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A Comprehensive Review of Epidemiology, Risk Factors, Classification, Diagnosis, and Therapeutic Strategies of Thyroid Cancer

Ergita Nelaj[1*], Sarah Ibërshimi[2], Irida Kecaj[1]

[1] Department of Internal Medicine, University Hospital Center "Mother Teresa", Tirana, Albania
[2] Department of Oncology, University Hospital Center "Mother Teresa", Tirana, Albania

Abstract

Thyroid cancer was the most common malignancy of the endocrine system worldwide in 2022. While its prognosis is generally favorable, with a 5-year survival rate of 98.4%, thyroid cancer remains a complex condition with various histological subtypes and evolving treatment strategies. The disease predominantly originates from follicular or parafollicular cells and includes differentiated, anaplastic, and medullary thyroid cancers. Genetic factors, environmental exposures like radiation, and autoimmune conditions are recognized as key risk factors. The diagnosis and management of thyroid cancer have been greatly enhanced through advanced imaging, fine needle aspiration biopsy, and molecular testing. However, challenges persist in determining the optimal surgical and adjuvant therapies. The introduction of the updated 2022 WHO classification of thyroid neoplasms provides more precise categories for tumor types and incorporates molecular data for better diagnosis and treatment planning. This review discusses epidemiology, risk factors, diagnostic approaches, staging, and treatment strategies for thyroid cancer, with an emphasis on the role of genetics and the evolving therapeutic landscape.

Keywords: Thyroid cancer, TIRADS, genetic mutations, Fine Needle Aspiration Biopsy

Address for correspondence: Ergita Nelaj*, Department of Internal Medicine, University Hospital Center "Mother Teresa", Tirana, Albania. Address: Dibra's Street, No 370, Tirana, Albania. Email: dr_ergi@yahoo.com

INTRODUCTION

Thyroid cancer is a malignancy that is increasing in incidence globally. Data from GLOBOCAN 2022 show that 821.214 new thyroid cancer cases and 47.507 thyroid cancer related cases have been estimated in 2022, worldwide (1,2). Approximately 44.020 new cases of thyroid cancer (respectively 12.500 in men and 31.520 in women), have been diagnosed in the United States for 2024. About 2170 deaths from thyroid cancer (990 in men and 1180 in women), have been reported during the last year (3). Despite the increase in incidence, thyroid cancer has a favorable overall prognosis, with a 5-year survival rate of 98.4% (4).

Thyroid neoplasms can originate from follicular cells or parafollicular cells (C cells). Differentiated thyroid cancer, which arises from follicular cells, includes papillary, follicular, oncocytic (Hürthle), poorly differentiated, and anaplastic carcinomas (5). These account for over 90% of thyroid cancers, with anaplastic carcinoma being rare and having a very poor prognosis, while poorly differentiated carcinoma is also aggressive and has an unfavorable prognosis. The 2022 fifth edition of the WHO histologic classification of thyroid neoplasms introduces several updates, including new tumor types, subtypes, and a grading system (6). Follicular cell-derived neoplasms are categorized into benign tumors, low-risk neoplasms, and malignant neoplasms. New terms like “follicular nodular disease” and “differentiated high-grade thyroid carcinoma” are introduced. The term “Hürthle cells” is replaced with “oncocytic cells,” and certain variants of papillary thyroid carcinoma (PTC), such as invasive encapsulated follicular and cribriform morular types, are now distinct tumor types. The term “variant” is now reserved for genetic alterations, and a grading system based on mitotic count, necrosis, and the Ki67 index is used to assess high-grade carcinomas. The 2022 classification also introduces new categories for “salivary gland-type carcinomas” and “thyroid tumors of uncertain histogenesis,” with a focus on their clinical relevance (6).

The detection and diagnosis of differentiated thyroid cancer have improved with advances in high-resolution ultrasound, fine needle aspiration biopsy (FNAB), molecular tests, and thyroglobulin as a serum marker. However, this progress has led to debates over optimal medical and surgical management, including decisions about surgical resection (lobectomy vs. total thyroidectomy), lymphadenectomy (central prophylactic vs. therapeutic), and the use of adjuvant treatments (7). These issues present unique challenges in patient care.

RISK FACTORS

Thyroid nodules are prevalent in the general population, depending on various environmental risk factors such as radiation exposure during childhood and on individual risk factors such as: age, sex, family history, lifestyle and genetic factor. Other factors include excess body weight, with higher BMI linked to increased risk, and

iodine intake, with low iodine levels associated with follicular thyroid cancer, while high iodine may raise the risk of papillary thyroid cancer (8). Chromosomal alterations, including mutations in the mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase–protein kinase (PI3K-AKT) signaling pathways, play a significant role in thyroid cancer growth, with activation often seen in papillary thyroid cancer through recombination events and point mutations in genes like RAS and BRAF (9). These genetic changes, such as rearrangements and point mutations, are linked to environmental factors like ionizing radiation and contribute to the development of both papillary and follicular thyroid cancers. Ionizing radiation is a well-established risk factor for thyroid cancer, as it causes DNA strand breaks and mutations that can lead to carcinogenesis (9). Studies of radiation exposure from the Chernobyl disaster found a 5 to 6-fold increase in thyroid cancer incidence among those under 18 at the time (10). Radiation-induced thyroid cancer is typically of the papillary type, but it may be more aggressive and less differentiated in those exposed at a young age, with the radiation dose and type influencing the cancer's behavior and associated genetic alterations.

Thyroid cancer (TC) has a significant hereditary component, with 3-9% of cases classified as familial non-medullary thyroid carcinoma (FNMTC), mostly papillary thyroid cancer (PTC) (11). FNMTC is typically non-syndromic, but familial PTC tends to be more aggressive than sporadic forms. Syndromic FNMTC is associated with inherited conditions like familial adenomatous polyposis, Cowden syndrome, and Carney complex. Medullary thyroid cancer (MTC), which arises from parafollicular C cells, makes up 3-5% of thyroid cancers, with hereditary MTC being linked to mutations in the RET proto-oncogene, particularly in MEN2A and MEN2B syndromes (11).

The role of estrogen in thyroid cancer development remains unclear. Some suggest that exogenous estrogen may increase the risk, while early loss of ovarian estrogen seems to lower it (12). Experimental studies indicate that estradiol can stimulate both benign and malignant tumors, though hormone therapy is generally associated with very low or no increased risk for thyroid cancer.

Studies suggest a possible increased risk of thyroid cancer (TC) in patients with autoimmune thyroid diseases such as Graves' disease and Hashimoto's thyroiditis (HT) (13). Mechanisms proposed include elevated TSH levels promoting follicular proliferation, proinflammatory cytokines, and oxidative stress in autoimmune thyroiditis, although some studies show no significant increase in papillary thyroid cancer (PTC) in HT patients (14).

CLASSIFICATION AND STAGING OF THYROID CANCER

Usually, thyroid nodules are asymptomatic, but due to the widespread use of imaging techniques and the introduction of fine-needle aspiration

biopsy (FNAB), detection of incidental nodules has increased, leading to overdiagnosis (15). The Thyroid Imaging Reporting and Data System (TIRADS), is a 5 point classification scale used to determine the risk of a thyroid malignancy based on ultrasound characteristics such as: nodule composition, nodule hypoechogenicity, irregular margins, microcalcifications, and a shape taller than wide on a transverse view (16). TIRADS categorizes thyroid nodules based on ultrasound features, with TIRADS 1 indicating a normal thyroid and TIRADS 2 showing benign features like cystic or spongiform nodules. TIRADS 3 denotes the absence of suspicious features, while TIRADS 4A to 4C and TIRADS 5 are based on increasing points from 1 to 5, reflecting a higher likelihood of malignancy (16). A study by Horvath et al. recommended follow-up for TIRADS 3 nodules, as their malignancy rate is under 5%, while TIRADS 4 and 5 nodules should be biopsied or surgically operated on due to a malignancy rate ranging from 5% to 80% (17).

The 5th edition of the WHO Classification of Endocrine and Neuroendocrine Tumors introduces significant changes to thyroid cancer classification, dividing thyroid tumors into benign, low-risk, and malignant categories based on cell origin, pathologic features, and molecular behavior (18). It introduces more distinct divisions, including benign tumors (such as follicular adenomas and oncocytic adenomas), low-risk neoplasms (like NIFTP- noninvasive follicular thyroid neoplasm with papillary like nuclear features, tumors of uncertain malignant potential, and hyalinizing trabecular tumors), and malignant neoplasms, which now include subtypes based on molecular characteristics. The malignant category includes revisions for papillary thyroid carcinoma (PTC), with a new emphasis on molecular profiles to distinguish between variants and subtypes. Notably, the invasive encapsulated follicular variant PTC is separated from PTC and reclassified as a distinct entity. New categories like high-grade differentiated thyroid carcinoma have been introduced to describe tumors that exhibit features between well-differentiated and anaplastic carcinomas. Additionally, anaplastic thyroid carcinoma now includes squamous cell carcinoma as a subtype, reflecting its similar aggressive nature and BRAF mutation profile. The classification also highlights the importance of incorporating molecular data for better diagnosis and treatment planning (18).

The TNM staging system for thyroid cancer is used to describe the size of the tumor, whether it has spread to lymph nodes, and if it has metastasized to other parts of the body. The "T" category indicates the tumor's size and extent, ranging from T0 (no cancer) to T4 (tumor has spread outside the thyroid, with T4 divided into subcategories based on the extent of spread to surrounding tissues) (19). The "N" category indicates if the cancer has spread to lymph nodes, with N0 meaning no spread, and N1 is divided into N1a (spread to lymph nodes near the thyroid or upper chest) and N1b (spread to lymph nodes

in the neck or behind the throat). The "M" category refers to metastasis, with M0 meaning no spread to other body parts, and M1 indicating spread to other areas such as the lungs or bones (19). Classification by the TNM system achieves a precise description and of the apparent anatomic extent of disease.

DIAGNOSIS

Thyroid cancer is frequently discovered incidentally during imaging studies, such as CT, MRI, PET, or ultrasound, typically performed for reasons unrelated to the thyroid. Most patients with thyroid cancer have no symptoms, though some may present with a new thyroid nodule, an increase in the size of a previously detected nodule, or pain from a hemorrhaging nodule. More concerning symptoms, like dysphagia, dysphonia, or dyspnea, are often associated with local invasion and may indicate undifferentiated thyroid cancer, which typically has a worse prognosis. The diagnostic process begins with a comprehensive medical history, including potential radiation exposure and family history of thyroid cancer. A physical exam should focus on signs of thyroid cancer spread, such as lymph node enlargement, tracheal deviation, or vocal cord paralysis. Preoperative assessments, including voice evaluation, are critical, especially for those with voice changes or surgical histories that may affect the laryngeal nerves (20)

When a thyroid nodule larger than 1 cm is identified, serum TSH levels should be measured, as high TSH levels are associated with a higher risk of malignancy (21). High-resolution neck ultrasound is essential for identifying nodule characteristics, gland size, and lymph node involvement. The ultrasound pattern, such as hypoechoic or solid nodules with irregular margins or microcalcifications, helps assess malignancy risk. Fine needle aspiration biopsy (FNAB), particularly ultrasound-guided for difficult-to-palpate nodules or those with cystic components, is the gold standard for evaluating suspicious nodules (21). Routine measurement of serum thyroglobulin or calcitonin is not recommended in the initial workup, as they are nonspecific for thyroid cancer. FNAB results can help guide the next steps, especially when nodules present high-risk features for malignancy.

TREATMENT

Surgical resection is the primary treatment for both Papillary Thyroid Cancer (PTC) and Follicular Thyroid Cancer (FTC), often followed by radioiodine ablation (RAI) and thyroid hormone suppression therapy (22). The surgical approach, whether hemithyroidectomy or total thyroidectomy, depends on factors such as tumor size, lymph node involvement, and patient health. For small tumors without invasion, a lobectomy may be sufficient, while larger or invasive tumors generally require total thyroidectomy (23). Lymph node dissection is performed when metastasis is suspected or confirmed. Postoperative risk stratification is essential, guiding decisions about further treatment,

including the use of RAI and thyroid hormone suppression to reduce the risk of recurrence. Patients are monitored through regular follow-up visits, with imaging and lab tests to assess disease persistence or recurrence, and treatment may be adjusted based on their response (24)

In cases of persistent or recurrent disease, additional therapies like RAI ablation, surgery, or radiofrequency ablation may be employed, depending on the cancer's iodine-avid characteristics. Systemic chemotherapy is reserved for cases where the disease is resistant to iodine, with targeted therapies such as kinase inhibitors being used for patients with specific gene mutations (25). For RAI-refractory DTC, multikinase inhibitors like lenvatinib and sorafenib are first-line therapies. Recent advances in molecular understanding have identified targetable genetic alterations, such as NTRK gene fusions and BRAF mutations, leading to new targeted therapies (26). Routine genomic testing is recommended to identify patients who may benefit from these therapies, enhancing treatment outcomes for advanced thyroid cancer. Monitoring continues after surgery, with dynamic risk stratification to assess how well the patient responds to treatment (27)

The treatment for Medullary Thyroid Cancer (MTC) primarily involves total thyroidectomy along with the resection of any local and regional metastases. If there is no evidence of pre-operative cervical lymph node metastasis, prophylactic central lymph node dissection is typically performed. For patients with confirmed lateral zone nodal metastasis, more extensive lymph node dissection, including central and lateral neck dissection, is required. Long-term monitoring of MTC patients is necessary, with regular testing of calcitonin levels, neck ultrasounds, and physical examinations (28). Because MTC is not derived from the follicular cells of the thyroid, radioiodine ablation and TSH suppression are not effective treatments. In cases where cancer is resistant to conventional therapies, kinase inhibitors, particularly RET-specific inhibitors for patients with a RET mutation, are used to target the disease (28). Molecular target agents such as multikinase inhibitors (MKIs) vandetanib and cabozantinib are used as first-line treatments. These agents target various receptors, including VEGFR, RET, and EGFR, and have shown efficacy in extending progression-free survival (PFS) in clinical trials (29). However, their use is associated with potential toxicities, and their efficacy may vary based on the presence of RET mutations. Recently, selective RET inhibitors like selpercatinib and pralsetinib have emerged as promising options, particularly for RET-positive MTC, showing high response rates with a more favorable side effect profile. These agents are particularly effective against the common RET M918T mutation and may overcome resistance associated with other mutations. Molecular testing to identify RET mutations is crucial in selecting appropriate therapies for MTC patients (29).

Anaplastic Thyroid Cancer (ATC) is a highly aggressive form of thyroid cancer with a poor prognosis, due to its advanced metastatic stage at diagnosis, making complete surgical resection difficult. Treatment typically involves surgical removal of the resectable disease and high-dose external beam radiation therapy (EBRT), followed by the use of targeted BRAF kinase inhibitors in patients with a BRAF V600E mutation (30). For patients without this mutation, targeted radiation and chemotherapy may be used post-surgery. However, ATC is often associated with rapid progression and metastasis, even at diagnosis. It frequently invades surrounding structures like the trachea or vasculature, which can make surgery impossible. Due to its aggressive nature, mortality rates for ATC are extremely high, and in cases where surgery is not feasible, palliative care may be considered to manage symptoms and improve quality of life (30).

CONCLUSIONS

Thyroid cancer is a highly frequent cancer worldwide with disparities across regions, genders, and age groups. TC, despite increasing in incidence globally, generally has a favorable prognosis with a high 5-year survival rate. Advances in diagnostic tools, such as high-resolution ultrasound, fine needle aspiration biopsy (FNAB), and molecular tests, have improved detection but also led to challenges in treatment decisions regarding surgery and adjuvant therapies. Regarding treatment, surgical resection remains the primary approach, particularly for differentiated thyroid cancers, often followed by radioactive iodine therapy and thyroid hormone suppression. Systemic therapies such as multikinase inhibitors (MKIs) and targeted treatments based on specific genetic alterations, like BRAF mutations or NTRK gene fusions, are being explored for persistent or recurrent disease. In MTC, which is not responsive to iodine treatment, RET-specific inhibitors and other kinase inhibitors are showing promising results.

In conclusion, personalized treatment plans based on molecular profiling, along with continued research into targeted therapies, are crucial for improving outcomes in patients with thyroid cancer, especially for those with advanced or metastatic diseases.

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