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Original Article

A Review-Thyroid Cancer

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ABSTRACT

With over 500,000 cases annually worldwide, thyroid carcinoma is the most common endocrine cancer. While poorly/undifferentiated thyroid cancers are uncommon (2% of all thyroid cancers), aggressive, commonly spread, and have a worse prognosis, differentiated thyroid cancers are the most prevalent and have the best prognosis. Since secondary plant metabolites can ensure the required biochemical diversity for therapeutic purposes, phytochemical products can be a logical and comprehensive source of novel anticancer agents for aggressive, metastatic, and advanced thyroid cancer. Resveratrol, curcumin, isoflavones, and glucosinolates are the most widely used bioactive compounds in experimental models that exhibit biological efficacy against thyroid cancer. Rarely have they been tested in clinical trials, although the majority have been investigated in vitro and in vivo for this cancer. Thousands of people worldwide suffer with thyroid cancer, a complicated and increasingly common illness. Improving patient care and results requires a thorough grasp of its pathology, diagnosis, available treatments, and current research. Although there are many different forms of thyroid cancer, each with its own hazards and prognoses, recent developments in treatment—such as surgery, radioactive iodine therapy, and ablation therapy—have improved recovery rates, particularly for older patients. Understanding these advancements helps empower patients, students, and healthcare professionals with knowledge of present and future treatment options. New medicines and ongoing clinical studies continue to improve care. The biology, diagnosis, treatment, and prognosis of the primary forms of thyroid cancer are reviewed in this study, with a focus on current research and treatment developments that enhance patient outcomes.

Keywords: Papillary thyroid carcinoma, External beam radiation, Radioactive iodine, Ablation therapy, Thyroid cancer Thyroidectomy, Radiofrequency ablation, and Personalized medicines.

INTRODUCTION

Common, representing less than 4% of thyroid cancers. Its Diagnosis can Thyroid cancer, while often having a favorable prognosis, presents a complex biochemical response and have resulted in the Inhibition of targ and Evolving landscape in terms of its biology and oncology. Advancements have Significantly deepened our understanding of its molecular underpinnings and opened new Avenues for diagnosis and treatment, particularly for advanced and aggressive forms [1]. Incidence of thyroid cancer of follicular cell derivation has risen considerably over the past Few decades, largely attributed to increased detection through widespread imaging and Fine-needle aspiration biopsies [2–4]. While many newly diagnosed cases are indolent, There is also a noted increase in advanced-stage disease. Thyroid cancer (TC) represents the most common endocrine malignancy, accounting for 3.4% Of all cancers diagnosed annually (3) . The transformation of thyroid follicular cells may result In differentiated or undifferentiated TC, through a multistep process that is the most accepted Theory of follicular cell carcinogenesis (4). In this model, distinct molecular alterations have been Associated with specific stages, driving progression from well-differentiated to undifferentiated Follicular-derived thyroid carcinomas. Thyroid cancer (TC) is the most common endocrine Malignancy. An estimated, 60 220 new cases of TC and 1850 TC-related deaths are expected in 2013 in the USA. Survival of patients with TC depends upon Multiple factors, including cancer type and stage. The 5-year survival rate is more than 90% in patients with Localized papillary thyroid cancer (PTC) and follicular Thyroid cancer (FTC), and only 53.9% in patients with Distant metastases (Schlumberger 1998). The prognosis for Patients with medullary thyroid cancer (MTC) depends on The stage of tumor progression at the time of diagnosis,

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With a mean 10-year survival rate of 100, 93, 71, and 21% for stages I, II, III, and IV respectively (Modigliani Et al. 1998). An increasing number of phase I and II studies have Been conducted to evaluate the efficacy of new molecular Targeted drugs, such as tyrosine kinase inhibitors, Inhibitors of angiogenesis, radio-immunotherapy, and Re-differentiation drugs (Lanzi et al. 2009, Liebner & Shah 2011). Several targeted therapies have shown Promising eted signaling pathways in TC cells. Most Of these therapeutic modalities, however, were associated Frequently with high toxicity rates.

Thyroid cancer (TC) represents the most common endocrine malignancy, accounting for 3.4% Of all cancers diagnosed annually (1). The transformation of thyroid follicular cells may result In differentiated or undifferentiated TC, through a multistep process that is the most accepted Theory of follicular cell carcinogenesis (2). In this model, distinct molecular alterations have Associated with specific stages, driving progression from well-differentiated to undifferentiated Follicular-derived thyroid carcinomas Thyroid cancer originates from hormone-producing thyroid gland cells, and its incidence has been consistently increasing worldwide [5,6]. It is classified into four major types, which account for approximately 98% of all thyroid malignancies: differentiated thyroid cancer (DTC), which encompasses both papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC); oncocytic thyroid carcinoma/anaplastic (undifferentiated) thyroid cancer (ATC/UTC); and medullary thyroid cancer (MTC) [6]. PTC is characterized by little colloid, hypercellularity, and enlarged, irregular, crowded nuclei with loss of polarity and presence of psammoma bodies.

PTC is the most prevalent malignant thyroid neoplasm, accounting for up to 80% of all thyroid cancers in countries with sufficient iodine intake. It occurs in all age groups, with its peak incidence noted in the third to fifth decades. These tumors typically grow at a slow pace and are often confined to a single lobe of the thyroid gland. They occa- sionally metastasize to the cervical lymph nodes and less commonly to the lungs and bones. FTC is the second most prevalent form of thyroid cancer, accounting for approxi- mately 10% of all thyroid malignancies. It is more preva- lent in regions with insufficient iodine intake. While FTC can occur across a broad age range, it most commonly affects individuals .While FTC Can occur across a broad age range, it most commonly Affects individuals in their fifth and sixth decades of life. Unlike PTC, FTC rarely spreads to lymph nodes; however, It has a greater tendency to metastasize to distant sites, such As the lungs and bones. On the other hand, MTC is less be challenging, as it may metastasize to the Lymph nodes, lungs, or liver even before a thyroid nodule Becomes clinically apparent. ATC is the most aggressive Yet rarest form of thyroid cancer, accounting for less than 2% of all cases.

Papillary thyroid carcinoma accounts for approximately 84% of all thyroid cancers. Papillary, follicular (≈4%), and oncocytic (≈2%) are termed well-differentiated thyroid cancer. Less common and more aggressive subtypes include poorly differentiated and ana- plastic thyroid carcinoma that arise from well-differentiated thy- roid cancer after accumulation of genetic mutations in the tumor thyroid cancer arises from parafollicu- lar C cells . Totally thyroidectomy with or without radioac- tive iodine therapy has been typically recommended for the treat- ment of most forms of thyroid cancer. Molecular profile testing has allowed for more personalized treatment. Specific genetic muta- tions define radioactive iodineand targeted thera- pies that can be used to tailor treatment. This review summarizes current evidence regarding pathophysiology, diagnosis, and man- agement of early-stage and advanced thyroid cancer

Thyroid cancer is a type of malignancy that arises from the cells of the thyroid gland, a butterfly-shaped endocrine gland located in the front of the neck. The thyroid gland plays a crucial role in regulating metabolism, growth, and development through the secretion of thyroid hormones such as thyroxine (T4) and triiodothyronine (T3).

Thyroid cancer is relatively uncommon compared to other cancers, but it is the most common endocrine malignancy. Its incidence has increased globally over the past few decades, partly due to improved diagnostic techniques such as ultrasound and fine-needle aspiration biopsy. There are several types of thyroid cancer, classified based on the type of cells involved: Papillary thyroid cancer (PTC) – the most common and slow-growing type Follicular thyroid

cancer (FTC) – spreads through the bloodstream Medullary thyroid cancer (MTC) – arises from parafollicular © cells Anaplastic thyroid cancer (ATC) – rare but highly aggressive The exact cause of thyroid cancer is not always known, but several risk factors have been identified, including: Exposure to ionizing radiation, especially during childhood Genetic mutations and family history Iodine imbalance (deficiency or excess) Female gender (more common in women) Clinically, thyroid cancer may present as a painless lump or swelling in the neck, difficulty swallowing, hoarseness of voice, or may remain asymptomatic in early stages. Early detection and appropriate treatment usually result in a good prognosis, especially for differentiated thyroid cancers like papillary and follicular types.

Pathophysiology Of Thyroid cancer –

Geographical location has a significant impact on the incidence of thyroid cancer , particularly in women .Higher-income nations, such as the Republic of Korea, Canada, Italy, France, Israel, Croatia, Austria, and the United States, as well as several middle- to upper-middle-income nations, such Turkey, Brazil, Costa Rica, and China, generally have the highest incidence (7, 8). Certain island states and territories, such as Cyprus, Cabo Verde, French Polynesia, New Caledonia, and Puerto Rico, also have high incidence rates (7). Although environmental exposures may also be a factor, geographic variations in access to care and diagnostic procedures are regarded to be the primary cause of this variation . Thyroid cancer mortality rates typically vary less widely and are significantly lower than incident [7]

Type of Thyroid Cancer -

1. Papillary thyroid cancer – most common and slow growing
2. Follicular thyroid cancer – spread through
3. Medullary thyroid cancer – Aries from c-cells and my be genetic
4. Anaplastic thyroid cancer – rare but highly aggressive.

Stages of thyroid cancer –

Stages I- Tumor confined to thyroid.

Stages II – Large tumor but still within thyroid.

Stages III – Spread to nearly lymph nodes.

Stages IV - Distant metastasis [8]

A frequent endocrine cancer, thyroid carcinoma is characterized by intricate genetic and epigenetic changes. RET/PTC gene rearrangements, BRAF^V600E, RAS point mutations, and PAX8/PPARγ rearrangements are common mutations that can profoundly alter tumor behavior and responsiveness to treatment (5). Papillary thyroid cancer (PTC) accounts for approximately 80% of all thyroid Cancers (6). Branching papillae and unique nuclear characteristics, such as nuclear inclusions and grooves, are histologically characteristic of PTC. It has an excellent Prognosis, largely due to its indolent course and High treatment responsiveness

Approximately 12% of thyroid cancers are follicular thyroid carcinoma (FTC) (7). It has a higher propensity for distant metastasis and vascular invasion, most frequently affecting the bones and lungs. FTC usually affects middle-aged women and is more common in areas with iodine shortage.About 3–4% of thyroid malignancies are medullary thyroid carcinoma (MTC), which is derived from parafollicular C cells (7). In contrast to PTC and FTC, MTC generates calcitonin, a valuable tumor marker. MTC can develop on its own or as a component of genetic disorders, such as Multiple Endocrine Neoplasia type 2 (MEN2). Less than 2% of instances of thyroid cancer are anaplastic thyroid carcinoma (ATC), which is the most dangerous type (6). It usually affects elderly persons, has a bad prognosis, and exhibits fast local invasion.

Less than 2% of instances of thyroid cancer are anaplastic thyroid carcinoma (ATC), which is the most dangerous type (6). It usually affects elderly persons, has a bad prognosis, and exhibits fast local invasion.Patients often present with a thyroid no-Dule incidentally detected during imaging Studies or identified on physical examination Approximately 4–7% of patients on physical. 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 Computed tomography (CT), magnetic resonance imaging (MRI), and radionuclide scanning are further diagnostic imaging modalities (10). When FNA results are nondiagnostic, radionuclide scanning can be used as a supplementary diagnostic method to assess the functional status of thyroid nodules. Because MRI has better soft tissue resolution than CT, it is recommended for assessing retrotracheal, mediastinal, or metastatic involvement of large thyroid nodules or goiters. Psammoma bodies, uneven nuclear outlines, and larger, elongated nuclei are among the nuclear characteristics of PTC . FTC may exhibit imaging characteristics such weakly defined margins, microcalcifications, and distinctive vascular patterns, and is frequently assessed with ultrasonography or FNA .Regarding the regular application of nuclear medicine, there is no agreement. Normal Thyroid Cell Function The thyroid gland consists mainly of: Follicular cells → produce thyroid hormones (T3, T4)Parafollicular © cells → produce calcitonin Normally, cell growth is tightly regulated by signaling pathways and hormonal control via thyroid-stimulating hormone (TSH).

2. Genetic Mutations and Molecular Changes Thyroid cancer begins with mutations in specific genes that control cell growth: Papillary Thyroid Cancer (PTC)Mutation in BRAF gene (most common)RET/PTC rearrangements Activates MAPK signaling pathway → uncontrolled cell proliferation [10]

a. Follicular Thyroid Cancer (FTC)RAS mutationsPAX8-PPARγ rearrangement Activates PI3K/AKT pathway → tumor growth and survival Medullary Thyroid Cancer (MTC) Mutation in RET proto-oncogene Arises from C-cells → excess calcitonin production

b. Anaplastic Thyroid Cancer (ATC)Multiple mutations: p53, BRAF, RAS Loss of differentiation → highly aggressive tumor[9]

3. Mechanism of Tumor Development

The pathogenesis follows these steps: Initiation

Genetic mutation caused by radiation, environmental, or hereditary factors Promotion Activation of oncogenes and inactivation of tumor suppressor genes Increased TSH stimulation may promote tumor growth Progression Rapid cell division Loss of normal cell differentiation Ability to invade surrounding tissues [11]

4. Tumor Growth and Spread

Local invasion → trachea, esophagus, muscles

Lymphatic spread → common in papillary carcinoma Hematogenous spread → seen in follicular carcinoma (to lungs, bones)

5. Hormonal Influence

Elevated TSH levels can stimulate tumor growth

Most thyroid cancers are non-functional (do not produce hormones)

Medullary carcinoma produces calcitonin

6. Dedifferentiation

Some tumors (especially ATC) lose their normal thyroid characteristics

Become more aggressive and resistant to treatment

Mechanism of Action of Drugs Used in Thyroid Cancer

Treatment depends on the type of thyroid cancer and includes radioactive iodine, hormone therapy, and targeted drugs.[8]

1. Radioactive Iodine Therapy (I-131)

Mechanism:

Thyroid cells (including cancer cells) absorb iodine via the sodium-iodide symporter (NIS)

Iodine-131 is taken up selectively by thyroid tissue

Emits beta radiation → destroys thyroid cancer cells from within

Minimal effect on other tissues

Use:

Mainly for papillary and follicular thyroid cancer [8]

2. Thyroid Hormone Suppression Therapy

Mechanism:

Levothyroxine suppresses TSH (thyroid-stimulating hormone)

TSH normally stimulates thyroid cell growth

Lower TSH → reduced stimulation of cancer cells → slows tumor growth [13]

3. Tyrosine Kinase Inhibitors (TKIs)

These are targeted therapies used in advanced thyroid cancer.

Examples:

Sorafenib

Lenvatinib

Mechanism:

Block tyrosine kinase receptors involved in tumor growth

Inhibit pathways like:

VEGF receptors → reduce blood vessel formation (angiogenesis)

RET, BRAF signaling → reduce tumor cell proliferation

Result: tumor growth inhibition and reduced metastasis

4. RET Inhibitors (Targeted Therapy)

Examples:

Selpercatinib

Pralsetinib

Mechanism:

Specifically block RET gene mutations

Prevent abnormal signaling → stop cancer cell growth

Use:

Medullary thyroid cancer and RET-mutated cancers

5. Chemotherapy (Less Common)

Example:

Doxorubicin

Mechanism:

Interferes with DNA replication

Causes cancer cell death

Drugs Act on Thyroid Cancer -

Treatment depends on the type and stage of cancer. The main drug classes include radioactive iodine, hormone therapy, targeted therapy, and chemotherapy.

1. Radioactive Iodine Therapy

Drug:

Iodine-131

Action -Selectively taken up by thyroid cells Emits radiation destroys cancer cells

Indication: Papillary and follicular thyroid cancer [13]

2. Thyroid Hormone Therapy

Drug:

Levothyroxine

Action: Suppresses TSH secretion Reduces stimulation of tumor growth

3. Tyrosine Kinase Inhibitors (TKIs)

Drugs:

Sorafenib , Lenvatinib

Action: Block tumor growth signaling pathways Inhibit angiogenesis (blood supply to tumor)

Use: Advanced or metastatic thyroid cancer

4. RET Inhibitors (Targeted Therapy)

Drugs:

Selpercatinib ,Pralsetinib

Action: Block RET gene mutation Stop cancer cell proliferation

Use: Medullary thyroid cancer [13]

5. Chemotherapy

Drug: Doxorubicin

Action: Inhibits DNA replication → cancer cell death

Use: Drugs Acting on Thyroid Cancer [13]

Treatment depends on the type and stage of cancer. The main drug classes include radioactive iodine, hormone therapy, targeted therapy, and chemotherapy. [14]

CONCLUSION

In the United States, there are about 44,000 new instances of thyroid cancer identified annually, with a 5-year relative survival of 98.5%. In the majority of well-differentiated thyroid cancer cases, surgery is curative. After surgery, radioactive iodine therapy increases overall survival in patients who are at high risk of recurrence. Metastatic illness is increasingly being treated with antiangiogenic multikinase inhibitors and tailored therapy to genetic abnormalities that cause thyroid cancer.[14]

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