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Decoding differentiated thyroid carcinoma: innovations in diagnosis, staging, and treatment

Abstract

Thyroid cancer is the most common endocrine malignancy, with differentiated thyroid carcinoma (DTC) accounting for approximately 90% of cases. DTC primarily includes papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and oncocytic thyroid carcinoma (OTC), each characterized by distinct histological and genetic profiles. Diagnostic strategies for DTC integrate advanced imaging modalities and cytopathological techniques. Cervical ultrasound is a cornerstone for evaluating suspicious thyroid nodules, complemented by systems like ACR-TIRADS for malignancy risk stratification. Fine-needle aspiration biopsy (FNAB) remains the gold standard, guided by the Bethesda System for Reporting Thyroid Cytopathology for risk-based management. DTC subtypes are defined by histopathological features. PTC, the most prevalent, exhibits hallmark nuclear changes and frequent lymphatic spread, driven by mutations such as BRAF p.V600E and RET fusions. FTC is characterized by hematogenous spread and key molecular drivers like RAS mutations and PAX8::PPARG fusions. OTC, a rare FTC variant, is less responsive to radioactive iodine (RAI) therapy due to limited iodine uptake. Staging systems such as the AJCC TNM and ATA risk stratification provide frameworks for prognosis and treatment decisions. While the TNM system incorporates tumor size, nodal involvement, metastases, and patient age, the ATA system emphasizes recurrence risk. Prognosis varies, with PTC generally showing excellent survival rates, whereas aggressive variants, widely invasive FTC, and OTC have poorer outcomes. Surgical management remains a cornerstone of treatment, ranging from lobectomy to total thyroidectomy with lymph node dissection. RAI therapy and long-term monitoring are integral to optimizing outcomes and mitigating recurrence. Molecular diagnostics, including genomic profiling, further refine risk stratification and personalized treatment strategies for DTC.

Keywords: differentiated thyroid carcinoma, papillary thyroid carcinoma thyroid cancer staging, fine-needle aspiration biopsy, radioactive iodine therapy

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Abbreviations: DTC, differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma; FTC , follicular thyroid carcinoma; OTC, oncocytic thyroid carcinoma; ACR-TIRADS, American college of radiology thyroid imaging, reporting, and data system; FNAB, fine-needle aspiration biopsy; TBSRTC, the bethesda system for reporting thyroid cytopathology; AJCC, American joint committee on cancer; TNM, tumor, node, metastasis; ATA, American thyroid association; RAI, radioactive iodine; TSH, thyroid-stimulating hormone; MRI, magnetic resonance imaging; PET, positron emission tomography; RAIU, radioactive iodine uptake.

Introduction

Thyroid cancer is the most prevalent endocrine malignancy, with DTC accounting for approximately 90% of cases.[1] These tumors originate from the follicular epithelial cells of the thyroid gland and exhibit a wide range of differentiation levels, resulting in distinctive histological and genetic profiles. A detailed understanding of these characteristics is essential for accurate diagnosis, the development of personalized therapeutic strategies, and optimizing clinical outcomes in patients. In 2022, an estimated 821,214 new cases of thyroid cancer and 47,507 related deaths were reported worldwide. In the United States, approximately 44,020 new cases are diagnosed annually, including 12,500 in men and 31,520 in women. This increasing trend is also observed in many other countries, including Mexico, where the incidence of thyroid cancer has significantly risen in recent years. The estimated incidence in Mexico is 8.6 per 100,000 individuals, with a prevalence of 47.0 per 100,000 individuals. The global rise in thyroid cancer incidence highlights the growing significance of DTC as a public health issue.[2]

Diagnosis

The diagnosis of DTC relies on a combination of radiological and pathological evaluations, with cervical ultrasound being a cornerstone in identifying suspicious thyroid nodules and cervical lymph nodes. Ultrasound aids in malignancy risk stratification by analyzing nodule composition, echogenicity, margins, microcalcifications, and internal vascularity, with features like hypoechoic texture and irregular margins being more indicative of malignancy.[3] Classification systems like ACR-TIRADS, ATA, EU-TIRADS, and K-TIRADS provide structured risk assessments, with ACR-TIRADS showing superior diagnostic accuracy. This system assigns nodules to one of five categories based on sonographic features, each with associated malignancy risks and management recommendations.[4–8] Additional imaging modalities complement ultrasound in specific scenarios. Thyroid scintigraphy, using radiotracers like technetium-99m or iodine-123, classifies nodules as “cold” (potentially malignant) or “hot” (usually benign), particularly useful in patients with suppressed thyroid-stimulating hormone (TSH) levels. Computed tomography (CT) is effective for detecting local invasion and lymph node involvement, while magnetic resonance imaging (MRI) is used for evaluating soft tissue invasion, especially in cases requiring minimal radiation exposure. Positron emission tomography (PET) plays a key role in advanced or recurrent DTC, particularly for detecting metastases when conventional imaging is inconclusive. The radioactive iodine uptake (RAIU) test assesses

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iodine uptake, vital for planning iodine-based therapies in iodine-avid tumors.[9] Fine-needle aspiration biopsy (FNAB) is the gold standard for evaluating suspicious nodules identified via ultrasound. Performed with a fine-gauge needle under ultrasound guidance, FNAB ensures precision and minimizes complications. Cytological evaluation of FNAB samples follows the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), which categorizes findings into six diagnostic groups, each with a corresponding malignancy risk and recommended management strategy.[10] Categories range from non-diagnostic (Category I) to malignant (Category VI). Category II indicates benign findings like nodular hyperplasia or Hashimoto's thyroiditis, while Category III represents indeterminate cases, often requiring repeat FNAB or molecular testing. Categories IV and V suggest increasing malignancy risks, typically necessitating surgical intervention. Category VI confirms malignancy, such as PTC, requiring near-total thyroidectomy. Cytological features of DTC subtypes are distinct. PTC exhibits overlapping oval nuclei, nuclear grooves, pseudoinclusions, and psammoma bodies, with papillary structures aiding diagnosis. FTC, however, displays uniform nuclei and microfollicular or trabecular patterns, often with densely packed colloid. FTC diagnosis requires histological evidence of capsular or vascular invasion, assessable only through surgical specimens. OTC is defined by large polygonal cells with eosinophilic granular cytoplasm and solid or trabecular growth patterns, differentiating it from the papillary or follicular features of PTC and FTC.

Classification of differentiated thyroid carcinoma

DTCs comprise PTC, FTC, and OTC, as classified in the 5th edition of the WHO classification system.[10] These subtypes are characterized by distinct histological and genetic features. PTC, the most prevalent form, accounts for 70–80% of thyroid cancers and is defined by its papillary architecture and unique nuclear features. FTC, representing 10–15% of cases, exhibits a follicular growth pattern without the nuclear changes characteristic of PTC. OTC, a rare variant of FTC, constitutes 3–5% of thyroid cancers and is characterized by granular eosinophilic cytoplasm due to mitochondrial proliferation. PTC is a malignant tumor of follicular origin, defined by its distinctive nuclear features and papillary, solid, or trabecular growth patterns. Clinically, it often presents as a painless thyroid nodule, occasionally accompanied by cervical lymphadenopathy or, less commonly, distant metastases to the lungs or bones.[5,11] Globally, PTC accounts for 80-85% of thyroid malignancies, with an increasing incidence largely attributed to improved detection methods.[12,13] While most cases are sporadic, risk factors include childhood radiation exposure, high dietary iodine intake, familial predisposition, and exposure to environmental chemicals.[14,15] Macroscopically, PTC typically presents as firm, infiltrative nodules with papillary structures and frequent calcifications. Its histological hallmarks include nuclear enlargement, grooves, pseudoinclusions, and psammoma bodies, which are present in 40–50% of cases. PTC demonstrates a strong propensity for lymphatic invasion, with regional lymph node metastases in ≥80% of cases.[16] Subtypes of PTC include the follicular variant, diffuse sclerosing variant, and aggressive subtypes such as tall cell, hobnail, and columnar variants. These aggressive variants are associated with higher proliferative activity and poorer outcomes.[17] PTC is driven by mutations in the MAPK signaling pathway, which regulates cell growth and survival. Two key genetic alterations are: BRAF p.V600E: A mutation that causes continuous activation of the BRAF kinase, leading to uncontrolled cell proliferation, and RET Fusions: Chromosomal rearrangements that abnormally activate the RET kinase, driving oncogenic signaling. Both alterations lead to MAPK pathway hyperactivation, promoting PTC development and serving as key targets for therapy. These mutations are particularly prevalent in aggressive subtypes. Additional genetic alterations, including TERT promoter mutations and NTRK fusions, contribute to the clinical variability and heterogeneity of PTC.[18–22] FTC is a well-differentiated malignant tumor that lacks the nuclear features of PTC. It predominantly affects adults, with a mean age of diagnosis between 45 and 50 years, and often presents as a painless thyroid tumor. Unlike PTC, FTC spreads hematogenously, with distant metastases frequently involving the lungs and bones, while regional lymph node involvement is rare.[23] FTC accounts for 10–15% of thyroid cancers, with its incidence remaining stable. However, iodine deficiency significantly increases its risk, and hereditary forms are associated with syndromes such as PTEN hamartoma tumor syndrome and DICER1 syndrome.[24,25] Pathologically, FTC is often encapsulated and exhibits solid or microfollicular growth patterns. Diagnosis requires histological evidence of capsular or vascular invasion, and FTC is classified as minimally invasive, encapsulated angioinvasive, or widely invasive based on the extent of invasion.[26] Key molecular drivers include RAS mutations, observed in up to 50% of cases, and PAX8::PPARG fusions. These genetic alterations, along with mutations in the PI3K/PTEN/AKT pathway, underscore the complexity of FTC tumorigenesis.[27,28] OTC, also known as Hürthle cell carcinoma, is a rare variant of FTC, comprising approximately 3–5% of thyroid cancers. It presents as a solitary, slow-growing nodule and predominantly affects women, with a mean age of diagnosis at 58 years.[29] Unlike FTC, OTC metastasizes through both lymphatic and hematogenous routes, often involving lymph nodes, lungs and bones. Macroscopically, OTC is encapsulated with solid or trabecular growth patterns. Diagnosis requires histological evidence of capsular or vascular invasion.[30,31] OTC is biologically distinct from FTC due to its limited iodine uptake capacity, making it less responsive to radioactive iodine therapy and more challenging to treat. Genetic mutations common in other thyroid cancers, such as BRAF and RAS, are rare in OTC, further differentiating it from other DTC subtypes.[29,31] Despite these differences, OTC shares some diagnostic criteria with FTC, including the requirement for evidence of invasion.

Staging of differentiated thyroid carcinoma

Staging of DTC is a critical component of its management, informing prognosis and therapeutic strategies such as surgery, RAI therapy, and TSH suppression therapy. Among various systems, the American Joint Committee on Cancer (AJCC) TNM staging system is the most widely utilized due to its robust validation and alignment with clinical practices.[32] The TNM system evaluates three components: primary tumor (T), regional lymph nodes (N), and distant metastases (M). The T category describes tumor size and local extension. Tumors ≤2 cm confined to the thyroid are T1, further classified into T1a (≤1 cm) and T1b (>1 cm but ≤2 cm). Tumors measuring >2 cm but ≤4 cm are T2, while those >4 cm or with minimal extrathyroidal extension are T3. Advanced tumors with significant extrathyroidal extension are T4, subdivided into T4a (invasion of adjacent structures like the larynx or trachea) and T4b (encasement of major vascular structures or invasion into prevertebral fascia). Minimal extrathyroidal extension (mETE) is categorized as T3 to avoid overstaging. The N category evaluates regional lymph node involvement. N0 indicates no nodal metastases, further divided into N0a (no clinical or microscopic evidence) and N0b (microscopic metastases without clinical significance). N1 denotes lymph node metastases, with N1a involving central compartment nodes and N1b involving lateral cervical or retropharyngeal nodes. Central compartment metastases

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(N1a) have minimal impact on survival but increase locoregional recurrence risk.[32] The M category assesses distant metastases, a major prognostic factor. M0 indicates no metastases, while M1 confirms their presence, commonly in the lungs, bones, or liver. Distant metastases significantly reduce the 10-year survival rate to approximately 40%, defining stage IVB. The TNM system incorporates patient age, with the 8th edition establishing a cutoff at 55 years. Patients younger than 55 years without metastases (M0) are classified as Stage I, while those with metastases (M1) are Stage II, reflecting their favorable prognosis. For older patients, staging follows traditional T, N, and M parameters due to worse outcomes associated with age. The American Thyroid Association (ATA) risk stratification system complements TNM staging by evaluating recurrence risk. Recurrence occurs in 10–30% of DTC cases, sometimes decades after initial treatment. The ATA system stratifies patients into low, intermediate, and high-risk categories based on clinicopathological characteristics.[5] Low-risk patients, with intrathyroidal tumors lacking aggressive features, have excellent prognoses and require minimal treatment, such as lobectomy or selective RAI therapy, with routine monitoring of thyroglobulin (Tg) levels. Intermediate-risk patients, characterized by features such as minimal extrathyroidal extension or nodal metastases, are treated with total thyroidectomy and RAI therapy to minimize recurrence risk. High-risk patients, who present with macroscopic extrathyroidal extension, extensive nodal involvement, or distant metastases, face significant recurrence risks and worse outcomes. Management includes total thyroidectomy, RAI therapy, TSH suppression, and advanced imaging for RAI-refractory disease detection. Alternative staging systems, including the AMES (Age, Metastases, Extent, Size),[33] MACIS (Metastases, Age, Completeness of resection, Invasion, Size)[34] and EORTC (European Organization for Research and Treatment of Cancer),[35] provide additional insights but are less commonly used in routine practice due to their limited precision in guiding current treatment strategies.

Prognosis of differentiated thyroid carcinoma

DTC is among the most treatable malignancies, with a 10-year survival rate exceeding 95% in most patients.[5] However, prognosis varies based on tumor biology, patient characteristics, and clinical presentation. PTC, the most common subtype, has an excellent prognosis due to its indolent nature and responsiveness to treatment. Most cases are diagnosed at early stages, further contributing to favorable survival rates. Aggressive variants such as tall cell and hobnail subtypes, however, are associated with higher recurrence rates and worse outcomes.[5,36] While lymph node metastases are frequent in PTC, their impact on survival is minimal, though they increase locoregional recurrence risk. Distant metastases, seen in 5–10% of cases, reduce the 10-year survival rate to approximately 40%.[37] FTC presents distinct challenges, primarily due to its hematogenous spread and propensity for distant metastases, particularly to the lungs and bones. Minimally invasive FTC has outcomes comparable to PTC, but widely invasive or metastatic FTC carries a poorer prognosis, with a 10-year survival rate of approximately 40%.[38,39] OTC, a rare and aggressive variant, is less responsive to RAI therapy due to its limited iodine uptake and exhibits higher rates of locoregional recurrence and distant metastases, complicating management.[40] Molecular diagnostics, including detection of mutations such as BRAF V600E and TERT promoter in PTC, and RAS mutations and PAX8::PPARG fusions in FTC, enhance risk stratification and inform personalized treatment plans. These advancements underscore the importance of integrating molecular insights into clinical practice to improve outcomes in DTC patients.

Surgical treatment of differentiated thyroid carcinoma

Differentiated thyroid carcinoma responds well to surgical treatment and typically has a favorable prognosis. The extent of surgery depends on the disease stage, the tumor's macroscopic and histological features, and the patient's overall condition. For patients with tumors larger than 4 cm, extrathyroidal extension (clinical T4), clinically evident metastatic lymph nodes (clinical N1), or distant metastases (clinical M1), the initial treatment should be a total thyroidectomy. In cases with distant metastases, total thyroidectomy facilitates subsequent radioactive iodine treatment. For small, unifocal tumors without extrathyroidal invasion or lymph node metastases, a lobectomy may be an appropriate alternative.[41] Modern thyroid surgeries are performed through small incisions. During thyroidectomy, it is critical to identify and preserve the recurrent laryngeal nerves and parathyroid glands. Neurostimulation is commonly used intraoperatively to locate the nerves and ensure their proper function.[42] If the parathyroid glands are inadvertently removed or devascularized, they should be auto transplanted into the pre thyroid muscles or the sternocleidomastoid muscle. Transient hypoparathyroidism occurs in 7% to 50% of patients undergoing total thyroidectomy, while permanent hypoparathyroidism is much less frequent, affecting only 1.5% to 4% of patients.[43] Additional surgical techniques, such as autofluorescence and indocyanine green fluorescence, help identify the parathyroid glands and reduce the risk of injury.[44] For patients with clinically or radiologically abnormal lymph nodes, therapeutic dissection of the central lymph node compartment (level VI) is recommended. Similarly, therapeutic dissection of the jugular compartments should be performed in cases of highly suspicious metastatic disease identified on imaging or biopsy-confirmed lymph node involvement. These dissections should focus on compartment-based approaches, preserving surrounding vascular and neural structures.[41] Following total thyroidectomy, radioactive iodine (I-131) therapy may be used for three primary reasons: to eliminate residual thyroid tissue and simplify follow-up using thyroglobulin levels, to destroy remaining tumor cells and reduce the risk of recurrence, and to target metastases, particularly in the lungs. The usual I-131 dose ranges from 100 to 200 mCi. To optimize absorption of the radiopharmaceutical in residual thyroid tissue, a state of iodine deficiency and elevated TSH levels must be achieved. This can be done by administering recombinant TSH (rhTSH) or by inducing hypothyroidism through temporary suspension of thyroid hormone replacement for 2 to 4 weeks.[41] Postoperative monitoring is critical to assess recovery and detect recurrences early. This includes periodic evaluation of TSH, thyroid hormone, and thyroglobulin levels, as well as cervical ultrasound and, in some cases, whole-body scans.[45] Recurrences may occur either early within the first 2–5 years, or late, after 10 or more years. Thus, long-term follow-up is essential.[46]

Conclusion

DTC encompassing papillary, follicular, and oncocytic subtypes is the most common endocrine malignancy. Advances in diagnostics, including ultrasound, FNAB, and molecular profiling, have enhanced risk stratification and personalized treatment. Frameworks like ACR-TIRADS and the Bethesda System improve diagnostic precision, while staging systems such as AJCC TNM and ATA risk stratification guide prognosis and management. Surgical intervention, from lobectomy to total thyroidectomy, remains the cornerstone of care, complemented by RAI and TSH suppression. Despite a favorable 10-year survival rate exceeding 95%, aggressive variants and invasive

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subtypes pose challenges. Long-term monitoring and integration of molecular insights drive the shift toward precision medicine in DTC management.

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Conflicts of interest

The authors declare no conflicts of interest.

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