Narrative Review Article

Thyroid Cancer: Pathological Subtypes and Contemporary Therapeutic Strategies

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ABSTRACT

Thyroid cancer is a complex and increasingly prevalent disease that affects thousands of individuals worldwide. A clear understanding of its pathology, diagnosis, treatment options, and ongoing research is essential for improving patient care and outcomes. Thyroid cancer includes various types with differing risks and prognoses; however, recent advancements in treatment—such as surgery, radioactive iodine therapy, and ablation therapy—have improved recovery outcomes, especially in older patients. Current clinical trials and new therapies continue to advance care, and understanding these developments can empower patients, students, and healthcare professionals with knowledge of both current and future treatment possibilities. This paper reviews the main types of thyroid cancer and discusses its pathophysiology, diagnosis, management, and prognosis, while emphasizing recent research and therapeutic advancements that improve patient outcomes.

Keywords: Thyroid cancer; Radioactive iodine; External beam radiation; Ablation therapy; Papillary thyroid carcinoma; Personalized medicine; Thyroidectomy; Radiofrequency ablation

INTRODUCTION

The thyroid is a quarter-sized, butterfly-shaped endocrine gland located anterior to the trachea. Thyroid cancer, though relatively rare compared to other malignancies, is the most common endocrine-related cancer (1). While most thyroid nodules are benign, a small but significant risk of malignancy remains. With a prevalence of approximately 5% in patients without a history of radiation exposure, the occurrence of thyroid nodules varies by patient population and the diagnostic method used to identify nodules (2). Thyroid cancer is approximately three times more prevalent in women than in men, and Africa is projected to have the highest future increase in thyroid cancer prevalence and mortality rates (3). African regions, along with other regions with low Human Development Index (HDI) scores, have higher mortality rates due to limited access to healthcare and additional environmental exposures. In 2020, low HDI regions accounted for approximately 73% of worldwide thyroid cancer mortality, an increase from 66% in 2018. As a result, populations in low HDI regions, particularly in Africa, face a higher risk of thyroid cancer, with females at the highest risk. Despite these disparities, treatments and therapeutic strategies have significantly advanced in recent decades, showing promise for improved patient outcomes.

In recent decades, the incidence of thyroid cancer has risen, partly attributed to improvements in diagnostic imaging techniques. Thyroid cancer demonstrates a wide biologic spectrum, ranging from indolent forms such as papillary thyroid carcinoma to highly

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aggressive variants such as anaplastic thyroid carcinoma. Traditionally, radioactive iodine (RAI) therapy has been used to eliminate residual thyroid tissue after surgical resection and was considered a preferred treatment modality. However, with the emergence of newer therapies such as external beam radiation and ablation therapy, treatment decisions have become more complex, requiring consideration of multiple factors rather than relying on direct comparisons. Physicians select surgical or radiative therapy after considering factors such as disease extent, patient eligibility, expected outcomes, and clinical experience (4). Notably, physicians with fewer thyroid cancer cases reported that patient and physician concerns about mortality were highly influential, whereas physicians with greater clinical experience in thyroid cancer did not report these concerns as strongly. Differences in how factors were ranked and reported revealed variability in the importance placed on specific considerations between more and less experienced clinicians. Additionally, factors influencing treatment decisions remain inconsistently defined across clinicians. Institution-specific practices, clinician beliefs regarding RAI, and availability of RAI were frequently cited influences on treatment selection. A limited body of literature restricts direct comparisons between treatment modalities, contributing to variability and potential bias in clinical decision-making.

This work reviews common treatment modalities, such as surgical resection, RAI therapy, radiation therapy, and local ablation techniques for thyroid cancer, focusing on their mechanisms, efficacy, and safety. In addition, thyroid cancer pathologies are discussed, as understanding the biologic diversity of thyroid cancers is essential for developing appropriate diagnostic and therapeutic strategies. Treatment selection should be guided by tumor subtype and patient eligibility, rather than by multiple clinician-dependent factors that vary in perceived importance. This paper establishes a foundational framework for understanding thyroid cancer and compares commonly used treatment approaches, including neck radiation, ablative therapies, and postoperative radioactive iodine therapy following thyroidectomy, to clarify the most appropriate treatment strategies.

THYROID CANCER TYPES, DIAGNOSIS, AND PROGNOSIS

Thyroid cancer is a common endocrine malignancy that involves complex genetic and epigenetic alterations. Common mutations include RET/PTC gene rearrangements, BRAF^V600E, RAS point mutations, and PAX8/PPARγ rearrangements—genetic changes that can significantly affect tumor behavior and response to therapy (5). Papillary thyroid cancer (PTC) accounts for approximately 80% of all thyroid cancers (6). It predominantly affects women and typically presents between the ages of 30 and 50 years. Histologically, PTC is characterized by branching papillae and distinctive nuclear features, including nuclear grooves and inclusions. It has an excellent prognosis, largely due to its indolent course and high treatment responsiveness.

Follicular thyroid cancer (FTC) comprises about 12% of thyroid malignancies (7). It has a greater tendency for vascular invasion and distant metastasis, most commonly involving the lungs and bones. FTC often occurs in regions with iodine deficiency and typically affects middle-aged women.

Originating from parafollicular C cells, medullary thyroid cancer (MTC) constitutes approximately 3–4% of thyroid cancers (7). Unlike PTC and FTC, MTC produces calcitonin, which serves as a useful tumor marker. MTC may occur sporadically or as part of hereditary syndromes, including Multiple Endocrine Neoplasia type 2 (MEN2).

Anaplastic thyroid cancer (ATC) represents the most aggressive form of thyroid cancer, accounting for less than 2% of cases (6). It typically affects older adults, demonstrates rapid local invasion, and is associated with a poor prognosis.

Patients often present with a thyroid nodule incidentally detected during imaging studies or identified on physical examination (2). Palpable thyroid nodules are reported in approximately 4–7% of patients on physical examination. Clinical features that raise suspicion for malignancy include rapid nodule enlargement, hoarseness, dysphagia, dyspnea, and unexplained weight loss. Firm or fixed nodules with associated cervical lymphadenopathy are particularly concerning for malignancy. ATC is also notable for causing rapidly progressive compressive symptoms (7).

Diagnosis relies on a combination of clinical evaluation, imaging, and cytologic assessment via fine-needle aspiration (FNA) biopsy (8). FNA is performed using a thin needle attached to a syringe and significantly reduces the need for thyroid surgery in patients with benign disease (9). Ultrasound features suggestive of malignancy include

hypoechogenicity, microcalcifications, irregular borders, and increased vascularity. In cases of indeterminate cytology, molecular testing for BRAF, RAS, and RET/PTC gene mutations improves diagnostic accuracy and assists with surgical planning.

Additional diagnostic imaging modalities include radionuclide scanning, computed tomography (CT), and magnetic resonance imaging (MRI) (10). Radionuclide scanning is useful for evaluating the functional status of thyroid nodules when FNA results are nondiagnostic, and it may serve as a secondary diagnostic tool in such cases. MRI is preferred over CT for evaluating retrotracheal, mediastinal, or metastatic involvement of large thyroid nodules or goiters due to its superior soft tissue resolution.

The nuclear features of PTC include enlarged, elongated nuclei, irregular nuclear contours, and the presence of psammoma bodies (11). FTC is commonly evaluated using ultrasound or FNA and may demonstrate imaging features such as poorly defined margins, microcalcifications, and characteristic vascular patterns (12). There is no consensus regarding the routine use of nuclear medicine imaging for MTC, which is typically diagnosed using ultrasound or FNA (13). However, CT and MRI may aid in the diagnosis and preoperative staging of MTC when serum calcitonin levels exceed 500 pg/mL (14).

Most anaplastic thyroid cancers present as a rapidly enlarging mass with low attenuation, dense calcifications, areas of necrosis, and invasion of adjacent structures on CT imaging (15).

Thyroid cancer prognosis is generally favorable, with a 5-year relative survival rate exceeding 95% for differentiated thyroid cancers (6). According to Surveillance, Epidemiology, and End Results (SEER) data reported by the American Cancer Society, the 5-year relative survival rate for treated PTC is 99% or higher for both localized and regional disease (16). In contrast, PTC with distant metastasis has a 5-year relative survival rate of approximately 71%.

For FTC and MTC, the 5-year relative survival rate for localized tumors also exceeds 99%, like PTC. However, regional and distant FTC demonstrate 5-year relative survival rates of 97% and 62%, respectively (16). Patients with regional MTC have a 5-year relative survival rate of 94%, whereas those with distant MTC have a survival rate of approximately 50%, representing a marked decline compared with localized and regional disease (16).

ATC has the poorest prognosis among thyroid cancer subtypes. Even with treatment, the 5-year relative survival rates are approximately 45% for localized disease, 14% for regional disease, and 5% for distant disease (16). Overall, ATC demonstrates a substantially lower 5-year survival rate compared with PTC, FTC, and MTC. Prognosis worsens in the presence of larger primary tumor size, distant metastases, advanced patient age, and poorly differentiated or anaplastic histology.

In contrast, the untreated prognosis of thyroid cancer is substantially worse than the reported 5-year relative survival rates for all four major subtypes. Among these, patients with PTC show a smaller disparity between treated and untreated outcomes, with an estimated stage I survival rate of approximately 86.3% and a stage II survival rate of about 66.0% without treatment (17). The median survival of untreated stage III PTC patients is approximately 108 months (9 years). Without intervention, early-stage PTC progresses more slowly than advanced-stage disease, and age, tumor stage, marital status, and sex have been identified as factors influencing prognosis in untreated PTC.

Fewer studies have evaluated the untreated prognosis of FTC and MTC, largely due to their lower prevalence compared with PTC. Nevertheless, both FTC and MTC demonstrate more aggressive behavior when untreated, with rapid proliferation and early metastasis, leading to progressively declining survival rates (12). ATC has an extremely poor untreated prognosis, with most patients dying within six weeks of diagnosis in the absence of treatment (18).

TREATMENT OF THYROID CANCER

Surgical Treatment

Surgical treatment is the primary management approach for most thyroid cancers and commonly involves thyroidectomy (19). Surgical options include lobectomy and total thyroidectomy. A lobectomy involves the removal of a single thyroid lobe and is typically used for small, low-risk tumors, whereas a total thyroidectomy involves the removal of the entire thyroid gland and is generally indicated for larger or bilateral tumors, aggressive histologic subtypes, or metastatic disease. When lymph node involvement is suspected, a lymphadenectomy may also be performed.

The decision to perform a lobectomy or total thyroidectomy depends on several factors, including clinical findings, cytologic results, and institutional practice patterns. Indications for surgical intervention include a confirmed malignant diagnosis, metastatic thyroid

cancer without a palpable mass, a diagnosis of follicular neoplasm, rapid tumor growth, airway or esophageal compression, vocal cord paralysis, and a history of neck radiation with a suspicious thyroid nodule (20). Patients meeting any of these criteria may be considered appropriate candidates for either lobectomy or total thyroidectomy.

In patients presenting with well-differentiated thyroid cancer and metastatic squamous cell carcinoma without evidence of a primary thyroid mass, surgical resection is unlikely to significantly alter the clinical course when postoperative external neck radiation is administered. Surgical management is individualized according to tumor type and stage (21).

Most PTCs are treated with a total thyroidectomy; however, small, low-risk tumors may be managed with lobectomy. Lymph node dissection is considered when nodal metastasis is suspected. Similarly, FTC is treated with either lobectomy or total thyroidectomy, depending on tumor extent, with lymph node dissection performed when indicated.

MTC stages I and II are most treated with total thyroidectomy, followed by thyroid hormone replacement therapy. Because MTC cells do not uptake radioactive iodine, RAI therapy is ineffective. In advanced stages (III and IV), surgery may be followed by external beam radiation therapy to reduce the risk of recurrence.

ATC, due to its highly aggressive behavior and tendency to extend beyond the neck, is rarely amenable to surgical management. ATC does not concentrate radioactive iodine and is typically managed with chemotherapy and/or external beam radiation, leaving PTC, FTC, and MTC as the thyroid cancer subtypes most treated surgically.

Surgical margins in thyroid tumor resection are classified as R0, R1, or R2 (22). An R0 resection indicates microscopically negative margins, with no residual cancer cells. An R1 resection represents a grossly complete excision with microscopically positive margins, meaning cancer cells are present at the tissue border despite removal of all visible tumor. An R2 resection indicates a grossly positive margin, reflecting incomplete tumor removal with macroscopic residual disease. This category is recognized by the American Thyroid Association as part of high-risk disease stratification. Additionally, the National Comprehensive Cancer Network (NCCN) includes any positive surgical margin as an indication for considering completion thyroidectomy in its 2019 clinical practice guidelines (22).

The efficacy of lobectomy versus total thyroidectomy varies depending on the thyroid cancer subtype. Although each surgical approach has distinct advantages and limitations, certain procedures may be more appropriate for specific cancers. For example, lobectomy may be preferable to total thyroidectomy for PTC, as total thyroidectomy increases the risk of transient parathyroid dysfunction (23). Importantly, total thyroidectomy does not improve overall, disease-specific, or recurrence-free survival in patients with PTC.

In contrast, patients with FTC treated with lobectomy demonstrated a 5-year overall survival rate of 98%, compared with 99% among those treated with total thyroidectomy (19). Although both approaches are effective, total thyroidectomy appears to be slightly more effective for FTC than lobectomy, unlike in PTC.

For MTC confined to the neck, total thyroidectomy is the preferred surgical approach, as it offers the highest likelihood of disease-free survival (24). Metastatic MTC and MTC with cervical lymph node involvement are best managed with total thyroidectomy combined with resection of involved lymph node compartments, as most patients present with nodal disease at diagnosis. Following total thyroidectomy, 40–80% of patients achieve a biochemical cure, with a 10-year survival rate of 97.7% (24). However, among patients who do not achieve biochemical cure after surgery, 5-year and 10-year survival rates decrease to approximately 80.2% and 70.3%, respectively (24).

Even in ATC, surgical intervention may confer a survival benefit. Compared with no treatment, surgical resection increased the 1-year overall survival rate from 0.6% to 30% (25). In patients with stage IVa and IVb ATC, surgical resection further improved 1-year overall survival from 21.5% to 71.8% and from 9.4% to 41.3%, respectively (25).

Furthermore, a clinical study involving 284 patients with a median age of 54 years examined recurrence-free survival among individuals who underwent thyroidectomy followed by RAI therapy, with or without additional adjuvant treatment. As shown in Figure 1, the 3-year recurrence-free survival rates differed based on response to adjuvant therapy, with rates of 96.3% among patients who achieved a successful response and 66.1%among those who did not respond (26). The overall mean recurrence-free survival rate across both cohorts was 85.8%. Among all documented recurrences, cervical lymph nodes were the most common site of disease recurrence (26).

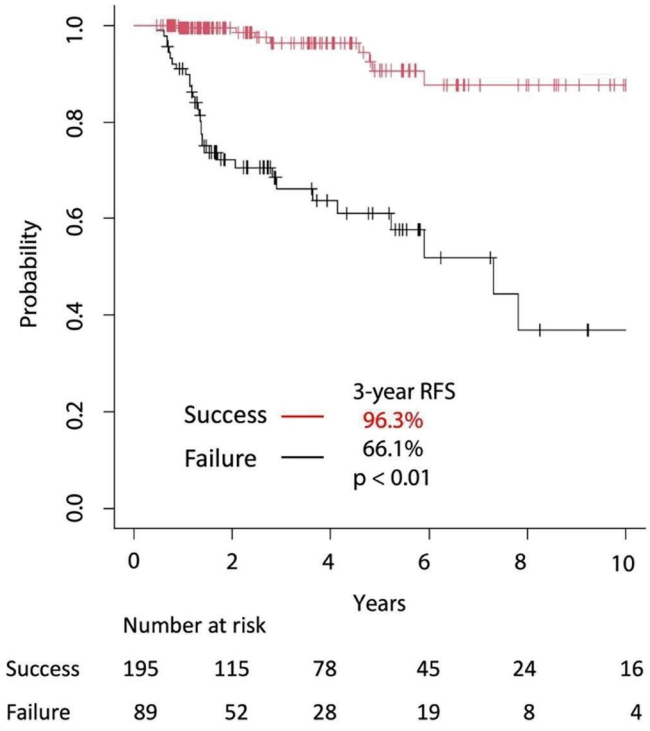

Figure 1. A Kaplan-Meier graph comparing three-year RFS rates of patients who successfully completed additional adjuvant therapy after a thyroidectomy and RAI treatment to those who did not is presented. The graph displays the number of successful and unsuccessful cases underneath the x-axis, and also includes a p-value (26).

Radioactive Iodine Therapy

RAI therapy is used postoperatively to eliminate residual thyroid tissue or microscopic disease (27). It is primarily indicated for differentiated thyroid cancers, such as papillary and follicular carcinomas, particularly in intermediate- and high-risk patients. The administered dose is adjusted according to risk stratification. Because thyroid tissue actively absorbs iodine from the bloodstream, RAI is effective in targeting remaining thyroid cells after surgical resection (28). However, RAI is ineffective in treating medullary and anaplastic thyroid cancers, as these tumor cells do not uptake radioactive iodine.

RAI may be used as monotherapy or as adjuvant therapy following surgical resection in papillary and follicular thyroid cancers. Its benefit is limited in patients with small, low-risk tumors, making it more suitable for advanced-stage or aggressive disease. Furthermore, patients undergoing RAI therapy typically require elevated thyroid-stimulating hormone (TSH) levels, which enhance iodine uptake by residual thyroid tissue. TSH elevation may be achieved through thyroid hormone withdrawal or recombinant human TSH administration. Common adverse effects of RAI therapy include neck tenderness, nausea, vomiting, taste alteration, fertility concerns, and xerostomia due to salivary gland involvement (29).

RAI remnant ablation is a specific application of RAI therapy used to destroy remaining thyroid tissue after surgery (30). The optimal dose for remnant ablation remains controversial, and dosing decisions are therefore made on a case-by-case basis. RAI adjuvant therapy, in contrast, is used to improve disease-free survival, particularly in patients at high risk of recurrence. In a study of 588 Chinese patients with PTC, the recurrence rate was 1% in the RAI-treated group compared with 5.8% in the non-RAI group (29). Because both cohorts underwent total thyroidectomy, these findings suggest that RAI therapy provides additional benefit beyond surgery alone.

Most patients with FTC survive approximately 156 months (13 years) with RAI therapy, with a 5-year survival rate of 88.8% and a 10-year survival rate of 67.4% (30). For FTC patients with distant metastases, however, survival outcomes are poorer, with 5-year and 10-year survival rates of 80.4% and 41.3%, respectively (30). Male patients with distant metastatic FTC demonstrate lower overall survival than female patients. As noted previously, medullary and anaplastic thyroid cancers do not uptake iodine, rendering RAI therapy ineffective for these malignancies (27). Accordingly, RAI therapy is primarily reserved for differentiated thyroid cancers.

RAI ablation and RAI adjuvant therapy represent distinct therapeutic strategies with different treatment objectives. RAI ablation targets residual thyroid tissue following surgical resection, regardless of evidence of metastatic disease (31). In contrast, RAI adjuvant therapy is intended to treat microscopic or known metastatic disease beyond the thyroid bed. These treatment targets define the respective therapeutic margins of RAI ablation and RAI adjuvant therapy.

Ablative Therapies

Locoregional interventions provide minimally invasive options for local tumor control. Types of locoregional therapies include ablative therapies and radiation-based treatments (32), each of which encom-

passes multiple techniques. Thermal ablation modalities include radiofrequency ablation (RFA), microwave ablation (MWA), and laser ablation (LA), all of which rely on heat-induced tumor necrosis.

RFA uses high-frequency alternating electrical currents to generate heat, resulting in tumor necrosis. It is effective for small, recurrent thyroid cancers and benign thyroid nodules (33). MWA delivers micro-wave energy to induce rapid tissue heating and destruction, offering advantages in the treatment of larger tumors (33). LA uses an optical fiber to deliver a focused laser beam to the tumor, which is converted into heat by the surrounding tissue. This localized temperature increase causes tumor necrosis. LA has been identified as a potential alternative therapy for low-risk PTC patients (34).

RFA achieves complete tumor necrosis in approximately 82% of patients with recurrent PTC (35). Additionally, PTC treated with MWA demonstrates a 5-year progression-free survival rate of 77.2% (36). MWA has also been shown to be a safe and effective treatment for FTC, with a low risk of disease progression. In one study, thyroid nodules completely resolved in 20.3% of 74 FTC patients treated with MWA, with a recurrence rate of 2.7% (37).

In a clinical study involving 428 patients with FTC, two comparably sized cohorts—one receiving postoperative ablation and one not—were evaluated (38). The postoperative ablation group demonstrated 100% cause-specific survival and distant metastasis–free survival. In contrast, the role of ablation therapy in MTC remains limited. RFA is primarily used in MTC patients who are not surgical candidates, such as those with high anesthetic risk or recurrent disease (39). Surgery remains the standard treatment for MTC (40). Few studies support RFA as an effective alternative to surgery for MTC, and the limited available evidence makes its role controversial.

Furthermore, due to its aggressive behavior and rapid growth, RFA has not demonstrated a significant reduction in tumor volume or meaningful improvement in outcomes for ATC (41). Studies evaluating ablation efficacy and survival outcomes in MTC and ATC remain scarce, largely due to the rarity of these malignancies.

Ablation therapy is administered within a defined safety margin surrounding the tumor to minimize recurrence risk (39). This margin typically ranges from 1–2 mm for benign thyroid nodules and 3–5 mm for malignant tumors. Establishing this margin helps ensure complete tumor destruction and reduces the likelihood of residual viable tumor cells.

In a separate study, two matched groups of 200 patients diagnosed with nodular goiter were followed: one group underwent surgical treatment, and the other received RFA. After a 1-year follow-up, mean nodule volume decreased from 5.4 mL to 0.4 mL in the RFA group. No patients in this group developed hypothyroidism. Overall, the RFA-treated group demonstrated a 0.05% recurrence rate and a 1% complication rate, with a mean hospital stay of 2.1 ± 0.9 days (42).

CONCLUSION

The present work reviews a range of treatment modalities and clinical pathways for the four major types of thyroid cancer: papillary, follicular, medullary, and anaplastic. With the development of advanced therapeutic options, understanding both established and emerging treatments can support improvements in standard clinical practice. Because thyroid cancer spans a broad clinical spectrum, ranging from indolent tumors to highly aggressive malignancies, optimal patient outcomes depend on accurate diagnosis, a comprehensive understanding of tumor biology, and the implementation of individualized treatment strategies.

Surgical management primarily includes thyroidectomy or lobectomy, which removes part or all of the thyroid gland containing malignant tissue. Postoperative RAI therapy may further enhance treatment efficacy by eliminating residual thyroid tissue following surgery. Locoregional ablative techniques apply thermal energy directly to tumors, resulting in tumor necrosis.

The future of thyroid cancer care is expected to progress through the integration of molecular diagnostics, targeted therapies, and minimally invasive approaches. Promising areas of ongoing research include antiangiogenic therapies and personalized medicine, particularly for patients with advanced or refractory disease. The development of refined treatment pathways supports a shift away from a “one-size-fits-all “approach toward patient-centered, evidence-based care.

CONFLICT OF INTEREST

The author declares no conflicts of interest related to this work.

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