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A REVIEW ON THYROID DISORDERS AND CLINICAL MANAGEMENT OPTIONS

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ABSTRACT

The thyroid gland is a vital, butterfly-shaped endocrine organ in the neck that regulates the basal metabolic rate (BMR), somatic, and psychic growth, and plays a role in calcium metabolism. It consists of two lobes joined by an isthmus, is richly vascularized, and is covered by true and capsules. Thyroid diseases are broadly classified into functional disorders (hypothyroidism and hyperthyroidism) and structural/ inflammatory disorders (goiter, thyroid nodules, and thyroiditis). Hypothyroidism (thyroid hormone deficiency) is primarily caused by chronic autoimmune thyroiditis (Hashimoto's disease) in iodine-sufficient areas. Treatment is mainly with levothyroxine monotherapy. Hyperthyroidism (excess thyroid hormone production/exposure, or thyrotoxicosis) has multiple etiologies, with Graves' disease, toxic multinodular goiter, and toxic adenoma being common. Definitive treatments include radioactive iodine (RAI) therapy, thionamide drugs (methimazole/propylthiouracil), and surgery (thyroidectomy). Goiter (enlargement of the thyroid) and thyroid nodules (discrete lesions) are common. Management for non-toxic goiter and benign nodules involves monitoring, while suspicious or malignant nodules require fine-needle aspiration (FNA) for diagnosis and potential surgery. Thyroiditis (inflammation) is often autoimmune (like Hashimoto's or Graves' disease) or subacute and is generally managed symptomatically or with anti-thyroid drugs/hormone replacement as needed. Thyroid cancer, primarily differentiated thyroid cancer (papillary and follicular), is treated with surgical resection (lobectomy or total thyroidectomy), followed by RAI ablation and

thyroid hormone suppression therapy based on risk stratification. Medullary and anaplastic thyroid cancers have distinct, more complex management strategies.

KEYWORDS: Thyroid gland, Hypothyroidism, Hyperthyroidism, Hashimoto's thyroiditis, Graves' disease, Goiter, Thyroid nodule, Thyroiditis, Thyroid cancer, Levothyroxine, Radioactive iodine, Thionamides, Thyroidectomy, Thyroid-stimulating hormone (TSH).

THYROID GLAND

The thyroid gland is a vital butterfly-shaped endocrine gland situated in the lower part of the neck. It is present in the front and sides of the trachea, inferior to the larynx. It plays an essential role in regulating the basal metabolic rate (BMR) and stimulating somatic and psychic growth, besides having a vital role in calcium metabolism.

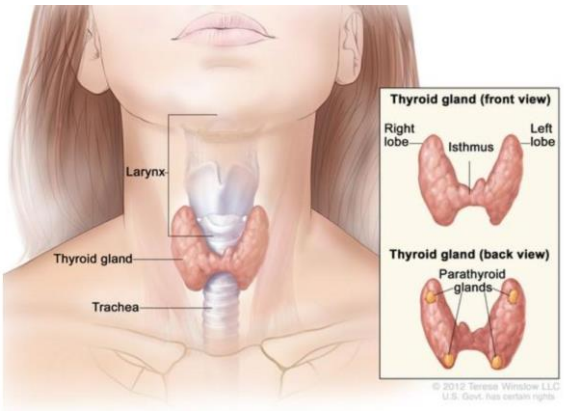
It is a gland consisting of two lobes, the right, and the left lobes, joined together by an intermediate structure, the isthmus. Sometimes a third lobe called the pyramidal lobe projects from the isthmus. It has a fibrous/fibromuscular band, i.e., levator glandulae thyroideae running from the body of the hyoid to the isthmus.[1] The lobes are 5 x 2.5 x 2.5 cm in dimension and weigh around 25 gm. It extends from the fifth cervical to the first thoracic vertebrae. The lobes extend from the middle of the thyroid cartilage to the fifth tracheal ring. The isthmus is 1.2 x 1.2 cm in dimensions and extends from second to third tracheal rings. It grows larger in females during the period of menstruation and pregnancy.

The lobes are conical in shape and have an apex, a base, three surfaces – lateral, medial, and posterolateral, and two borders – the anterior and posterior. The isthmus, however, has two surfaces – anterior and posterior and two borders – superior and inferior.

The lobes are related anteriorly to the skin, superficial and deep fascia, and platysma. Posteriorly, the lobes are associated with the laminae of the thyroid cartilage and tracheal rings and laterally to the external carotid artery and internal jugular vein.[2]

The thyroid gland is a richly vascular organ supplied by the superior and inferior thyroid arteries and sometimes by an additional artery known as the thyroidea ima artery (see Image 1). The Thyroid Artery).[3] The venous drainage is by superior, middle, and inferior thyroid veins. Sometimes a fourth thyroid vein might be present, called the vein of Kocher. The nerve supply is mainly from the middle cervical ganglion and partly from the superior and inferior cervical ganglia.

Two capsules completely cover the thyroid gland. The true capsule is made up of fibro-elastic connective tissue. The false capsule comprises the pre-tracheal layer of the deep cervical fascia. It consists of a deep capillary plexus, deep to the true capsule. Hence, it is crucial to remove the plexus with the capsule during thyroidectomy.[4]



Conditions and Disorders

A. FUNCTIONAL DISORDERS

1. Hypothyroidism

Hypothyroidism refers to the common pathological condition of thyroid hormone deficiency. If untreated, it can lead to serious adverse health effects and ultimately death. Because of the large variation in clinical presentation and general absence of symptom specificity, the definition of hypothyroidism is pre-dominantly biochemical. Overt or clinical primary hypothyroidism is defined as thyroid-stimulating hormone (TSH) concentrations above the reference range and free thyroxine concentrations below the reference range. Mild or subclinical hypothyroidism, which is commonly regarded as a sign of early thyroid failure, is defined by TSH concentrations above the reference range and free thyroxine concentrations within the normal range. Subclinical hypothyroidism has been reviewed in a previous Lancet Seminar1[5] and is therefore not the focus here.

Treatment

Levothyroxine monotherapy in solid formulation, taken on an empty stomach, is the treatment of choice. The presence of clinical features of hypothyroidism, with biochemical confirmation of overt hypothyroidism, is the indication for treatment initiation. No rationale exists for avoiding the prescription of generic preparations, but switches between levothyroxine products in patients who are stable are not recommended.[6] The optimal daily dose in overt hypothyroidism is 1·5—1·8 μg per kg of bodyweight.[7-9] In patients with

coronary artery disease, the starting dose is generally 12·5—25·0 μg per day and should be gradually increased on the basis of symptoms and TSH concentrations.[10] This regimen is often preferred in the elderly, especially in patients with many co-morbidities.[11-12] In younger patients without comorbidities, the full dose can usually be given from the start with adequate monitoring to avoid overtreatment. After the initiation of therapy, TSH measurement is repeated after 4–12 weeks and then every 6 months and, once stabilised, annually. Adjustments should be made according to laboratory findings, keeping in mind that in some patients (ie, those with low bodyweight or older patients) small changes in dose can have substantial effects on serum TSH concentrations. The clinical significance of low tri-iodothyronine concentrations in some patients despite reaching normal TSH concentrations is unknown. Routine measurement of tri-iodothyronine should not be used to assess treatment effectiveness.[13]

2 Hyperthyroidism

Introduction

Hyperthyroidism is a common thyroid disorder. "Hyperthyroidism" defines a syndrome associated with excess thyroid hormone production.[14] It is a common misconception that the terms thyrotoxicosis and hyperthyroidism are synonyms. The term "thyrotoxicosis" refers to a state of excess thyroid hormone exposure to tissues.[15] Although hyperthyroidism can lead to thyrotoxicosis and can be used interchangeably, it is essential to note their differences. For the sake of simplicity, this topic covers hyperthyroidism and thyrotoxicosis. Hyperthyroidism has multiple etiologies, clinical manifestations, and treatment modalities. Hyperthyroidism can be overt or subclinical. Overt hyperthyroidism is defined as low or suppressed thyroid stimulating hormone (TSH) levels with elevated triiodothyronine (T3) levels and/or elevated thyroxine (T4) levels.[16] When T3 levels are elevated with low/suppressed TSH and normal T4 levels, this is called 'T3 toxicosis'.[17] Subclinical hyperthyroidism is low or suppressed TSH with normal T3 and T4 levels.[18] Both overt and subclinical hyperthyroidism are associated with significant long-term complications.[19][20][21][22][23]

Treatment / Management

Treatment of hyperthyroidism depends on the underlying etiology and can be divided into symptomatic and definitive therapy. The symptoms of hyperthyroidism, such as palpitations, anxiety, and tremors, can be controlled with a beta-adrenergic antagonist such as atenolol. Calcium channel blockers, such as verapamil, can be used as second-line therapy for patients

who are beta-blocker intolerant or have contraindications to beta-blocker treatment.[24] This topic only covers the treatment for the most common causes of hyperthyroidism: Graves disease, toxic multinodular goiter, and toxic adenoma in non-pregnant patients.

B. Structural and inflammatory disorders

1. GOITER

Introduction

Goiter means enlargement of the thyroid gland and is a general term that conveys the information that the volume of the thyroid gland is larger than normal. The presence of goiter can be determined by inspection, palpation, or by an imaging study.

Normal thyroid gland measures 4 to 4.8 cm in sagittal, 1 to 1.8 cm in transverse, and 0.8 to 1.6 cm in anteroposterior dimensions. This corresponds to a volume of 7 to 10 mL on ultrasonography calculations and 10-20 grams in weight. Thyroid size increases with age and body size. It is larger in males as opposed to females. The size decreases with higher iodine intake.

The thyroid gland can enlarge due to a variety of physiological or pathological stimuli. Goiter during adolescence and pregnancy are two causes of a physiological goiter. Goiter can be associated with euthyroidism, hypothyroidism, or hyperthyroidism.[25] It can be diffuse, nodular, or multinodular. The thyroid gland usually grows anteriorly in the neck, because the enlarging thyroid is not constrained by the weak anterior cervical muscles, subcutaneous tissue, or the skin. The term goiter is usually used to denote cervical goiter. If the thyroid gland enlarges inferiorly and passes through the thoracic inlet, then it is called a substernal or retrosternal goiter.

Treatment / Management

The aim of goiter treatment is to relieve compression and to restore euthyroidism. By definition patients with nontoxic goiters are euthyroid or in lower frequency hypothyroid. If there is any coexistent hypothyroidism, treatment includes thyroid hormone administration. Patients with toxic goiter require modalities that address thyroid enlargement and thyrotoxicosis.

2. THYROID NODULES

Introduction

The American Thyroid Association (ATA) defines the thyroid nodule as a discrete lesion within the thyroid gland. It is radiologically distinct from the surrounding thyroid parenchyma.[26] Nodules may be solitary, multiple, cystic, or solid.[27]

Nodules in the thyroid gland are a common entity and are detected in approximately 5% to 7% of the adult population by physical examination alone. However, autopsy data have shown a 50% prevalence of thyroid nodules larger than one centimeter in patients without previously diagnosed thyroid disease.[28][29] Nodules are found with increasing frequency, likely due to the widespread use of modern imaging modalities, particularly ultrasound (US), but also computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET).[30]

Although more than 90% of detected nodules are clinically insignificant benign lesions,[31] thyroid nodules are clinically important as they may represent thyroid cancer in approximately 4.0% to 6.5% of cases.[32]

Treatment / Management

Initial management of thyroid nodules depends on the type of lesion found, US characteristics, and whether it is functional or not. FNA results will ultimately guide treatment.[33]

FNA cytology results provide 6 major diagnostic categories (Bethesda classification), all of which indicate different subsequent management.[34]

Non-diagnostic: Cancer risk 5% to 10%

Benign: Cancer risk 0% to 3%

Atypia of undetermined significance or follicular lesion of undetermined significance: Cancer risk 10 to 30%

Follicular neoplasm (or suspicious for follicular neoplasm): Cancer risk 25% to 40%

Suspicious for malignancy: Cancer risk 50% to 75%

Malignant: Cancer risk 97% to 99%

Non-diagnostic biopsies (Bethesda I) are considered cytologically inadequate. The absence of malignant cells should not be interpreted as a negative biopsy if scant follicular tissue is obtained. FNA is usually repeated in 4 to 6 weeks.[35]

Patients with benign nodules (Bethesda II), such as macrofollicular, colloid adenomas, nodular goiter, and Hashimoto thyroiditis, are usually followed without surgery. Periodic US monitoring initially at 12 to 24 months, with increasing intervals, is preferred. If the US shows highly suspicious findings, then FNA should be repeated within 12 months despite a benign initial biopsy.[36][37]

For nodules with indeterminate cytology (Bethesda III and IV), the approach varies with institutional practices. Some institutions obtain an additional FNA sample for molecular testing, while other centers repeat the FNA after 6 to 12 weeks. A radionuclide scan may also be obtained if repeat aspirates show only architectural atypia.[38][39]

For nodules that fall within the category of Bethesda V, suspicious for malignancy, treatment should include surgery. Molecular markers should not be used. Bethesda VI includes papillary cancer, MTC, thyroid lymphoma, anaplastic cancer, and cancer metastatic to the thyroid. These patients should also be referred for surgery.[40]

3. THYROIDITIS

Introduction

The term thyroiditis reflects inflammation of the thyroid gland. Thyroiditis can be classified based on the onset of symptoms, underlying etiology, and clinical symptoms. The most common cause of thyroiditis is an autoimmune disease. In the United States, Hashimoto thyroiditis is the most common cause of hypothyroidism.[41] Thyroiditis can cause transient or permanent hypo and hyperthyroidism.

Treatment / Management

Acute Thyroiditis

Infectious thyroiditis: Patients with suppurative thyroiditis can be managed with nonsurgical management. Antibiotics are used to control infection. NSAIDs are used to control severe neck pain and inflammation. Surgical intervention, like abscess drainage, can be done if clinically indicated.[42] Radiation-induced thyroiditis: Treatment is symptomatic with

NSAIDs or prednisone in severe cases. These patients are increased risk of hypothyroidism and should be followed with a thyroid function test.[43]

Subacute Thyroiditis

It is usually self-limiting, and symptomatic management is all that is needed. NSAIDs are preferred for pain control. In case of severe pain and severe symptoms of thyrotoxicosis, corticosteroids, and beta-blockers can be used for the treatment of inflammation and tachycardia due to thyrotoxicosis. The hypothyroid phase is usually mild and does not require treatment.[44]

Chronic Thyroiditis

Autoimmune thyroiditis: Hashimoto thyroiditis with normal thyroid function can be monitored without treatment with levothyroxine.[45] Hyperthyroidism or Graves disease can be treated with methimazole or propylthiouracil. Methimazole is the drug of choice, but propylthiouracil is preferred during the first trimester of pregnancy and for treatment of the thyroid storm. Permanent treatment of Graves disease included radioactive iodine treatment and thyroidectomy.[46]

C. AUTOIMMUNE DISORDERS

1. HASHIMOTO`S THYROIDITIS

Hashimoto thyroiditis is an autoimmune disease that destroys thyroid follicular cells through cell- and antibody-mediated immune processes. This disease is also known as chronic autoimmune thyroiditis and chronic lymphocytic thyroiditis. Hashimoto thyroiditis is the most common cause of hypothyroidism in developed countries.[47] The pathophysiology of this disease involves the formation of antithyroid antibodies and T-cell activation that attack the thyroid tissue, causing progressive fibrosis. Together with Graves disease, this condition comes in the category of autoimmune thyroid disorders.[48] This condition was initially described by a Japanese physician, Haruto Hashimoto, in 1912 as "struma lymphomatosa" after he found enlarged thyroids having lymphocytic infiltration.[49]

Women are more commonly affected. The female-to-male ratio is at least 7 to 10:1.[50] The incidence of Hashimoto thyroiditis increases with age, with most cases found between ages 45 and 55 years. The incidence tends to be higher in countries with a lower prevalence of iodine deficiency.[51] Hashimoto thyroiditis can occur alone, or it can occur as a part of autoimmune polyglandular syndrome (APS).[52] Some individuals with Graves disease might

transform into Hashimoto thyroiditis and vice versa. This could indicate a common pathogenesis for these disorders but different clinical presentations.[53][54][55][56]

2 GRAVES DISEASE

Introduction

Graves' disease is an autoimmune disease which primarily affects the thyroid gland. It may also affect multiple other organs including eyes and skin. It is the most common cause of hyperthyroidism.[57] In this chapter, we attempt to review different aspects of Graves' disease.

D.MALIGNANT DISORDER

Thyroid cancer

Introduction

Thyroid cancer is a malignancy of the thyroid parenchymal cells. The thyroid parenchyma consists of two major cell types, the thyroid follicular cells that give rise to differentiated thyroid cancer(DTC) and the parafollicular or C-cells that give rise to medullary thyroid carcinoma (MTC). DTC comprises papillary thyroid cancer(PTC), follicular thyroid cancer(FTC), and Hurthle cell cancer which account for 90-95% of all thyroid malignancies. MTC accounts for around 1 to 2%, and anaplastic thyroid carcinoma accounts for less than 1% of all thyroid cancers.[58]

Treatment / Management

Papillary and Follicular Thyroid Cancers

Surgical Treatment

Surgical resection remains the main treatment modality of both PTC and FTC, followed by radioiodine ablation (RAI ablation) when indicated and suppression therapy with thyroid hormone.[59][60] Systemic radiation and chemotherapy seldom play a significant role in treatment, although they may be used in advanced cases refractory to conventional methods. To minimize the risk of complications, specifically recurrent laryngeal nerve injury and hypoparathyroidism, surgery is recommended, performed by experienced, "high-volume" thyroid surgeons.[61]

Pre-operative neck ultrasound is pivotal in deciding the appropriate surgical procedure. Surgical resection can be hemithyroidectomy or total thyroidectomy, with or without lymph node dissection. The choice of surgery depends on tumor size, presence of lymph node metastasis, extra-thyroidal extension, age of the patient, and the presence or absence of co-

morbid conditions. In patients with locally advanced disease, additional imaging of the neck is advised.

A thyroid lobectomy is preferred for unilateral DTC < 1 cm, without any extra-thyroidal or lymph node invasion, unless there are clear indications for total thyroidectomy, such as childhood head and neck irradiation or a strong family history of thyroid cancer. Lately, there is also a trend for just active surveillance without immediate surgery, but more studies are needed to show the difference, if any, in the outcomes and prognosis.[62]

For tumor sizes between 1 and 4 cm with no extrathyroidal or lymphatic invasion, the procedure of choice can either be a total thyroidectomy or lobectomy, depending on patient preferences and risk factors, as described above. This decision should be made with the patient aware that a completion thyroidectomy may be necessary depending on pathology results.

For tumors > 4 cm or tumors with extra-thyroidal or lymph node invasion, a total thyroidectomy is the preferred surgical procedure as there is a high risk of multifocal carcinoma in such cancers. It is also intended to facilitate RAI ablation and future surveillance with thyroglobulin as a tumor marker.

The decision for lymph node dissection should be made on a patient-by-patient basis, and there is still a lot of controversy about the proven survival benefit of prophylactic node dissection. Regardless, all patients with proven or suspected PTC should undergo a thorough examination of both the central and lateral neck for possible nodal metastasis. The lateral neck compartments are not routinely entered in thyroidectomy and should be assessed preoperatively with ultrasound and subsequent FNAB if there is a concern for lymphatic spread. If pathologic nodes are confirmed, an ipsilateral neck dissection should be carried out, with a formal clearance of defined lymph node compartments as opposed to isolated "berry-picking" of diseased nodes. The central neck lymph nodes are difficult to assess preoperatively due to their location. A careful inspection and palpation of the central neck should be performed at the time of surgery, with subsequent compartmental neck dissection if abnormal nodes are found.

Postsurgical Risk Stratification

Postsurgical risk stratification must be performed to determine the need for additional treatment, especially with RAI ablation. The TNM (Tumor, Node, Metastasis) risk stratification by the American Joint Commission on Cancer(AJCC) predicts disease-specific mortality, while the American Thyroid Association (ATA) risk stratification system, which is widely used, helps predict the persistence or recurrence of residual cancer.[63]

The ATA system classifies patients as low, intermediate, or high risk based on clinicopathologic findings, including but not limited to tumor size, histologic type, vascular or lymph node involvement, local invasion, distant metastasis, the extent of tumor resection, post-operative thyroglobulin levels, and post-operative radioiodine uptake outside of the thyroid gland.[64][65][66]

The TNM-AJCC system accounts for factors such as the tumor size, the presence and extent of extra-thyroidal invasion, the number of nodal metastases, and whether there is the presence of distal metastasis. Age is a significant factor in predicting mortality in thyroid cancer patients, and its role is also significant in staging the disease. Patients under 55 years old at the time of diagnosis will receive a stage II diagnosis at the most.[67]

Radioiodine (RAI) Ablation Therapy

RAI therapy after thyroidectomy is used for remnant ablation of normal residual thyroid tissue, as adjuvant therapy for subclinical micrometastases, or as treatment of apparent local or distant metastasis.[68] High-risk and some selected intermediate-risk patients, per the ATA risk stratification system, will benefit from RAI ablation. Patients who are candidates for RAI therapy should maintain a low iodine diet for 1 to 2 weeks before the treatment to ensure iodine depletion of the cells; they should also be cautioned against large iodine administrations such as through iodinated contrast or amiodarone to improve the avidity of the thyroid follicular cells to iodine. RAI ablation works best when thyroid hormone has been withdrawn, with a goal thyroid-stimulating hormone (TSH) of 30mIU/liter or higher. This level of TSH can be achieved either through the withdrawal of thyroid hormones or the administration of exogenous recombinant human TSH.

Thyroid Hormone Suppression Therapy

Thyroid hormone suppression therapy to suppress TSH and thereby potentially minimize its stimulation of thyroid cancer growth is recommended in most patients after surgery. For

patients with ATA high-risk, the goal TSH should be no more than 0.1m IU/liter, and for patients in the intermediate-risk category, the goal TSH should be between 0.1 and 0.5 mIU/liter. For the ATA low-risk category, a goal TSH between 0.5 and 2.0 mIU/liter is acceptable.[69][70][71]

Persistent or Recurrent Disease

For recurrent minimal iodine-avid disease, RAI ablation is the preferred therapy. For invasive neck disease, surgical resection is recommended. Percutaneous ethanol injection[72] has been tried for cervical lymph node metastasis. For small distant metastasis to bones or lungs, radiofrequency ablation has been used. Other treatment options are external beam radiation and systemic chemotherapy.

Systemic Chemotherapy

Systemic chemotherapy is usually only considered in a group of carefully selected patients with a high metastatic disease burden or rapidly progressive metastatic disease despite the above treatment (Iodide-refractory). Because of the significant adverse effects associated with such therapy, it should be considered only when the associated benefits exceed the risks.[73]

Systemic chemotherapy for DTC is preferably administered through a clinical trial. The common agents of choice are the kinase inhibitor class of drugs such as anti-angiogenic multi-targeted kinase inhibitors (aaMKI- lenvatinib, sorafenib), BRAF kinase inhibitors (vemurafenib, dabrafenib), MEK inhibitors (trametinib, cobimetinib), NTR kinase inhibitors (larotrectinib), and RET inhibitor (selpercatinib).[74] The choice of agent depends on the occurrence of specific gene mutations or signaling irregularities such as those described above. For patients with no identifiable mutations, aaMKIs are the recommended first-line therapy.

Dynamic Risk Stratification

After the initial postsurgical risk stratification and appropriate treatment as above, patients should be re-stratified during each follow-up visit depending on their response to therapy into one of the following clinical outcomes: 1. Excellent response, 2. Biochemical incomplete response, 3. Structural incomplete response, 4. Indeterminate response.[75][76][77]

Monitoring in the first postsurgical year primarily involves a thyroid ultrasound scan every 6 to 12 months and TSH and thyroglobulin levels every 3 to 6 months, depending on risk. For

higher-risk patients, additional imaging such as CT scan, MRI, FDG-PET, or whole-body radioiodine scanning is required.

After one year, the frequency of monitoring depends on the dynamic risk stratification.

Medullary Thyroid Cancer

Surgical therapy that includes total thyroidectomy with resection of local and regional metastases is the mainstay of treatment for MTC. In most patients with confirmed MTC and no evidence of pre-operative cervical lymph node metastasis on ultrasound, prophylactic central lymph node dissection should be performed at the time of the total thyroidectomy. Patients with confirmed lateral zone nodal metastases should receive lateral compartment dissection, central neck dissection, and total thyroidectomy. Serum calcitonin, carcinoembryonic antigen, and biochemical testing for coexisting hyperparathyroidism and pheochromocytoma should be performed. Patients should be monitored long-term with serial calcitonin levels, neck ultrasound, and physical examination. Of note, as MTC is not of follicular origin, there is no role for radioiodine ablation or TSH suppression in its management.[78] For refractory MTC, systemic chemotherapy with kinase inhibitors has been shown to be beneficial. RET-specific kinase inhibitors are preferred in patients with RET mutation, while in patients negative for RET mutation, aaMKIs are the preferred drugs.

Anaplastic Thyroid Cancer

In patients diagnosed with anaplastic thyroid cancer, BRAF V600E mutation testing and staging are performed. Resectable disease is surgically removed, followed by specific BRAF kinase inhibitors in patients with BRAF V600E mutations. Other patients received targeted radiation treatment and cytotoxic chemotherapy after surgery. However, distant metastases are common in patients even at initial diagnosis due to their rapidly progressive course, and local invasion into the trachea or vasculature may occur, making it unresectable. Mortality is near 100% for these cancers, and a conservative surgical approach for palliation can be considered in such high-risk patients.

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