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Thyroid Carcinoma: From Histopathology To Prognosis

Mahinar M Alhartani[1], Huda Fatima[2], Sarah Kaleem Ather[3], Ayesha Shrouq Amin[4], Saleha Khan[5], Jumana H. Timraz[6], Husna Irfan Thalib[7], Sara Khalid Fagih[8]

[1]General Medicine Practice Program, Batterjee Medical College, Jeddah, Saudi Arabia Email: Mahinaralhartani@gmail.com
[2]General Medicine Practice Program, Batterjee Medical College, Jeddah, Saudi Arabia Email: huda.firdous10@gmail.com
[3]General Medicine Practice Program, Batterjee Medical College, Jeddah, Saudi Arabia Email: sarahkaleem05@gmail.com
[4]General Medicine Practice Program, Batterjee Medical College, Jeddah, Saudi Arabia Email: ayesha.amin1112@gmail.com
[5]General Medicine Practice Program, Batterjee Medical College, Jeddah, Saudi Arabia Email: salehashafi05@gmail.com
[6]General Medicine Practice Program, Batterjee Medical College, Jeddah, Saudi Arabia Email: jomana1420@gmail.com
[7]General Medicine Practice Program, Batterjee Medical College, Jeddah, Saudi Arabia Email: husnairfan2905@gmail.com
[8]General Medicine Practice Program, Batterjee Medical College, Jeddah, Saudi Arabia Email: fagihkhalidsara@gmail.com
Correspondence Author:
Husna Irfan Thalib,
General Medicine Practice Program, Batterjee Medical College, Jeddah, Saudi Arabia, Email: husnairfan2905@gmail.com

Abstract
Thyroid carcinomas are fairly uncommon and include disease types that range from indolent localized papillary carcinomas to the fulminant anaplastic carcinomas. Surgical resection is the cornerstone of primary treatment for most thyroid carcinomas, and is often followed by adjuvant radioactive iodine treatment for both papillary and follicular types of cancer. Thyroid hormone replacement therapy is used for two main reasons: to rectify postsurgical hypothyroidism, and to prevent disease recurrence in patients with papillary or follicular carcinomas. Treatment for progressive metastatic disease is often of limited benefit. In families with inherited thyroid cancer syndromes, early diagnosis and intervention based on genetic testing might prevent poor prognosis. Multimodality treatments are widely recommended, although there is little evidence from prospective trials to support this approach. Care should be carefully coordinated by members of an experienced multidisciplinary team, and patients should be provided with education about diagnosis, prognosis, and treatment options to allow them to make informed contributions to decisions about their care.

Keywords: Papillary thyroid carcinoma, BRAF, Radioactive iodine, Fine-needle aspiration

Introduction

Thyroid carcinomas are a diverse group of malignancies originating from the thyroid gland. As of late, there has been a visible rise in incidence partly due to improved diagnostic methods, increased awareness amongst the vulnerable populace, radiation exposure, dietary reasons etc. It consists of several subtypes, each with their own specific clinical behaviours and outcomes. Amongst the rest, papillary thyroid carcinoma (or PTC) is the most common cancer of thyroid, known for its highly indolent nature and elevated survival rates relative to other carcinomas [1]. Other types include;, follicular thyroid carcinoma (FTC), medullary thyroid carcinoma (MTC), and anaplastic thyroid carcinoma (ATC) [2]. Note that most

of the aforementioned carcinomas are derivatives of thyroid follicular epithelium except for medullary carcinomas.

Key genetic mutations, such as BRAF and RET/PTC (corresponding to papillary carcinomas mostly) rearrangements, drive thyroid carcinogenesis and offer targets for improved pharmacotherapy [3]. This evolving understanding has refined classification, prognosis, and personalized treatment approaches. Management typically involves a multidisciplinary approach, including surgery, radioactive iodine therapy, and thyroid-stimulating hormone suppression. Emerging targeted therapies and immunotherapies show promise for advanced and refractory cases [4].

Thyroid cancer is the most common endocrine cancer among women and the ninth most common among men in the Kingdom of Saudi Arabia (KSA). Its incidence has been rising over recent years, although the exact cause remains ambiguous [4]. Internationally, thyroid cancer incidence also continues to rise, with women showing a significantly higher prevalence than men. Age trends indicate that thyroid cancer primarily affects middle-aged adults, with peak incidence typically occurring between 45 and 54 years of age. The trend of increasing incidence in younger populations, especially women, may be attributed to a combination of heightened awareness, advanced diagnostic capabilities, and potential lifestyle or environmental factors influencing thyroid health [5].

In the presented article, we present an overview of the current literature of thyroid carcinoma from types, histopathology, clinical picture, diagnosis, treatment to prognosis, focusing on morphological differences and treatment.

Papillary Thyroid carcinoma

Papillary thyroid carcinoma (or PTC) is the most commonly occurring malignant neoplasm of the thyroid, originating from the follicular cells of the latter. PTC usually presents as a low grade, indolent nodule on the thyroid gland, although it could also present as a metastatic disease (could spread through lymphatics) in the neck, albeit rarely, and is usually diagnosed via fine-needle aspiration (FNA) by chance when afflicted patients come in for routine medical examinations. However, it is to be noted that even if certain nuclear alterations (for e.g., the characteristic Orphan Annie Eye nuclei) are observed, it is still difficult to diagnose PTC cases in isolation. Relative widespread of the tumour in addition to the aforementioned unique characteristics are the only diagnostic method of PTC using FNA. PTC is associated with the BRAF V600E and RET/PTC genetic aberrations. This tumour accounts for approximately 80% of all cancers at this site, and occurs in all age groups, with peak incidence during the third to fourth decades, and with females being more at risk (M-F ratio is 1:3). It is generally not fatal, and bears a decent prognosis, thus mortality due to this tumour is highly uncommon [6,7].

Histopathological morphology of PTC is particularly significant. PTC is labelled as such due to the presence of certain finger/fern-like projections that protrude from the tumour, called papillae. Papillae are usually lined by one layer of cuboidal-to-columnar epithelium. The central axis of each papilla is composed of a fibrous core supplied by blood vessels; the fibrovascular core.

The nucleus of this tumour could undergo several variations, most of which are common amongst all the variants of PTC; it usually has longitudinal grooves (visualized with alcohol-fixed Papanicolaou-stained preparations and less conspicuous with air-dried, Romanowsky-stained smears) and is elongated, several nuclei could overlap thus contributing to a crowded appearance etc. Another significant nuclear variation; Orphan Annie Eye appearance due to chromatin being finely dispersed, leading to a 'ground-glass' nuclear appearance. Intranuclear cytoplasmic inclusions appearing as round, eosinophilic bodies are also often present within the nucleus. Multinucleated giant cells are also common [6].

Extracellularly within the stroma of the tumour or at the fibrovascular core, certain concentric and lamellated structures are observed; called Psammoma bodies. They are a result of dystrophic calcification

due to tumour necrosis. Psammoma bodies are a key diagnostic feature of PTC. The amount of colloid is variable and may be string in appearance. Hürthle cell (oncocytic) metaplasia is sometimes seen or even squamous metaplasia. It is noted that these histopathological findings are common in all types of PTC, thus serving as a major criterion, based on which the variants of PTC are classified as indicated in **Figure 1.**

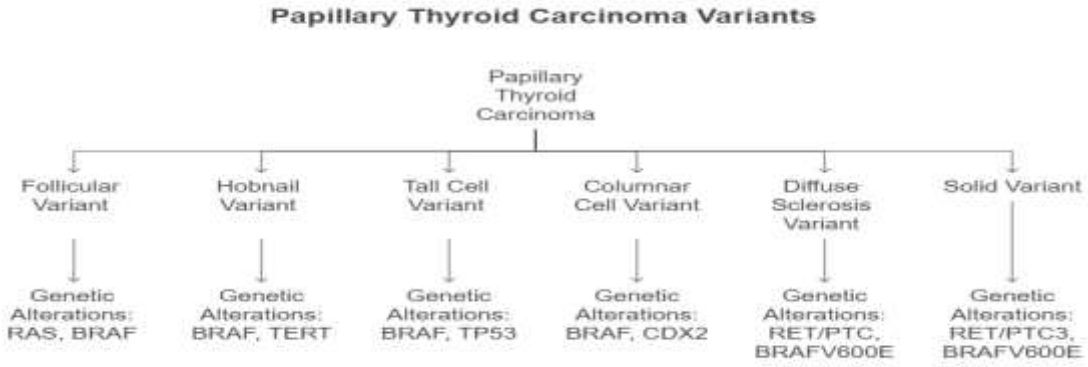

Figure 1: Genetic Alterations in Papillary Thyroid Carcinoma Variants

Follicular Variant of PTC (FVPTC): One of the most commonly occurring variants, medium-sized follicular cells instead of papilla are the dominant observation in this variant but overall nuclear features of PTC are retained. Psammoma bodies, multinucleated giant cells and papillae are absent in this variant. Hypercellular samples with syncytial-like fragments contain 'rosettes' formed of micro follicles. Dispersed microfollicular clusters, isolated neoplastic follicles, and some sheets with branched irregular contours may be present.
Clinically, it is said to be indistinguishable from PTC, and even resembles the follicles in normal thyroid tissue or other follicular patterned lesions including but not limited to; follicular adenomas (due to encapsulation; however, it may be absent). To help differentiate from these adenomas, vascular invasion is an important discerning element. Unfortunately, the FVPTC are diagnosed as 'suspicious for PTC' instead of reporting malignancies, thus impacting prognosis. Similarly, due to its morphological consistencies alongside follicular neoplasms, FVPTC may be misdiagnosed. In order to prevent misdiagnoses, ovoid/cerebriform nuclei must be highlighted, using FNA. FVPTC is frequently associated with RAS mutations, less commonly with BRAF V600E and PAX8-PPARγ. [8,9,10]

Hobnail variant of PTC (HVPTC): This variant features a hobnail cell appearance that denotes a unique feature whereby the tumour cell nuclei are located in the middle/apex of the cytoplasm appearing as bulging of the nuclei at the tip of the cell. A rather clinically aggressive variant, HVPTC is characterized by a specific growth pattern of micro papilla, similar to ovarian papillary carcinoma, breast, lung, kidney adenocarcinomas etc. [11,12]. The BRAF genes are mutated in most cases, however some may involve TERT, GNAS and TP53. These tumours express thyroid transcription factor-1 (TTF-1), thyroglobulin, cyclin D1, and p53 upon immunohistochemistry [11-13].

Tall Cell Variant of PTC (TCV PTC): Previously referred to as poorly differentiated carcinoma of the thyroid, this variant is characterized by foci of tall columnar cells containing abundant cytoplasm that is eosinophilic. TCV PTC is relatively aggressive (extrathyroidal invasion leads to higher mortality within in a span of 5 years) in comparison to the classic presentation of PTC, and accounts for 1.3-12% of all PTCs, and usually presents at the median age of 54.3 years. The neoplastic cells of TCV PTC have an elongated shape, with a height-to-width ratio of 3:1 [14].

A notable feature; some TCV PTC tumours are refractory to radioactive iodine treatment, aiding in diagnosis of this specific variant of PTC. More importantly, this tumour is very prone to metastasis beyond the thyroid gland. Thus, metastatic foci are observed. Locoregional recurrences may exhibit more TCV/consist entirely of TCV cells. Similar to the hobnail variant, the BRAF proto-oncogene is mutated here, along with loss of heterozygosity for chromosome 1 (D1S243) and the p53 gene (TP53) 19 and RET/PTC3 rearrangement [14-16].

Columnar Cell Variant of PTC (CCV): A rare, highly malignant tumour characterised by columnar cells (arranged in a papillary manner) containing hyperchromatic, oval and stratified nuclei alongside subnuclear vacuoles. However, follicular, solid and trabecular growth patterns may also be noted. In contrast to the classic presentation of PTC, the nuclear features of PTC such as nuclear grooves are focal and less prominent, the nuclear chromatin tends to be hyperchromatic and the colloid and cystic change (macrophages) are typically not seen [17,18].

Grossly, these tumours might be encapsulated or infiltrative; the encapsulated type may follow an indolent clinical course. The genes implicated in CCV PCT are BRAF (in 30% of the cases) and the immunological profile of the Columnar Cell Variant (CCV) of Papillary Thyroid Carcinoma (PTC) includes selective expression of CDX2, a nuclear transcription factor from the caudal homeobox family, in 50% of cases. It also features cyclin D1 expression, bcl-2 expression, a high Ki67 proliferation index, membranous localization of beta-catenin, and expression of estrogen and progesterone receptors, irrespective of the patient's gender. Clinically, the cardinal manifestation is an asymptomatic neck mass [17,18].

Diffuse sclerosis variant (DSV) of PTC: Due to its unique histopathology, i.e., diffuse involvement of one/ both lobes of the thyroid gland, it is known as diffuse sclerosis variant. Grossly, a hard tumour is palpable due to calcification and sclerosis. Classic papillary nuclear features are observed, with dense sclerosis, extensive squamous metaplasia, focal to diffuse lymphocytic infiltration, numerous psammoma bodies, and small papillary to solid tumour deposits within intraglandular lymphatics [19].

Notably, DSV always affects younger adults and children (due to the survivors of the Chernobyl accident, the morphology of DSV has been revealed), with background of thyroid showing chronic lymphocytic thyroiditis. Clinically, most cases present with extrathyroidal extension, lymph node metastasis with extra nodal extensions and sometimes even distant metastases (usually to lungs). Locoregional recurrences are normal [19].
Common genetic alterations in DSV PTC are RET/PTC rearrangements (RET/PTC1 > RET/PTC3) and BRAFV600E mutations. RET/PTC3 alterations are seen in patients who have a poor clinical outcome, usually in the advanced stage of the disease [19,20].

Solid variant of PTC: Histologically, SV PTC displays tumour cells in solid nests separated by collagenous bands, with typical nuclear features of PTC. It often includes areas of follicular and papillary growth patterns intermixed with solid growth. Vascular invasion and extrathyroidal extension occur in about 40% of cases. It is important to distinguish SV PTC from insular carcinoma, which lacks the nuclear features of PTC and has a more uniform cell population arranged in nests surrounded by thin-walled vessels [21].

The diagnosis of the solid variant (SV) of papillary thyroid carcinoma (PTC) requires a solid growth pattern of more than 50%. A Japanese study found that even a 10% solid component was associated with shorter disease-free survival. While commonly seen in children, SV PTC can also occur in adults and was notably prevalent among those exposed to radiation, such as after the Chernobyl nuclear accident (similar to DSV). The RET/PTC3 rearrangement is commonly associated with SV PTC, particularly in irradiated tumours. Additionally, a specific BRAF mutation (BRAFV600E + K601) has been identified in SV PTC [21,22].

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) arises from thyroid neuroendocrine C cells, with about 80% of cases being sporadic. The rest are associated with inherited tumour syndromes like multiple endocrine neoplasia (MEN) types 2A and 2B, or familial MTC. Inherited MTC syndromes are autosomal dominant with mutations in the RET proto-oncogene, detectable in most affected family members. Diagnosis typically occurs in the fifth or sixth decade, with women slightly more affected than men. MTC may present with cervical adenopathy in about 50% of cases and can cause symptoms like diarrhoea, flushing, or Cushing's syndrome due to hormone secretion. This is due to the tumour's ability to oversecrete calcitonin, ACTH, calcitonin-gene related peptide etc. [23,24].

Medullary thyroid cancers (MTCs) are usually firm, solid tumours with a greyish-tan colour. They lack a clear, defined outer shell (capsule) and contain a high number of C cells. These C cells can be round, oval, spindle-shaped, or many-sided. The tumour is often divided into lumps by wide bands of connective tissue containing blood vessels. The nuclei of the cancer cells are round or oval and have a speckled pattern of chromatin (the genetic material) inside them. Deposits of a protein called amyloid, derived from calcitonin, are frequently found within the supporting tissue (stroma) surrounding the tumour cells. [23-25].

Follicular thyroid carcinoma

Follicular thyroid carcinoma (FTC) comprises of 5-15% of thyroid cancers, and is characterized by follicular differentiation without the nuclear features of PTC. Grossly, FTC presents as a solitary encapsulated tumour with a grey-tan sometimes salmon-like appearance. These tumours often exhibit focal areas of haemorrhage [26].

FTC's diagnosed is based on invasion of follicular cells into the tumour capsule and/or blood vessels. Most of the FTCs are minimally invasive, showing only slight invasion of the tumour capsule. These minimally invasive FTCs closely resemble follicular adenomas and rarely metastasize (similar to PTCs). In contrast, widely invasive FTCs, although less common, have a much higher propensity for distant metastasis, occurring in approximately 80% of cases and resulting in a mortality rate of around 20%. Genetic mutation of RAS and PAX8-PPAR rearrangements are responsible for the condition [27,28].

Anaplastic carcinoma

Anaplastic thyroid carcinoma or ATC is one of the most aggressive human malignancies, accounting for 3-5% of thyroid cancers. Its targeted demographic is older individuals, whilst being rare in those under 55 years. Grossly, ATC presents as large masses with a flesh-like appearance, often illustrating extensive haemorrhage and necrosis. These tumours grow rapidly and typically invade surrounding tissues leading to potential ulcerations of the dermis [29-31].

Notably, ATC shows several forms including spindle cells, giant cell, rhabdoid, and angiomatoid forms. These patterns can occur singly or in combination within a single tumour. Histopathological features include extensive tumour necrosis, abnormal mitoses, and venous invasion. Polymorphonuclear leukocytes are usually present within the tumour, especially in proximity to necrotic areas. Eosinophilic leukocytic infiltrate is also found [29-31].

Risk Factors

Thyroid carcinoma represents a multifaceted disease influenced by various risk factors as summarized in

Table 1, encompassing iodine intake, oestrogen, TSH levels, genetic, environmental, and lifestyle determinants. Exposure to ionizing radiation, particularly during childhood, is a well-documented risk factor.

Chromosomal and genetic alterations, such as those involving the MAPK and PI3K-AKT signalling pathways, contribute to thyroid cancer growth, with mutations like RET/PTC and BRAF/AKAP9 being notable examples. Hereditary conditions, including familial non-medullary thyroid carcinoma (FNMTC), carry increased risks, with certain syndromes like familial adenomatous polyposis and Cowden syndrome being linked to thyroid cancer. Medullary thyroid cancer (MTC), while largely sporadic, has a significant hereditary component, especially in cases associated with multiple endocrine neoplasia (MEN) syndromes [32].

Estrogen, whether endogenous or exogenous, appears to modulate thyroid cancer risk, with studies suggesting a correlation between estrogen levels and malignancy. Radiation exposure, whether from medical diagnostics or environmental sources, can induce chromosomal rearrangements and somatic mutations, notably increasing the risk of thyroid cancer, especially in children [33]. Iodine intake, through its influence on thyroid hormone synthesis and TSH secretion, is another critical factor, with both excessive and insufficient consumption potentially affecting thyroid function and malignancy risk. Autoimmune thyroid diseases like Hashimoto's thyroiditis and Graves' disease may elevate risk, possibly through chronic inflammation and hormonal dysregulation [34].

Lifestyle factors also play a role, with smoking potentially reducing the risk of certain thyroid cancers, while obesity and high BMI are associated with an increased risk, particularly in men. Alcohol consumption, dietary habits, and exposure to environmental pollutants, including pesticides, nitrates, and metals, further contribute to the complexity of thyroid cancer risk [32,35]. Physical activity may offer protective effects against thyroid malignancy, potentially through mechanisms such as DNA repair and anti-inflammatory pathways. Screening for individuals with heightened risk factors is crucial for early detection and management, though efforts to prevent overdiagnosis and overtreatment are also imperative [36].

Risk Factor	**Risk Level**	**Summary**
Ethnicity	Varies	Incidence differs globally, influenced by factors like screening and access to care.
Heredity	High	Genetic syndromes and mutations increase thyroid cancer risk.
Sex Effects/Hormones	High	Women have higher incidence, possibly due to hormonal factors.
Comorbidity	High	Conditions like goiter and thyroiditis elevate thyroid cancer risk.
Radiation Exposure	High	Ionizing radiation, especially in childhood, significantly raises risk.
Obesity	High	Obesity is a recognized risk factor, possibly linked to rising incidence.
Diet (iodine)	Low	Iodine deficiency may influence risk; high intake (>300 mg/d) may be protective.
Lifestyle (smoking)	Low	Smoking has been associated with reduced risk, potentially due to its effect on estrogen metabolism.

Environmental Pollutants	Low	Pollutants like pesticides may disrupt endocrine function, contributing to risk.
Nitrate and Radiation	Low	Nitrates in water, alongside radiation exposure, may synergistically increase risk, especially in areas with agricultural runoff.
Endocrine Disruptors	Low	Industrial pollutants, acting as endocrine disruptors, may contribute to risk.

Table 1: Risk factor, risk level and findings

Clinical features

Thyroid carcinomas encompass several histological subtypes, each with distinct clinical presentations. Among these, papillary thyroid carcinoma (PTC) is the most prevalent, often presenting as a thyroid nodule that is discovered incidentally during routine physical exams or imaging studies. In many cases, these nodules are asymptomatic and do not cause immediate discomfort. However, PTC can also present with more concerning signs such as lymph node metastasis in the neck or hoarseness due to involvement of the recurrent laryngeal nerve. These symptoms may arise from tumour infiltration or compression of nearby structures. In rare instances, PTC may present with distant metastasis, although this is exceptionally uncommon at the time of initial diagnosis. Follicular thyroid carcinoma and follicular adenoma tend to present similarly, most often as solitary thyroid nodules. These tumours are typically non-functional, and patients are often euthyroid and asymptomatic. However, when tumours grow larger, they may compress surrounding tissues, leading to symptoms such as dyspnoea, coughing, choking spells, hoarseness, or difficulty swallowing (dysphagia). Neck pain may also occur, particularly if the tumour undergoes rapid enlargement due to intertumoral haemorrhage or cystic degeneration. Though follicular carcinomas are less likely to present with distant metastasis, when they do, they commonly affect the lungs or bones. The presence of such metastases is rare at the time of initial diagnosis but can become apparent as the disease progresses [24,37-39].

Medullary thyroid carcinoma (MTC), which can be either sporadic or familial, usually presents as a solitary thyroid mass or nodule, frequently discovered incidentally during a physical exam or imaging study. In sporadic cases, MTC typically presents in adulthood, often in the fifth or sixth decade of life. The clinical presentation may be subtle, with patients reporting no symptoms or only mild discomfort from the neck mass. However, as the tumour grows or metastasizes, more pronounced symptoms may develop, including difficulty swallowing, speaking, or breathing due to compression of adjacent structures. Lymph node involvement, particularly in the cervical and mediastinal regions, is common at the time of diagnosis, with two-thirds of patients presenting with nodal metastasis. While distant metastasis to the lungs, liver, or bones is more commonly observed in later stages of the disease, a small percentage of patients may present with these metastases at initial diagnosis. In advanced MTC, patients may also experience hormone-mediated symptoms such as persistent diarrhoea, which is the most prominent feature of the disease, along with occasional flushing. In rare cases, MTC tumours can secrete ectopic hormones like ACTH, leading to symptoms of Cushing's syndrome. Medullary thyroid carcinoma is also linked to genetic syndromes such as Multiple Endocrine Neoplasia (MEN) type 2, in which patients may present with characteristic features like Hirschsprung's disease or cutaneous lichen. Additionally, in younger patients, certain facial features, such as a Centro-facial ganglioneuroma, may suggest an underlying MEN2B syndrome. Hence, the clinical presentation of thyroid carcinomas can vary significantly depending on the subtype and stage of the disease, ranging from asymptomatic nodules to more severe manifestations of local invasion or distant metastasis. Early detection and timely intervention are essential

for improving outcomes, as the management strategies differ based on the tumour type and extent of disease spread [24,37,38].

Diagnosis

For the initial testing in the suspected thyroid nodule, serum thyroid stimulating hormone (TSH) levels must be checked, along with a neck ultrasound [39,40]. Performing an ultrasound scan helps to differentiate between benign and malignant masses as mentioned in **Figure 2**. Since ultrasounds are safe and do not expose patients to radiation, it not only helps detect primary thyroid neoplasms, but can also be used to assess nearby lymph nodes for metastasis. Thyroid nodules in ultrasounds are distinguished according to their dimensions, any irregularity in shape, margins, presence of micro-calcifications and hypo-echogenicity [40].

Fine needle aspiration cytology (FNAC) is conducted in cases where ultrasound reveals features indicative of potential malignancy. FNAC can be done either by using palpation or ultrasound guidance. Ultrasound guided FNAC is more favoured, particularly for nodules that are difficult to palpate, are located posteriorly or have a cystic component. This method also minimizes the need for repeat biopsies due to insufficient samples [41].

Magnetic Resonance Imaging (MRI) is utilized for assessing tumours in suspected regions. It is used as a secondary option in comparison to other imaging methods due to cost constraints and limited accessibility. MRI is preferred for surveillance of recurrence in high-risk patients, such as those with a family history of neoplasms or cancers that start with aggressive growth and has positive margins, etc. The newer and more advanced MRI techniques aid in differentiating between benign and malignant thyroid lesions by providing improved contrast and detailed assessment about the extent of tumour and its infiltration into surrounding tissues [40]. Serum Calcitonin levels and Carcinoembryonic antigen (CEA) tumour marker should be assessed only if patient is suspected to have MTC [39].

In the age of precision medicine, identifying genetic mutations is crucial for the diagnosis and staging of thyroid cancer. PTC patients show BRAF or RAS gene mutations, while patients with radiation related PTC show a higher frequency of RET mutations. RAS gene mutations are most commonly seen in FTC, and TP53 gene mutations in ATC [42,43]. Mutations in RET proto-oncogene are responsible for majority of MTC cases, while a minority of cases are attributed to sporadic RAS mutations. RET mutations may arise sporadically or as inherited germline mutations showing autosomal dominant character. RET germline mutations can increase the risk of early onset of MTC as a part of multiple endocrine neoplasia's (MEN) type 2A and 2B syndromes [44].

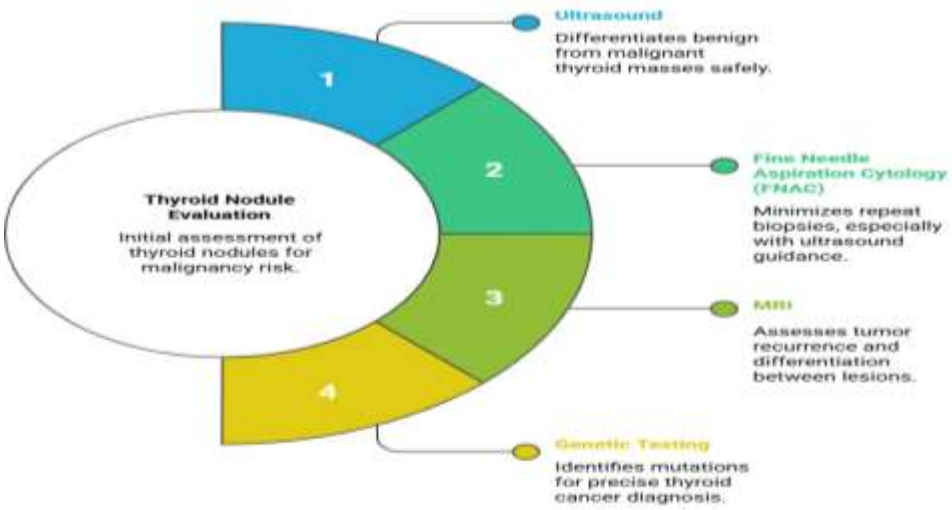

Figure 2: Comprehensive evaluation of thyroid nodules

Surgical Treatment

Surgery is the primary treatment option for differentiated cancers as indicated in **Figure 3**. For primary tumours, surgical procedure options consist of near total thyroidectomy in which less than one gram of thyroid tissue near the recurrent laryngeal nerve is left; hemi-thyroidectomy, either with or without isthmectomy.

For managing thyroid cancer with primary tumour sizes ranging from 1-2cm or larger, near total or total thyroidectomy is preferred. Due to the significant occurrence of thyroid carcinoma's multifocal distribution, complete removal of the thyroid gland decreases the possibility of malignancy remaining in the residual parenchyma. Thyroidectomy also allows for accurate tumour risk evaluation, which relies on size and extracapsular infiltration [41].

Recent technological advancements in total thyroidectomy devices like nerve monitoring and hemostatic vessel-sealing devices have improved both the procedure's safety and the effectiveness of removing the affected tissues in cancer patients. According to studies, an initial thyroidectomy for suspected malignant nodules based on FNAC biopsy is also more cost effective than an initial lobectomy and intraoperative frozen section surgery [41]. Even so, ipsilateral thyroid lobectomy is a viable option in low-risk differentiated thyroid cancers instead of total thyroidectomy [42].

Radioactive Iodine Therapy

Radioactive iodine or isotope ^{131}I, in coordination with thyroidectomy is used to thoroughly ablate the thyroid gland and eliminate any potential remaining cancer post-surgery. In this therapy, through sodium iodide transporters, ^{131}I enters thyroid cells and causes rapid cell death by emission of short-wavelength beta rays. When administered the first-time following thyroidectomy surgery, it is known as iodine ablation and the administrations after are called as treatment [41,45].

By removing the remnant thyroid tissue, the risk of recurrence is reduced and the sensitivity of diagnostic tests (such as serum thyroglobulin levels and whole-body scintigraphy scans) that are used to detect residual or metastatic illness is increased. This approach is especially beneficial for differentiated thyroid carcinoma [41]. In addition, adjuvant treatment with radioiodine is recommended to improve long-term results by destruction of occult microscopic foci of cancerous cells in the thyroid remnant or in other parts of the body. According to current guidelines, radioactive iodine should be used sparingly and with the lowest activity necessary to ensure successful course of treatment, taking into account each patient's risk [46].

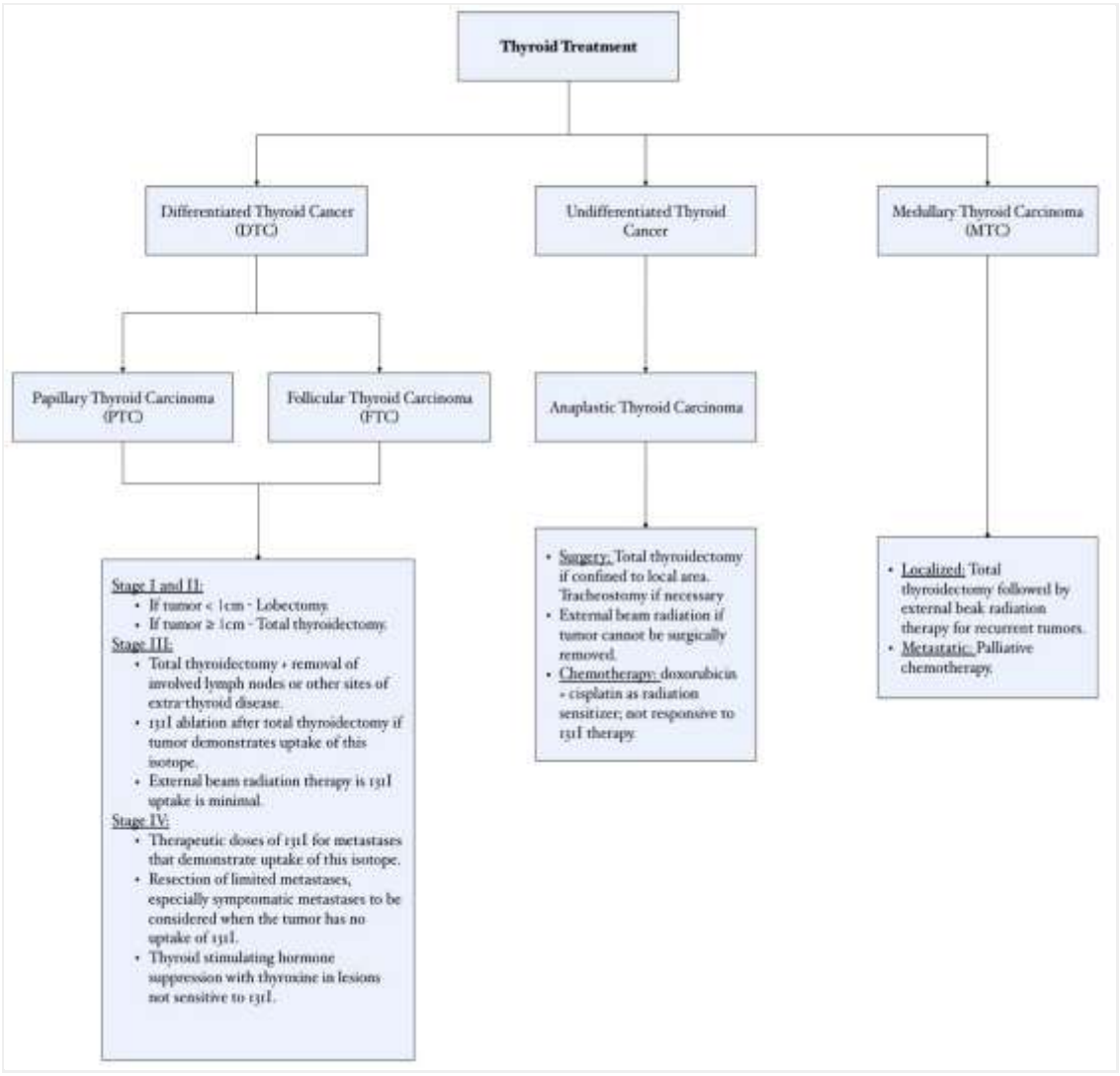

Figure 3: Treatment of different thyroid carcinomas [41]

Prognosis

When determining the prognosis of thyroid carcinoma, the "tumour-node-metastasis" (TNM) classification scheme is used based on size of the tumour, neighbouring structures infiltration, along with distant and lymph-node metastases. Age, genetic factors, and specific histological type of carcinoma are also considered important determinant factors for prognosis. Patients with stage I or stage II disease usually have a very good prognosis. These patients are usually less than 45 years in age and are diagnosed at an early stage. Patients who are 45 years old or above may have less favourable stages III and IVA-IVC, with a poor prognosis [45].

Follicular thyroid carcinoma (FTC), Papillary thyroid carcinoma (PTC), Hürthle cell carcinoma (HTC) are all different types of differentiated thyroid carcinomas (DTC). A 10-year survival rate in 90 – 95% patients has been seen in DTC with excellent prognosis, majorly in the younger patients. A small number of patients may develop recurrence or advanced, metastatic DTC which can be unresponsive to treatment. In this case, the overall survival is poor, with 5-year or 10-year survival rates respectively [47,48]. FTC patients usually present with advanced stage and distant metastases, and are usually older in age at diagnosis, leading to a very poor prognosis. A mutation in the TERT promoter is also seen in DTC, which is an important prognostic marker, particularly in FTC patients [28]. Moreover, multiple studies have reported a link between BRAF mutation and recurrence of PTC, leading to a worse prognosis [49].

Medullary thyroid carcinoma (MTC) is a very rare type of cancer that has a favourable prognosis if detected early. However, for patients with advanced or metastatic disease, there are no effective treatment options. The recurrence rates of 5-years and 10-years is less than 1% - 8.5% in patients who respond better to treatment. Familial MTC is often linked to multiple endocrine neoplasia type 2A (MEN2A) or multiple endocrine neoplasia type 2B (MEN2B), and MTC associated with MEN2A tends to show a favourable prognosis. Additionally, the presence of a mutation in the RET proto-oncogene can also indicate a poor prognosis. Calcitonin is a significant marker for MTC used to determine prognosis. High levels of calcitonin could indicate an overall poor prognosis [50]. Recently, elevated levels of a biomarker called carbohydrate antigen 19.9 (Ca 19.9) in the blood have been identified as a prognostic indicator for poor prognosis of MTC [51].

Anaplastic thyroid cancer (ATC) is another rare type of aggressive carcinoma characterized by rapid onset, local and distant metastases, and local progression [50]. Undifferentiated (anaplastic) thyroid tumours are classified as stage IV disease, indicating a very poor prognosis [45]. The prognosis for ATC remains poor, with a 1-year overall survival rate ranging from 20% - 50%. However, recent treatments have shown some potential for improving the prognosis [29]. TERT promoter mutations have a lower prevalence in PTC compared to poorly differentiated thyroid cancer (PDTC) and ATC. These mutations are highly frequent (up to 50%) in PDTC and ATC and have been linked to poor prognosis, including increased recurrence and mortality rates [49].

Conclusion

Treatment should be based on their increased risk for recurrence instead of overall mortality, and lifelong follow up is required because recurrence and death may not occur for decades after diagnosis. Initial treatment will generally include total thyroidectomy and central compartment lymph node dissection especially if lymph node disease is found in the preoperative evaluation. Radioiodine ablation should be individualized and given to those with a higher risk of recurrence. Large multicentre studies are needed to better under-stand optimal treatment approaches to this unique population. All care of thyroid carcinoma should be delivered by multidisciplinary specialized teams minimize possible complications and ensure competent follow-up.

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