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## Thyroid carcinoma: A review

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### Abstract

Cancer is a malignant growth resulting from uncontrolled division of abnormal cells. Thyroid cancer is 9<sup>th</sup> most common cancer. The cause of thyroid cancer is exposure to radiation, excess iodine intake westernized lifestyle and due to genetics. Symptom is usually presence of palpable thyroid nodule which is usually detected by routine examination of thyroid gland. Diagnostic tests include ultrasound, Positron Emission Tomography (PET) Scan, Radio Iodine Scan & Fine Needle Aspiration Cytology. Treatment includes surgery in which thyroidectomy or lymphadenectomy or lobectomy is done, Radio iodine therapy, thyroid hormone treatment, chemotherapy. Identifying the potential risk factors and being away from them can help a person prevent thyroid cancer. As cancer can metastasise at any time point after treatment regular follow up is needed.

**Keywords:** Thyroid cancer, thyroidectomy, lymphadenectomy, radio iodine therapy

### Introduction

Thyroid gland is located in front of neck just below the larynx. It produces hormones that regulate metabolism <sup>[1]</sup>. Thyroid gland produces has 2 types of cells Follicular cells & C- cells. Follicular cells are responsible for production of thyroid hormone that controls the basic metabolism of the body. C cells make calcitonin hormone that participates in calcium metabolism. Thyroid cancer happens when tumors grow in thyroid gland. Thyroid cancer is the most common endocrine malignancy <sup>[2]</sup>. It is the fifth most common cancer in women in USA. Thyroid cancer is the 9<sup>th</sup> most common cancer. It is more frequently encountered in early age highest incidence is in 2<sup>nd</sup> 3<sup>rd</sup> & 4<sup>th</sup> decades of life <sup>[3]</sup>. In India Male to female ratio of Thyroid cancer is 1:4. In the Thiruvananthapuram region, thyroid cancer comprised one of every 10 cancers diagnosed in females <sup>[4]</sup>

### Types <sup>[5]</sup>

Thyroid cancers are classified on the basis of histology into

1. Differentiated Thyroid cancers
2. Undifferentiated Thyroid cancers

Differentiated thyroid cancers include Papillary and Follicular thyroid cancer. Undifferentiated Thyroid cancers include Medullary and Anaplastic thyroid cancer.

### Papillary thyroid cancer (PTC)

Papillary thyroid carcinomas are the most common Thyroid cancers and constitute more than 70% of thyroid malignancies <sup>[6]</sup>. It is a well differentiated cancer of thyroid. Papillary thyroid cancers develops from follicular cells. It is usually found in 1 lobe <sup>[7]</sup>. Papillary thyroid carcinoma is characterized by low mortality but a high recurrence rate such as lymph node recurrence and lung metastases <sup>[8]</sup>. *RET / PTC* is an important oncogene in the initiation events in the pathogenesis of cancers and is rearranged, particularly in patients who have been exposed to radiation <sup>[9]</sup>. The activation of the *BRAF* gene accounts for approximately 45% of sporadic mutations that result from increased *BRAF* kinase activity. Approximately 80% of all mutations have transversion events, that is, the transversion from thymine to adenine at nucleotide 1799. In thyroid cancer, point mutations, chromosomal rearrangement or small in-frame insertions or deletions can lead to the activation of *BRAF* <sup>[10]</sup>. *BRAF* is the most common mutation observed in patients with PTC. Three members of the *RAS* gene family (*HRAS*, *NRAS* and *KRAS*) have been shown to be mutated in thyroid cancer. The most common *RAS* mutations were detected in the *NRAS* gene, followed by *HRAS*, and least frequently, *KRAS*. Role of *RAS* is more inclined to progression rather than initiation of PTC <sup>[11]</sup>.

PTC is usually gray-white color and shows a variety of gross appearance such as tumors with central scar and infiltrative borders, encapsulated tumor and lesional calcification. Nearly half of PTCs have multifocal lesions and regional lymph node metastasis [12].

### Causes

Potential etiologic factors for thyroid cancer are exogenous factors such as radiation exposures, high iodine intake, nitrate, westernized life style or unknown environmental pollutants and endogenous factors such as high thyroid stimulating hormone (TSH), presence of Hashimoto's thyroiditis or obesity [13].

### Risk factors

Radiation exposure is most common and well-known risk factor for Papillary thyroid carcinoma. Ionizing radiation causes DNA strand breaks and somatic mutations that are thought to be a risk factor for cancer [14, 15].

Level of iodine intake affects thyroid functions, but mechanisms linking with thyroid cancer are not clear. Chronic stimulation of the thyroid-stimulating hormone (TSH) and *BRAF* mutations in PTC are possible pathways [15].

Obesity & diabetes - Mechanisms for a possible link between obesity, diabetes, and thyroid cancer include elevated levels of insulin resistance and TSH. Insulin resistance may activate insulin and the IGF pathway, which are important to cell proliferation and apoptosis [16].

Hashimoto's Thyroiditis - Elevated levels of TSH found in hypothyroid patients with autoimmune thyroid disease may stimulate follicular epithelial proliferation, promoting the development of papillary carcinoma. Autoimmune thyroiditis might also induce thyroid tumorigenesis via the production of proinflammatory cytokines and oxidative stress [15, 17].

Diet - The changing diet and growing varieties of food additives may also be associated with the incidence of thyroid cancer. For example, nitrate, with its increasing presence in our dietary composition, was postulated to be a risk factor for thyroid cancer. It competitively inhibits iodide uptake by the thyroid, potentially affecting thyroid functions [15].

### Epidemiology

PTC accounts for 1% of all malignancies. It accounts for 85% of all thyroid cancers. It is the most prevalent form of thyroid cancer [9].

### Signs and Symptoms [8].

Most frequent presentation is a palpable thyroid nodule, cervical lymphadenopathy

Locally advanced disease presents with Hoarseness or voice alteration.

### Follicular thyroid carcinoma (FTC)

Follicular thyroid cancer is a tumor of the follicular cells that are lined by cuboidal epithelial cells and have capsular and vascular invasive properties [17]. It usually grows slowly and rarely spreads to lymph node [18]. Compared to follicular carcinoma, follicular adenoma is benign and occurs more commonly with a ratio estimated to be 5 to 1. FTC is more likely to metastasize to distant organs rather than to regional lymph nodes because of its tendency to invade blood vessels thus resulting in hematogenous dissemination [19]. They are very often curable especially when found early. FTC is solitary encapsulated tumor with gray tan pink colour usually

focal haemorrhage. FTCs are minimally invasive. Hurthle cell carcinoma is a subtype of FTC but its prognosis is worse than FTC [20].

### Causes

Radiation exposure, diabetes, iodine, obesity, diet and Hashimoto thyroiditis are observed as potential causes for thyroid carcinoma [21]. The position of thyroid makes it a target for radiation exposure. Hashimoto thyroiditis leads to an increase in the production of pro-inflammatory cytokines and oxidative stress [15]. Food such as cabbage, broccoli, cauliflower, chicken, pork, and poultry have been found to cause an increased incidence of thyroid cancer. Too much multivitamin use has been shown to cause an increased incidence of thyroid cancer due to iodine content [22].

### Epidemiology

FTC is more common in older females, with a female to male ratio of 3 to 1. It is the 2<sup>nd</sup> most prevalent thyroid cancer. It accounts for 10 – 15% of all thyroid cancers. Its peak incidence is between 40 – 60 years.

### Risk Factors [23].

Risk factors for Follicular thyroid carcinoma include radiation exposure especially in childhood, history of thyroid cancer in first degree relative.

### Signs and symptoms

Most follicular carcinomas are generally asymptomatic. Patients with large nodules may notice a Palpable mass. Patients with very large nodules face difficulty in swallowing, shortness of breath when lying and with advanced disease patient may develop hoarseness.

### Medullary thyroid cancer (MTC)

Medullary thyroid carcinoma is undifferentiated form of thyroid cancer and develops from parafollicular C- cells [24]. It accounts for 1 – 2% of thyroid cancers. majority of MTCs are sporadic, 25% of cases are hereditary and are found in Multiple Endocrine Neoplasia (MEN) 2A or 2B syndromes, or as part of familial MTC based on a specific germline mutation in the *RET* proto-oncogene [25]. Production of calcitonin is a characteristic feature of this MTC [26]. Undifferentiated thyroid cancers are more aggressive than differentiated thyroid cancers. The *RET* gene plays an important role in cell signalling in neural tissue, especially during the early stages of development. Mutations in this gene lead to abnormalities in cell proliferation and differentiation of tissues that are derived from neural crest cells [27]. The C-cells of the thyroid and the chromaffin cells in the adrenal medulla are both affected, resulting in MTC and pheochromocytoma. MTCs exhibit gray tan colour, firm solid tumors and do not have well-formed capsule. MTC cells are round to oval, spindle or polyhedral. Broad fibro vascular bands separates tumors to nodules.

### Causes [26].

Majority of MTCs are sporadic, but the familial form, responsible for about 25% of cases, is usually represented by multiple endocrine neoplasia (MEN) 2A or 2B or pure familial MTC syndrome. The hereditary disorders are caused by *RET* proto-oncogene germline mutations, located on chromosome 10 (5-7) and typically are bilateral and preceded by premalignant C-cell hyperplasia.

## Epidemiology

It is a rare thyroid malignancy. Patients with sporadic MTC may have a less favourable prognosis than Familial medullary thyroid carcinoma (FMTC) [28].

## Signs and symptoms

### Sporadic

Patient presents a palpable nodule or neck mass. Other features include cervical lymphadenopathy (can be detected in more than 50% of patients) and less common systemic symptoms like diarrhea and flushing, secondary to increased secretion of calcitonin, prostaglandins, serotonin or vasoactive intestinal peptide (VIP). Very rarely tumors may also secrete ACTH causing Cushing's syndrome [25]. Larger tumors result in dyspnoea, dysphagia or hoarseness [29].

### Hereditary MTC [29].

Patients with hereditary MTC may have a positive family history or present with clinical features of other components of the MEN 2 syndrome. For example, MEN 2A, which accounts for 80% of hereditary MTC, is associated with pheochromocytoma in 10–50% of cases and hyperparathyroidism in 10–30% cases.

## Anaplastic thyroid cancer (ATC)

Anaplastic thyroid carcinomas are undifferentiated aggressive tumors with a high mortality rate [30]. It is rare and accounts for 1 – 2% of all thyroid malignancies and 30 – 40% of thyroid cancer deaths [31]. The average survival is 6–12 months with a 10-year survival of approximately 3 percent. Anaplastic thyroid cancer starts from differentiated thyroid cancer or a benign thyroid tumor. Mutations, amplifications, activation of oncogenes and silencing of tumour suppressor genes contribute to its aggressive behaviour [32]. ATC extensively invades to surrounding structures. Large pleomorphic giant cells resembling osteoclasts are hall marks of ATC.

## Etiology [33]

Exact cause of anaplastic cancer is unknown. It might be mutation of another aggressive form of tumor. It is caused due to genetic mutations. *TP53* gene inactivation plays a role in the progression from differentiated to undifferentiated carcinoma. The most common mutations are in *TP53* (nuclear expression), while *BRAF V600E*, *RAS*, *PIK3CA*, and *PTEN* are also present in a range of 10% to 20% each.

## Epidemiology

Incidence of anaplastic cancer is 1 to 2 per million persons [34]. About 40% of the cases have cervical lymph node metastases, 90% directly invade the surrounding soft tissues and organs such as trachea and larynx and 75% have distant metastases [30]. ATC is primarily a disease of elderly.

## Risk Factors [35].

History of goitre

## Signs and symptoms

Local symptoms – rapidly evolving central mass, noticeable dysphagia, voice change or hoarseness.

Regional symptoms – local lymph node mass, neck pain.

Systemic symptoms – anorexia, weight loss, shortness of breath with pulmonary metastases.

## Pathogenesis

Thyroid cancer is initiated by genetic alterations and epigenetic changes in driver oncogenes or tumor suppressor genes. The genetic mutation underlying tumorigenesis in thyroid is the activating mutation of *RET* oncogene [9]. In follicular cell derived cancers, other molecular alterations such as the *RAS* pathway and the *PI3K-AKT* pathway are identified. *BRAF* point mutation (T1799A) in exon 15 leads to the expression of *BRAF-V600E* mutant protein and results in constitutive serine/threonine kinase activation [36]. *BRAFF600E* mutation, occurs in approximately 45% (30 to 70%) of sporadic PTC whereas about 15% in follicular variant PTC [37]. Among genes of three *RAS* isoforms (*HRAS*, *KRAS*, and *NRAS*), *NRAS* is predominantly mutated in thyroid tumors [38]. *RAS* mutation activates *PI3KAKT* pathway in thyroid tumorigenesis. Tumor suppressor gene *PTEN* is a negative regulator of *PI3KAKT* signalling pathway by opposing function of *PI3K*. Mutation or deletion of *PTEN* causes follicular thyroid cell tumorigenesis. Other genes like *CTNNB1*, *TP53*, *IDH1* and *NDUFA13* are also mutated in thyroid carcinoma [39]. Chromosomal rearrangements of tyrosine kinase *RET* oncogene are responsible for 15–45% of PTC [20].

**Table 1:** Genes involved in thyroid Follicular variant tumors [20].

Genes	Types of Tumors	Associated pathways
<i>BRAF<sup>V600E</sup></i> (mutations)	PTC	MAPK
	FVPTC	
	TCPTC	
	ATC	
RET/PTC (translocation)	PTC	MAPK and P13 – AKT
	FTC	
	PDTC	
HRAS, KRAS, NRAS mutation	FA	MAPK and P13 – AKT
	FTC	
	PTC	
	FVPTC	
	PDTC	
	ATC	
PAX8/PPAR $\gamma$ Translocation	PTC	PAX8 associated nuclear transcription.
	FVPTC	
	FTC	
	PDTC	
PTEN (mutation)	FA	P13K-AKT
	PTC	
	FTC	
	ATC	
PTEN (deletion)	FTC	P13K-AKT
CTNNB1 (mutation)	PDTC	WNT B-Catenin
	ATC	
TP53 (mutation)	PDTC	P53 coupled pathways
	ATC	
IDH1 (mutation)	PTC	IDH1 associated metabolic pathways
	FVPTC	
	FTC	
	ATC	
NDUFA13 (GRIM19) (mutation)	HCTC	Mitochondrial function

**Abbreviations:** FVPTC: Follicular Variant PTC; TCPTC: Tall Cell Variant PTC; FA: Follicular Adenoma; PDTC: Poorly Differentiated Thyroid Cancer; HCTC: Hürthle Cell Thyroid Cancer; IDH1: Isocitrate Dehydrogenase 1; NDUFA13: NADH Dehydrogenase (Ubiquinone) 1 $\alpha$  Subcomplex 13

## Diagnosis

Thyroid cancer is usually diagnosed after thyroid nodules are discovered on imaging<sup>[40]</sup>. Majority of patients have no clinical symptoms at time of diagnosis. The initial workup for newly diagnosed thyroid nodule should include measuring serum TSH level. The TSH is released from the anterior pituitary and signals the thyroid gland to make thyroid hormone as appropriate. When thyroid hormone levels are low, the TSH rises responsively and vice versa; thus, measuring a TSH level allows differentiation between functional and non-functional nodules. This is an important characteristic, because hyperfunctioning nodules are rarely malignant. However, if a TSH is subnormal, indicating a hyperactive gland, a nuclear medicine imaging study (thyroid uptake and scan) should be performed, to document whether the nodule itself is hyperfunctioning (hot), isofunctioning (warm), or non-functioning (cold) compared with the surrounding thyroid tissue. If the nodule is hot or warm, no cytologic evaluation is necessary<sup>[41]</sup>.

### Calcitonin<sup>[42]</sup>.

Levels of calcitonin rises in MTC so if MTC is suspected blood tests for calcitonin levels can help look for MTC. This test is also used to look for recurrence.

### Carcinoembryonic antigen (CEA)<sup>[42]</sup>.

Patients with MTC usually have a high level of CEA this test is used to monitor Cancer.

### Imaging tests

Ultrasound, CT, MRI and PET scan are used to evaluate MTC. It is used to determine if the nodules are solid or filled with fluid<sup>[42]</sup>. This test is decision making test. CT MRI and PET are used for patients who have extensive primary tumor with invasion of adjacent structures and nodal metastases<sup>[40]</sup>.

### Radio Iodine scan<sup>[42]</sup>.

Radioiodine scans can be used to help determine if someone

with a lump in the neck might have thyroid cancer. They are also often used in patients who have already been diagnosed with differentiated thyroid cancer to help show if it has spread. Because medullary thyroid cancer cells do not absorb iodine, radioiodine scans are not used for this cancer. For this test, a small amount of radioactive iodine (called I-131) is swallowed (usually as a pill) or injected into a vein. Over time, the iodine is absorbed by the thyroid gland (or thyroid cells anywhere in the body). A special camera is used several hours later to see where the radioactivity is. For a thyroid scan, the camera is placed in front of neck to measure the amount of radiation in the gland. Abnormal areas of the thyroid that have less radioactivity than the surrounding tissue are called cold nodules, and areas that take up more radiation are called hot nodules. Hot nodules usually are not cancerous, but cold nodules can be benign or cancerous. Because both benign and cancerous nodules can appear cold, this test by itself can't diagnose thyroid cancer.

### Fine needle aspiration biopsy (FNAC)<sup>[41]</sup>.

FNAC is the most accurate and best diagnostic method for evaluating nodules. The goal of the FNA biopsy is to obtain at least 6 follicular cell groups, each containing 10 to 15 cells from at least 2 different aspirates of a nodule for cytologic evaluation. FNA is not recommended unless sonographic appearance of nodules is suspicious. If abnormal lymph nodes are detected, an FNA biopsy should be performed on the lymph node in addition to the thyroid nodule. In case of a multinodular gland that consists of 2 or more nodules measuring >1 cm, the nodule with suspicious sonographic features should be biopsied preferentially. However, if none of the nodules is suspicious, only the largest nodule should be aspirated, and the rest should be observed with serial ultrasound examination. FNA biopsy results are categorized as nondiagnostic, malignant, suspicious for malignancy (50%–75% risk), indeterminate or suspicious for neoplasm (20%–30% risk), follicular lesion of undetermined significance (5%–10% risk), and benign.

**Table 2:** Staging of cancer according to American Joint Cancer Committee (AJCC) TNM<sup>[43]</sup>

Stage	Definition
<b>Tumor</b>	
T1a	tumor ≤1 cm limited to the thyroid
T1b	tumor >1 cm but ≤2 cm limited to the thyroid
T2	tumor >2 cm but ≤4 cm limited to the thyroid
T3a	tumor >4 cm limited to the thyroid
T3b	gross extrathyroidal extension invading only strap muscles (Sternohyoid, Sternothyroid, Thyrohyoid, Omohyoid) from a tumor of any size
T4a	gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, oesophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	gross extrathyroidal extension invading Prevertebral fascia or encasing the carotid artery or Mediastinal vessels from a tumor of any size
<b>Node</b>	
Nx	regional lymph nodes cannot be assessed
N0a	one or more Cytologically or histologically confirmed benign lymph nodes
N0b	no radiologic or clinical evidence of locoregional lymph node metastasis
N1a	Ipsilateral or bilateral metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes; this can be unilateral or bilateral disease
N1b	metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph node
<b>Metastasis</b>	
M0	No distant metastasis
M1	Distant metastasis

**Goals of treatment for DTC [2].**

- Remove the primary tumour and involved lymph nodes
- Minimise treatment related morbidity
- Allow accurate staging of the disease
- Facilitate post-operative treatment with radioactive iodine in appropriate patients
- Enable long-term surveillance for disease recurrence
- Minimise the risk of disease recurrence and distant metastases

**Treatment**

Treatment options for thyroid cancer include

1. Surgery
2. Adjuvant Radio Iodine Therapy (RIT)
3. Thyroid hormone treatment
4. Chemotherapy
5. External beam radiography

**Differentiated thyroid carcinoma****1. Surgery**

Initial treatment for DTC include Surgery, radioactive iodine treatment, and thyroid hormone suppression therapy [44]. For widely invasive FTC with vascular infiltration thyroidectomy is recommended. For all papillary thyroid carcinomas >1 cm and/or metastasized or macroscopically invasive PTC irrespective of size, thyroidectomy is recommended [45]. If lymph node metastases is detected lymph node dissection of affected compartment is done to reduce the risk of recurrence [46]. Accurate histopathological examination of the specimen after (hemi) thyroidectomy and lymphadenectomy (if done) is regarded as the gold standard and is indispensable for the management and further diagnostic and therapeutic approach. Lobectomy is only considered if tumors are small isolated less than 1cm without evidence of local spread [44].

**2. Adjuvant radio iodine therapy**

A small amount of thyroid tissue, called the thyroid remnant, is often left after total thyroidectomy. Radioactive Iodine (RAI) can be administered postoperatively to destroy any remaining thyroid cells, normal or malignant [44]. RIT is defined as the systemic administration of I-131 (radioiodine as sodium iodide or potassium iodide) to irradiate thyroid remnants as well as non-resectable or incompletely resected DTC. RAI is administered after total thyroidectomy for several reasons:

- To eliminate the normal thyroid remnant, thereby ensuring undetectable serum
- Tg levels (in the absence of neoplastic tissue), which facilitate follow-up (remnant ablation);
- To irradiate presumed foci of neoplastic cells, thereby reducing the recurrence risk (adjuvant therapy); and/or
- To treat persistent or recurrent disease (treatment of known disease) [47].

In all three cases, RAI administration must be followed by an iodine-131 (131I) whole-body scan (WBS) to stage the disease and document the 131I avidity of any structural lesion. To optimise isotope uptake, RAI should be given after thyroid-stimulating hormone (TSH) stimulation, which can be achieved by withdrawing levothyroxine for 4–5 weeks, ideally until serum TSH levels reach  $\geq 30$   $\mu\text{IU/mL}$ . Alternatively, recombinant human TSH (rhTSH) can be given (2 daily injections of 0.9 mg of rhTSH followed by RAI on day 3). Levothyroxine withdrawal is preferred if distant metastases are present [47].

Absolute contraindications of RIT are pregnancy and breastfeeding. Relative contraindications include depression of the bone marrow, a restriction of salivary gland function, pulmonary function restriction and symptomatic metastases of the central nervous system, because local edema and inflammation caused by RIT and hypothyroidism can lead to severe compression effects [48].

Long-term risks and side effects include permanent bone marrow depression, second primary malignancy after RIT with a high cumulative activity (leukemia and solid tumors) [49], chronic sialadenitis (including abnormalities of taste and smell, xerostomia,) and pulmonary fibrosis (in patients with diffuse iodine-avid pulmonary metastases). Due to the risk of chronic hypospermia or azoospermia, sperm banking should be considered if high cumulative activities are expected [50]. These risks have to be weighed against the expected benefits of the RIT.

**3. Thyroid hormone treatment**

After thyroidectomy, life-long thyroid hormone therapy is required, usually as monotherapy with levothyroxine (LT4). Since TSH is able to promote the growth of remaining DTC cells, the dosage of LT4 should initially be high enough to achieve a suppression of thyrotropin. The thyroid function should be checked after 6 to 8 weeks. Depending on the result the dosage should be adjusted. An elevated level of triiodothyronine has to be avoided. According to the guidelines of the ATA, serum TSH should be maintained between 0.1 and 0.5 mU/L in patients with high-risk disease [46].

**Follow up**

Life long follow up is usually required because relapse can occur at any time. Initial follow up should be carried for every 6 months for 5 years after 5 years follow up should be annually [51]. The follow-up examination is based on the medical interview, clinical examination, cervical sonography, determination of TSH, triiodothyronine, levothyroxine, and thyroglobulin including Tg antibodies. A diagnostic whole-body scan is obligatory 6–12 months after initial RIT, a second scan is only needed in the case of relapse [52].

**4. Tyrosine kinase inhibitors**

For poorly differentiated carcinomas with very low iodine uptake RAI is not an appropriate option. For these patients a strict LT4 regime with TSH suppression is the best way.

Tyrosine kinase inhibitors like vandetanib, sorafenib and lenvatinib are a relatively new approach to systemic therapy in these cases. Tyrosine kinase receptors, the target structure of TKI, are trans-membrane proteins that mediate cell survival and proliferation [53]. TKIs block receptors of the vascular endothelial growth factor (VEGF), fibroblast growth factor receptors and platelet-derived growth factor and thus inhibit tumor angiogenesis and lymphangiogenesis and cause hypoxia in malignant tissue [54].

**Vandetanib:** This drug was approved in 2011. Drug targets *RET*, *EGFR*, and VEGF receptor for the treatment of patients with symptomatic or progressive, unresectable, locally advanced or metastatic medullary thyroid cancer [55]. Dose- 300 mg PO q day.

**Cabozantinib:** In 2012, the FDA approved the second TKI. This drug is a TKI that targets 3 potentially important

pathways in medullary thyroid cancer: *MET*, VEGF receptor 2, and *RET* [56]. Cabozantinib had significant grade 3 or 4 side effects, including diarrhea, hand-foot syndrome, fatigue, and hypertension. Dose – 140 mg PO q day

**Sorafenib:** In 2013, sorafenib, which is a multikinase inhibitor of *RET*, wild-type and *BRAF* V600E mutation, VEGF receptors 2 and 3, among others, was the third drug to be approved by the FDA for the treatment of <sup>131</sup>I-refractory, locally recurrent or metastatic, progressive, differentiated thyroid cancer [57]. Dose – 400 mg PO q12hrs

Therapy with kinase inhibitors may be accompanied by severe side effects. Vasoconstriction following reduced nitric oxide production via inhibition of the VEGF-PI3K pathway is discussed. A reduction of peripheral arterioles due to antiangiogenic effects resulting in increased peripheral resistance and an activation of the endothelin-1-system causing vasoconstriction have also been suggested. This therapy should be reserved for patients with rapid tumor progression and severe to life threatening symptoms [46].

### Medullary thyroid cancer

All patients with MTC should undergo total thyroidectomy and central compartment node clearance even if disease is local. Radiotherapy is used for controlling local symptoms in patients with inoperable disease and improving the relapse-free rate following central or lateral compartment surgery where residual disease is present macroscopically or microscopically.

Tyrosine kinase inhibitors can be effective in controlling symptoms in patients with metastatic disease. Cabozantinib targets 3 potentially important pathways in medullary thyroid cancer: *MET*, VEGF receptor 2, and *RET* [56].

Somatostatin analogues may be effective in alleviating the unpleasant gastrointestinal symptoms that patients with advanced cases of MTC experience.

Lifelong follow-up is recommended for all patients with MTC. Screening should include calcitonin and CEA. Thyroid-stimulating hormone suppression is not necessary. Rising calcitonin levels should trigger investigations to identify potentially treatable metastatic disease [2].

### Anaplastic thyroid cancer

Therapeutic strategies for ATC focus on the use of combination therapy with surgery, chemotherapy using taxanes, anthracyclines, and platins, and external beam radiation therapy [31].

### External beam radiography

External beam radiation therapy is only used for palliative treatment of patients with advanced or inoperable thyroid cancer. It is usually considered in patients aged >45 years who have grossly visible extrathyroidal extension and a high likelihood of residual disease during surgery. It is also reserved for tumors that are unresponsive to therapy with [13, 41].

Before any treatment, patients should have an upper airway evaluation, generally via flexible fiberoptic laryngoscopy, to evaluate the function of the vocal cords and any degree of laryngeal edema, compression, or invasion. If the patient does not have a tracheostomy tube before radiation therapy, the airway can quickly become unstable as a result of radiation-induced tumor and/or laryngotracheal inflammation, edema, and thickened mucous, which compound pre-treatment airway compromise related to direct effects of the tumor and/or vocal cord paralysis.

The benefit of adjuvant chemotherapy as a single modality is uncertain and it is usually not indicated in patients with intrathyroidal (stage IVA) anaplastic thyroid carcinoma; however, chemotherapy is often used in combination with radiation therapy after R0 or R1 thyroidectomy, at the cost of increased toxicity [58].

**Table 3:** Adjuvant chemotherapy for anaplastic thyroid carcinoma [59].

Drug	Radio sensitizing Chemotherapy Dose	Chemotherapy Full Doses for Advanced Disease	Frequency
<b>Combination regimens</b>			
Paclitaxel + carboplatin	Paclitaxel 50 mg/m <sup>2</sup> , carboplatin AUC 2 mg/m <sup>2</sup> IV	Paclitaxel 60-100 mg/m <sup>2</sup> , carboplatin AUC 2 mg/m <sup>2</sup> IV	Once a week
		Paclitaxel 135-175 mg/m <sup>2</sup> , carboplatin AUC 5-6 mg/m <sup>2</sup> IV	Every 3 – 4 weeks
Docetaxel + doxorubicin + pegfilgrastim	Docetaxel 60 mg/m <sup>2</sup> , doxorubicin 60 mg/m <sup>2</sup> IV	Docetaxel 60mg/m <sup>2</sup> IV, doxorubicin 60mg/m <sup>2</sup> IV	Every 3 – 4 weeks
Docetaxel + doxorubicin	Docetaxel 20 mg/m <sup>2</sup> , doxorubicin 20 mg/m <sup>2</sup> IV	Docetaxel 20 mg/m <sup>2</sup> IV, doxorubicin 20 mg/m <sup>2</sup> IV	Once a week
<b>Single agent regimens</b>			
Paclitaxel	30-60 mg/m <sup>2</sup> IV	60-90 mg/m <sup>2</sup> IV	one a week
		135-200 mg/m <sup>2</sup> IV	every 3 -4 weeks
Cisplatin	25 mg/m <sup>2</sup> IV	-	once a week
Doxorubicin	60 mg/m <sup>2</sup> IV	60-75 mg/m <sup>2</sup> IV	every 3 weeks
	20 mg/m <sup>2</sup> IV	20 mg/m <sup>2</sup> IV	once a week

### Patient counselling

Hearing that one has Cancer will be devastating for the patient and patient may be depressed and loose hope that they can live so they need support and care no matter what stage of illness they are in, talking to other patients who have been diagnosed with cancer and leading a normal healthy life can help them to cope up and come out of depression.

Communicating with cancer care team is important so that patient understands ways to maintain or improve quality of life. Thyroid cancer can be treated very successfully and can be cured.

After surgery neck incisions heal rapidly, bruising and swelling can develop in area around incision 1-3 days after surgery.

Person may also have some difficulty swallowing.

Patients voice may be slightly hoarse or weak after surgery.

Patient should consult doctor if he experiences trouble talking or breathing, production of yellow sputum.

Cancer metastasis can occur even after treatment so regular follow up is needed.

Exact cause of thyroid cancer is unknown so it is not possible to reliably prevent thyroid cancer.

After RAI ablation women should avoid conceiving for six months and men should avoid fathering a child for four months.

### Diet for thyroid carcinoma

Decreased thyroid cancer risk is associated with high levels of fish, shell fish and sea food intake.

High intake of fruits and vegetables containing active micronutrients (e.g., vitamins and minerals) and phytochemicals provide antioxidant activity that helps to protect against cancers.

In Norway, a high intake of citrus fruits was positively associated with thyroid cancer risk, but other fruits such as apples and oranges were not associated with an increased risk. Cruciferous plants (e.g., Brussels sprouts and cabbage) contain a degraded form of thioglucosides, such as thiocyanates (e.g., Goitrogen), and may increase thyroid cancer risk by inhibiting iodine transport to the thyroid gland at low concentrations

While cooking red meat at a high temperature, carcinogenic compounds such as heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAH), N-nitroso compounds, or heme iron are formed and carcinogenesis is promoted by increasing cell proliferation in the mucosa<sup>[60]</sup>.

A high exposure to organophosphate insecticides was associated with a higher TC incidence

Cruciferous vegetables contain large amounts of glucosinolates, which are a nutritional source of thiocyanates and isothiocyanates. Those molecules can block the action of carcinogenic substances and suppress the expression of neoplasia in initiated cancer cells<sup>[61]</sup>.

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