A Comprehensive Guide to Thyroid Cancer

Shazma Qasim[1,*], Uswa Afzal[1], Javeria[1], Brida[1], Farah Shoukat[1], Muhammad Qasim Raza[1], Nasib Ur Rehman[1], Humaira Batool[1] and Saba Inayat[1]

[1]Department of Zoology, Government College University, Faisalabad, Pakistan
*Corresponding author: shazmaqasimo@gmail.com

Abstract

Over the past few decades, the incidence for thyroid cancer has increased significantly in the United States. Thyroid cancer is a disease that results from the growth of thyroid parenchyma cell. Approximately 43 720 new cases of thyroid carcinoma are expected to be diagnosed in 2023 in the US. Recent study about pathogenesis, diagnosis, and treatment of both early-stage and advanced thyroid cancers is compiled in this chapter. All forms of thyroid cancer, papillary thyroid carcinoma (PTC) make up around 84% and anaplastic thyroid cancer about 1%. The cause of hereditary medullary thyroid cancer (MTC) is germline RET missense mutations. The treatment options for patients with thyroid cancer include the surgical removal of the entire thyroid gland (total thyroidectomy), radioactive iodine therapy and molecular-targeted therapies with tyrosine kinase inhibitors. The best-established risk factor for TC is exposure to ionizing radiation, particularly in childhood. Multi-kinase inhibitors including motesanib, sorafenib, vandetanib, sunitinib, lenvatinib, imatinib and cabozantinib have been utilized for advanced differentiated thyroid carcinoma.

Keywords: Carcinoma, Tyrosine kinase inhibitor, Thyroidectomy, Goiter, Radiation exposure, Hyperthyroidism

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Introduction

Thyroid gland is the first endocrine gland to develop in human embryos among all endocrine glands (Benvenga et al., 2018). The thyroid gland is a butterfly- shaped organ lying interiorly to the trachea, inferior the larynx in the lower neck (Braverman and Cooper, 2012). It secreted thyroid hormone, its main product, preformed essential function in human physiology. These functions involve the metabolic rate, thermo genesis, reproduction, female ovarian cycle, and lactation and in organs functioning such as heart and brain (Rothenberg et al., 2015). Thyroxin (T4), triiodothyronine (T3) and calcitonin sis hormone released by thyroid gland. The first two respectively combine various serum proteins as thyroid-binding globulin, transthyretin and albumin (Schussler, 1990).

Thyroid-stimulating hormone (thyrotropin) released by the pituitary gland and regulates the thyroid growth and function from fetal development to maturity (Maenhaut et al., 2015). The abnormal and uncontrollable cell growth in the tissue of thyroid gland is known as thyroid cancer. These cells can be metastasized and spread in other parts of the body such as lymph node, lungs, liver, bone and brain. National Cancer Institute updates the prevalence of thyroid cancer has grown by 5.5% annually on average over the last ten years between 2002 to 2011, the death rate rose by 0.8% yearly (NCI, 2015). In 2015 thyroid cancer is the 5th common cancer in women in USA and roundabout 62000 cases occurred in both male and female (Cabanillas et al., 2016).

In United States is the third most common cancer in women by 2019, with the annual cost of $19–21 billion and it will predict the fourth cancer diagnosis by 2030 (Aschebrook-Kilfoy et al., 2015; Nettore et al., 2018). Nearly 43720 new cases of thyroid carcinoma are possible to be diagnosed in 2023 in US (Boucai et al., 2024). Thyroid gland is one and only source of thyroid hormone. The oxidative stress, radiation exposure in early ages, hereditary reasons including positive family history, hyperthyroidism, iodine deficiency, abstinence from alcohol and smoking consumption are the common factors of thyroid cancer (Iqbal et al., 2021). The objective of this chapter is to provide a comprehensive overview of thyroid cancer, including its pathogenesis, clinical presentation, diagnostic modalities, risk factors, treatment options, and current management strategies. It aims to integrate current research findings to aid students, clinicians, and researchers in understanding both early-stage and advanced thyroid cancers.

Symptoms and Diagnosis

During the early stages thyroid cancer doesn't show the signs but as it grows gives physical appearance like difficulty in swallowing, shortness of breathing, formation of goiter due to iodine deficiency, pain in neck and throat, swollen lymph node in neck and changes in voice (hoarseness) as shown in Figure 1 (Neff et al., 2008).

Diagnosis

An initial and accurate diagnosis of thyroid cancer is essential for effective treatment and improving patient health. Diagnosis begins with

the clinical evolution like patient history, physical examination, thyroid nodule and irregular secretion of thyroid hormone etc. The diagnosis of thyroid cancer depends on its type, tumor size, metastasis rate and patient's age. Disturbance factors in diagnosis consist of large tumor size, extra-thyroidal extensions or metastases, older age and unfavorable tumor types such as undifferentiated cancer (Table 1) (Lee et al., 2023).

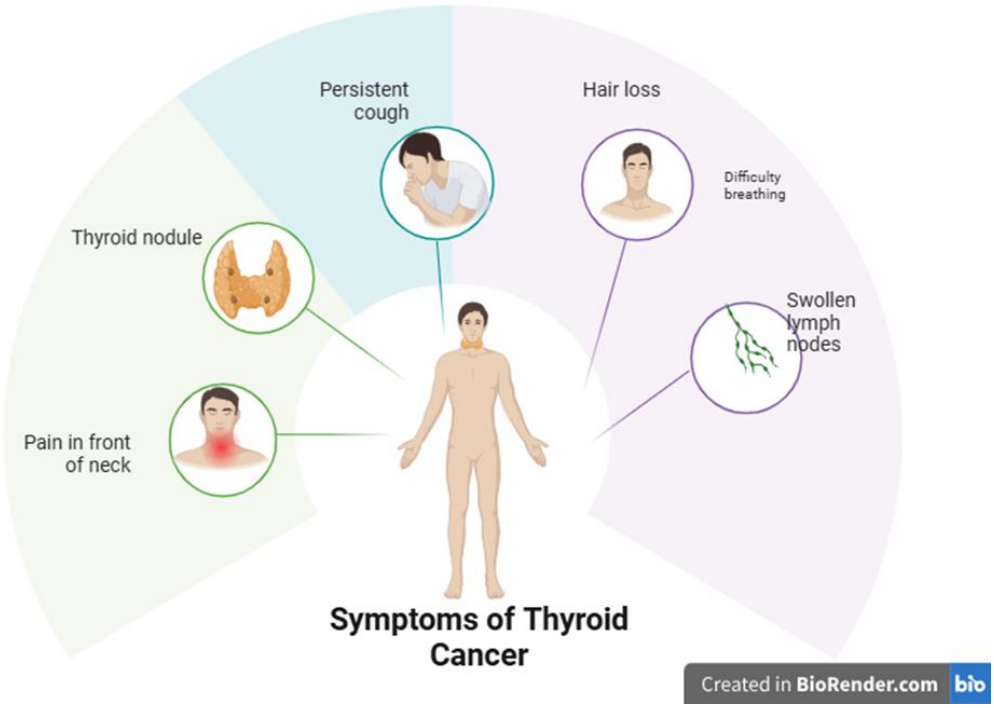

Fig. 1: Symptoms of thyroid cancer

Table 1: Techniques, purpose and features of thyroid cancer

Techniques	Purpose and Features	Citation
Physical examination	Determine the patient history and physical examination for the presence of thyroid nodule.	(Nikiforov et al., 2013)
Serum TSH measurement	Separation of functional and dysfunctional nodules is identified by TSH level.	(Cooper et al., 2009)
Laboratory investigation	Includes TSH, Free T4 and T3.	(Filetti et al., 2006)
Neck ultrasound	Perform for the confirmation of suspected nodule size and existence.	
Thyroid scan	Determine either the nodule is hyperfunctioning (hot), isofunctioning (warm) or nonfunctioning (cold).	(Lee et al., 2023)
Fine -needle aspiration	Use to assess the malignancy risk in nodules >1cm.	(Nikiforov et al., 2013)

Types of Thyroid Cancer

There are four types of thyroid cancer, Papillary, Follicular, Medullary and Anaplastic thyroid cancer (ATC).

Papillary Thyroid Cancer

PTC is the most common type of thyroid cancer that accounts for 89.1% of all TC (Megwalu and Moon, 2022). Annually, twenty thousand new cases of cancer were detected in the US. PTC occurs in any year; it has a double peak pattern with the first peak at 25 to 30 and the second peak at 55 to 60 years. Forty-four is the intermediate detecting age (Sosa and Udelsman, 2006).

Anaplastic Thyroid Cancer

It is a rare form of thyroid cancer, and it accounts for 1-2% of all cases. With no effective psychotherapy it is usually lethal to older adults. The viability is less than 6 months from the time of diagnosis and, regrettable, this outcome is not essentially altered by convenient treatments (Neff et al., 2008). ATC is responsible for 1.7% of all thyroid cancer, while geographically the occurrence ranges from 1.3% to 9.8% in the United State (Sallmridge and Copland, 2010).

Medullary Thyroid Cancer

Medullary thyroid cancer accounts for 3-4 % of all TC (Hundahl et al., 2000). The clinical course of medullary thyroid cancer can be assertive; they cannot change for years and associated with the death of lots of peoples. Although the overall cases of medullary thyroid cancer are sporadic, more or less 20 are hereditary by the reason of germline mutation (Pelizzo et al., 2023).

Follicular Thyroid Cancer

Follicular Thyroid cancer is the second prevalent type of thyroid cancer. Its amount may decisive from the dietary iodine content. The neoplastic papillae have a central core of fibrous material covered by one or more layers of cells with compacted oval nuclei. Death rate of follicular thyroid cancer is second highest (Sun et al., 2022).

Risk Factors of Thyroid Cancer

Environmental Pollutants

The industrialize food, including nitrate from cured meat and few vegetables, can compete with iodine uptake and can cause thyroid cancer (Pellegriti et al., 2013). Recent studied shown that the nitrate levels in drinking water sources are also related with high risk of thyroid cancer (Cherrat et al., 2014).

Obesity

Obesity rates can increase the thyroid cancer incidence in recent decades and well-known risk factor of TC (Simard et al., 2012). Goodman et al. determined that the highest correlation to the least categories of weight enhanced the risk for TC within at least five times for males and more than twice for females (Goodman et al., 1992).

Radiation

Particularly in childhood, the IR exposure, especially in the head and neck region, extensively increase risk of TC. Therefore, one way to lessen thyroid cancer is to avoid the ionization radiation (Dal Maso et al., 2009). A dose- response association has been reported during childhood. The Gray1 dose is about 7 times the risk of thyroid cancer and linear- dose risk has been seemed to be at least Gray2. The thyroid cancer risk is aspect to the radiation is about 3 times higher than in areas with iodine deficiency (Cardis et al., 2005; Ron et al., 1995).

Iodine

Iodine is the trace element that is important in the synthesis of thyroid hormone. Iodine deficiency may produce begin illness and extreme intake affects thyroid function (Dal Maso et al., 2009). Iodine deficiencies affect the thyroid function and decrease the thyroid hormone levels and then increase TSH secretion which can lead to hypothyroidism (Horn- Ross et al., 2001).

Treatment

The treatment procedures of thyroid cancer involve surgery, radioactive iodine therapy (RIT) and the enzymatic actions i.e. tyrosine kinase inhibitor in case of molecular targeted therapy. Kind and level of thyroid carcinoma verify the common therapy option (Nguyen et al., 2015).

Surgery

Total thyroidectomy is advised when the underlying malignancy is between 1.0 and 2.0 cm in size for the treatment of thyroid cancer (Nguyen et al., 2015). Total thyroidectomy decreases return rates and improves survival for PTC ≥1.0 cm compared to lobectomy (Bilimoria et al., 2007). Hemostatic vascular closure devices and neuro-monitoring are two examples of advancements in total thyroidectomy equipment that have increased surgery safety and tissue removal efficacy in cancer patients (Rudolph et al., 2014).

Recurrent laryngeal neural damage (5%–11%) and hypocalcaemia (20%–30%) are the two causes of early postoperative issues followed thyroidectomy. The threat of postoperative hypocalcaemia is increased by the following factor: Appearance of large goiters, later stage of thyroid cancer, Graves's disease that results in a complex dissection of lymph nodes, the upper parathyroid glands' venous drainage, the parathyroid glands' location and difficulty in determining it, ongoing cervical region exploration that causes adhesions, young age and female sex. Six to twenty-four hours after surgery, the levels of calcium and parathyroid hormone are examined. Oral calcitriol is also added to patients with low parathyroid hormone levels in order to optimize calcium absorption (Christou and Mathonnet, 2013).

Radioactive Iodine Treatment

Iodine-131 has been a key component of thyroid cancer treatment and medicine since 1946 (Wartofsky and Van Nostrand, 2012). By entering the thyroid cells using sodium iodide transporters and producing short-wavelength beta rays, 131I causes abrupt cell death (Luster et al., 2008; Wartofsky and Van Nostrand, 2012). For nonsurgical or partly resectable thyroid cancers, that involve microscopic or metastatic disease.131I therapy remains as being the usual method of therapy. A patient should be initiated on 131I therapy shortly after several aspects are taken into consideration. During surgery, radioactive iodine is delivered directly as I131 that has a half-life of 7 to 8 days (Cooper et al., 2009; Tuttle, 2014; Mazzaferri and Kloos, 2000).

TSH concentration should be at least 30 mU/L, that stimulates intracellular uptake of isotope. This rise in TSH levels may be obtained in several ways. With the typical method, the patient will cease using thyroid hormone replacement for up to six weeks (Sawka et al., 2004).

Recombinant human TSH (rhTSH) administration is the latest method. Radioactive iodine takes place on the third day in rhTSH is applied as intramuscular injections on the first two days. One advantage of this therapy is that, in contrast with hormone withdrawal, the patient does not suffer from hypothyroidism for a prolonged period of duration (Ma et al., 2010; Klubo-Gwiezdzinska et al., 2012). The common problems facing during radioiodine include dryness and pain in oral cavity, salivary gland puffiness, altered taste, conjunctivitis and tiredness (Mazzaferri et al., 2000; Mandel and Mandel 2003; Almeida et al., 2011).

Thyroxine Suppression

Thyroid stimulating hormone increases the growth of thyroid follicular cells, iodine consumption and the production and elimination of thymoglobulin, thyroxine (T4) and 3,5,30 -L-triiodothyronine (T3) through its G-protein coupled receptor (TSHR). According to retrospective research, giving patients T4 doses that lower the level of circulating TSH during the initial stages of surgery and radioiodine treatment lowers the threat of cancer repetition and disease-specific death (Sawka et al., 2008). TSHR is expressed by thyroid cancer cells. Conversely, a prospective non-randomized investigation shows that reduced TSH suppression is an independent predictor of illness progression in people at high risk of disease recurrence (Cooper et al., 1998). TSH suppression can have several negative effects, especially on cardiovascular and skeletal systems, but its effects are questionable in the majority of low-risk individuals after first treatment (Biondi and Wartofsky, 2014).

External Beam Radiation

External-beam radiation can occasionally be used to treat thyroid carcinoma, while 131I is the chosen adjuvant therapy designed for the disease. Tumors that tend to be persistent, frequent, anaplastic, or poorly differentiated can never remain in 131I. Since ATCs frequently cannot be entirely eliminate and not focus on iodine, external-beam radiation is literally always used in their treatment, mostly EBRT used for PDT (Poorly Differentiated Tumor) to minimize the risk of reoccurrence despite currently has never been evidence of any improvement in overall survival (Brierley and Tsang., 1999; Ma et al., 2010). External-beam radiation may be valuable in patients with regional recurrence in a previously operated field, unrespectable disease, and incompletely removed tumors (Patel and Shaha, 2006; Brierley and Tsang., 1999).

Chemotherapy and Molecular Targeted Therapies

Generally cytotoxic chemo has not been investigated for metastatic TC as radioactive iodine often succeeds well for treat well-differentiated tumors that have expanded. For individuals with disease burden, chemo becomes a crucial part of treatment after surgery if it is poorly DT (Xing et al., 2005).

Thyroid cancer remains the most frequent endocrine cancer, and its incidence is still rising. While there is presently no viable systemic treatment for medullary or iodine-refractory differentiated thyroid cancer, recent research into the path physiology of the conditions have identified key targets that are currently being studied in the clinic (Perez et al., 2012).

Many new agents have shown encouraging results. By eliciting clinical responses and stabilizing the disease process, tyrosine kinase inhibitors, such as Sorafenib, lenvatinib, vandetanib, and cabozantinib, show to be the most effective of the medications examined (Wells et al., 2010).

Tyrosine Kinase Inhibitors (TKI)

TK signaling pathways, that include the RAF, RAS or RET protein kinase genes, have been responsible for many genetic variations that activated the tyrosine kinase domain (Smit et al., 2010; Ouyang et al., 2006). Drug as target these pathways can be significant in minimizing the disease's progression. Thyroid-derived carcinomas frequently display an excessive expression of VEGF along with various growth factors, particularly when mutations in BRAF are prominent (Cabanillas et al., 2010).

Sorafenib

Sorafenib has been approved as first TKI in November 2013 by FDA to treat progressive metastatic DTC that was resistant to RAI therapy. RET, FLT, c-kit, VEGFR 1-3 and PDGFR are targets of sorafenib. Four hundred seventeen patients were involved in progressive DTC during the DECISION trail, that area phase-III, multicenter (MC), double-blind (DB), placebo-controlled trial that fail to response to regular treatment, is the basis of the approval (Brose et al., 2014).

Compared to the placebo (5.8 months), sorafenib was related to a noticeably higher mean progression-free survival of 10.8 months. Most frequently adverse effects exhibited by patients with sorafenib were rash, gastrointestinal and dermal reaction (Brose et al., 2014; Dawkins and Webster, 2019).

Lenvatinib

Lenvatinib targets EGFR, VEGFR2, RET, VEGFR3, KIT, and PDGFR. It was licensed in February 2015 which is used in progressive DTC treatment. It is RAI based SELECT trail which is a P III, DB, MC research which is conducted on two hundred sixty one patients that have progressive DTC second TKI. A long-term median PFS of 18.3 months vs. t 3.6 months in the placebo group were associated with lenvatinib. Six patients were using lenvatinib out of 20 which died as TKIs because deadly tachyarrhythmia's and prolong the QT interval. Adverse responses resulted in dose reductions and, in 18% of cases, termination of lenvatinib treatment in 68% of patients (Al-Jundi et al., 2020).

Vandetanib

The FDA approved vandetanib in 2011 to treat patients with medullary thyroid carcinoma that is symptomatic or advancing, incurable, locally evolved, or metastatic. Vandetanib targets the EGFR, VEGF and RET receptors. The first drug to be approved for this signal was based on information from phase 3 ZETA research (Sandor at el., 2002). Vandetanib significantly increased progression-free survival in the study as compared to a placebo (0.46; 95% CI hazard ratio [HR]0.31-0.69; belief (P<.007)). In the randomized phase, the median length of vandetanib and placebo treatment was 39.9 weeks and 90.1 weeks, respectively (Wells at el., 2012).

Cabozantinib

The FDA authorized cabozantinib, a TKI, in 2012; it has the same suggestion for the findings of EXAM trail as vandetanib. This medication is a TKI that target three possible pathways in MTC. Various studies demonstrated that cabozantinib increased progression-free survival to 11.2 months (HR, 0.28; 95% CI, 0.19-0.4; P<.001) compared to 4 months for a placebo. Hand-foot syndrome, diarrhea, weariness, and hypertension were the major grade 3 or 4 unfavorable effects at cabotinib (Elisei at el., 2013).

Management of Thyroid Cancer

Radiation Safety

High-energy gamma rays, or photons, are the primary source of radiation exposure to patients receiving 131I radiation. A person's exposure to radiation from a treated patient will be affected from three variables: the patient's retained radioactivity, the distance from the patient and duration of exposure. Patients of thyroid cancer who are hypothyroid or euthyroid at the time of treatment (Hanscheidet al., 2006) and patients who are hyperthyroid will receive substantially various cumulative external exposures from a given activity of 131I (Reinhardt et al., 2002).

Radiation safety is based on two main principles: following the law and using good medical practices. The NRC advice, 131I therapy for thyroid disease can be performed by identifying the individual's requirements and giving advice on reducing the radiation exposure through appropriate and patient-specific precautions. Patients' evaluations of the adherence to precautions are regarded as routine reassessments of programs and procedures (Vigário et al., 2014).

Dietary Protocol

It has been investigated that lowering the metabolic rate causes hyperthyroidism due to decline in physical activities and increase in dietary energy load at same time in a patient may result in obesity. Most bodily tissues perform poorer when energy is converted incorrectly, and metabolism, especially glucose metabolism, is disrupted (Tuchendler et al., 2009).

According to the results of the Polish study conducted between 2001 and 2010, approximately 27% of HT participants had a documented case of diabetes, and over 17% of HT subjects had either impaired glucose tolerance or a fasting blood glucose level (Gierach et al., 2012). The main treatment for (Hashimoto's thyroiditis) HT is medical management with thyroid hormone replacement (Biondi and Cooper, 2008; Ruchala et al., 2015).

Since dietary micronutrients contribute to the synthesis of thyroid hormones, nutrition can aid in the treatment of thyroid disorders and diet has an undeniable effect on thyroid function (Krysiak et al., 2019; Liontiris et al., 2017; Wojtas et al., 2019). The roles of gluten, vitamin D, selenium, and iodine in the diets of patients with HT. HT patients were thought to benefit from a gluten-free diet regardless of whether they also had celiac disease (Krysiak et al., 2019; Liontiris et al., 2017; Wojtas et al., 2019; Szostak-Węgierek et al., 2018).

Conclusion

In the United States, it is expected that 43,720 new cases of thyroid cancer are identified in 2023. Relative survival after five years is nearly 98.5%. Current research on the pathogenesis, diagnosis, and treatment of both early-stage and advanced thyroid carcinoma is compiled in this chapter.

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