

# Carcinoma of the Thyroid Gland: Insights into Etiology, Pathogenesis, Diagnosis and Possible Lines of Management

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**Abstract** Thyroid carcinoma is one of the most common malignancies of the endocrine system worldwide. Over the recent years, there has been a significant increase in the newly reported cases of thyroid cancer which may be attributed to the wide use of imaging techniques in the diagnosis and treatment of a wide range of human diseases. Papillary thyroid cancer is the most common type of thyroid malignancies. Lines of treatment include total thyroidectomy, radioactive iodine therapy, and molecular-targeted therapies. Prognosis of thyroid carcinoma depend on many factors including age of the patient, the tumor type and its stage at the time of diagnosis of the disease. This review sheds light on carcinoma of the thyroid gland in view of the recent trends regarding its prevalence, risk factors, types, clinical picture, methods of diagnosis and possible lines of management.

**Keywords:** carcinoma, thyroid gland, etiology, pathogenesis, diagnosis, management

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## 1. Introduction

Thyroid carcinoma represents one of the most common malignancies that affect the endocrine system all over the world [1]. The incidence of thyroid carcinoma was significantly increased in the last decades. This increase may be a true rise in incidence or due to the progress in the diagnostic tools that participated efficiently in the early discovery of subclinical cases [2]. This increase has generated significant interest in exploration of the pathophysiologic mechanisms of thyroid carcinoma and encouraged the researchers to develop new lines of management of this disease [3].

Most cases of thyroid carcinoma usually start in the follicular cells of the thyroid gland. Most cases of thyroid carcinoma are generally well-differentiated and not usually aggressive [4]. However, they may mutate at any time to more aggressive forms. About 85% of patients with thyroid carcinoma have an excellent prognosis following treatment. Between 10% and 15% of cases may eventually mutate into more aggressive forms of the disease especially those presenting with tall-cell features [5]. These aggressive forms are usually poorly differentiated and carry a worse prognosis requiring more aggressive interventions, both surgically and non-surgically because they are often resistant to therapy

with radioactive iodine and have a higher mortality rate. Less than 2% of thyroid carcinomas present as anaplastic carcinomas which carry the highest mortality rates among the different types of thyroid carcinoma [6].

The clinical presentation of thyroid carcinoma is highly variable, ranging from asymptomatic early cases to symptoms of metastasis in advanced cases [5]. Depending on the stage of the disease, lines of treatment of thyroid carcinoma include surgical removal of the tumor with adjuvant radioactive iodine therapy [7]. Recently, molecular-targeted therapies were approved for treatment of refractory cases and exhibited promising results [8]. The aim of this review is to shed light on thyroid carcinoma regarding its prevalence, risk factors, types, clinical picture, methods of diagnosis and possible lines of management in view of the recent trends.

## 2. Etiology of Thyroid Carcinoma

The exact etiologic factors that predispose to thyroid carcinoma are not yet fully understood. However, exposure to radiation has been implicated as the principle etiological factor for many decades [3]. Recent reports had proven that exposure to low-dose radiation during childhood may be associated with an increased incidence of thyroid carcinoma later in life [1]. Also, children with acne vulgaris who were treated with low-voltage

radiation were reported to have an increased risk of development of thyroid carcinoma [9]. Although radiation exposure plays a crucial role in the development of thyroid carcinoma, it does not appear to play a role in determining the aggressiveness and prognosis of the disease [10].

### 3. Epidemiology of Thyroid Carcinoma

In 2010, thyroid carcinoma was reported to be responsible for 36,000 deaths globally [11]. Thyroid carcinoma occurs most frequently in younger age groups, with the highest incidence among the second, third, and fourth decades of life [1]. In the United States, occult thyroid carcinomas were reported in approximately 10% of autopsy among individuals who died of causes other than thyroid carcinoma. Occult carcinoma might be present in the thyroid glands of these individuals during their life without becoming clinically significant [3].

### 4. Clinical Presentation of Thyroid Carcinoma

In a vast majority of cases, the first symptom of thyroid carcinoma is a nodule in the thyroid region of the neck [4]. However, the presence of small nodules in the thyroid gland is considered a normal finding in up to 65% of adults and less than 10% of these nodules are found to be cancerous [12]. In some cases, the patient may present with an enlarged lymph node. With progress of the disease, the patient may suffer from pain in the anterior region of the neck with hoarseness of voice due to extension of the tumor to involve the recurrent laryngeal nerve [13]. Signs and symptoms of hypo- or hyperthyroidism might be evident in patients suffering from large metastatic tumors [3]. Some individuals may present with hemoptysis or airway obstruction from tumors growing into the trachea and obstructing the airway. In some patients, the only symptom is a mass in the neck that turns out to be a metastatic lymph node [14].

### 5. Diagnosis of Thyroid Carcinoma

When multiple intrathyroid nodules are discovered on routine imaging of the neck, thyroid carcinoma should be suspected [6]. The most important tests for proper decision-making in management of this disease are ultrasound of the thyroid gland and fine-needle aspiration biopsy [5]. Following confirmation of diagnosis, further radiologic investigations should be carried out particularly for those patients with extensive primary tumor with involvement of the surrounding structures or in patients who present with extensive nodal metastases [15]. They include computerized tomography (CT) scan or magnetic resonance imaging (MRI) which efficiently aid in proper anatomic assessment of the primary tumor and its invasion to local structures. This assessment is vital for the surgeon to decide whether he can perform a definitive R0 resection of the tumor or not [16].

## 6. Management of Thyroid Carcinoma

Lines of treatment of thyroid carcinoma include total thyroidectomy, radioactive iodine therapy, and molecular-targeted therapies [8]. Surgical resection of differentiated thyroid carcinoma is the main line of treatment associated with thyroid ablation with radioactive iodine and suppression of thyroid stimulating hormone (TSH) secretion [17]. Radiation and systemic chemotherapy may be needed in metastatic cases refractory to conventional methods of treatment [18]. The choice of the line of treatment depends on several factors including the goal of therapy, prognosis of the tumor, the relative risk of recurrence, and the morbidities associated with each line of treatment [8,19].

Surgical resection of thyroid carcinoma can range from hemithyroidectomy, thyroid lobectomy to total thyroidectomy, with or without lymph node dissection according to the stage of the tumor [20]. Total thyroidectomy is usually indicated for lesions greater than 1cm in diameter to ensure complete removal of the tumor and to improve the results of radioactive iodine ablation [21].

The use of radioactive iodine therapy after surgical resection of the gland helps to ablate the remaining thyroid tissues to decrease the risk of recurrence of the tumor and to suppress the detected or occult metastasis [22]. Therapy with radioactive iodine should be recommended for any patient with extrathyroidal spread or distant metastasis [23]. Individuals who are candidates for therapy with radioactive iodine should maintain a low iodine diet for two weeks to ensure iodine depletion of the cells and to improve the iodine uptake by the cells [24].

Suppression of TSH secretion is another line for treatment of refractory thyroid carcinoma due to the fact that TSH receptors are highly expressed in the tissues of thyroid carcinoma and TSH was proven to be an important growth factor for thyroid carcinoma [26]. A high dose of exogenous thyroid hormone is given, although there must be a balance between the risks of malignancy versus the multiple adverse effects caused by hyperthyroidism [27].

Although lines of treatment of cases with advanced metastatic thyroid carcinoma are limited, developments in the last years in understanding of the pathogenesis of these malignancies resulted in identification of novel targeted therapies that were proven to improve the survival rates of patients with these malignancies [27]. These targeted therapies have the ability to block the oncogenic kinases or signaling kinases that are largely involved in the growth and proliferation of the tumor cells [28]. For example, sorafenib and lenvatinib (Kinase inhibitors) are able to inhibit angiogenesis and can target some of the proteins produced by cancer cells that normally help them to grow [29]. These drugs can stop cancer growth for a time for refractory cases of differentiated thyroid carcinoma [30]. Also, dabrafenib and trametinib inhibit the production of some proteins that are involved in growth of the tumor [31]. These drugs can be used together to treat mutant types of anaplastic thyroid carcinomas that can't be removed completely with surgery [32]. Common adverse effects of targeted therapies include rash, loss of appetite, fatigue, nausea, vomiting, diarrhea, hypertension, and hand foot syndrome [28].

## 7. Prognosis of Thyroid Carcinoma

Prognosis of cases with thyroid carcinoma depends on different factors related to the patient himself and the tumor [5]. Young-aged patients less than 45 years have a favorable prognosis compared to older patients. The ten-year survival rate is about 98% in patients younger than 45 years while the mortality rates may reach up to 20% in patients older than 70 years [33]. Also, the histologic grade of the tumor often represents an important prognostic factor for thyroid carcinoma. Well-differentiated tumors have a more favorable prognosis than poorly differentiated and anaplastic types of the tumor [34]. Moreover, the degree of extension of the tumor is a key stone in determination of the prognosis of the tumor. Cases with minor extension in the structures surrounding the thyroid gland have better prognosis than cases with major extension to the trachea, the larynx or the esophagus [33]. Also, large-sized tumors have an increased risk of local recurrence after total thyroidectomy and have a relatively higher mortality rate than those with smaller sizes [35].

## 8. Conclusion

Carcinoma of the thyroid gland is one of the common tumors worldwide. A vast majority of cases with thyroid cancer remain stable and indolent. Total thyroidectomy remains the main line of treatment as it increases survival rates and decreases the liability for recurrence. Adjuvant therapy with radioactive iodine ( $I^{131}$ ) plays a crucial role for complete cure of thyroid cancer. Also, molecular-targeted therapies that were approved in the last few years participate efficiently in improvement of the morbidity and mortality rates of the different types of thyroid carcinoma. Prognosis of thyroid carcinoma largely depends on the histological type of the tumor and its stage at the time of diagnosis.

## Conflict of Interest

The authors had no conflict of interest to declare.

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