Alterations	Clinical Characteristics	Typical Management
Medullary thyroid carcinoma (MTC)	~3–4%	Parafollicular cells	RET mutations (germline in MEN2, somatic in sporadic cases)	Secretes calcitonin; may be hereditary; early nodal and distant metastasis possible	Total thyroidectomy with lymph node dissection; targeted therapy (RET inhibitors) in advanced disease
Poorly differentiated thyroid carcinoma (PDTC)	~3–5%	Follicular cells	BRAF, RAS, TERT, TP53, EIF1AX alterations	Intermediate behavior between DTC and ATC; higher metastatic potential	Surgery when feasible; RAI if iodine-avid; systemic therapy for advanced disease
Anaplastic thyroid carcinoma (ATC)	~1–2%	Dedifferentiated follicular cells	TP53, TERT, BRAF, PI3K/AKT pathway alterations	Highly aggressive; rapid local invasion and distant metastasis; very poor prognosis	Multidisciplinary treatment: surgery when possible, radiotherapy, systemic targeted therapy, palliative care

More recently, the thyroid tumor immune microenvironment (TIME) has emerged as an important area of investigation. The TIME includes tumor-associated lymphocytes, macrophages, myeloid-derived suppressor cells, and other immune populations that may shape tumor progression and therapeutic response (14). Current evidence suggests that immune landscapes differ substantially across thyroid cancer subtypes, particularly between PTC and ATC, which may partly explain differences in clinical behavior and sensitivity to immunotherapy (14). These findings support the development of immune-based biomarkers and checkpoint-targeted treatment strategies, although this field remains under active investigation.

Diagnosis and Biomarkers

Most well-differentiated thyroid cancers are asymptomatic and are detected either incidentally or during evaluation of a thyroid nodule (1). Diagnostic workup relies heavily on neck ultrasound and ultrasound-guided fine-needle aspiration (FNA), with risk stratification guided by American Thyroid Association (ATA) recommendations for thyroid nodules and differentiated thyroid cancer (15).

However, FNA has important limitations, particularly for follicular and Hürthle cell neoplasms, in which cytology often cannot confirm capsular or vascular invasion and therefore cannot definitively distinguish benign from malignant disease (6). This is a major clinical gap and continues to complicate management decisions.

Regarding biomarkers, serum thyroglobulin remains central for surveillance of differentiated thyroid cancer, while calcitonin and carcinoembryonic antigen are established markers in medullary thyroid carcinoma (1,16). Newer circulating biomarkers, including mutant DNA fragments, microRNAs, exosomal proteins, and other genomic and proteomic markers, are under investigation to improve

diagnosis, recurrence detection, and treatment monitoring. However, their clinical utility remains limited by issues of standardization, sensitivity, and validation (16).

Management and Evolving Therapies

The management of thyroid cancer has shifted toward a more risk-adapted and personalized model. For selected patients with papillary thyroid microcarcinomas measuring 1 cm or less, active surveillance is now considered an acceptable option, reflecting recognition of the indolent nature of many small tumors and the need to reduce overtreatment (1). For larger or clinically significant disease, surgery remains the cornerstone of treatment, with the extent of resection determined by tumor features, patient risk profile, and guideline-based recommendations (1,15,17).

Radioactive iodine (RAI) remains an important adjuvant treatment in higher-risk differentiated thyroid cancer, but current practice favors selective rather than routine use in order to avoid unnecessary treatment in low-risk patients (1,17). This risk-adapted approach has become a key principle in contemporary thyroid cancer management (17).

In recurrent or metastatic disease, local therapies such as surgery, ablation, or focused radiotherapy are preferred when feasible (1). For RAI-refractory DTC, metastatic MTC, PDTC, and ATC, systemic therapy has expanded considerably. Multikinase inhibitors such as sorafenib, lenvatinib, cabozantinib, and vandetanib have improved progression-free survival in advanced disease, though toxicity and acquired resistance remain important limitations (18,19).

More importantly, molecularly selective therapies have transformed the management of subsets of advanced thyroid cancer. Agents targeting RET, NTRK, BRAF, and MEK alterations have enabled genotype-directed treatment, particularly in advanced DTC, MTC, and ATC (18,19). In

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ATC, the 2021 ATA guidelines emphasize urgent multidisciplinary care integrating surgery when feasible, radiotherapy, systemic therapy, targeted treatment when actionable mutations are present, and palliative care when appropriate (11).

A further area of interest is re-differentiation therapy, in which MAPK pathway inhibition may restore RAI uptake in selected tumors, potentially re-sensitizing them to radioactive iodine treatment (18,19). Although promising, this strategy still faces practical and biologic limitations.

Discussion

The current thyroid cancer literature is shaped by a tension between two realities. The first is the overidentification of low-risk disease, especially papillary microcarcinomas detected through modern imaging, which has prompted a move toward less aggressive treatment and, in selected cases, active surveillance (1,2,5). The second is the persistent challenge posed by aggressive subtypes such as PDTC and ATC, which continue to cause substantial mortality despite improvements in molecular characterization and therapy (3,10,11).

A major strength of the field is the rapid integration of molecular biology into clinical care. The identification of key drivers such as BRAF, RAS, and TERT promoter mutations has improved the understanding of disease progression and opened the door to more precise treatment strategies (7,12,13). Even so, the assumption that molecular insight automatically translates into better outcomes is too simplistic. Resistance, intratumoral heterogeneity, and variable tumor microenvironmental influences still limit the long-term success of targeted therapy (4,12,14).

Another persistent problem is that not all thyroid cancer subtypes are equally well studied. Papillary thyroid cancer dominates the literature, while follicular and Hürthle cell carcinomas remain comparatively underrepresented despite their distinct biology and clinical challenges (6). Similarly, the growing interest in circulating biomarkers and immunotherapy is justified, but much of this work remains investigational and has not yet changed routine practice in a robust way (14,16).

Overall, the field has progressed from a largely morphology-based discipline to one increasingly informed by molecular profiling, risk stratification, and individualized treatment. That said, the literature still contains major gaps regarding optimal sequencing of systemic therapies, biomarkers of response, and the best integration of targeted therapy, immunotherapy, and conventional treatment modalities.

CONCLUSION

Thyroid cancer is a heterogeneous group of malignancies ranging from indolent differentiated tumors with excellent prognosis to highly aggressive undifferentiated cancers with poor survival. Current evidence supports a risk-adapted management model grounded in histology, imaging, guideline-based stratification, and increasingly, molecular

profiling. The rise in incidence is largely explained by increased detection of low-risk tumors, though a subset of clinically significant aggressive disease remains a major therapeutic challenge.

Advances in molecular pathogenesis, targeted therapy, and understanding of the immune microenvironment have improved the management of advanced disease and expanded personalized treatment options. However, important limitations remain, including overdiagnosis, unequal evidence across subtypes, treatment resistance, and lack of validated novel biomarkers. Future research should focus on refining biologic risk prediction, improving subtype-specific evidence, and integrating molecular and immune-based approaches into more effective and less harmful treatment algorithms.

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