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Cross-Sectional Imaging Evaluation of Thyroid Carcinoma and Histopathological Variants: A Primer for Radiology Trainee

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Abstract

Thyroid cancer is the most common of endocrine malignant tumors with the most common endocrine cancer related deaths. The incidence of thyroid cancer is approximately 2.1% worldwide and 3.3% in the United States [1]. The incidence of thyroid cancer has increased greatly during the last few decades due to improved diagnosis of subclinical cancers and environmental factors [2]. The role of radiologists is paramount in proper diagnosis of thyroid cancer without causing psychological, physical, or financial burden on the patient or health care system [2,3]. A challenge to radiologists is how to accurately report clinically significant thyroid nodules among those incidentally found in CT, MRI or nuclear studies such as PET/CT [4-6]. In this review, we will discuss the imaging features of thyroid carcinomas and their histological variants and subtypes.

Keywords: Thyroid cancer; Radiologists; Columnar cells; Cytopathologists; Microcalcifications; Health care system

Imaging Modalities

Ultrasonography

High-resolution ultrasonography is the imaging modality of choice for pre-operative evaluation of thyroid nodules and determination of nodal metastasis with 51-62% sensitivity, and 79-98% specificity [6-10]. The common sonographic findings that indicate a benign nature of the nodule include uniform halo around the nodule, predominantly cystic, and an avascular appearance on color flow Doppler [11]. Suspicious imaging criteria include internal microcalcifications, capsular interruption, extrathyroidal extension, markedly hypoechoic nodules which appear taller than wide in transverse plane and cervical nodal metastasis [11,12]. Ultrasound imaging evaluation criteria are summarized in table 1. The American College of Radiology (ACR) has developed the thyroid imaging reporting and data system (TI-RADS) as a standard system to better evaluate thyroid nodule and provide guidance for further management [3,13]. The ACR TI-RADS is a scoring system based on ultrasound imaging features which classify thyroid nodules into five categories: TR1 benign and TR5 highly suspicious [3]. Each nodule should be evaluated for internal composition, echogenicity, shape, margin and internal echogenic foci [13]. Each imaging feature is recorded and given points. The nodules are categorized according to the cumulative score into five categories.13 Contrast-enhanced ultrasound and ultrasound elastography are recent imaging modalities which may help in further characterization of the thyroid nodules [14].

Computed tomography

Although CT is not optimal in characterization of thyroid nodule, CT is helpful to demonstrate extrathyroidal extension and invasion of surrounding structures [2,4,15]. Evaluation of vascular and osseous invasion as well as airway involvement is more easily identified on CT [2]. The thyroid gland typically appears hyperattenuating on non-contrast CT scan with homogenous enhancement on contrast-enhanced exams [2,4]. The updated guidelines show the importance of iodinated contrast CT studies for locoregional evaluation of thyroid nodules. Prolonged delay of radioactive iodine therapy of longer than one month following iodinated contrast administration is likely unnecessary and is not recommended by the American thyroid association [16-18].

Magnetic resonance imaging

Routine MRI lacks the optimal spatial resolution for evaluation of thyroid nodules. However, it is excellent in demonstrating extra-

thyroid extension, infiltration of peritracheal and prevertebral muscles, as well as vascular and osseous invasion [2,4,15]. Diffusion-weighted MRI can help to evaluate thyroid nodules and differentiate benign from malignant lesions [14,19-21]. Noda et al. [22] reported the cut-off ADC value to differentiate benign from malignant thyroid nodule was 1.12 x 10-3mm/s with sensitivity and specificity of 86% and 100% respectively [22]. Hoang et al. [23] proposed a 3-tiered system strategy for further work up on incidentally recognized thyroid nodules on cross-sectional imaging (CT and MRI) [23]. Fine needle aspiration cytology is recommended in highly suspicious nodules with lymphadenopathy and extrathyroidal extension [4]. Ultrasound is recommended in indeterminate nodules with high-risk history, nodules > 1cm in patients <35 years or nodules >1.5cm in patients >35years [2,4]. Indeterminate nodules < 1.5cm without high-risk factors usually don't require further evaluation [4].

Table 1: Ultrasound imaging features for evaluation of thyroid nodules.

Benign	Intermediate	Suspicious
Surrounding uniform hypoechoic halo	Lack of the surrounding halo	Internal microcalcifications
Avascular on Doppler	Increased internal vascularity	Capsular interruption with extra-thyroid extension
Predominantly cystic	Solid	Cervical nodal metastasis
	Ill-defined outline	Taller than wide
	Irregular margins	Markedly hypoechoic

Nuclear Scans

Nuclear thyroid scintigraphy

Thyroid scintigraphy is routinely used for evaluation of thyroid nodules with reduced serum thyroid-stimulating hormone level [12]. It assesses the functional activity of the thyroid nodule which may be functioning which appear as hot nodule or non-functioning which appear as cold nodule [12]. Rarely, the hot nodule is malignant. However, the cold nodule carries a higher risk (approximately 27%) of malignancy [12].

$^{131/123}$I-whole body scan

131/123I WBS is usually utilized postoperatively to assess locoregional residual tumor or occult distant metastasis [14,15]. The presence of normal thyroid tissue after total thyroidectomy can represent a diagnostic dilemma due to normal uptake within the thyroidectomy surgical bed [15]. It has been proposed that administration of high doses of ^{131}I (ablative dose) rather than low diagnostic dose in post-surgical cases. This approach allows ablation of thyroid remnants, screening for locoregional residual or distant metastasis and eradication of any tumor focus which uptakes the radioactive iodine [14,15].

^{111}In-octreotide SPECT/CT

This is a somatostatin receptor scintigraphy which is widely utilized in imaging of neuroendocrine tumors [24]. ^{111}In-octreotide SPECT/CT is not recommended in routine evaluation of medullary thyroid carcinomas however it is helpful for tumor localization and metastatic detection in postoperative patients with elevated calcitonin [24-26]. This imaging modality depends on the fact of somatostatin receptor (SSTR) expression in medullary thyroid carcinomas [24,27]. Five subtypes of somatostatin receptors have been identified SSTR 1-5; SSTR2 and SSTR-5 are the most common [27]. Many somatostatin analogs could be labelled with several radiotracers e.g. 111In-octreotide or ^{99m}Tc-HYNIC-TOC [27].

Positron emission tomography

The role of 18F fluorodeoxyglucose (FDG) positron emission tomography (PET) in evaluation of thyroid nodules is unclear, yet it has a high negative predictive value [15]. Thyroid carcinoma typically appears with avid ^{18}F FDG activity [15]. ^{18}F FDG PET is useful in evaluation the extent of cervical lymphadenopathy or in patients with suspected distant metastasis [15,28]. 68Ga-DOTATATE PET/CT was shown to accurately localize the tumor in recurrent or metastatic MTC with elevated calcitonin (>1000pg/ml) [28]. 18F-fluorodeoxyphenylalanine (^{18}F- FDOPA) is a recent modality which can detect subtle foci of tumor in recurrent MTC with even mildly elevated calcitonin (~ 150 pm/ml) [28].

Fine needle aspiration cytology

Fine needle aspiration biopsy remains the gold standard for diagnosis of thyroid nodules.9 Some histological PTC variants represent a notable challenge for cytopathologists on FNA specimens.29,30 In such situation, ultrasound guided core biopsy is recommended [11]. The adequacy and diagnostic accuracy of specimens are variable due to the technique and biopsied site.11 FNA is recommended in patients with intermediate-high suspicion (TI-RADS 4-5) if the nodule > 1cm. In case of low suspicion (TI-RADS 3), FNA might be performed if the nodule is > 1.5cm. Generally, FNA is preferred in nodule > 2cm even with very low suspicion [3,13].

Thyroid Carcinoma Types and Variants

Thyroid carcinoma is classified into differentiated, poorly differentiated, anaplastic and medullary carcinoma [31]. The differentiated thyroid carcinoma includes both papillary and

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follicular carcinomas [10,31]. The diagnosis is based histologically on characteristic nuclear features such as intra-nuclear pseudo-inclusions, nuclear grooves, and psammoma bodies [9,10] Table 2 summarizes the common imaging features of each thyroid carcinoma and its variant.

Table 2: Histological variants of papillary thyroid carcinoma.

Favorable	Less Favorable	Aggressive
Classic-conventional	Solid variant	Tall cell variant
Follicular variant	Diffuse sclerosing	Columnar cell variant
Microcarcinoma	Papillary thyroid carcinoma with nodular fasciitis-like variant	PTC with prominent hobnail features
Oncocytic variant		Clear cell variant
Warthin-like variant		Insular variant
Cribriform morular		

Papillary thyroid carcinoma

PTC is the most common thyroid malignancy which accounts for 80% of thyroid cancers and 1% of all malignancies [1,6,7,29,32-36]. It is more common in women [9]. PTC has an excellent prognosis, with an overall 90% 10-year survival rate [4,31,32,37-39]. Most patients respond to surgery and targeted therapy with radioactive iodine [9]. The prognosis is associated with age, tumor size, extra-capsular invasion, extra-thyroid extension, nodal or distant metastasis and histological variants (subtypes) [7,9,31,37]. Papillary thyroid carcinoma typically manifests as a painless thyroid nodule which is incidentally discovered on routine examination. Patients are less frequently present with nodal metastasis as a primary presentation.9 Ultrasonography is the imaging modality of choice for pre-operative evaluation of thyroid nodules and determination of nodal metastasis with 51-62% sensitivity, and 79-98% specificity [7-9]. The common sonographic findings are a solid hypoechoic nodule with micro or macro-calcifications [9]. Nuclear thyroid scans are another imaging modality to evaluate thyroid nodules with a cold nodule pattern as the common finding [9]. Fine needle aspiration cytology is the gold standard for diagnosis of papillary thyroid carcinoma with an accuracy ≥ 95 %.9 The management of PTC depends on tumor characteristics, occult versus evident nodal metastasis, and distant metastasis [7]. Risk factors include genetic factors, exposure to ionizing radiation, and nodular disease of the thyroid. PTC has many histopathological variants. The histopathological subtype (variant) represents the most important prognostic factor and determinant of survival [7,31]. Each variant has a specific growth pattern, cell types, and stromal changes [7]. These variants can be divided into favorable, less favorable, and aggressive according to the prognosis (Table 2).

Papillary thyroid carcinoma, classic variant

The classic or conventional PTC variant is the most common subtype which comprises approximately 80% of PTC. This variant is characterized by complex papillae with thin fibrovascular core, covered by cuboid and columnar cells with eosinophilic cytoplasm [9]. Other histological criteria include intra-nuclear pseudo-inclusions resemble Orphan Annie eye appearance (nuclei with uniform staining, which appear empty due to powdery chromatin and marginal micro nucleoli), nuclear grooves, and psammoma bodies [9,40]. Classic PTC variant has a strong association with RET/BRAF mutations [7]. Typically, classic PTC presents clinically as a painless growing thyroid nodule with possible cervical lymphadenopathy. On ultrasound it appears as a hypoechoic nodule with ill-defined margins, irregular outlines, and internal microcalcifications. Color flow Doppler shows increased internal vascularity of these nodules [30]. The classic PTC has a good prognosis with an approximately 76.6% overall 10-year survival [31]. Extrathyroidal extension, cervical nodal metastases, and vascular invasion are associated with poor prognosis (Figure 1) [31].

Papillary thyroid carcinoma, microcarcinoma variant

The microcarcinoma variant refers to tumor less than 1cm at its widest diameter that is undetectable in preoperative examination [7,41-43]. This subtype also has been termed occult papillary carcinoma [7]. Microcarcinoma PTC variant has female predominance with a wide age range between 27-74 years [43]. This tumor is the most frequently encountered PTC at autopsy [7]. Histologically these are characterized by frosted glass appearing nuclei, with nuclear grooves, desmoplasia and proximity to thyroid capsule [7]. Immunohistochemical characteristics of this variant include positive stating for thyroglobulin transcription factor-1, thyroglobulin, galectin-3, and Hector Battifora Mesothelial-1 (HBME-1) [7]. However conservative surgical treatment is the treatment of choice for microcarcinoma PTC, patients are kept under surveillance to exclude possibility of occult metastasis [7,41]. Following prompt and adequate treatment, there is usually no tumor recurrence, distant metastasis, nor effect on survival [7,42].

Papillary thyroid carcinoma, follicular variant

Follicular variant PTC is the second most common subtype of PTC which accounts for 9-30% of all PTC [1,8,30,44]. The follicular variant of PTC was first described by Lindsay in 1960,

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followed by Cheng and Rosai in 1977 and 1983 [1,44]. Follicular variant PTC is characterized by nuclear features of PTC and a follicular growth pattern [1,33]. Two clinically and genetically distinct subtypes have been described; encapsulated (EFVPTC) and non-encapsulated (NFVPTC) [1,44]. Encapsulated FVPTC presents a diagnostic challenge as it is difficult to be differentiated from a benign follicular adenoma [1,30,33,44]. The non-invasive encapsulated subtype has been reclassified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) [44]. Macrofollicular variant of the papillary thyroid carcinoma is another follicular variant subtype which has larger follicles ≥ 250mm.45,46 EFVPTC usually behaves as follicular tumors with rare (5%) metastatic lymphadenopathy.1 These are associated with high-rate RAS mutations (36%) without BRAF mutations [1,33]. In contrast, non-encapsulated FVPTC behaves like classic PTC with cervical lymphadenopathy (65%), high rate of BRAF mutations (26%) and less RAS mutations (10%) [1,8]. On ultrasound the encapsulated subtype appears as well-demarcated isoechoic nodule without macrocalcifications (Figure 2) [8,30]. Cystic and partial cystic appearance without other aggressive features have been described.30 The non-encapsulated (infiltrative) subtype has a more aggressive and suspicious appearance on ultrasound.30 These appear as ill-defined nodules with irregular margins, internal microcalcifications and locoregional lymphadenopathy [8,30].

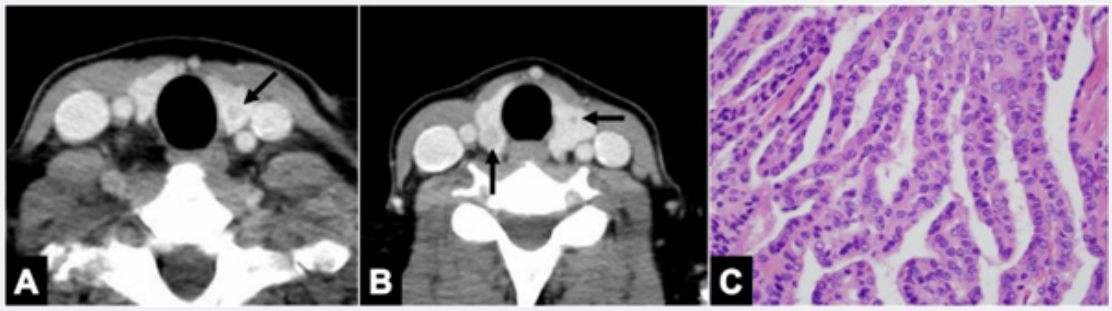

Figure 1: Classic variant, multi-focal papillary thyroid carcinoma in a 65-year-old female. Axial contrast-enhanced CT images (a and b) show multi-focal hypodense nodules within both thyroid lobes (arrows). High-power photomicrograph (c, hematoxylin-eosin, original magnification ×400) reveals classic variant with characteristic architectural and cytologic features: papillae with fibrovascular cores; nuclear enlargement, overlapping, and elongation; irregular nuclear membranes with longitudinal grooves; intranuclear pseudo inclusions and empty appearance of nucleoplasm.

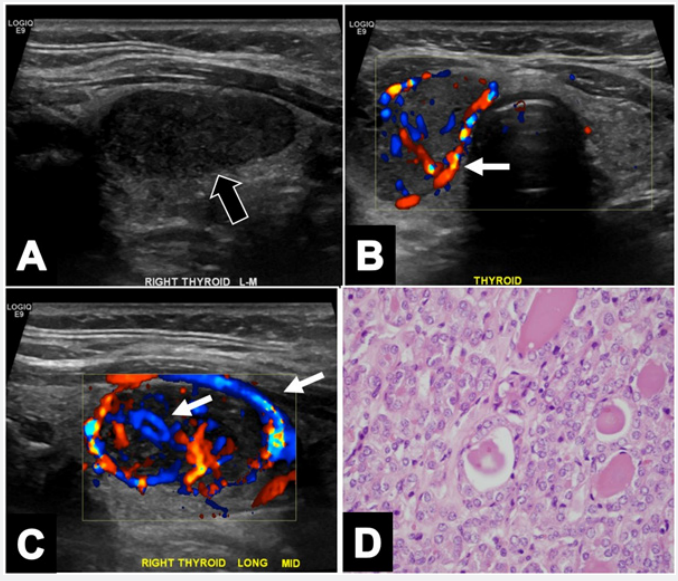

Figure 2: Follicular variant, papillary thyroid carcinoma in a 48-year-old female. Longitudinal B-mode ultrasound image (a) shows a well-defined ovoid hypoechoic thyroid nodule (outlined arrow). Transverse and longitudinal color Doppler ultrasound images (b, and c) demonstrate "type 4" flow pattern, intense hypervascularity, (white arrows). High-power photomicrograph (d, hematoxylin-eosin, original magnification ×400) reveals follicular variant with same nuclear features of the classic PTC variant but the neoplastic cells grow in a predominately follicular pattern with irregularly shaped small-medium sized follicles and hyper eosinophilic colloid. The cells are cuboidal in shape and have variable cytoplasm

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Papillary thyroid carcinoma, oncocytic cell variant

The oncocytic (Hurthle) variant represents approximately 1-11% of all PTC and was first described by Karl Hürthle in 1894 [8,40,47]. Histologically the oncocytic variant is characterized by large irregularly clustered oncocytes with marked eosinophilic granular cytoplasm, "Orphan Annie" nuclei, and other features of classic PTC [7-9,40]. These tumors usually have no psammoma bodies or areas of calcification [7]. Several studies found an association between the oncocytic variant and autoimmune (Hashimoto's or lymphocytic) thyroiditis [8,33,40]. Whereas other articles advocate that presence of thyroiditis is a differential key point between the oncocytic and Warthin like PTC variants [9]. This variant has variable prognosis and biological behavior but usually better than classic PTC [7,8,40]. On ultrasound these tumors appear as well-defined nodules with less frequent internal calcifications (Figure 3) [8].

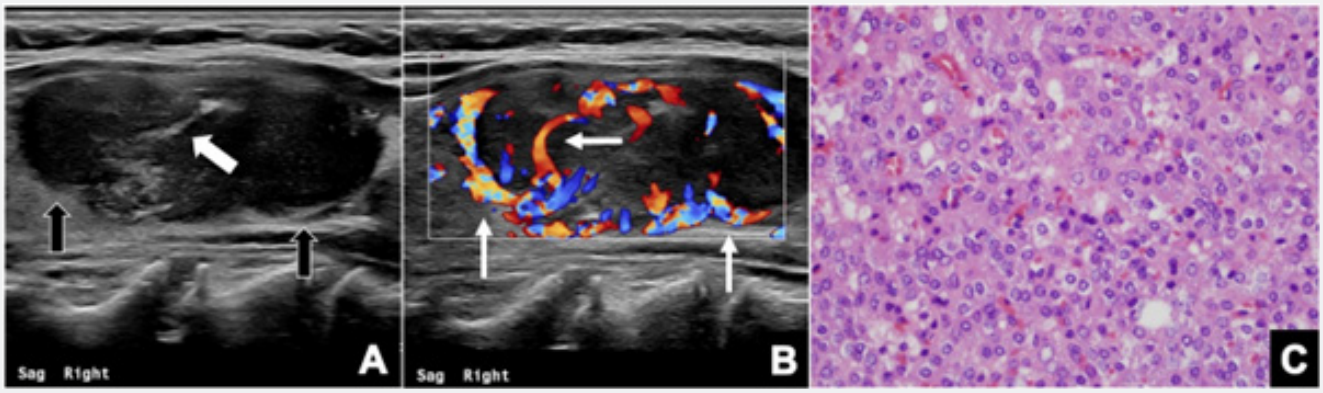

Figure 3: Oncocytic variant, papillary thyroid carcinoma in a 59-year-old female. Longitudinal B-mode ultrasound of the thyroid gland (a) demonstrates a well-circumscribed ovoid shaped hypoechoic thyroid nodule (outlined arrows) with internal hyper echoic band (central scarring) (white wide arrow). Longitudinal color Doppler US image (b) shows type 4 flow pattern, extensive peripheral and internal hypervascularity (white arrows). High-power photomicrograph (c, hematoxylin-eosin, original magnification ×400) revealed similar nuclear features of the classic variant but with abundant granular eosinophilic cytoplasm.

Papillary thyroid carcinoma, warthin-like variant

This uncommon, recently recognized variant resembles a Warthin tumor of the salivary glands histologically [8]. Apel et al. first described this entity in 1995 [8,10,48]. Microscopically, this variant is characterized by oncocytic cells on background of lymphocytic (Hashimoto) thyroiditis with papillary architecture and characteristic nuclear feature of papillary thyroid carcinoma [8-10,33]. Warthin-like PTC variant has lower BRAF mutations compared to classic PTC [10]. A few reports had described ultrasound imaging features of Warthin-like variant which include well-circumscribed nodules with irregular margins and internal microcalcifications [49-52]. The thyroid parenchyma typically appears heterogenous due to associated thyroiditis (Hashimoto thyroiditis) [8]. The propensity of lymphocytic infiltration within the tumor might contribute to the control of tumor growth with favorable prognosis of this variant, and less nodal metastasis [8].

Papillary thyroid carcinoma, cribriform morular variant

A rare variant (0.2% of all PCT), this carcinoma has a strong association with autosomal dominant inherited familial adenomatous polyposis and Gardner syndrome [9,10,33,53]. These are usually multiple and may precede colonic manifestations in 50% of cases [8,10,53]. Therefore, additional work up and screening with colonoscopy for early detection of colon cancer is recommended [8,53,54]. Cribriform morular variant of PTC is common in young female with female-to-male ratio of 17:1 [7,8,10]. Microscopically, these tumors are characterized by cribriform pattern with solid and spindle cells, squamoid morules, and focal papillary architecture [7,33]. The tumor has positive nuclear staining to β-catenin, thyroglobulin and lymphoid enhancing factor-1 (LEF-1) [10,32,33,53,54]. The cribriform morular variant presents as a well-circumscribed capsulated mass with cervical lymphadenopathy like classic PTC [7,55]. This cribriform variant has an indolent course with good prognosis and low incidence of recurrence [8,53]. Preoperative diagnosis of this variant based on imaging criteria is not easy [10,53]. However, the most common features on ultrasound include well defined solid nodule of heterogenous hypo echogenicity [8,10,55]. These masses typically lack internal microcalcifications, hypoechoic halo, or other malignant features [8,10].

Papillary thyroid carcinoma, solid variant

The solid cell variant is also rare and comprises approximately 3% of all PTCs [8-10]. The tumor consists of sheets and solid nests of cells with typical nuclear morphology of PTC [8,9,33]. These are common in children and are related to prior radiation exposure with RET/PTC3 rearrangement [7,8,10,33,56]. Many articles reported a high percentage of vascular invasion, extrathyroidal

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extension, and distant metastasis with less favorable prognosis and survival rate compared to classic PTC [7,8,33]. This aggressive variant should be treated promptly with total thyroidectomy, central neck dissection and thorough work up for detection of distant metastasis [7]. On ultrasound, the tumors manifest as an irregularly outlined unencapsulated nodule with high-intermediate suspicious criteria i.e. cervical lymphadenopathy and distant metastasis [9,10]. This variant should be distinguished from poorly differentiated thyroid carcinomas due to similar insular, solid, and trabecular growth patterns [56].

Papillary thyroid carcinoma, diffuse sclerosing variant

Diffuse sclerosing PTC variant accounts for 0.3-5.3% of all PTC [7,57]. These tumors tend to be more common in young female patients with an age range of 15-30 years [33,57]. Histologically, these tumors are characterized by diffuse thyroid involvement, extensive squamous metaplasia, scattered macrocalcifications which correlate to abundant psammoma bodies, stromal fibrosis, and prominent lymphocytic infiltration [33,57]. This variant is usually associated with elevated serum thyroid antibodies and has unfavorable prognosis compared to classic PTC [7,57]. On US, these tumors manifest with thyroid enlargement, heterogeneous hypo echogenicity, diffuse microcalcifications, and may resemble a "snow-storm" appearance, with or without a dominant mass [57]. DSV-PTC typically present with extra-thyroid extension, bilateral cervical lymphadenopathy, and lung metastasis [7,33,57].

Papillary thyroid carcinoma with nodular fasciitis like stroma

PTC-NFS is an uncommon papillary thyroid carcinoma variant (0.17%-0.5% of all PTC) which was first described in 1991 by Chan et al. [58,59] This variant typically has abundant stroma (approximately 60-80%), composed of both fibroblasts and smooth muscle cells, with sparse papillary carcinoma features on histopathology [32,58,60]. Some authors described immunoreactivity to transforming growth factor -β which is known to activate fibroblasts and induce scarring [60]. Other studies demonstrate BRAF-V600E and CTNNB1 mutations in the epithelial and mesenchymal components respectively [32,61]. Clinical features are usually like classic PTC variant [60]. PTC-NFS share similar imaging features with thyroid lymphoma and anaplastic carcinoma [33,58,60]. On ultrasound, PTC-NFS appear as homogenous mass with well-circumscribed margins and low echogenicity, owing to its homogenous internal composition of abundant fibromatosis like stroma [58]. The mass is usually hypovascular with scanty vascular flow on Color flow Doppler ultrasonography [58]. Typically, there was no extra-thyroid extension or associated enlarged cervical lymph nodes. One should pay close attention to the fact of its prominent stroma which could make FNA cytology difficult [58]. Hence, core-needle biopsy is recommended when FNAC results are inconclusive. In this variant, the size and extension of the neoplastic epithelial component is important for prognosis [58].

Papillary thyroid carcinoma, tall cell variant

The tall cell variant is a well-recognized aggressive PTC-variant which was first described by Hawk and Hazard in 1976 [7,8,37,62-64]. TCV accounts for approximately 4-17% of all PTC [7-10,35]. This tumor is characterized by tall cells 2-3 times than width [33,37,40,65,66]. Histologically, the tumor cells have nuclear features of conventional PTC, abundant eosinophilic cytoplasm, and other aggressive features i.e. extensive necrosis, brisk mitotic activity, and nuclear pleomorphism [33,65]. BRAFV600E mutation is found in up to 92.6% of TCV tumors, which is believed to be associated with its aggressive behavior [10,65]. This tumor is characterized by high expression of mucin 1 and matrix metalloproteinase, which contribute to tumor aggressiveness through increase of stromal degradation and invasion potential [8]. Some reports also advocated the contribution of overexpression of c-Met (tyrosine kinase receptor) with tumor aggressiveness [7]. Most patients are older and present with large bulky tumors, which often usually have a more aggressive course than the usual PTC [10,33]. The World health Organization determined certain criteria for diagnosis of the tall cell variant which include tall cells 2-3 times as wide, and the tall cells form > 30% of the tumor volume [7,10,37,67]. The tumor is associated with aggressive criteria e.g. extrathyroidal extension, nodal and distant metastasis with increased tumor recurrence [7,35,37,55,63,64]. On ultrasound the tall cell variant appears as markedly hypoechoic nodule with internal microcalcification, irregular spiculated margins, and evident extra-thyroid extension [8,10,35,68]. Cervical lymph node metastasis is a typical finding [8,35]. TCV PTC should be included in the differential diagnosis of aggressive thyroid tumors because it almost always appears as a highly suspicious nodule in the US [10]. 18F-FDG PET is an important imaging modality in evaluation of patients with high thyroglobulin and negative whole-body radio iodine scanning which is sometimes referred as thyroglobulin-elevated negative iodine scintigraphy (TENIS) [65] 18F-FDG–avid disease is associated with tumor aggressiveness and relative resistance to radio- iodine therapy even in patients with differentiated thyroid carcinoma who demonstrate avid radioiodine uptake (Figure 4) [65]. Poor prognostic factors include older age at presentation, larger tumor size, and presence of extra-thyroid extension [7,66].

Papillary thyroid carcinoma, columnar cell variant

This is a very rare variant accounting 0.15-0.2% of all papillary thyroid carcinoma which was first described by Evans in 1986 [7,39,69]. Columnar cell variant is considered an aggressive PTC subtype according to the revised American Thyroid Association guidelines [39]. Many reports indicated fast tumor growth with high incidence rate of local invasion, and nodal metastasis which contribute to high recurrence rate [39]. However, other reports described a well-defined capsulated form with indolent clinical

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course and more favorable prognosis [33,39,56,70]. This variant may resemble the tall cell variant however columnar cell variant is made up of pseudo stratified elongated columnar cells with clear cytoplasm [7,9]. Some cells may have supranucleur and subnuclear cytoplasmic vacuoles and resemble endometrial or colonic adenocarcinomas.9 Due to lack of clear nuclear features of conventional PTC in these tumors, the metastatic lesions could be mistaken as originating from colon, lung, or endometrium [29]. The tumor cells are usually positive for thyroid transcription factor 1 (TTF-1) and thyroglobulin [7,29]. The BRAFV600E mutation is found in one-third of these tumors which might be associated with nuclear overexpression of estrogen and progesterone, and increased cyclin D1 and Ki-67 proliferation [7,10]. On ultrasound the encapsulated form typically appears as small, well-circumscribed, hypoechoic nodule with internal microcalcifications and variable metastatic lymphadenopathy [10,39]. The aggressive (extra-capsulated) form manifests as large microlobulated/infiltrative, markedly hypoechoic nodule with capsular interruption and extrathyroidal extension [10,29,39]. Locoregional nodal and distant metastasis are frequently encountered [7,39]. Further research studies are recommended to accurately stratify the aggressive from non-aggressive subtypes.

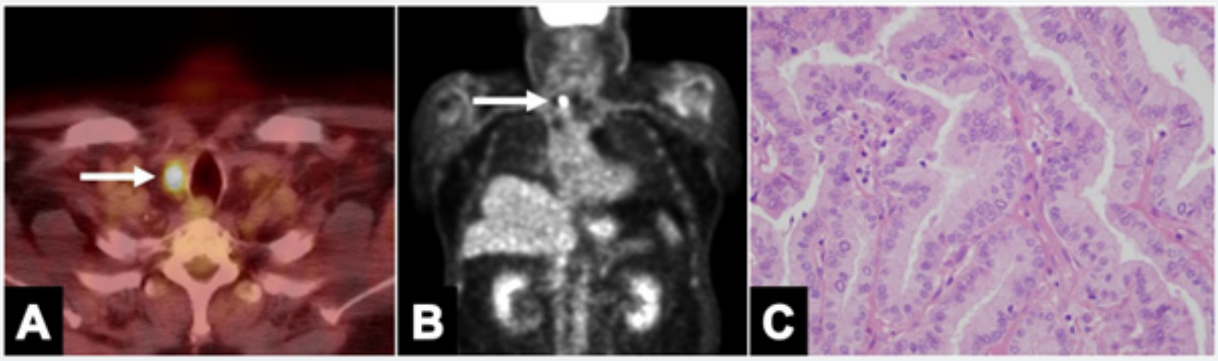

Figure 4: Tall cell variant, papillary thyroid carcinoma in a 61-year-old male. Axial fused PET/CT (a) and coronal PET (b) images demonstrate focal intense FDG activity within right thyroid lobe (arrows). High-power photomicrograph (c, hematoxylin-eosin, original magnification ×400) shows a papillary architecture with greater than 30% of the tumor cells being 2-3 times tall as they are wide with abundant eosinophilic cytoplasm. The same basally located nuclei have features of the classic variant are present, though nuclear pseudo inclusions are more common in this variant than others and there is little to no nuclear overlap due to the abundant cytoplasm.

Papillary thyroid carcinoma, with prominent hobnail features

This is a rare variant which has single cells with loss of polarity with > 30% of the cells having a surface bulge and apically placed nuclei [10,33,71]. This variant is associated with aggressive behavior compared to classic PTC [10,71]. BRAFV600E mutations are commonly found in the hobnail variant which contribute to increased incidence of extrathyroidal extension, nodal, and distant metastasis, tumor recurrence, and poor survival [71-73]. On ultrasound, this variant typically appears as micro lobulated hypoechoic nodule with internal microcalcification and cervical nodal metastasis [10].

Papillary thyroid carcinoma, clear cell variant

This is an extremely rare aggressive variant that accounts for about 0.52% of all PTC [74]. Clear cell carcinoma can affect multiple organs i.e. kidney, lungs, liver, vagina and thyroid.74 Histologically, it has a characteristic abundance of glycogen, mucin and lipids within the cytoplasm giving its clear appearance.74 Immunostaining with thyroid transcription factor-1 (TTF-1) and thyroglobulin has been described.75 Primary follicular derived tumor and metastatic clear cell renal cell carcinoma share similar morphological characteristics. Multiple studies reported that positive thyroglobulin staining is the most helpful tool to differentiate between the two entities [74,76].

Papillary thyroid carcinoma, insular cell variant

Insular type thyroid carcinoma is a rare aggressive subtype of papillary thyroid carcinoma which accounts for about 5% of all thyroid tumors [77,78]. Insular variant PTC was first described by Carcangiu et al [79]. This tumor occurs more frequently in females with a median age of 55 years [77]. The typical clinical presentation is a long-standing thyroid goiter (25%) patients [77]. Histologically, these are characterized by islands of malignant cells called insulae, which contain thyroglobulin filled small follicles [77]. They are typically separated by clefts and associated with capsular and vascular invasion, as well as internal areas of necrosis [77]. Ultrasound typically demonstrates an ill-defined mass with foci of calcifications [77]. CT is more accurate in assessing the tumor which appears ill defined heterogenous mass with internal foci of calcifications. The mass effect on surrounding structures is better evaluated on CT [77].

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Follicular thyroid carcinoma

Follicular thyroid carcinoma is the second most common thyroid carcinoma (15-18%) [11,15,80]. The risk of distant metastases is greater in follicular than in papillary carcinoma, and usually involves lungs, mediastinal lymph nodes, and skeleton [31]. Follicular neoplasm is a cytologic term which includes proliferation of thyroid follicular cells in both follicular adenoma and carcinoma. Follicular adenoma is much more common than carcinoma and accounts for (80-90%) of follicular neoplasms [80]. Histologically follicular carcinoma, classic type, is characterized by small follicles of fairly uniform cells containing scant colloid and lack characteristic nuclear features of papillary carcinoma [80]. Follicular carcinomas require thorough histologic evaluation to be differentiated from follicular adenoma [80]. Follicular adenomas share similar histological features to carcinoma without vascular or capsular invasion [11,80]. A recognized subtype has been reported which is composed of cells with prominent granular and eosinophilic cytoplasm, termed as Hurthle cell variant [11,15,47,80]. Insular cell variant is a 3rd uncommon variant which is characterized by poorly differentiated cells with solid infiltrating nest-like (insulae) appearance [80]. The prognostic significance of these subtypes is uncertain [80]. Vascular invasion is a frequent finding, and associated with distant metastasis to bones and lungs, which indicates a poor prognosis [15,80]. On ultrasound follicular carcinoma manifests as well-circumscribed, iso-hypoechoic nodule which lacks surrounding hypoechoic halo and has increased internal vascularity (Figure 5) [11,12,80]. Interruption of the capsule with evident parenchymal invasion is a frequent finding in large tumors [12,15,80]. Interruption of the capsule with evident parenchymal invasion is a frequent finding in large tumors [12,15,80]. Locoregional nodal metastasis is typically uncommon in follicular carcinoma [4,12,80].

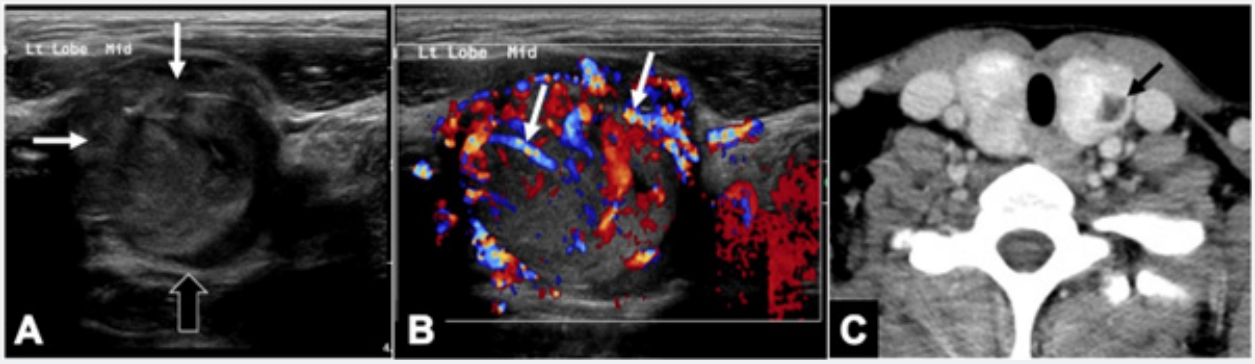

Figure 5: Classic variant, follicular thyroid carcinoma in a 29-year-old female. Transverse US (a) image of the left thyroid lobe shows fairly defined mass of heterogenous slightly isoechoic echotexture (arrow), and loss of well-defined surrounding hypoechoic halo. Transverse color Doppler (b) image shows type 4 flow pattern, peripheral ring with intense internal vascularity "green arrows". Axial contrast-enhanced CT (c) image demonstrates ill-defined iso-dense mass with internal areas of necrosis (black arrow).

Anaplastic thyroid carcinoma

Anaplastic thyroid carcinoma is the highly aggressive with the worst prognosis of all thyroid malignancy. It accounts for 1-2% of thyroid malignancy and more than 50% of thyroid cancer related deaths [81]. Anaplastic thyroid carcinoma occurs in the 6th-7th decade of life with slight female prevalence [81]. ATC can arise through 2 mechanisms: de novo or from differentiated thyroid carcinoma [81]. This tumor typically manifests as rapidly enlarging neck mass with infiltration of adjacent structures i.e. pre-tracheal muscles, larynx, trachea, esophagus, carotid sheath, and recurrent laryngeal nerve [81]. In addition, ATC has propensity for nodal metastasis (40%) and distant metastasis (43%). The most common locations for distant metastasis are lungs (78%), adrenals (24%), liver (20%), and brain (18%) [81]. All cases of ATC are considered as stage IV according to the American Joint Committee on Cancer TNM system [81]. It is further subdivided into stage IVa and IVb depending on presence of extrathyroidal extension.81 Stage IVc is considered when distant metastasis is present [81]. Preoperative imaging is imperative for accurate tumor localization and proper management planning [81]. On ultrasound, ATC typically manifests as large heterogeneously hypoechoic infiltrative mass with increased internal vascularity on color flow Doppler [81]. Ultrasound is useful in evaluation of locoregional lymph node metastasis and guidance of percutaneous biopsy [81]. However, FNAC is usually sufficient to reach diagnosis, core needle biopsy is preferred as it provides adequate tissue for molecular testing [81]. Owing to its rapid growth, contrast-enhanced CT could be the initial imaging modality for evaluation of ATC. Contrast-enhanced CT is helpful in delineation of the tumor, detection of tumor extension and invasion to adjacent structures e.g. larynx, trachea, esophagus and vascular involvement [81]. Typical CT imaging features include large poorly differentiated mass with extensive internal necrosis, evidence of extrathyroidal extension and local invasion (Figure 6) [81]. Preoperative staging with CT chest, MRI brain, and whole-body PET/CT is recommended to detect distant metastatic disease [81].

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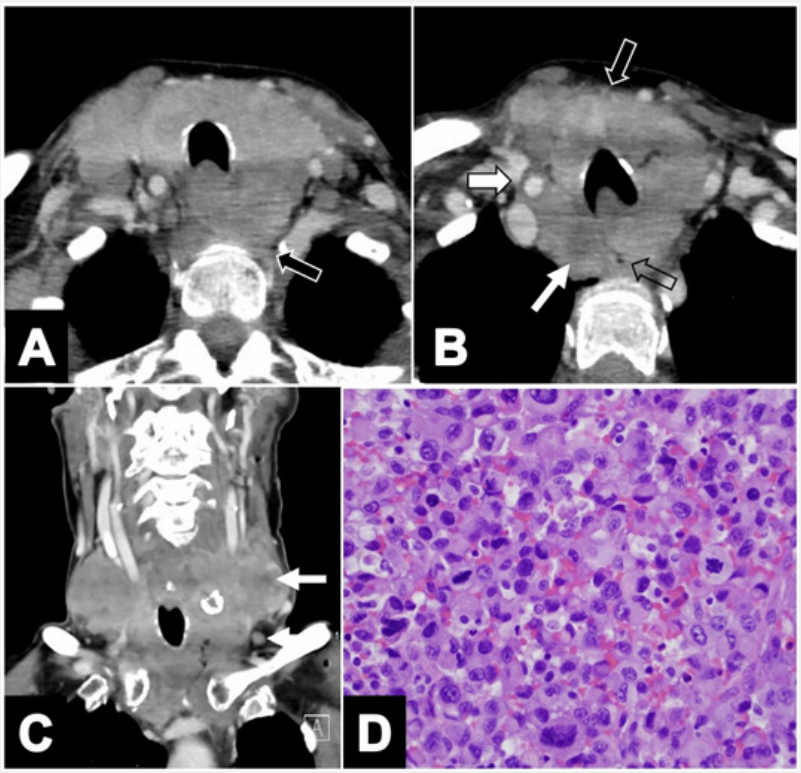

Figure 6: : Anaplastic carcinoma of the thyroid gland in an 81-year-old female. Axial and coronal contrast-enhanced CT (a, b, and c) images demonstrate extensive thyroid mass with internal areas of necrosis, encasement of right CCA (black outlined arrow), posterior extension into tracheo-esophageal groove with infiltration of esophagus (outlined arrows), prevertebral muscles (white outlined arrow), extra-thyroid infiltration of pre-tracheal muscles (white outline arrow in B) and lymphadenopathy. High-power photomicrograph (d, hematoxylin-eosin, original magnification ×400) shows anaplastic thyroid carcinoma with classic features: enlarged cells with dense eosinophilic cytoplasm; bizarre nuclei with prominent nucleoli; increased mitotic activity; infiltrating inflammatory cells.

Medullary thyroid carcinoma

MTC accounts for 1-2% of all thyroid cancers [82]. MTC arises from calcitonin producing parafollicular C cells and is considered as neuroendocrinal tumor [82]. It is associated with high incidence of distant metastasis, tumor recurrence and poor prognosis [82,83]. Majority of cases of MTCs are sporadic, yet 25% are hereditary and associated with multiple endocrine neoplasia (MEN) type-2 syndromes and familial non-MEN MTC [82,84]. Hereditary MTCs are frequently multifocal and bilobar, compared to the sporadic forms [82,84]. RET protooncogene associated germline mutations have been reported in 88-95% of hereditary MTC [82,85]. Medullary thyroid carcinoma has a slight female predilection with mean age 40-65 years [82,83]. The sporadic MTC typically manifests clinically as painless growing thyroid nodule with cervical adenopathy [82]. Whereas hereditary MTC typically has positive family history and could present with clinical manifestations of other associated tumors i.e. pheochromocytoma and hyperparathyroidism [82,83]. Histologically, the classic MTC is characterized by round polygonal or spindle-shaped tumor cells with uniform nuclei that have coarsely clumped chromatin, and granular cytoplasm. The presence of stromal amyloid deposits is a unique feature for medullary thyroid carcinomas [82]. Necrosis and hemorrhage occur in large tumors. Some reports described an oncocytic variant of the medullary carcinoma of the thyroid [40]. This carcinoma is characterized by prominent oncocytic cells on areas of medullary carcinoma with lack of PTC characteristic nuclear features of PTC [40,86,87]. Immunohistochemical staining is typically positive for calcitonin, carcinoembryonic antigen (CEA), chromogranin and synaptophysin [82]. Genetic testing helps in MTC treatment planning, risk stratification, and prognosis prediction [82,88]. On US, it can be classified into b-MTC and m-MTC; the latter has more metastatic LN, extra-thyroid extension, distant metastasis and higher CTN levels [68]. The typical sonographic features of medullary carcinomas include hypoechoic nodule with spiculated margins and increased internal vascularity [68,82]. Medullary carcinoma sometimes shows punctate calcification [15]. CT could depict the dense irregular coarse calcifications within the tumor and metastatic lymph nodes (Figure 7) [82]. Imaging evaluation of the abdomen is recommended if serum or urine metanephrines are elevated to exclude associated pheochromocytoma specially in hereditary MTC [82,89].

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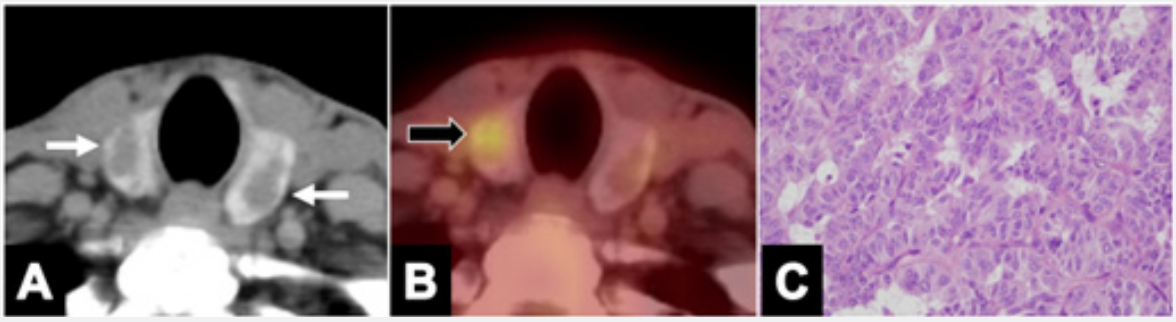

Figure 7: Metastatic medullary thyroid carcinoma in a 52-year-old male. Axial non-contrast CT (a) image of the neck shows bi-lobar thyroid nodules(arrows), hypodense relative to remaining normal thyroid parenchyma. Axial fused PET/CT (b) image shows focal FDG activity within the right thyroid lobe nodule (outlined arrow). High-power photomicrograph (c, hematoxylin-eosin, original magnification ×400) shows nests of C cells that extend beyond basement membrane and destroy thyroid follicles. These cells are polygonal to spindle-shaped, separated by thin fibro-vascular cores, with eosinophilic cytoplasm, round to oval nuclei with small nucleoli, and chromatin that varies between finely granular and dispersed to coarsely clumped.

Conclusion

Thyroid carcinoma has four main types with several histological subtypes and variants. Histological variant was shown to be the most important prognostic factor. Imaging criteria overlap between the various subtypes. However, awareness of suspicious imaging features of malignant nodules could help to predict the underlying variant and expect the outcome and prognosis. Radiologists should pay attention for characterization of incidentally detected thyroid nodules on CT, MRI, or PET/CT to minimize unnecessary aggressive interventions. Table 3 summarizes the imaging features of each histological type of thyroid carcinomas.

Table 3: Summary of common imaging features of thyroid carcinomas and variants.

Thyroid Carcinoma/Variant	Imaging Features
	– Hypoechoic nodule.
Papillary thyroid carcinoma Classic-conventional	– Ill-defined margins.
	– Irregular outlines
	– Internal microcalcifications
	– Color flow Doppler shows internal hypervascularity
	– Extrathyroidal extension, cervical nodal metastases, and vascular invasion are associated with poor prognosis
Microcarcinoma variant	– Tumor less than 1cm at its widest diameter
	– Good prognosis
Follicular Encapsulated (EFVPTC)	– Good prognosis
	– Isoechoic nodule.
	– No microcalcifications.
	– Cystic and partially cystic appearance
Non-encapsulated (infiltrative) (NFVPTC)	– More aggressive and suspicious appearance.
	– Ill-defined nodules.
	– Irregular margins.
	– Internal microcalcifications.
	– Locoregional lymphadenopathy
Oncocytic variant	– Well-defined nodules with less frequent internal calcifications.

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Warthin-like variant	– Well-circumscribed nodules.
	– Irregular margins.
	– M microcalcifications
	– Heterogenous background due to associated thyroiditis (Hashimoto thyroiditis)
Cribriform morular	– Well-circumscribed capsulated mass with cervical lymphadenopathy similar to classic PTC
	– Heterogeneous hypoechogenicity
	– Lack internal microcalcifications
Solid variant	– Irregular outlined unencapsulated nodule with high-intermediate suspicious criteria e.g. cervical lymphadenopathy and distant metastasis
Diffuse sclerosing	– Diffuse thyroid enlargement.
	– Heterogeneous hypoechogenicity.
	– Dispersed microcalcifications, may resemble snow-storm appearance.
	– With or without dominant mass
	– Typically present with extra-thyroid extension, bilateral cervical lymphadenopathy and lung metastasis
PTC variant with nodular-fasciitis-like stroma	– Homogenous mass with well-circumscribed margins and low echogenicity
	– Usually hypovascular
	– No extra-thyroid extension or associated enlarged cervical lymph nodes
Tall cell variant	– Markedly hypoechoic nodule.
	– Internal microcalcification.
	– Irregular spiculated margins.
	– Evident extra-thyroid extension
	– Cervical lymph node metastasis
	– Poor prognostic factors include older age at presentation, larger tumor size and presence of extra-thyroid extension
Columnar cell variant Encapsulated form	– Small, well-circumscribed, hypoechoic nodule with internal microcalcifications.
	– Variable metastatic lymphadenopathy
Aggressive (extra-capsulated) form	– Large microlobulated/infiltrative.
	– Markedly hypoechoic nodule.
	– Capsular interruption with extrathyroidal extension.
	– Locoregional nodal and distant metastasis are frequently encountered
PTC with prominent hobnail features	– Microlobulated hypoechoic nodule.
	– internal microcalcification.
	– Cervical nodal metastasis
Insular cell variant	– Ill-defined mass with foci of calcifications
Follicular thyroid carcinoma Classic variant	– Well-circumscribed.
	– Iso-hypoechoic nodule.
	– Lacks surrounding hypoechoic halo.
	– Increased internal vascularity.
	– Interruption of the capsule with evident parenchymal invasion is a frequent finding in large tumors
Hurthle cell variant	– Similar to classic variant with more prominent locoregional cervical lymphadenopathy
Anaplastic carcinoma	– Large heterogeneously hypoechoic infiltrative mass.
	– Increased internal vascularity on color flow Doppler
	– Locoregional lymph node metastasis
	– Contrast-enhanced CT is helpful in delineation of the tumor, detection of tumor extension and invasion to adjacent structures
	– Preoperative staging with CT chest, MRI brain, and whole-body PET/CT

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Medullary thyroid carcinoma	– Hypoechoic nodule with spiculated margins and increased internal vascularity
	– Medullary carcinoma sometimes shows punctate calcification
	– CT could depict the dense irregular coarse calcifications within the tumor and metastatic lymph nodes
	– Abdominal imaging to exclude associated pheochromocytoma.

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