Evaluating the diagnosis and treatment of thyroid cancer

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Abstract
The most common endocrine disease worldwide is still thyroid cancer (TC). Papillary (PTC), follicular (FTC), medullary (MTC), and anaplastic thyroid carcinoma (ATC) are the main histological types of TC; each has a distinct clinical and molecular profile. TC is more common in women, and regrettably, it has been rising over the past few years. However, new advancements in immunotherapy and targeted medications, like as PD-1 inhibitors and tyrosine kinase inhibitors (e.g., lenvatinib, sorafenib), have revolutionised the treatment of advanced or aggressive TC types. The diagnostic procedure uses imaging, molecular testing, and fine-needle aspiration biopsies, for example; looking for mutations that could influence prognosis and offer the best course of treatment. The current standard of care for TC includes chemotherapy, immunotherapy, radioactive iodine therapy (RAI), surgery (such as a total thyroidectomy), and molecularly targeted medicines. Improved diagnostic accuracy and customised treatment plans based on the genetic profile and tumour subtype are necessary to optimise patient outcomes. Understanding the complicated aetiology of TC and the evolving treatment landscape is essential to improving survival and quality of life.

Introduction
Thyroid carcinoma (TC) is still the most common endocrinological cancer worldwide, with a startlingly high incidence rate in recent years [1,2]. This is because there is a greater understanding of this malignancy, a comprehensive diagnostic that enables the early detection of less common clinical symptoms, and the fact that it is getting more prevalent because of environmental risks and a constantly changing world. Recent research has highlighted exposure to radiation, heavy metals, air pollution, and the increasing usage of environmental chemicals as potential risk factors for TC [3,4,5,6,7]. Exposure to the aforementioned causes is a growing worldwide issue that may lead to an increase in the incidence of TC and other endocrinological disorders and cancers. 91% of new cases of TC occur in nations with a high or very high Human Development Index (HDI), which is linked to an increase in the TC occurrence rate [8]. We sought to provide an overview of the most recent information on TC in the narrative review that follows, including details on its epidemiology and changes in trends, causes, prognostic and diagnostic factors, classification, and—above all—the most recent developments in TC treatment strategies and innovative therapeutic approaches.

Epidemiology of Thyroid Cancer
As of right now, TC is the seventh most common cancer in the world, and its death rate is the 24th highest of all malignancies [9]. Females are three times more likely than males to have TC; the more aggressive histologic subtypes are equally common in both sexes, whereas the less aggressive subtypes are more common in females [10]. Compared to other adult cancers, TC is typically discovered at a younger age;

the average age at diagnosis is 51 age. [11]. The clinicopathological signs of TC vary according to the patient's age; for example, younger patients are more likely to exhibit neurovascular, capsular, or lymph node metastases, suggesting that the disease typically progresses more aggressively in younger people [12]. Additionally, TC is half as common in black people as in white people. The current ranking of TC incidence rates is as follows: white people have the highest prevalence, followed by Asians and Pacific Islanders, American Indians and Alaskan natives, and black people [13]. In general, non-Hispanic males and females are more likely than Hispanic males and females to experience TC [13]. Between 1992 and 2018, the incidence of TC rose by more than 200%, although the fatality rate stayed constant [14]. The majority of countries had a rise in the incidence rate of TC; this increase was particularly pronounced in younger people, but rates usually rose across all age categories [15]. According to the epidemiological picture based on the GLOBOCAN database, the mortality rate of TC is less than 1 per 100,000 for both genders in the majority of the nations under investigation; South Korea was found to have the highest incidence-to-mortality-rate ratio for both sexes [16]. Additionally, it was observed that the mortality rates in high-HDI nations and low- and medium-HDI countries do not differ significantly [16].

Thyroid Cancer Classification

1. Thyroid Papillary Cancer

Nearly 90% of all occurrences of thyroid cancer are papillary thyroid cancer (also known as papillary thyroid carcinoma, or PTC) [17,18]. PTC accounts for over 90% of TC in children, despite being the most frequent paediatric thyroid cancer [19]. The peak of its most likely incidence is seen to occur between the ages of 30 and 50, despite the fact that it is the most common type of TC and can occur in any age group [20].

Tall cell variant (TCV), diffuse sclerosing variant (DSV), columnar cell variant (CCV), hobnail variant (HV), and solid variant (SV) are some of the aggressive variations of PTC [21]. About 70% of patients have this kind of metastasis, which typically spreads to the neck's lymph nodes (mostly the pretracheal and paratracheal lymph nodes) [22]. However, it should be noted that in the case of PTC, the presence of lymph node metastases is not linked to a greater mortality rate, despite the fact that malignant dissemination via lymph nodes may be associated with a worse recovery and a higher risk of recurrence [23,24]. Metastases are thought to occur in only 10% of PTC patients when the disease first manifests [25]. Although distant metastases are uncommon in PTC, they most frequently occur in the brain, liver, lungs, and bones [26]. A poor prognosis for PTC is linked to a number of factors, but the most common ones are older age at diagnosis (patients over 55), extrathyroidal growth and distant metastases, large tumour size, male sex, aggressive subtypes of PTC, aneuploid cell population, vascular invasion, and solid and less differentiated areas [27,28].

2. Thyroid Cancer with Follicles

About 20% of all occurrences of thyroid cancer are follicular thyroid carcinoma (FTC), the second most frequent cancer of the thyroid gland [36]. FTC is thought to be responsible for 10% of thyroid cancers in iodine-sufficient regions and 25–40% in iodine-deficient regions [29, 30]. Like PTC, this kind of cancer is more common in women, with a female-to-male ratio of 3:1; the peak onset age is between 40 and 60 years old, and the mean age at diagnosis is estimated to be 60 years old [31, 32, 33]. About 80% of FTC cases are thought to have moderate symptoms and a favourable prognosis, while the other 20% exhibit aggressive behaviour [33]. It has been found that the size of the tumour affects the prognosis of FTC, with carcinomas less than 1.5 cm showing a favourable prognosis [34]. There are three subtypes of FTC: broadly invasive, encapsulated angioinvasive, and minimally invasive [35]. Hurthle cell carcinoma, another subtype of FTC that was previously identified, is now categorised by the World Health Organization as a distinct kind of thyroid cancer [35]. Although younger individuals are more frequently diagnosed with minimally invasive FTC, it is important to remember that this variety has also been found to be a likely forerunner of more aggressive forms [37]. Vascular invasion and extension outside of the thyroid gland are the main characteristics of invasive follicular carcinoma [38, 39]. When compared to other thyroid cancers, FTC progresses more slowly [40,41,42,43]. About 20% of follicular adenomas that are not functional may have oncogenic alterations that eventually cause FTC [44]. However, it is important to remember that cytologic characteristics alone cannot differentiate FTC from follicular thyroid adenoma [45]. Although distant metastases are less common in FTC than in PTC, they are more frequently seen in this kind of carcinoma [46,47,48]. FTC is more aggressive than PTC and tends to metastasise considerably more frequently. Distant metastases, which are most frequently found in the lungs, followed by the bones, liver, brain, and skin, may occur in 6–20% of FTC patients [49,50]. When it comes to FTC, elderly patients have a higher chance of metastases [47]. Vascular invasion is a hallmark

of FTC, while lymph node metastasis is uncommon [51]. Less than 10% of patients are thought to have lymph node metastases [52,53]. 3.3. Thyroid Cancer in the Medullary

The thyroid parafollicular C cells that produce calcitonin are the source of medullary thyroid cancer (MTC), a relatively uncommon neuroendocrine disease [54]. This cancer, which makes up 1–5% of all TC cases, can develop on its own or as a component of a number of genetic disorders, such as familial medullary thyroid cancer (FMTC) and multiple endocrine neoplasia (MEN) types 2A and 2B [55]. Approximately 25% of MTCs are linked to MEN2 syndrome, but the majority of MTCs are sporadic [56]. While the hereditary form of MTC is equally common regardless of gender, sporadic MTC has been found to be more common in females [57]. MTC is thought to be the least prevalent of all TCs, making up less than 5% of all thyroid cancers.[58]. Spontaneous MTC peaks between 40 and 60 years of age, with a mean age of 50; cases of MTC linked to hereditary disorders show different patterns [59]. While this cancer typically manifests in the second to fourth decade when it is a component of FMTC, MTC linked with either MEN2A or MEN2B may manifest in early childhood [60,61,62,63,64,65]. Prophylactic surgery may be carried out to stop the beginning of MTC in patients who have a family history of MTC and/or MEN2 and test positive for the RET gene mutation [66]. Due to delayed detection and a higher likelihood of metastasis than other thyroid cancers, MTC has a somewhat poor prognosis [55]. Furthermore, due to a higher prevalence of distant metastases and a higher risk of local recurrence, high-grade tumours have lower overall survival rates than low-grade carcinomas. Distant metastases of medullary thyroid cancer can arise in the brain, liver, lungs, or bones in addition to lymph nodes [67].

3. Thyroid Cancer Anaplastic

An extremely uncommon but extremely aggressive type of undifferentiated thyroid cancer is called anaplastic thyroid carcinoma (ATC). About 2% of all TCs are caused by this thyroid cancer [68]. ATC is responsible for over 50% of mortality related to thyroid cancers, although being extremely rare [69]. Females are more likely to receive an ATC diagnosis, and individuals over 65 are typically affected by this form of cancer [70,71]. There is still much to learn about the aetiology of ATC. Since the majority of these tumours develop in the context of a persistent goitre, it is thought that the development of these malignancies may be linked to an undetected differentiated TC [72,73]. Metastases to distant regions of the body are thought to occur in 20–50% of ATC patients, with the brain, lungs, and bones being the most prevalent sites [74,75,76]. Less than 20% of patients are still alive a year after receiving an ATC diagnosis, with an average survival rate of five to six months [77,78]. Younger patients, tumours less than 6 cm, unilateral tumours, and the absence of distant metastases and lymph nodes are factors that may help improve the prognosis [79].

4. Thyroid Cancer Risk Factors and Causes

One of the most prevalent cancers, TC, can result from a variety of causes. These can be classified as either modifiable or unmodifiable [80]. Obesity, smoking and secondhand smoke (SHS), heavy alcohol use, inactivity, and high radiation exposure are all changeable variables. Sex, genetic factors such inherited genetic disorders or gene mutations, and preexisting benign thyroid illness can all be considered unmodifiable factors [81].

5. Adaptable Elements

Obesity (5.1)

Unquestionably, obesity is a risk factor for a number of illnesses, including cancer. It might be emphasised as one of the main causes of TC [82,83]. A body mass index (BMI) of 25.0–29.9 is linked to a higher risk of thyroid cancer than a lower BMI, regardless of gender. Numerous factors, such as immunological dysfunction, oxidative stress, increased thyroid-stimulating hormone (TSH), insulin, and chronic inflammation, may link obesity to thyroid cancer. resistance, elevated aromatase activity, and adipokines. Reactive oxygen species can be produced, cell division can be accelerated, and tumour suppression can be compromised by persistent low-grade inflammation. Increased TSH levels may promote the growth of thyroid cells, genetic alterations, you can see below (figure 1.)

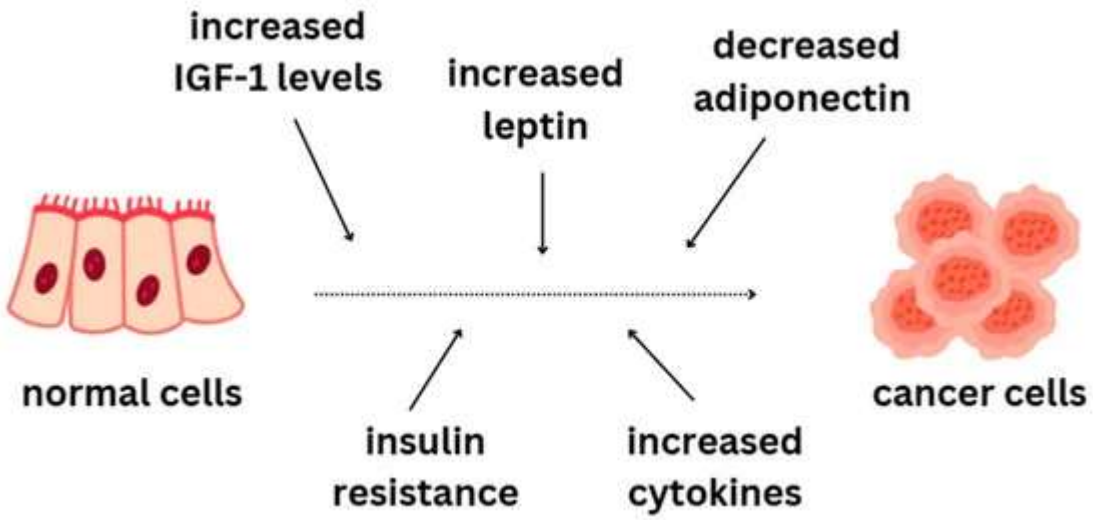

Figure 1. Molecular obesity mechanisms associated with thyroid cancer.

5.2. Secondhand smoke and smoking

SHS and cigarette smoking have been linked to TC and are known risk factors for numerous illnesses. Hours-long inflammatory reactions are triggered by even a little amount of SHS exposure [84]. Toxic substances such thiocyanate, which interferes with the production of thyroid hormones,

5.3. Drinking Alcohol

Contrary to popular opinion, current research indicates a negative correlation between alcohol use and the incidence of TC [85]. It has been observed that smoking, SHS, and light to severe alcohol intake have a submultiplicative effect on TC [86]. Alcohol's protective effects may be caused by changes in thyroid hormone metabolism, disruptions in thyroid gland function, as well as dysregulation of the hypothalamic-pituitary-thyroid axis [87].

5.4. Insufficient Exercise

While regular activity successfully lowers the chance of acquiring cancer, there is substantial scientific evidence that obesity and physical inactivity both independently increase the risk of many malignancies [88]. Long non-coding RNAs (lncRNAs) may play a significant role as molecular mediators between physical activity and cancer prevention, according to recent research. It has been demonstrated that regular exercise modifies the expression of several lncRNAs, which are generally elevated in cancer.

5.5. Radiation Exposure at High Levels

In the past, only certain groups were exposed to high radiation levels. Today, a new, persistent source of radiofrequency (RF) radiation has been introduced by the widespread usage of mobile phones. Recent research links cell phone RF exposure to a higher risk of TC [89,90].

6. Unchangeable Elements

6.1. Sex

The incidence of thyroid cancer is much higher in women than in men; this difference is believed to be caused by oestrogen exposure and reproductive activity. By modifying thyroxine-binding globulin (TBG) levels, changing the availability of free thyroxine, and inducing TSH secretion, variations in oestrogen levels throughout the menstrual cycle impact circulating TSH concentrations. By encouraging cell division, causing DNA damage, and regulating stress reactions, oestrogens have an impact on TC development.

6.2. Genetic Variables

A population-based analysis from 2021 reveals trends in TC prevalence worldwide. It displays a variety of patterns among distinct subtypes. PTC has experienced the biggest increase, particularly in wealthy and developing nations, primarily as a result of improved detection through sophisticated imaging. Other subtypes, such as FTCs and MTCs, have not shown any discernible temporal trends and have stayed rather steady. Fortunately, the incidence rates of ATC, the rarest and most aggressive form, have been

declining in most areas. These increases have been mostly attributed to overdiagnosis, especially of PTC, which has prompted demands for more cautious screening and diagnosis methods [91].

6.3. Genes

6.3.1. Thyroid Papillary Cancer

Regardless of age, PTC is the most prevalent thyroid cancer in the world. Over time, its diagnostic standards have changed. Along with environmental factors like obesity, radiation exposure is a known risk factor [92].

6.3.2. Cancer of the Medullary Thyroid

Three to five percent of thyroid cancers are MTC, an uncommon neuroendocrine tumour. A sizable percentage of TC-related deaths are caused by MTC, despite its low prevalence. It can happen occasionally or as a component of genetic disorders such as FMTC and multiple endocrine neoplasia type 2 (MEN2). Carcinoembryonic antigen (CEA) and calcitonin are important markers for MTC diagnosis and prognosis [93,94]. The development of MTC is significantly influenced by mutations in the RET proto-oncogene, which are divided into somatic and germline mutations. A receptor tyrosine kinase involved in cell survival, proliferation, and differentiation is encoded by the RET gene.

6.3.3. Thyroid Cancer with Follicles

The second most common kind of differentiated TC is FTC. It comes from follicular cells, which are in charge of making and releasing thyroid hormones. FTC usually manifests in the fifth and sixth decades of life and is more prevalent in women. Iodine deficiency, age above 50, and female sex are risk factors for FTC [31].

6.3.4. Thyroid Cancer Anaplastic

ATC is a very aggressive tumour with poor survival rates, accounting for 5–10% of TCs. Thirty to forty percent of cases have distant metastases at the time of diagnosis. It shows a varied cellular structure and a total loss of follicular differentiation when examined under a microscope. ATC is often associated with coexisting.

6.3.5. Benign Thyroid Disease Preexisting

TC is more common in people with a history of benign thyroid conditions, such as goitre and hyperthyroidism. Chronic changes in TSH levels, which may encourage aberrant thyroid cell proliferation, are probably the mechanism behind this connection. Furthermore, research has demonstrated that a family history of benign thyroid disorders increases the risk of TC, suggesting a possible genetic connection [95].

7. Thyroid cancer symptoms and diagnosis

The symptoms of thyroid carcinoma (TC) can vary greatly. More than half of participants in studies on the discomfort, anxiety, and depression of people with advanced TC report experiencing a variety of symptoms, with sleep difficulties, exhaustion, and emotional distress being the most common and severe. Furthermore, the tumor's interaction with the parathyroid gland and recurrent laryngeal nerve is usually the cause of symptoms including hoarseness, numbness, and a prominent lump in the thyroid area. Depression and anxiety symptoms are reported by more than 30% of patients [96].

However, an enlarged thyroid, which may be structurally aberrant, is frequently discovered by accident—typically after a neck or chest X-ray taken for purposes unrelated to thyroid cancers. About half of thyroid cancer cases are found by accident, especially in people who don't have any symptoms. Small papillary thyroid cancers (PTCs) are frequently involved in these. Furthermore, when thyroid glands are removed for benign illnesses, TC is often detected histologically, unintentionally exposing tiny tumours [97]. TC is usually diagnosed by a combination of fine-needle aspiration biopsy (FNAB), imaging techniques (such as ultrasound), and physical examination. The kind and extent of the malignancy are ascertained by further testing, such as radioactive iodine scans and molecular markers [98]. Gland enlargement, which can be identified during routine examinations, is caused by the aberrant and ongoing proliferation of malignant cells within the thyroid. If the growth is small and asymptomatic, the patient might not notice the enlarged thyroid, but if it causes discomfort or makes swallowing difficult, it might be obvious [134]. During a physical examination, the existence of visible nodules or an enlarged gland may indicate a rise in the number of malignant cells. Palpation-identified alarm signs frequently result in additional

diagnostic testing, such as neck ultrasonography and blood TSH levels. Microcalcifications, neovascularisation, disorganised internal vascularity, uneven edges, and a taller-than-wide form are concerning ultrasonography findings that could lead to a biopsy [99].

Diagnostic Markers of Thyroid Cancer

Because they enable early disease detection, which is essential for efficient treatment and a better prognosis, diagnostic markers are crucial in the diagnosis of TC. Precise diagnosis is made possible by the identification of pertinent markers, which affects therapy choice and progress monitoring.

1.Thyroglobulin

Thyroglobulin (TG), a crucial substrate for the synthesis of thyroid hormone, is a significant tumour marker for DTCs, and over 90% of DTCs are PTCs [100]. TG, a 330 kD, 2750 amino acid protein made by the thyroid's follicular epithelial cells [102], is normally synthesised by differentiated thyroid cells [101]. Thyroid follicular cells and follicular lumens are the main locations for these cells [103]. Thyroid tumours that start in follicular epithelial cells may have greater circulating levels of TG due to autoantibodies to the TSH receptor [103]. TG is used to follow residual disease and identify recurrent disease, highlighting the importance of vigilant monitoring [101].

In patients with ambiguous cytology, preoperative serum TG levels may be able to distinguish between benign and malignant thyroid nodules [104]. Serum TG levels should be measured using validated immunoassays calibrated against authorised reference materials. TG test laboratories are required to follow approved national or international quality assurance programs [105]. Both benign and well-differentiated malignant thyroid tissue are known to secrete Tg [106]. In fact, the presence of anti-TG antibodies (TgAb) may affect TG test results, and the presence of normal thyroid remnants reduces the utility of TG [107]. A study found that preoperative TG levels greater than 1.39 ng/mL are significantly associated with an increased risk of distant metastases in PCT [108]. Serum TG levels may be linked to HbA1c levels in people with diabetes and TC; this relationship is more pronounced in those with changing TG levels, which calls for more research [109]. This correlation emphasises the necessity of closely observing and clarifying the intricate connections between TC and other metabolic diseases.

2.Calcitonin

MTC is an aggressive neuroendocrine tumour that arises from thyroid parafollicular cells and releases the neurotransmitter calcitonin gene-related peptide (CGRP). It often has a bad prognosis [110]. Aberrant dendritic cell (DC) development in MTC is associated with CGRP expression [111]. One of the main characteristics of MTC is known to be calcitonin (Ctn) secretion [113]. C-cell hyperplasia, autoimmune thyroiditis, chronic renal disease, hyperparathyroidism, and some lung and neuroendocrine tumours can also cause slight elevations in Ctn, which could result in false-positive or false-negative readings [112]. The National Comprehensive Cancer Network and American Thyroid Association (ATA) Guidelines for Management of MTC [114] suggest Ctn and CEA as biochemical markers for MTC. Serum proteases break down the hormone more rapidly in human plasma, which contains one or more Ctn-degrading enzymes [115]. Thirty minutes after thyroidectomy and central neck lymph node dissection (LND), a decrease in Ctn levels of less than 50% indicates that tumour tissue may still be present in MTC patients [116]. Long-term postoperative Ctn normalisation as a biochemical cure is a positive prognostic feature linked to a better result, with a 10-year survival rate of 97.7% [117]. In advanced MTC, serial CT scans might be more sensitive than radiological follow-up [118]. Serum Ctn levels are a reliable and accurate biochemical predictor of tumor development for postoperative monitoring [119]. In addition, higher Ctn levels may play an important role in the early diagnosis of MTC, especially in patients with a family history of medullary thyroid cancer [120,121]. Therefore, Ctn serves as both a diagnostic and prognostic biomarker, improving the precision of treatment and follow-up strategies in patients with MTC.

3.Antigen Carcinoembryonic

The glycoprotein CEA was first discovered to be involved in intercellular adhesion. During foetal development, the gastrointestinal tract's neuroendocrine tissues express it [122]. When used alone, CEA does not exhibit specificity for MTC, while being widely acknowledged as a marker of several malignant illnesses. But when used in conjunction with Ctn, it greatly improves MTC diagnostic sensitivity [123].

4.Procalcitonin Thyroid

C cells produce procalcitonin (Pct), a 116-amino acid precursor that is thought to be a more stable and dependable biomarker than Ctn for the diagnosis and tracking of MTC, which is released by the thyroid's parafollicular cells [124]. Apart from its function in MTC, PCT is frequently employed to track inflammatory activity and is a crucial marker in differential diagnosis, particularly when identifying bacterial infections [125].

5.Hormone Thyroid-Stimulating

TSH is essential for thyroid function and is mostly produced by basophils in the distal region of the adenohypophysis. Thyroxine (T4) and triiodothyronine (T3) are two thyroid hormones that are produced and released when it binds to TSH receptors (TSHRs) in thyroid tissue [126]. TSH influences the production and secretion of these hormones by stimulating the development and activity of thyroid follicular cells through its receptor [127]. Additionally, TSH promotes thyroid follicular cell development, which causes the thyroid to expand [128]. DTC cells have TSH receptors on their cell membrane. When these receptors are activated, thyroid-related proteins like TG are expressed more frequently, which promotes cell growth [128].

6.MicroRNA

Exosomal microRNAs (miRNAs) have shown great promise as biomarkers, with the potential to improve prognostic evaluations in PTC and other malignancies [129]. By attaching to the 3′ untranslated sections of target messenger RNAs (mRNAs) in the cytoplasm, miRNAs—small, non-coding RNA molecules that normally range in length from 19 to 25 nucleotides—act as negative regulators of gene expression [130]. Translation suppression and mRNA degradation are the outcomes of this interaction, and they have a significant impact on gene expression in cells [131]. Because of their stability, miRNAs can be extracted from a variety of biological materials, including blood, tissue biopsies, and even formalin-fixed paraffin-embedded tissues [131].

Discussion

1.The prevalence of thyroid carcinoma

Surgical excision continues to be the mainstay of care for the majority of patients with well-differentiated thyroid carcinoma (WDTC), especially those classified as low-risk. However, those with high-risk characteristics frequently need a more complex treatment plan that includes things like radioiodine therapy (RAI) and thyrotropin (TSH) suppression [132]. A revolutionary period in the treatment of thyroid cancers has begun with the development of immunotherapy in recent years. The basic goal of immunotherapeutic approaches is to either use targeted pharmacological drugs with specific goals for antineoplastic effects or alter endogenous immune responses. Interestingly, immunotherapy is mostly used for subtypes that do not respond to standard therapies.

2.Medullary thyroid carcinoma (MTC) is a minority of thyroid cancers, accounting for 3–5% of occurrences [133]. Finding and then focusing on actionable mutational events is the treatment tenet for MTC. Furthermore, a significant tumour mutational burden is a selection criterion for immunotherapeutic intervention; in situations without such characteristics, conventional chemotherapy is typically used. As a result, immunotherapy's uptake in MTC is still limited. Despite being uncommon, anaplastic thyroid carcinoma (ATC) is the most aggressive type of thyroid cancer, with a one-year survival rate of 20–40% and a median survival length of 5–12 months [133]. Because of these dire prognostic indicators, immunotherapy is a crucial area for ATC therapeutic research.

Our study supports the expedited development of immunotherapeutic modalities in thyroid cancer by using both scientometric analysis and a review of clinical trials. The ramifications of these findings are then thoroughly examined.

3.Targeted therapy for MTC and ATC

Targeted treatments for particular genetic alterations have developed in tandem with our growing understanding of the genetic and molecular causes of thyroid cancers. For example, BRAF-V600E correlates with the therapeutic efficacy of BRAF inhibitors like vemurafenib and dabrafenib and is a diagnostic cornerstone across several clinical subtypes of thyroid cancer [134, 135]. The proto-oncogene RET is often mutated in medullary thyroid cancer (MTC) [136]. For MTC patients with these particular mutations, drugs that target this gene, including pralsetinib and selpercatinib, have showed potential [13]. NTRK1, NTRK2, and NTRK3 are members of the NTRK gene family. Numerous tumour types have NTRK gene fusion as a carcinogenic driver [137]. Thyroid cancer is one of the uncommon tumours

where NTRK gene fusion is most common. It also happens in solid tumours, however the likelihood is very low [138]. New targeted medications have been created to treat associated malignant tumours in response to these genetic defects. One subtype of anaplastic large cell lymphoma contains anaplastic lymphoma kinase (ALK). Anaplastic thyroid carcinoma, non-small cell carcinoma, and other ALK-positive tumours are becoming more common each year [139]. Patients have benefited from tailored cancer treatment by using RNA interference, monoclonal antibodies, and small molecule inhibitors to target ALK [139, 140].

4.ATC and MTC chemotherapy

Chemotherapy is still a vital treatment option for both MTC and ATC. A commonly used chemotherapy drug, dacarbazine has shown promise in MTC and is more successful when paired with other chemotherapeutic drugs like cyclophosphamide, vincristine, and 5-fluorouracil or adjuvant therapies like radiation [141,142]. A chemotherapy medication called docetaxel disrupts microtubule networks to prevent cells from being classified. Thyroid tumours are markedly inhibited following combination treatment with radiotherapy, and docetaxel has been demonstrated to have an active role in the treatment of ATC [143].

5.Immunotherapy's microenvironment for thyroid cancer

Tumour cells' internal and external environments, which include surrounding blood arteries, different cells, signal molecules, and extracellular matrix, are directly linked to the development, growth, and metastasis of tumours. Immune surveillance processes, which include the removal of developing tumour cells via complex immunological pathways, help to preserve cellular balance under homeostatic settings. When cancer cells emerge in the body, dendritic cells will harvest fresh tumour antigens for T cells, which will subsequently collaborate with B cells to create appropriate antibodies [144]. NK cells first eliminate the cancer cells. Tumour cells, on the other hand, frequently use a variety of tactics to avoid immune detection, such as attracting immunosuppressive cells and altering their own immunogenicity [145]. Immature bone marrow cells called myeloid-derived suppressor cells (MDSC) are markedly increased in thyroid cancer patients and can have potent immunosuppressive effects [146]. MDSC and M2 macrophages can assist thyroid cancer cells in avoiding immune system destruction during their escape from immune surveillance [147].

6.Thyroid cancer immunotherapy indicators

Finding biomarkers to direct the application of immunotherapy is essential when tumour treatment moves into the precise immunotherapy stage. By preventing T cell activation, programmed cell death 1 (PD-L1), a significant immunosuppressive molecule, stimulates tumour growth [148]. By activating PD-1 and impairing the crucial dephosphorylation step in the T cell receptor pathway, it can prevent T cell growth and activation, alter its metabolism and function, and even cause T cell death [149]. Notably, it has been demonstrated that the BRAF^V600E mutation causes PD-L1 expression, which makes it a promising target for immunotherapy in thyroid cancer [150]. A quantitative indicator of genetic abnormalities in tumours is the tumour mutation burden (TMB). The effectiveness of ICB treatment will increase with a greater TMB value [151]. Thyroid cancer had the third-lowest TMB (between 0.1 and 1 mut/Mb) among 27 tumours, according to whole exome sequencing [152]. The FDA authorised TMB in 2020, and research on it has steadily advanced in recent years. It has also emerged as a possible marker. It has been demonstrated to be a marker available in some cancer types, particularly when paired with PD-L1.

7.Using immunotherapy

Immune checkpoint barriers

Immunotherapy for cancer has undergone a paradigm change thanks to immune checkpoint blockades. These checkpoints protect against autoimmunity and preserve immunological homeostasis, making them essential immunoregulatory components [153] [154] clinical trials pertaining to immune checkpoint blockades are included in our study; many of these trials use combination treatments for thyroid cancer.

8.Multiple immune checkpoint blockades

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death-1 (PD-1) are the most commonly used immune checkpoint inhibitors [155].

9.Adoptive cell therapy
In order to target neoplastic cells, immunocompetent cells from cancer patients are isolated, amplified, and functionally characterised before being reinfused into the patient as part of adoptive cell therapy (ACT).

10.Tumor-infiltrated lymphocytes (TIL)
Autologous immune cells extracted from the tumour microenvironment are used therapeutically in TIL treatment, a new cell-based immunotherapy approach [156].

11.Immunisation
Six clinical studies (6.98%) involving cancer vaccines were found in our analysis; two were in Phase II and four were in Phase I. Interestingly, most of these trials were started before 2015.

12.The cytokine
Many immune and non-immune cells produce and secrete cytokines, a family of tiny molecular proteins with a wide range of biological actions. They either promote or inhibit carcinogenesis in the tumour microenvironment [156].

13.Immunotherapy's prospects for thyroid cancer
Surgical resection is still the recommended course of treatment for thyroid cancer that can be removed, but it has drawbacks, including a high likelihood of recurrence and the possibility of harm to neck nerves, notably the recurrent laryngeal nerve. In addition, there are dangers connected with using iodine-131 to treat thyroid cancer, such as parotid gland damage, neck swelling, and gastrointestinal problems. However, the development of immunotherapies, especially immune checkpoint inhibitors, has started to change the therapeutic landscape for a number of cancers, including recurring and advanced thyroid tumours. The core of this advancement is immunotherapy, namely immune checkpoint inhibition.

Treatment
1.Surgery
Hemithyroidectomy, with or without isthmusectomy; near-total thyroidectomy (leaving less than 1 g of thyroid tissue next to the recurrent laryngeal nerve); and total thyroidectomy (removing all visible thyroid tissue) are surgical treatments for primary tumours.[157]In general, near-total or total thyroidectomy is advised for the treatment of thyroid cancer in which the primary tumour measures **≥1.0 cm to 2.0 cm**. [158] Although subtotal lobectomy and unilateral lobectomy were previously performed, they are now considered unsuitable for the treatment of patients with thyroid cancer; instead, extracapsular dissection is advised.[158,159]

Because of the high percentage **(42.7%)** of the multifocal distribution of thyroid cancer, removing the thyroid gland in its entirety reduces the chance for malignancy in the residual parenchyma.[160]. It also allows for the correct risk assessment of the tumor, which is based on size and extracapsular infiltration. [160]
Thyroidectomy is also recommended because 5% to 10% of thyroid cancer recurrences are found in the contralateral lobe.[158]

The haemostatic vessel sealing device and nerve monitoring, two major technological advancements in total thyroidectomy devices, have improved both the procedure's safety and the effectiveness of tissue removal in cancer patients.[161]. Research also demonstrates that an initial total thyroidectomy is more cost-effective than an initial lobectomy and intraoperative frozen section surgery for nodules that are suspected for malignancy based on a FNA biopsy. [167,162]

When lymph nodes are clinically affected, a therapeutic central compartment neck dissection should be carried out in addition to the complete thyroidectomy because 20% to 90% of patients with papillary cancer may have lymph node metastases.[157]. Even if there are no clinically affected lymph nodes, prophylactic central compartment neck dissection is advised for T3 or T4 tumours. [157] For smaller T1 or T2 noninvasive tumours, no prophylactic dissection is advised. [157].

Nowadays, the majority of thyroidectomies are done as outpatient procedures.[163] Patients are more likely to select outpatient surgery if they receive appropriate education and counselling; However,

contraindications must be taken into account for the patient's safety. Non compensated cardiac and/or respiratory conditions, dialysis-dependent renal failure, anticoagulant medication, seizures, obstructive sleep apnoea, mental impairment, pregnancy, unilateral vocal fold paralysis, thyrotoxicosis, and morbid obesity are all contraindications for outpatient thyroidectomy.[164]. The success of the outpatient surgery depends on additional elements including emotional stability and family or friend support.

With 0.92% of patients experiencing perioperative morbidities and 2.17% of patients being readmitted within 30 days following the procedure, a review of 5121 patients receiving outpatient thyroidectomy revealed extremely low rates of morbidity and readmission.[163]. However, problems are possible with any surgery. Hypocalcaemia (20%–30%) and recurrent laryngeal nerve damage (5%–11%) are the two most frequent early postoperative problems following thyroidectomy.[164].

The venous drainage of the upper parathyroid glands, the location and difficulty of identifying the parathyroid glands, the presence of large goitres, Graves' disease, thyroid cancer that necessitates extensive lymph node dissection, repeated cervical exploration that results in adhesions, young age, and female sex are some of the factors that increase the risk of postoperative hypocalcaemia.[165]. Although bilateral recurrent laryngeal nerve palsy is an uncommon consequence, there is little chance of damage to the recurrent laryngeal nerve. The amount of the resection, the invasion of nearby structures, the underlying thyroid pathology, and reoperation all raise the risk of nerve damage.[165]. The incidence of postoperative haemorrhage, another consequence, increases with the weight and size of the thyroid gland.[165].

Compared to a total thyroidectomy, a unilateral lobectomy requires a narrower operating field. About 1% of patients get haematomas, which usually happen during the first six hours following surgery.[9]. Significant anterior swelling, a tight feeling, and a purple discolouration of the skin are early indicators of a haematoma. Respiratory discomfort and stridor are late indications of a haematoma. Same-day hospital discharge has been demonstrated to be safe with early care and patient education regarding haematoma symptoms.[164, 165]

2.Preoperative and intraoperative procedures are necessary to prevent recurrent laryngeal nerve damage. Patients should be checked for any preexisting laryngeal dysfunctions prior to surgery. Careful nerve dissection, nerve monitoring, and the selection of haemostatic procedures are crucial during surgery.19th Nerve monitoring is becoming more popular since it may verify the functional integrity of the nerve at the conclusion of the thyroidectomy, despite the absence of conclusive data on nerve preservation.[166] New energy devices, such as electrothermal bipolar vascular sealing systems and ultrasonic dissection, are haemostatic procedures that minimise both intraoperative bleeding and the duration of surgery.

3.Inhibitors of Tyrosine Kinase
The standard treatment for recurring or metastatic thyroid tumours is radioactive iodine therapy; however, patients whose cancer no longer absorbs iodine require an alternative course of treatment.

4.The Vandetanib.
Vandetanib, which targets the RET, EGFR, and VEGF receptors, was licensed by the FDA in 2011 to treat patients with medullary thyroid carcinoma that is symptomatic, progressing, unresectable, locally progressed, or metastatic. Data from the phase 3 Zactima Efficacy in Thyroid Cancer Assessment (ZETA) study were used to approve the first medication for this indication.

5.It is **Sorafenib.** The third medication approved by the FDA in 2013 for the treatment of 131I-refractory, locally recurrent or metastatic, progressive, differentiated thyroid cancer was sorafenib, a multikinase inhibitor of RET, wild-type and BRAF V600E mutant, VEGF receptors 2 and 3.

6.Therapy using External Beam Radiation
Patients with advanced or incurable thyroid cancer are the only ones who can benefit from external beam radiation therapy.[157]. Patients over 45 who have clearly apparent extrathyroidal extension and a high risk of residual disease during surgery are typically given consideration.[157] It is also saved for tumours that do not respond to 131I therapy.

7.Management After Treatment
Because differentiated thyroid tumours produce TSH receptors that react to TSH stimulation, TSH

suppression medication is advised following surgery and 131i therapy.[157]. In response, the cells produce more sodium iodide symporters, which promotes cell proliferation. Levothyroxine supraphysiologic dosages can be used to reduce TSH to less than 0.1 mU/L or, in lower-risk patients, up to 0.5 mU/L.5 Since 25% of patients with thyroid cancer will produce antithyroglobulin antibodies, which erroneously lower the amount of serum thyroglobulin, serum thyroglobulin should be examined every 6 to 12 months in the same laboratory as antithyroglobulin antibodies.[157]. A single rhTSH-stimulated blood thyroglobulin measurement of less than 0.5 ng/mL without antithyroglobulin antibody can identify patients who are totally tumor-free around a year after ablation.[157] When there is no imaging evidence of a tumour (negative whole-body scan), no clinical indication of a tumour, and an undetectable serum thyroglobulin level after TSH stimulation in the absence of antibodies, the patient is considered disease-free.[157]. Thyroid hormone supplementation and yearly thyroglobulin testing can subsequently be used to monitor such people.[157].

For five to ten years, patients with high-risk disease should have their TSH suppressed to 0.1 to 0.5 mU/L, whereas those with low-risk disease or those who are disease-free should keep their TSH levels between 0.3 and 2.0 mU/L.5 A PET scan should be undertaken to rule out any metastatic illness that would necessitate additional workup if a patient is thyroglobulin positive (>10 ng/mL) and the 131I whole-body scan is negative.[157]. TSH should always be kept below 0.1 mU/L in patients with chronic illness. [157].

Conclusions

Immunotherapy has grown in significance in the treatment of advanced TC and ATC in recent years. Every year, there are more articles about TC immunotherapy. At the same time, there is active research being done on combining immunotherapy with conventional treatments like chemotherapy, radiation, and targeted therapy. Research on the TME and immune cell functions, as well as clinical trials aimed at ICIs, are still in progress. Future studies should concentrate on a number of important areas, such as maximising the use of ICIs, particularly for patients who don't respond to conventional therapies or who have recurrences focusing on immune cells like T cell subsets, cancer-associated fibroblasts (CAFs), and macrophages in the TC microenvironment, as well as fundamental studies on immune infiltration and associated mechanisms, in order to harness the patient's immune system while precisely targeting tumour cell key points. In general, it is anticipated that these investigations and clinical trials will provide TC patients more accurate and efficient treatment options, thereby enhancing their quality of life and survival rates.

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