Papillary Thyroid Carcinoma

5

Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy, accounting for 80 % of thyroid carcinomas in adults and 90 % in children [1]. PTC is a malignant epithelial tumor showing follicular differentiation and distinctive nuclear features [2]. Patients usually are 20–50 years old, but those of any age may be affected [2]. PTC is more common in women than men. Most PTCs are sporadic but may occur with syndromes such as Gardner syndrome, Cowden syndrome, and ataxia telangiectasia [3, 4]. PTC may arise in ectopic thyroid tissue such as struma ovarii, adrenal glands, and trachea [5–7]. Radiation exposure is a risk factor for PTC [8]. Histologic variants of PTC are important to recognize prognostically and for association with other diseases. Aggressive variants include tall cell, columnar cell, solid, and the recently described hobnail variant. The cribriform-morular variant often is associated with familial adenomatous polyposis. PTCs are positive for thyroglobulin, thyroid transcription factor 1 (TTF1), and keratins and are negative for calcitonin, chromogranin, and synaptophysin. Markers useful in confirming a diagnosis of PTC are HBME-1, keratin 19, galectin-3, and CITED1. *BRAF* mutations occur in about 60 % of PTCs, and *RET/PTC* rearrangements occur in 20–30 % of adult PTCs. *BRAF* mutation and *RET/PTC* rearrangement are mutually exclusive abnormalities in PTCs. *RET/PTC1* is more common in papillary microcarcinomas and PTCs with classic architectural features, whereas *RET/PTC3* is more common in the solid variant. *BRAF* mutations occur in classic, Warthin-like, and oncocytic PTCs; microcarcinomas; and aggressive variants such as tall cell, columnar, and hobnail PTCs. Poorly differentiated and anaplastic thyroid carcinomas also may show *BRAF* mutation, particularly if associated with or dedifferentiated from a PTC. *BRAF* mutation is not common in pediatric or radiation-associated PTCs. The follicular variant of PTC (FVPTC) is associated with *RAS* mutations (as are follicular neoplasms), thus RAS is not useful in separating FVPTC from follicular neoplasms. PTCs usually metastasize to cervical nodes, particularly ipsilateral nodes, before spreading to the lung and other sites [1]. Unfavorable prognostic features are older age, male sex, large tumor size, multicentricity, angiolymphatic invasion, necrosis, mitoses, extrathyroid extension, distant metastases, high grade, marked nuclear atypia, and progression to poorly or undifferentiated carcinoma [1, 9]. PTCs are treated by thyroidectomy and removal of involved lymph nodes. Radioactive iodine may be used to ablate any remaining tumor, including metastatic sites. Overall, PTC has an excellent prognosis, with >90 % survival, and most patients survive even with metastatic disease.

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Classic PTC

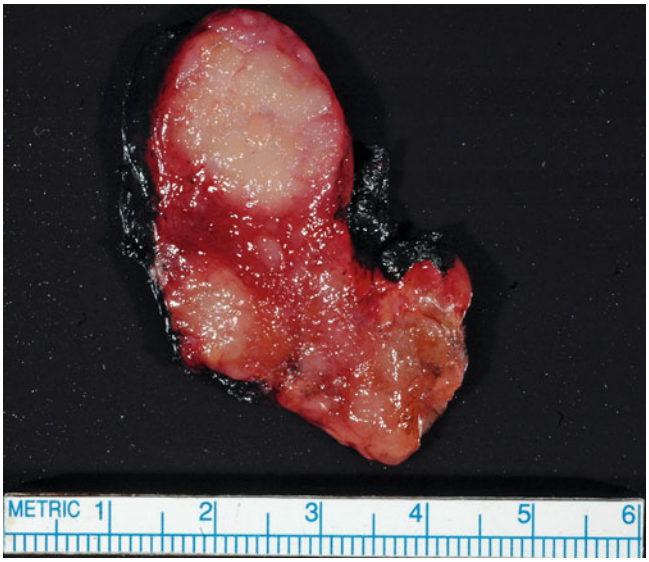

Fig. 5.1 Classic papillary thyroid carcinoma. This thyroid has multiple ill-defined firm masses of PTC with a granular white cut surface. Tumors may be single or multifocal and bilateral. The mean tumor size is 2–3 cm, although size may vary greatly

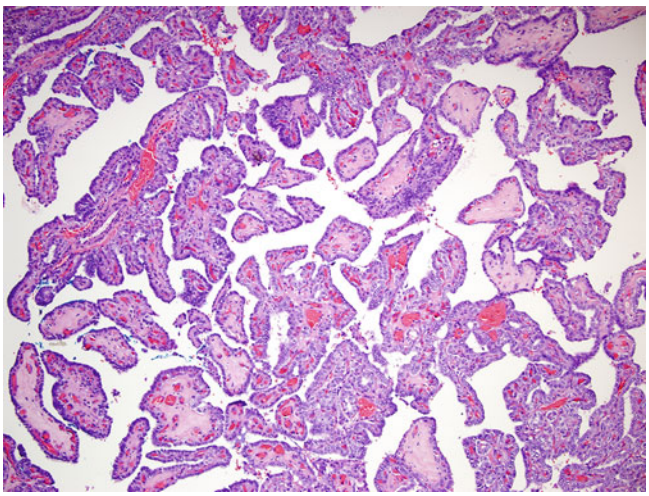

Fig. 5.3 Classic papillary thyroid carcinoma. Prominent papillae with fibrovascular cores lined by epithelial cells with characteristic cytologic features are seen in this PTC. The differential diagnosis includes papillary hyperplasia, both focal and diffuse, as seen in Graves disease. Nuclear features are used to differentiate PTC from papillary hyperplasia and Graves disease. Also, Graves disease diffusely involves the entire thyroid rather than forming a distinct mass, as often is seen in PTC. In difficult cases, p27 protein expression has shown some promise in separating these entities, as it has shown significantly higher expression in papillary hyperplasia of Graves disease than in PTC [10]

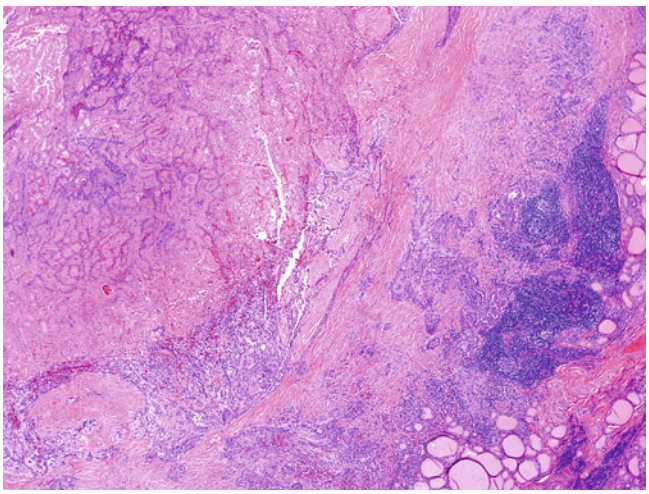

Fig. 5.2 Classic papillary thyroid carcinoma. Invasive PTC is shown with a lymphocytic infiltrate at the periphery. The stroma in PTC often is abundant, fibrous, and sclerotic

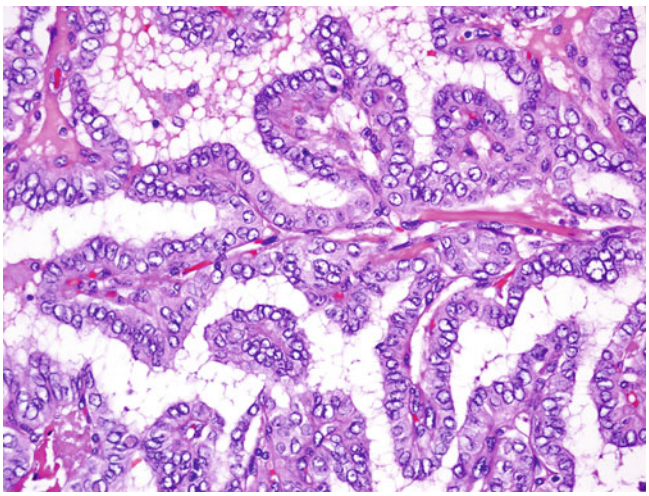

Fig. 5.4 Classic papillary thyroid carcinoma. This classic PTC shows papillae with fibrovascular cores and lined by cells with cytologic features of PTC. The cells show nuclear enlargement, irregular nuclear membranes, nuclear clearing ("Orphan Annie" nuclei), nuclear grooves, intranuclear holes, and cytoplasmic clearing. Although Graves disease may show papillary fronds, the cells lining the papillae in Graves lack cytologic features of PTC. PTC usually is positive for HBME-1, galectin-3, CITED-1, and keratin 19. These immunohistochemical markers may be helpful in difficult cases

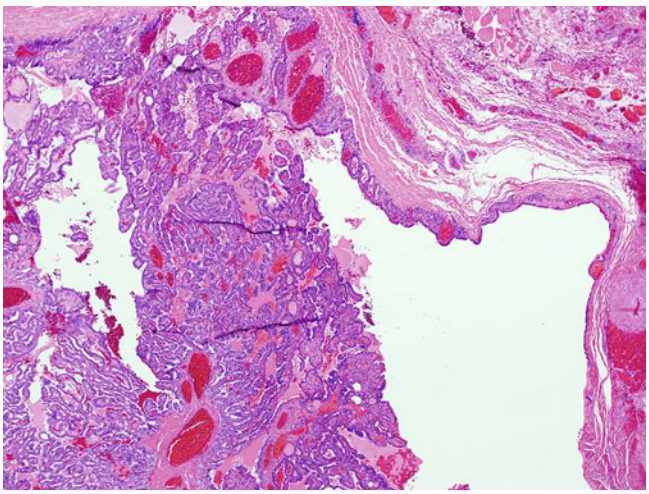

Fig. 5.5 Classic papillary thyroid carcinoma. Classic PTC with papillae with fibrovascular cores and cystic change. Focal areas of more solid growth and squamous metaplasia may be seen in some cases. The proportion of papillary structures in PTC may vary

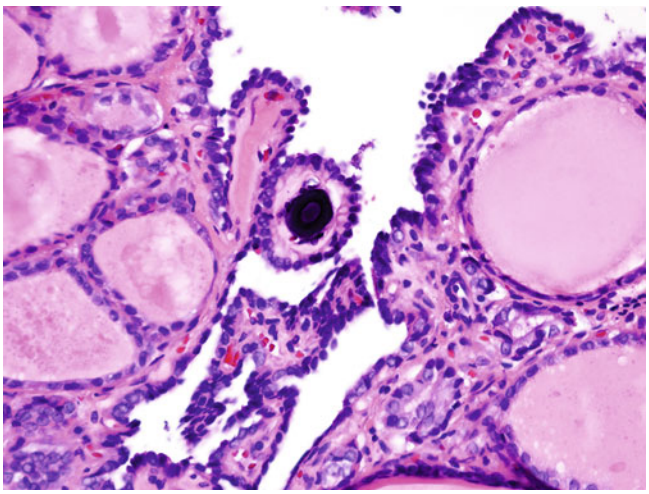

Fig. 5.7 Classic papillary thyroid carcinoma. Psammoma bodies are calcifications with concentric lamellations that are seen in 50 % of PTCs, particularly those with prominent papillary architectural features [1]

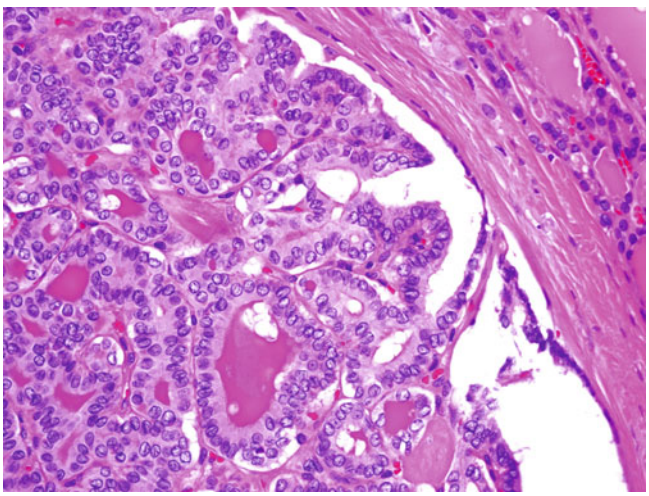

Fig. 5.6 Classic papillary thyroid carcinoma. This partially cystic PTC has prominent papillae. Cystic areas are not uncommon in PTC

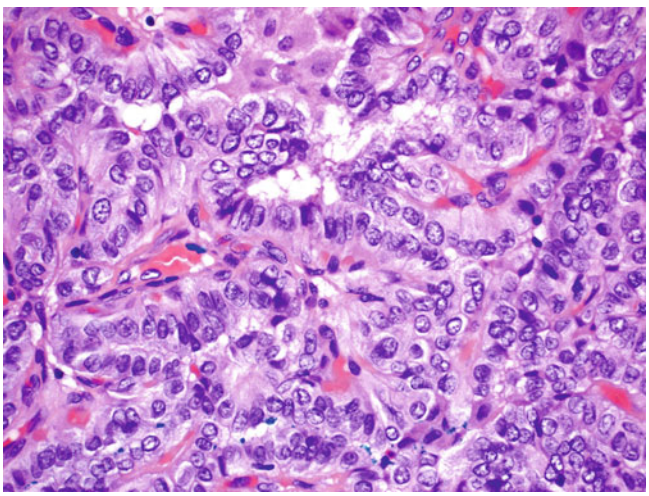

Fig. 5.8 Classic papillary thyroid carcinoma. The characteristic cytologic features of PTC are seen in this image. The nuclei are enlarged, overlap, and show clearing, irregularity, grooves, and intranuclear holes. Mitotic figures are uncommon

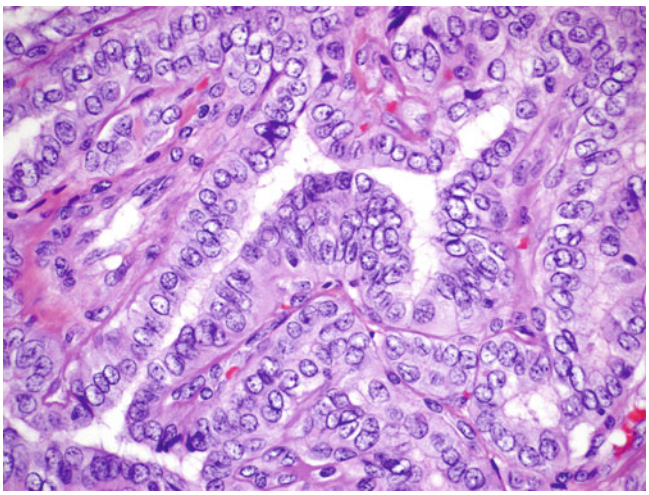

Fig. 5.9 Classic papillary thyroid carcinoma. Intranuclear holes are eosinophilic invaginations of the cytoplasm. They are well defined, round to ovoid, and eosinophilic. Intranuclear holes, when present, are characteristic of PTC; however, they are not specific for PTC because they may be seen in parathyroid tissue, occasionally in Hurthle cell tumors, and in medullary thyroid carcinoma

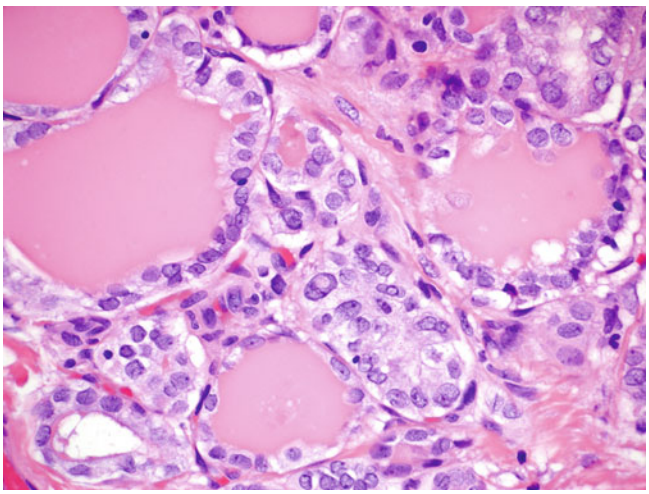

Fig. 5.11 Classic papillary thyroid carcinoma. Growth patterns in PTC are variable. In this image, there is an area of follicular growth in a PTC that shows papillae in other areas of the tumor. If a PTC has both a papillary and follicular growth pattern, it is classified as a classic PTC rather than an FVPTC, which would require the tumor to have cytologic features of PTC and the entire tumor to have a follicular growth pattern

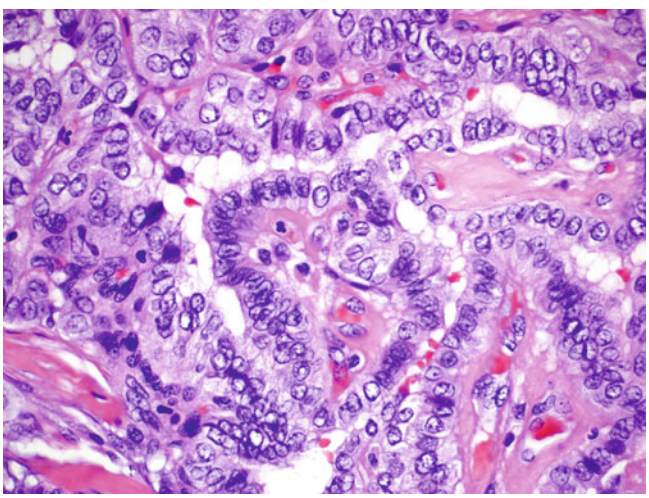

Fig. 5.10 Classic papillary thyroid carcinoma. The cells in PTC are enlarged, with irregular nuclei, nuclear clearing, nuclear grooves, nuclear overlap, and intranuclear holes. The cytologic features are diagnostic in PTC. Colloid in PTC often is darker than in the benign thyroid, although this feature is variable

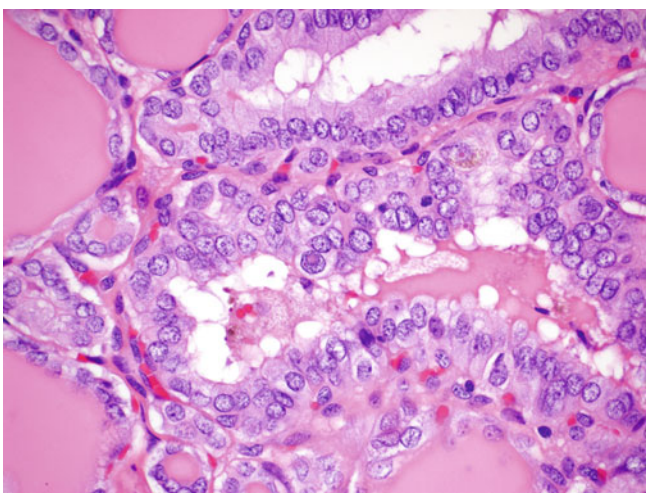

Fig. 5.12 Classic papillary thyroid carcinoma. The colloid in PTC often is darker than that of the surrounding thyroid parenchyma. The cytologic features are characteristic of PTC, with enlarged, irregular nuclei; nuclear clearing; intranuclear pink holes; and longitudinal nuclear grooves. The intranuclear holes are cytoplasmic invaginations of the cytoplasm that are eosinophilic, comprise >50 % of the nucleus, and show condensation around the periphery of the hole

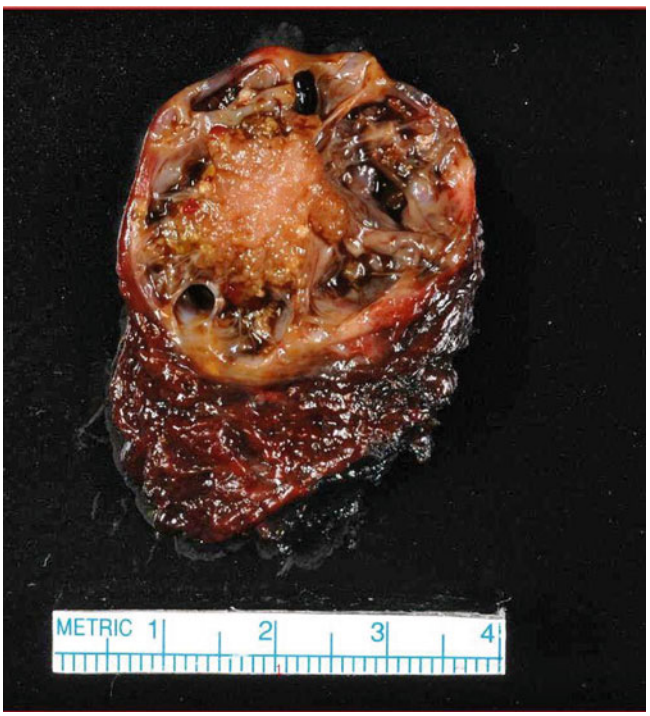

Fig. 5.13 Classic papillary thyroid carcinoma. Shown is a cystic PTC. PTCs often are white-tan, firm masses grossly and may be gritty as the result of psammoma bodies. However, a cystic gross appearance or a cystic PTC with a mural nodule of tumor is not uncommon. This cystic PTC is multiloculated, with the bulk of the tumor cells in the center

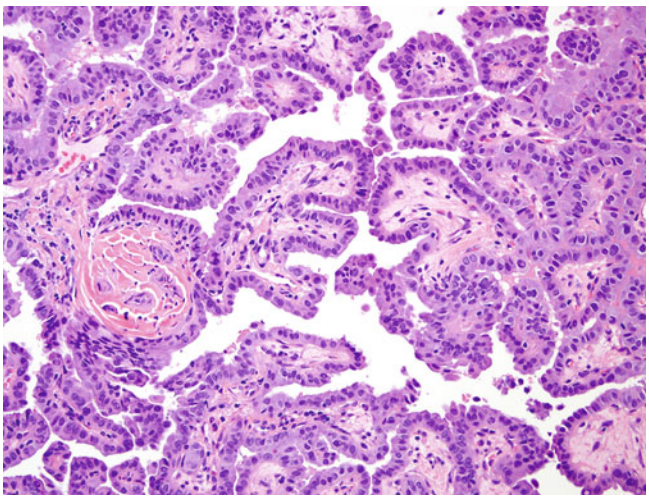

Fig. 5.15 Classic papillary thyroid carcinoma. The papillae in this cystic PTC have fibrovascular cores and are lined by cells with characteristic features of PTC, including enlarged, irregular nuclei; nuclear clearing; intranuclear pink holes; and longitudinal nuclear grooves

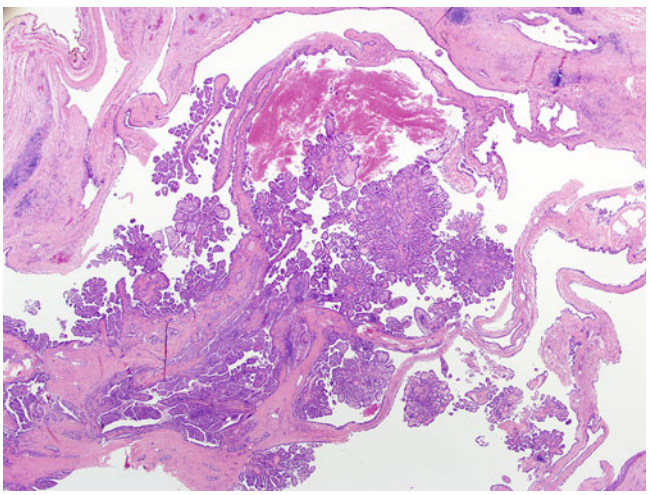

Fig. 5.14 Classic papillary thyroid carcinoma. Low-power photomicrograph of multiple cystic spaces in a PTC. These tumors often have prominent papillary architectural features. Cystic PTC must be differentiated from an adenomatous or a hyperplastic nodule with papillary hyperplasia

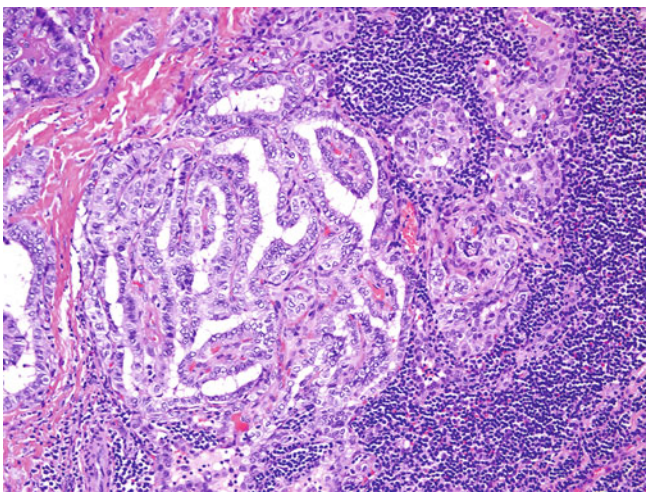

Fig. 5.16 Classic papillary thyroid carcinoma. PTC metastatic to a lymph node. Cervical and ipsilateral lymph nodes are the most common sites of metastasis for classic PTC. Patients with lymph node metastases of PTC still may have long-term survival and be cured of their disease

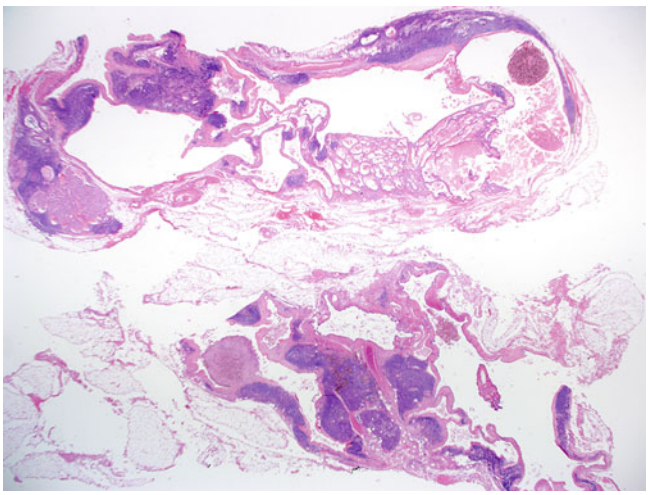

Fig. 5.17 Classic papillary thyroid carcinoma. Cystic metastases of PTC to regional lymph nodes. Cystic change in lymph node metastases is not uncommon in PTC

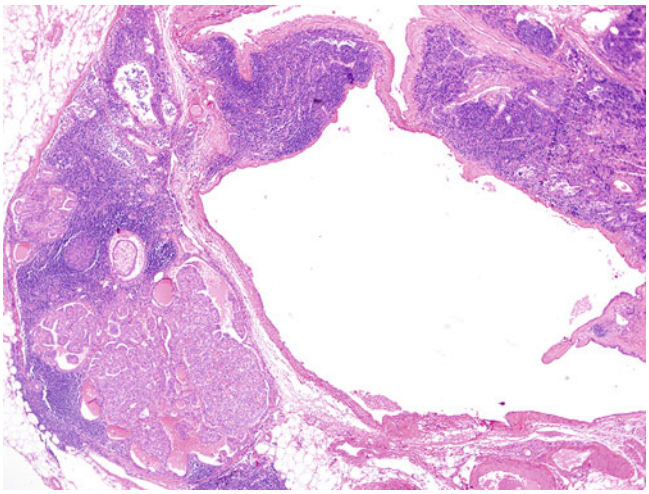

Fig. 5.18 Classic papillary thyroid carcinoma. An area of solid growth is present in a cystic-appearing lymph node metastasis of PTC

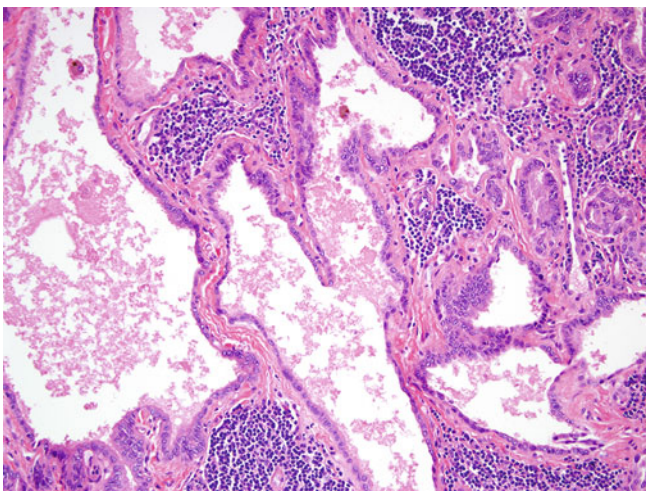

Fig. 5.19 Classic papillary thyroid carcinoma. In some cases, lymph node metastases of PTC may be difficult to diagnose, as they do not always show the prominent features of classic PTC. In difficult cases, immunoperoxidase studies may be helpful, as PTC is positive for TTF1 and thyroglobulin

Papillary Thyroid Microcarcinoma

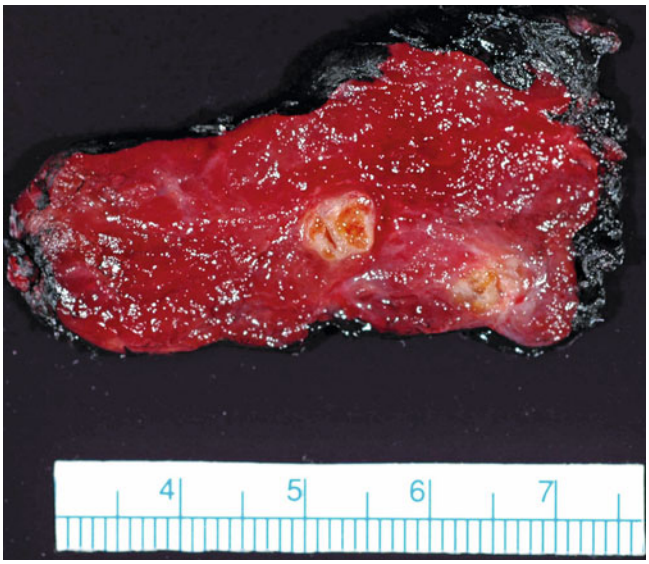

Fig. 5.20 Papillary thyroid microcarcinoma. Two papillary thyroid microcarcinomas are seen in this gross photograph. Papillary thyroid microcarcinoma is defined as measuring 1 cm or less. This tumor often is an incidental finding in thyroid glands removed for benign disease [11]. Autopsy and surgical series identify these tumors in 7–35 % and 7 % of cases, respectively [12–15]. Incidental, clinically occult tumors are less aggressive than those presenting clinically. If a tumor is clinically apparent, regardless of size, it is a clinical carcinoma and usually treated as such. Clinically overt microcarcinomas are larger than occult tumors and more often show multifocality, extrathyroid extension, vascular invasion, recurrence, and metastases and usually are treated as clinical cancer [16–18]. A meta-analysis of 1,586 microcarcinomas found multifocality related to nodal metastases [19]. Microcarcinomas may be aggressive and may present as distant metastases [20, 21]. Familial occurrence has been noted in 5.9 % of papillary microcarcinomas, and these tumors may be aggressive [22]

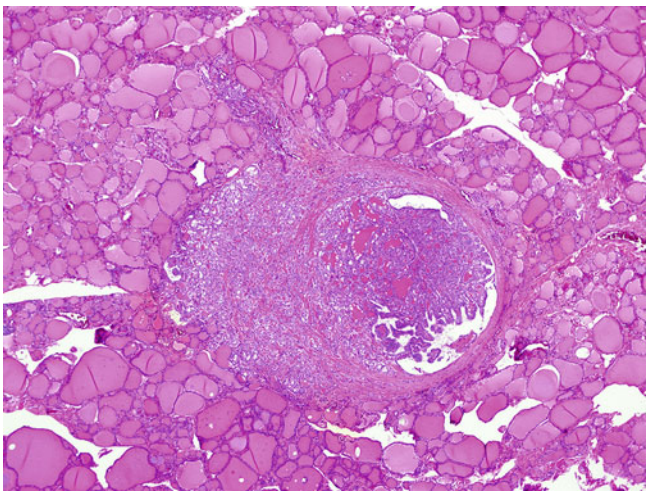

Fig. 5.21 Papillary thyroid microcarcinoma. This papillary thyroid microcarcinoma was discovered incidentally in a patient undergoing surgery for benign thyroid disease. Cases presenting clinically usually are treated as clinical cancer [11]; however, treatment of incidental microcarcinoma is more controversial. Another focus of microcarcinoma is identified in the contralateral lobe in 15–20 % of cases, and 20 % of patients may have long-term recurrent disease without complete resection. Capsular invasion or distant metastases occur in up to 5 % of microcarcinomas [23]. Of 115 clinically overt and 75 occult papillary microcarcinomas, the overt tumors were larger and more often had extrathyroid extension, multifocality, vascular invasion, and nodal metastases, and recurrence occurred only in the overt microcarcinomas [18]. However, clinically incidental papillary microcarcinomas also may behave aggressively; thus, treatment remains controversial

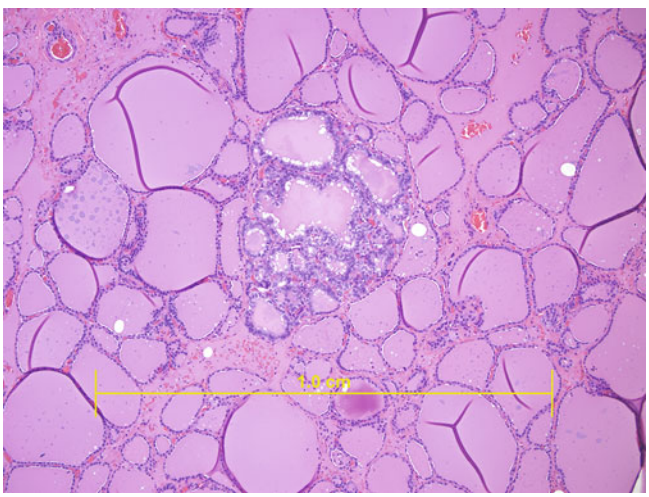

Fig. 5.22 Papillary thyroid microcarcinoma. Although papillary microcarcinomas have an excellent prognosis overall, they have 1 % mortality, 2.5 % local recurrence, 1 % nodal recurrence, and 1 % distant metastatic rates [24]. Comparing subtypes of papillary microcarcinomas, tall cell microcarcinomas are larger (7.1 mm) than the classic type (5.3 mm) and have higher rates of multifocality and extrathyroid extension than classic microcarcinomas (47.2 % vs. 34 %) [25]. Diffuse sclerosing microcarcinomas have higher rates of nodal metastases (57 % vs. 33 %) and extrathyroid extension than classic papillary microcarcinomas (13 % vs. 6 %) [25]. However, no differences in survival were found among the three groups [25]

FVPTC

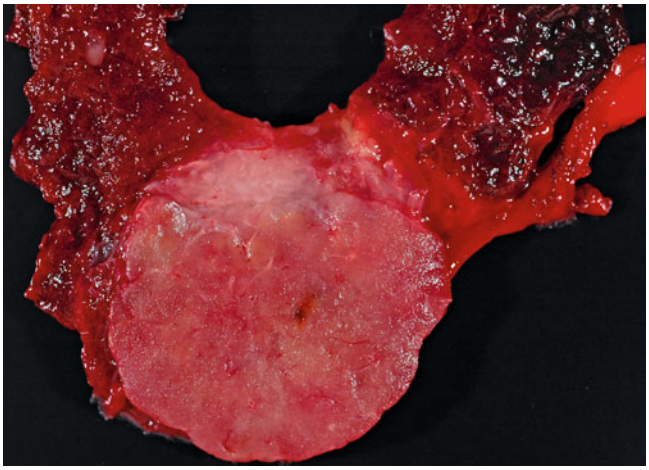

Fig. 5.23 Follicular variant of papillary thyroid carcinoma, gross. This FVPTC appears circumscribed. Encapsulated tumors with vascular or capsular invasion may behave more aggressively than those without invasion [26, 27]. Encapsulated FVPTCs with no invasion have minimal metastatic potential, and FVPTCs that are not fully encapsulated or infiltrative but are partially encapsulated or well circumscribed also have very low metastatic potential/recurrence risk, unlike more aggressive infiltrative FVPTC [28]. Both encapsulated and partially encapsulated FVPTCs often have *RAS* mutations (46 %) and lack *BRAF* mutations (which are found in some infiltrative FVPTCs) [29]

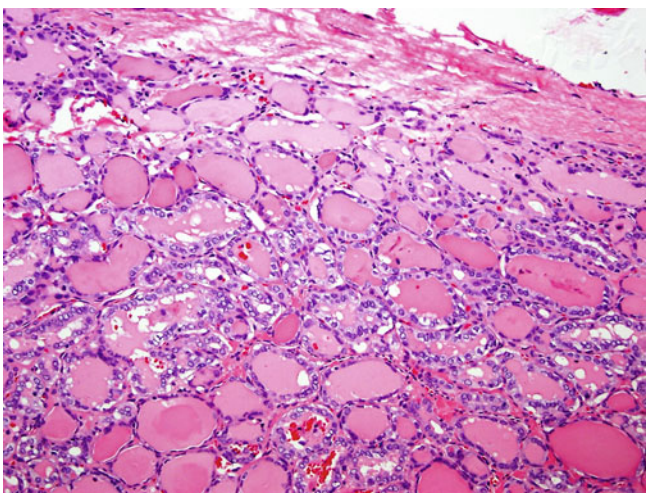

Fig. 5.24 Follicular variant of papillary thyroid carcinoma. FVPTC has a follicular growth pattern and cytologic features of PTC. Classic cytologic features may not be present throughout the tumor; thus, differentiation from follicular neoplasms may be difficult. FVPTC is the second most common PTC and one of the most difficult to diagnose. Ten thyroid pathologists evaluated 87 FVPTCs, and all ten made a concordant diagnosis of FVPTC in 39 % [30]. Seven of the pathologists made a diagnosis of FVPTC in all cases associated with metastases, but the cumulative diagnosis of all ten reviewers in these cases was 66.7 % [30]. Comparing FVPTC with classic PTC, patient age (46–48 years) and female predominance (77–79 %) are similar [31–33]. These tumors do not differ in size, multifocality, or capsular, lymphovascular, or perineural invasion, but FVPTCs have fewer lymph node metastases and less extrathyroid extension than classic PTC [31]. Older age, male sex, high T stage, extrathyroid extension, and nodal disease are associated with decreased survival [32, 33]. Ten-year survival (96–98 %) is similar for FVPTC and classic PTC [31–33]

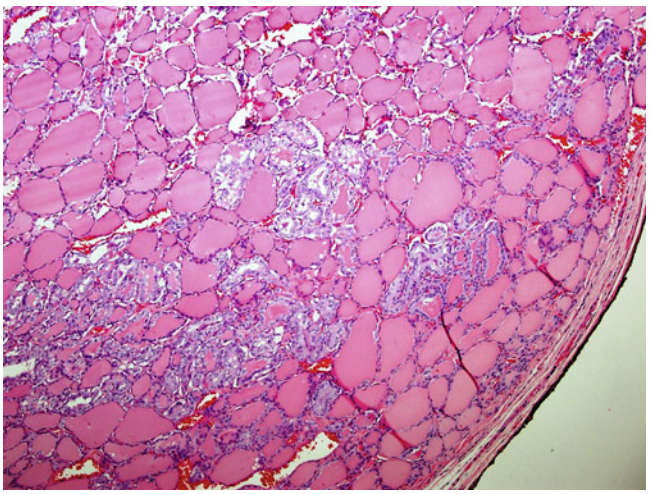

Fig. 5.25 Follicular variant of papillary thyroid carcinoma. FVPTC may not have classic features of PTC throughout the tumor. Foci of characteristic features may be identified along the periphery of the tumor. Unlike classic PTC, FVPTC does not show papillary growth. If this tumor showed areas of papillary growth, it would be classified as classic PTC

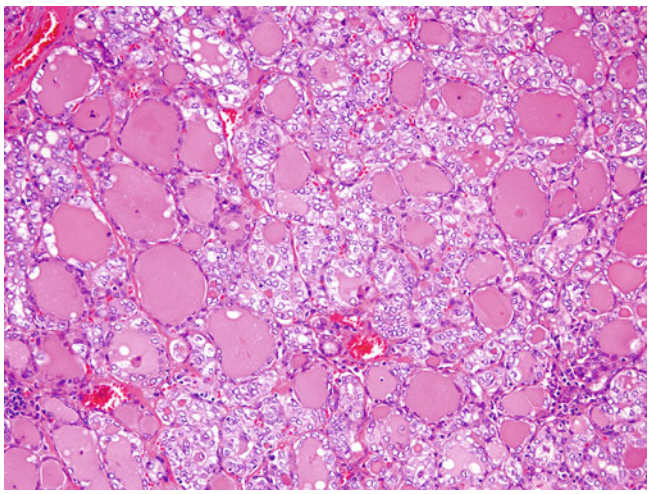

Fig. 5.27 Follicular variant of papillary thyroid carcinoma. Numerous patterns have been identified in FVPTC, including microfollicular, macrofollicular, diffuse, and adenoid cystic patterns, as well as combinations of these. From low to medium power, a pattern of small follicles intermixed with larger follicles is a clue to the diagnosis of FVPTC

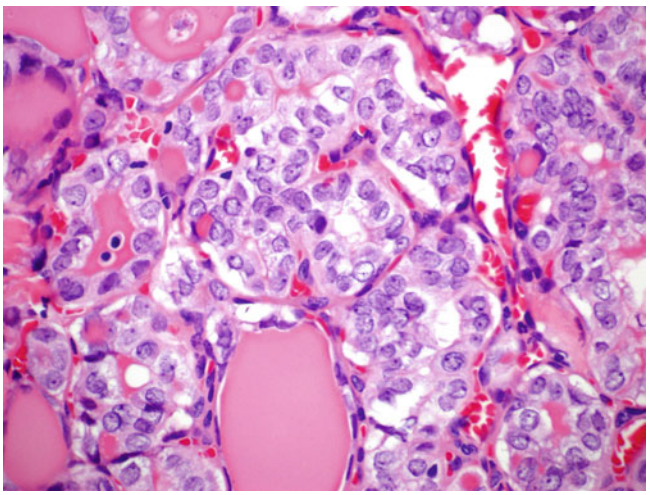

Fig. 5.26 Follicular variant of papillary thyroid carcinoma. This photomicrograph shows features of FVPTC, with variably sized follicles lined by cells with large, irregular, back-to-back nuclei; nuclear groves; and chromatin clearing. Less nuclear overlap is seen in FVPTC than in classic PTC. Although dark colloid may be seen, it is not diagnostic for malignancy

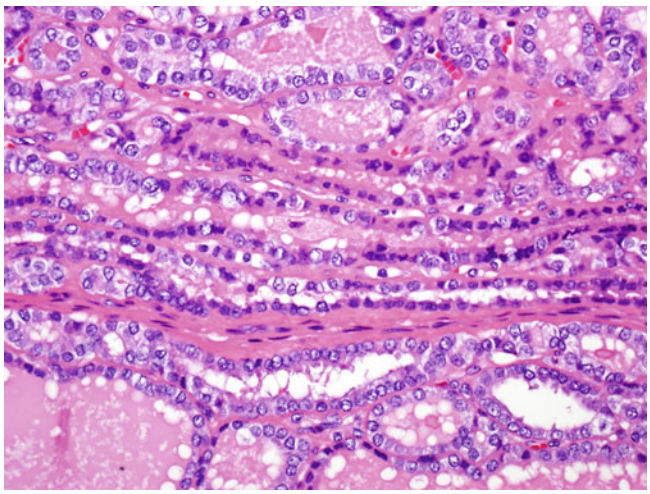

Fig. 5.28 Follicular variant of papillary thyroid carcinoma. The elongated follicles in this thyroid tumor are a clue to the diagnosis of FVPTC. Elongated follicles in parallel cords also may be seen in the columnar and tall cell variants of PTC

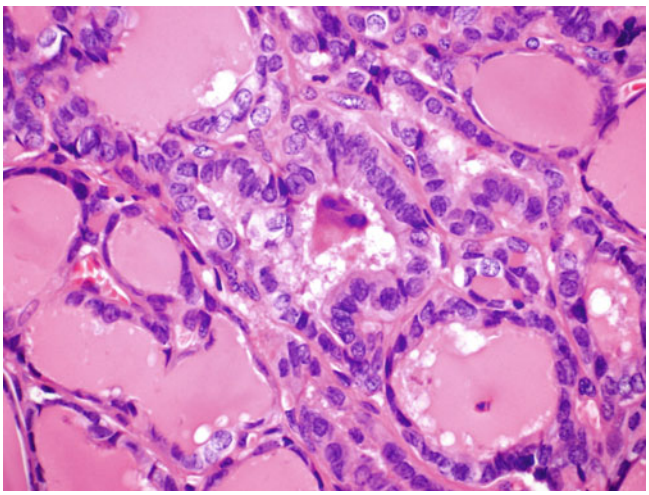

Fig. 5.29 Follicular variant of papillary thyroid carcinoma. The cells in FVPTC have large, irregular, back-to-back nuclei; grooves; and chromatin clearing and show less nuclear overlap than classic PTC. The nuclei in FVPTC appear somewhat rectangular and squared off. Although dark colloid may be seen, it is not diagnostic of malignancy. Giant cells may be seen in PTC, including FVPTC, but are nonspecific

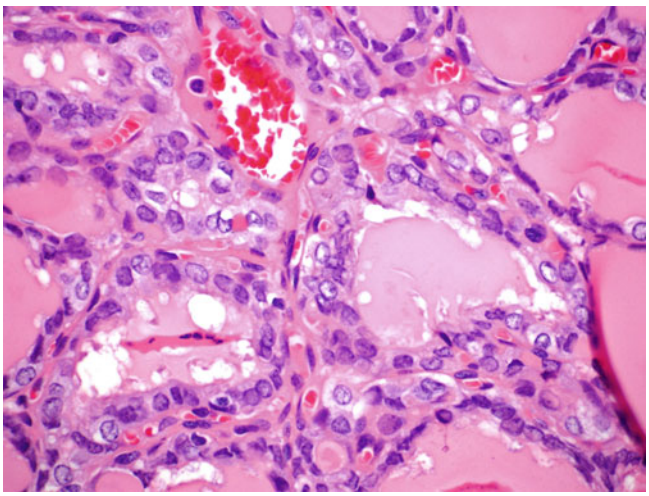

Fig. 5.30 Follicular variant of papillary thyroid carcinoma. Intranuclear pink holes are helpful in the diagnosis of FVPTC, but they are seen in only a minority of the cases. Intranuclear pink holes are less common in FVPTC than in classic PTC. These intracytoplasmic invaginations into the nuclei must comprise >50 % of the nucleus, are eosinophilic, and have condensation around the periphery. Intranuclear pink holes are not specific for FVPTC or PTC, as they also are seen in medullary thyroid carcinoma, some Hurthle cell neoplasms, and parathyroid tissue

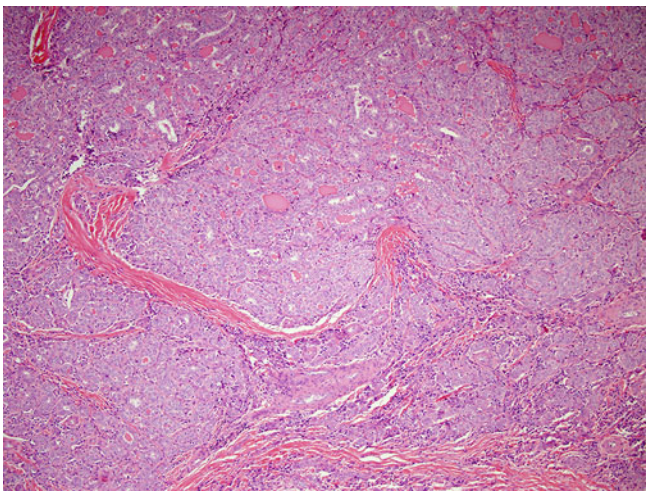

Fig. 5.31 Follicular variant of papillary thyroid carcinoma. Low-power photomicrograph of an FVPTC showing infiltrative/diffuse growth. This growth pattern is more common in younger patients, often multicentric, and associated with extrathyroid extension, nodal metastases, and vascular invasion [34, 35]. Encapsulated FVPTCs have less intratumor fibrosis (18 %), extrathyroid extension (5 %), positive margins (2 %), and lymph node metastases (5 %) than nonencapsulated FVPTCs with diffuse/infiltrative growth (88, 65 , 50, and 65 %, respectively) [27]. Encapsulated tumors with vascular or capsular invasion may be more aggressive than those without invasion [26, 27]. Encapsulated FVPTCs with no capsular or vascular invasion have minimal metastatic potential, and FVPTCs that are not fully encapsulated or infiltrative but are partially encapsulated or well circumscribed also have a very low metastatic potential/recurrence risk, unlike more aggressive infiltrative FVPTC [28]. Both encapsulated and partially encapsulated FVPTCs often have *RAS* mutations (46 %) and lack *BRAF* mutations (which occur in some infiltrative FVPTCs) [29]

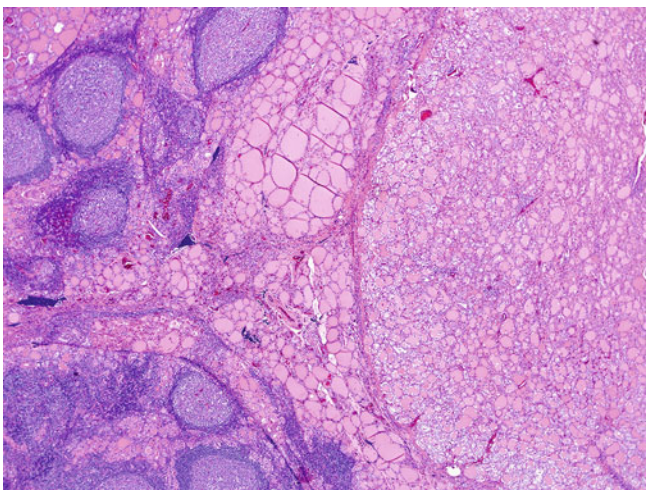

Fig. 5.32 Follicular variant of papillary thyroid carcinoma. This is an encapsulated, noninvasive FVPTC. The surrounding thyroid parenchyma shows thyroiditis, which often is seen in cases of PTC. From low power, the tumor cells appear lighter in color, likely because of the nuclear clearing and the areas of scalloped-appearing colloid. Note that the colloid in this example does not appear darker than in the surrounding thyroid parenchyma

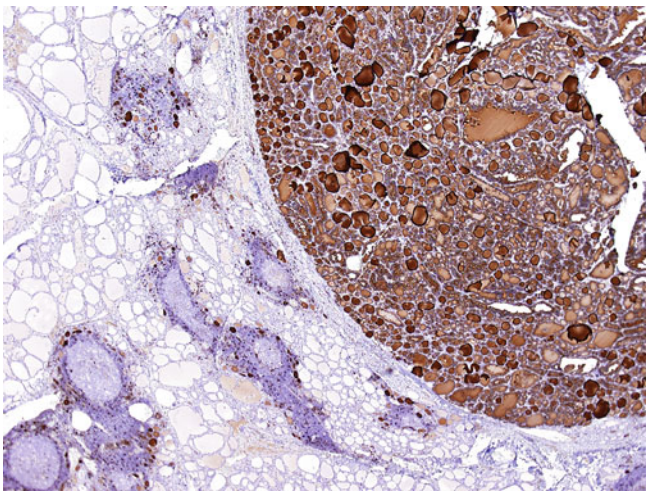

Fig. 5.33 Follicular variant of papillary thyroid carcinoma. HBME-1 immunostain is positive in the FVPTC on the right side of the photomicrograph. This is a helpful feature to confirm a diagnosis of FVPTC. Notice that in the surrounding thyroid parenchyma, there is focal nonspecific staining of colloid and a few cells around areas of inflammation. It is important to recognize that this occurs, so these inflamed foci are not diagnosed as PTC

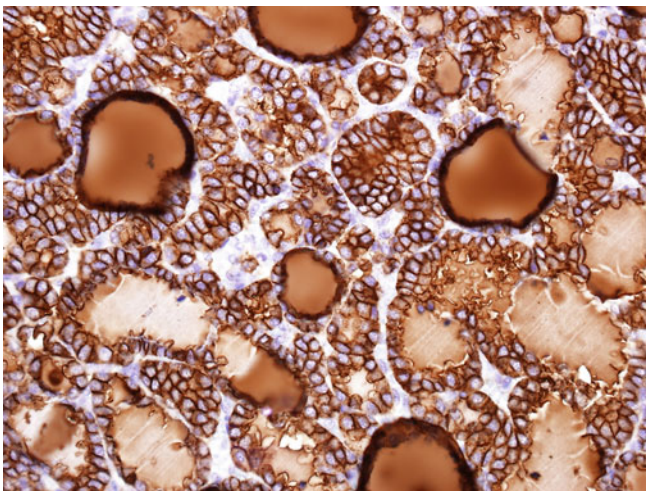

Fig. 5.34 Follicular variant of papillary thyroid carcinoma. HBME-1 shows membranous and some cytoplasmic staining of the tumor cells in this FVPTC. The colloid also shows staining, but this is not specific. Several immunohistochemical markers, such as HBME-1, galectin-3, CITED-1, and keratin 19, may be helpful in confirming a diagnosis of FVPTC [36]. Although a panel of immunostains may be most helpful, HBME-1 is probably the best single marker to assist in differentiating FVPTC from a follicular neoplasm or adenomatous nodule

Cribriform-Morular Variant of PTC

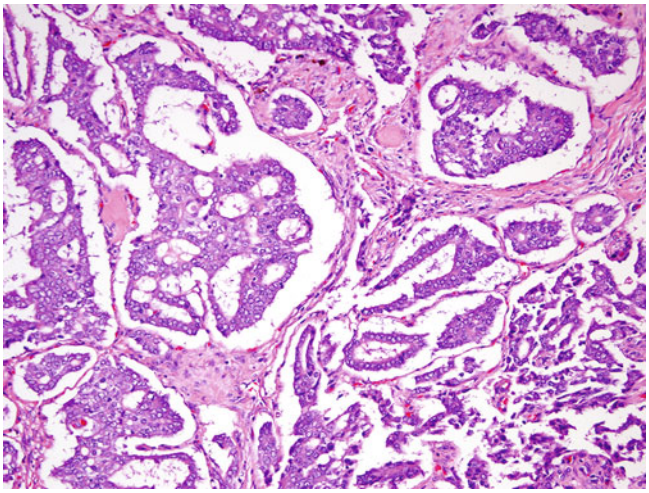

Fig. 5.35 Cribriform-morular variant of papillary thyroid carcinoma. The cribriform-morular variant of PTC has unique histologic features and is associated with familial adenomatous polyposis (FAP) and germline *APC* mutations [37–41]. Although sporadic cases of cribriform-morular PTC occur, this variant often occurs in FAP, an autosomal dominant syndrome of gastrointestinal adenomas and carcinomas, endometrial cancer, and medulloblastomas [39]. Patients with FAP may present with the cribriform-morular variant of PTC [38]; thus, patients diagnosed with cribriform-morular PTC should be evaluated for FAP

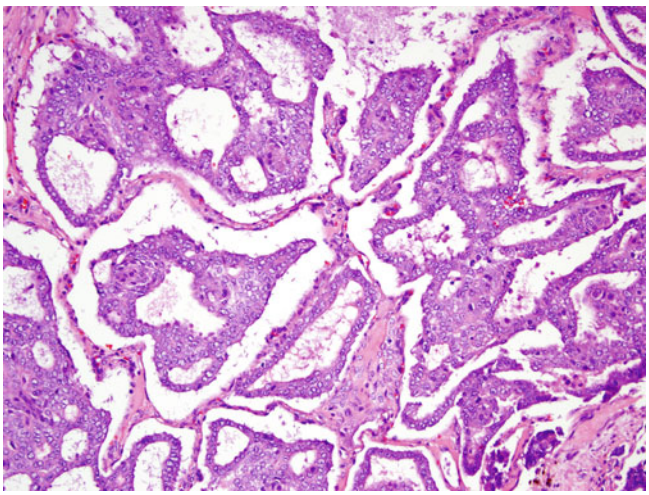

Fig. 5.36 Cribriform-morular variant of papillary thyroid carcinoma. The cribriform areas in the cribriform-morular variant of PTC have arches and anastomosing bars of cells. The arches and bars of cells lack intervening fibrovascular stroma [40]. These tumors have cytologic features of PTC, and areas of follicular and papillary growth may be seen. The architectural features are the most distinguishing in separating cribriform-morular PTC from other types of PTC. These tumors occur most commonly in women, they may be single or multifocal, and their prognosis is similar to that of classic PTC

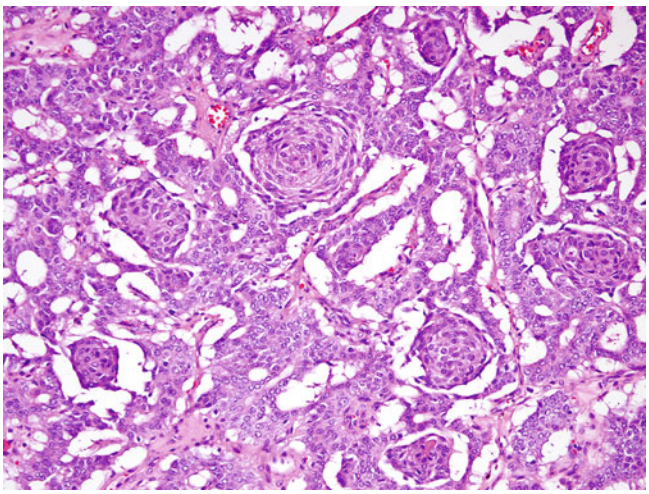

Fig. 5.37 Cribriform-morular variant of papillary thyroid carcinoma. Shown is an area of prominent morules in a cribriform-morular PTC. The morules are composed of spindle/oval tumor cells, which are positive for TTF1 and sometimes thyroglobulin. The tumor cells show aberrant nuclear and cytoplasmic expression of β-catenin. The morular areas may show absent or focal keratin expression [42]. Nuclear expression of estrogen and progesterone receptors and Bcl-2 also has been reported [43]

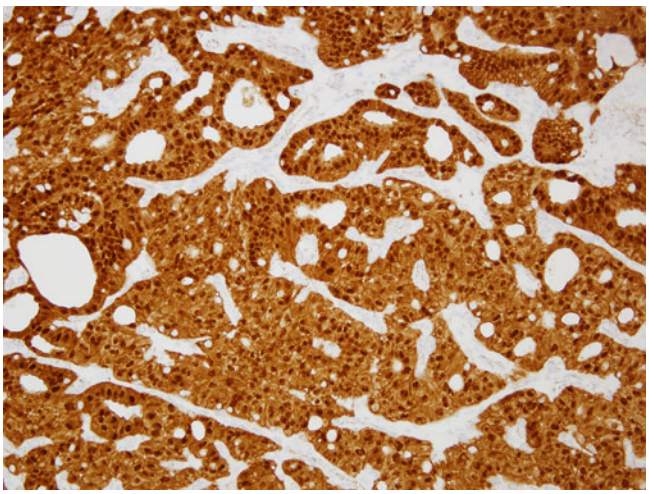

Fig. 5.39 Cribriform-morular variant of papillary thyroid carcinoma. Aberrant nuclear and cytoplasmic staining for β-catenin is present in cribriform-morular PTC. The follicular cells in the surrounding thyroid may show membranous staining for β-catenin, but aberrant cytoplasmic and nuclear staining for β-catenin is seen in cribriform-morular PTC

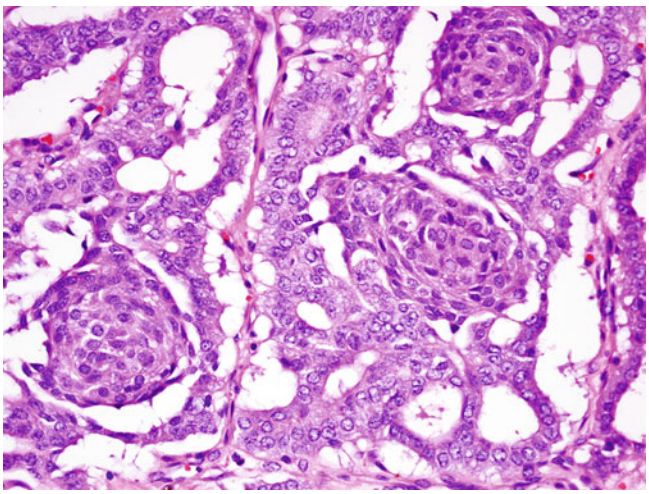

Fig. 5.38 Cribriform-morular variant of papillary thyroid carcinoma. High-power view of morules in the cribriform-morular variant of PTC. The morules are a helpful diagnostic feature but must be distinguished from those of squamous metaplasia [42]. Unlike in squamous metaplasia, the morules may lack or show decreased staining for keratin [42]

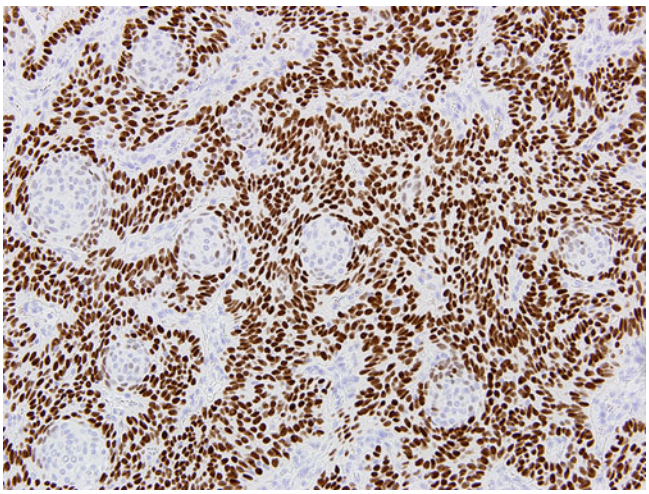

Fig. 5.40 Cribriform-morular variant of papillary thyroid carcinoma. Cribriform-morular variant of PTC shows nuclear staining for TTF1

Warthin-Like Variant of PTC

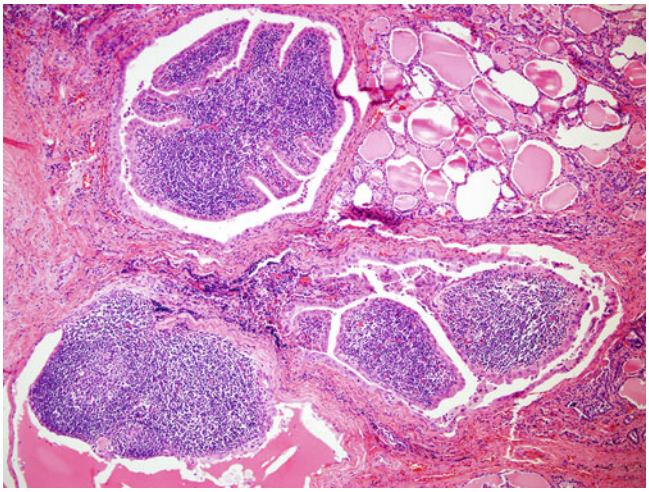

Fig. 5.41 Warthin-like variant of papillary thyroid carcinoma. The Warthin-like variant of PTC shows papillary nuclear features, oxyphilic cytoplasm, and lymphocytic infiltrates filling papillary cores lined by the tumor cells. In 1995, Dr. LiVolsi described this tumor as "a peculiar thyroid tumor of follicular epithelial differentiation with distinctly papillary architecture, oxyphilic cytology, and lymphocytic infiltrates in papillary stalks" [44]. This Warthin-like variant of PTC resembles Warthin tumor of the salivary glands [44]. These tumors occur in adults, have a female predominance, and usually are solitary, circumscribed small tumors. The prognosis is similar to that of classic PTC

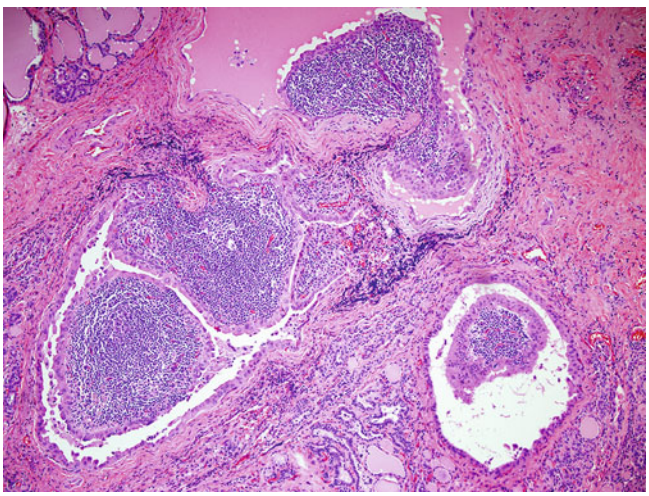

Fig. 5.42 Warthin-like variant of papillary thyroid carcinoma. This low-power view of Warthin-like variant PTC shows papillary cores filled with lymphocytic infiltrates and lined by epithelial cells with eosinophilic cytoplasm. This low-power appearance is quite characteristic and helpful in identifying this tumor. The surrounding thyroid parenchyma often shows lymphocytic or Hashimoto thyroiditis

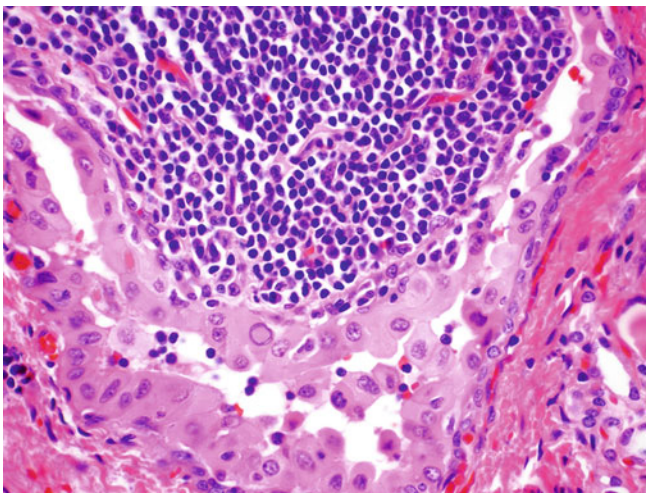

Fig. 5.43 Warthin-like variant of papillary thyroid carcinoma. In addition to the characteristic low-power architecture of the Warthin-like variant of PTC, the nuclear features are classic for PTC. The cells have eosinophilic cytoplasm. The tall cell variant of PTC also shows fairly eosinophilic cytoplasm, but the cells in the Warthin-like variant of PTC are not elongated as those of the tall cell variant, in which the cells are twice as tall as they are wide. The papillary cores filled with lymphocytic infiltrates lined by epithelial cells help separate the Warthin-like variant from the oxyphilic/Hurthle variant of PTC. The architectural and nuclear features separate the Warthin-like variant of PTC from Hurthle cell thyroid neoplasms

Diffuse Sclerosing Variant of PTC

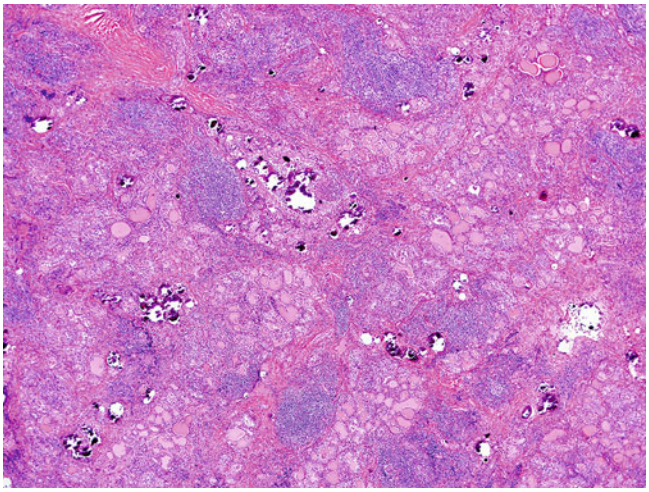

Fig. 5.44 Diffuse sclerosing variant of papillary thyroid carcinoma. The diffuse sclerosing variant of PTC has prominent calcifications, numerous psammoma bodies, fibrosis, squamous metaplasia, and a marked lymphocytic infiltrate. This variant, described in 1985, is more common in females and young patients [45]. This tumor often has aggressive features of large size, diffuse involvement of both lobes, prominent angiolymphatic invasion throughout the thyroid, and increased lymph node and lung metastases [46, 47]. Ultrastructurally, the dissemination in the thyroid is the result of lymphatic invasion [48]. The prognosis varies in the literature, with some studies showing a worse prognosis than that of conventional PTC [46, 49]. Other studies report distinctive and unfavorable features but an outcome similar to that of conventional PTC [47, 50]

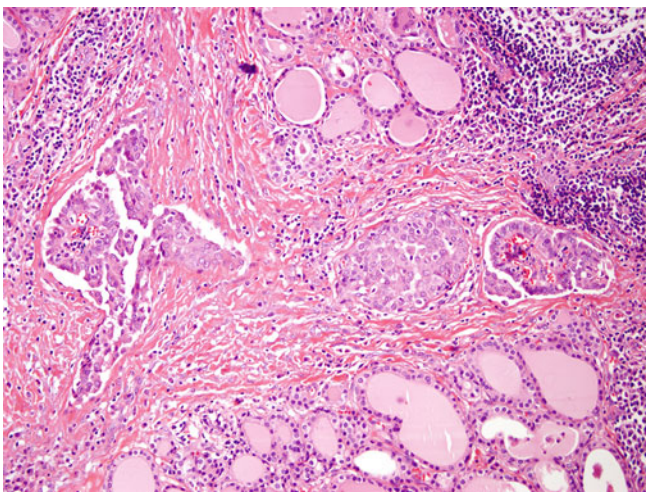

Fig. 5.45 Diffuse sclerosing variant of papillary thyroid carcinoma. Diffuse sclerosing PTC showing widespread intrathyroidal angiolymphatic permeation, which may appear as micropapillary formations in cleft-like spaces [46]. Although an earlier study did not identify thyroglobulin staining in the squamous metaplasia [51], a subsequent study reported that both PTC and squamous metaplasia cells stain strongly with keratin 19, thyroglobulin, and TTF1 [50]. Prominent S100 dendritic cells also are seen in these tumors [50, 51]

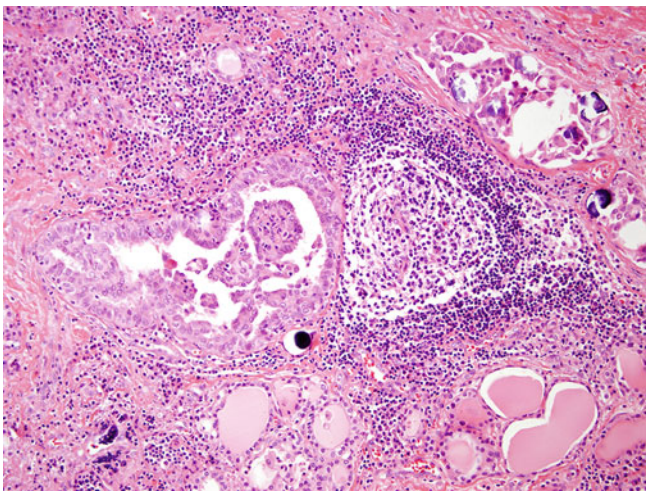

Fig. 5.46 Diffuse sclerosing variant of papillary thyroid carcinoma. Diffuse sclerosing variant of PTC with fibrosis, lymphocytic infiltrate including lymphoid follicles with germinal centers, and extensive angiolymphatic invasion

Oxyphilic (Oncocytic/Hurthle Cell) Variant of PTC

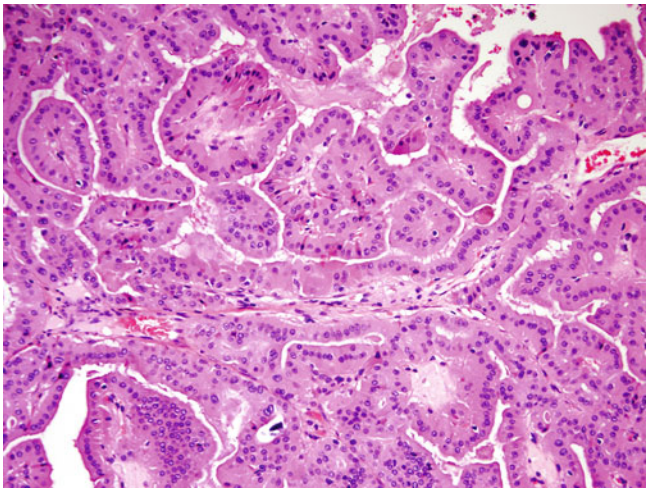

Fig. 5.47 Oxyphilic (oncocytic/Hurthle cell) variant of papillary thyroid carcinoma. Low-power photomicrograph of the papillary architecture in an oxyphilic variant of PTC. This is an uncommon variant of PTC and one of the most difficult to diagnose. Oxyphilic PTC has cytologic features of PTC and abundant eosinophilic cytoplasm. Because of the abundant cytoplasm, the nuclei do not show the prominent overlapping often seen in other types of PTC. Oxyphilic PTC must be differentiated from Hurthle cell neoplasms and papillary hyperplasia with oxyphilic change, both of which lack the characteristic nuclear features of PTC

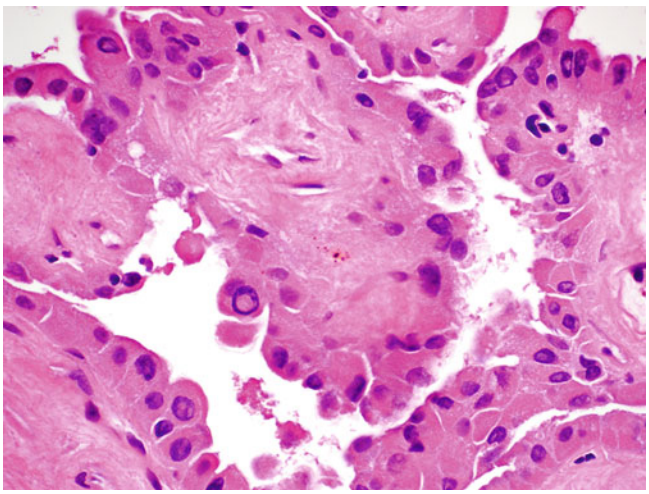

Fig. 5.48 Oxyphilic (oncocytic/Hurthle cell) variant of papillary thyroid carcinoma. The papillae in this oxyphilic variant of PTC are lined by a single layer of oxyphilic cells with cytologic features of PTC, including intranuclear inclusions. These tumors may behave similarly to classic PTC, although some studies have reported more aggressive behavior [52]. Tumors with features of both oxyphilic and tall cell PTC may behave more aggressively [53]. In a study of 42 oxyphilic PTCs, the tumors ranged from 1 to 9 cm (median, 3 cm), 19 tumors had extrathyroid extension, 13 tumors had lymph node metastases, 2 tumors had distant metastases, 4 patients had locoregional recurrence, 1 patient had disseminated disease, and 3 patients died from the disease [54]. The 5- and 10-year survival rates were 94 and 87 %, respectively [54]. Prognostic factors were age, extrathyroid extension, primary tumor stage, and regional and distant metastases [54]. In this study, extrathyroid tumor growth was common (45 %), but the tumors still had a favorable prognosis with radical resection, radioiodine ablation of the thyroid remnant, and external irradiation [54]

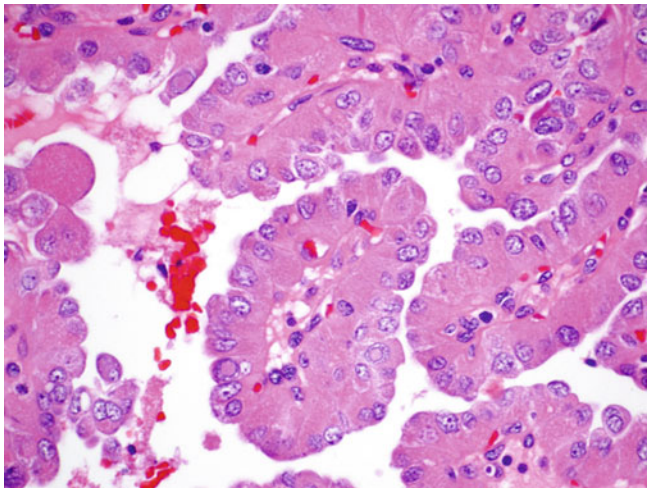

Fig. 5.49 Oxyphilic (oncocytic/Hurthle cell) variant of papillary thyroid carcinoma. Oxyphilic variant of PTC with papillae lined by a single layer of epithelial cells with abundant eosinophilic cytoplasm and nuclear features of PTC, including large nuclei with irregular nuclear membranes, focal nuclear grooves, and eosinophilic intranuclear inclusions ("holes"). The oxyphilic variant of PTC shows an immunophenotype similar to that of classic PTC, but the immunostains may be difficult to interpret because there may be nonspecific staining in the cytoplasm

Solid Variant of PTC

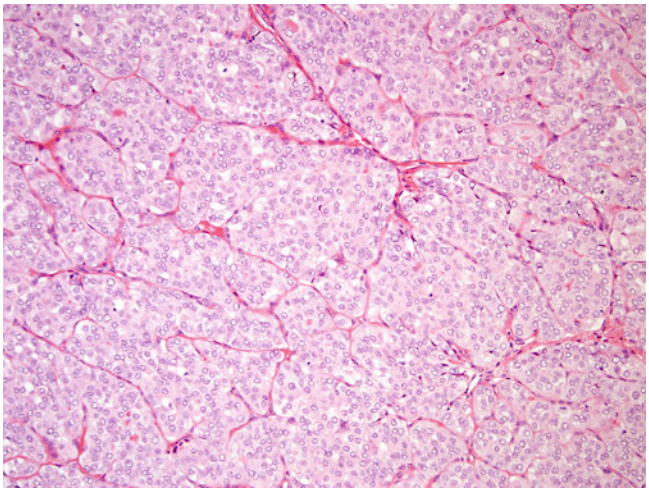

Fig. 5.50 Solid variant of papillary thyroid carcinoma. The solid variant of PTC is uncommon, accounting for 2–3 % of PTCs, but is more common in children [55]. In a study from the Mayo Clinic, the solid variant of PTC was defined as having predominantly (>70 %) solid growth, a lack of necrosis, and the presence cytologic features of PTC [55]. This variant must be differentiated from poorly differentiated thyroid carcinoma. Both may show solid growth, but the solid variant of PTC has cytologic features of PTC and lacks necrosis. The solid variant has a less favorable prognosis than classic PTC but higher survival than poorly differentiated carcinoma [55]. In a study of 121 PTCs, the solid cell variant had the highest proportion (75 %) of high-risk tumors classified by AMES (age, metastases, extent, and size) criteria (75 %), followed by the tall cell variant (33.3 %), with only 8.3 % of classic PTC being high risk [56]

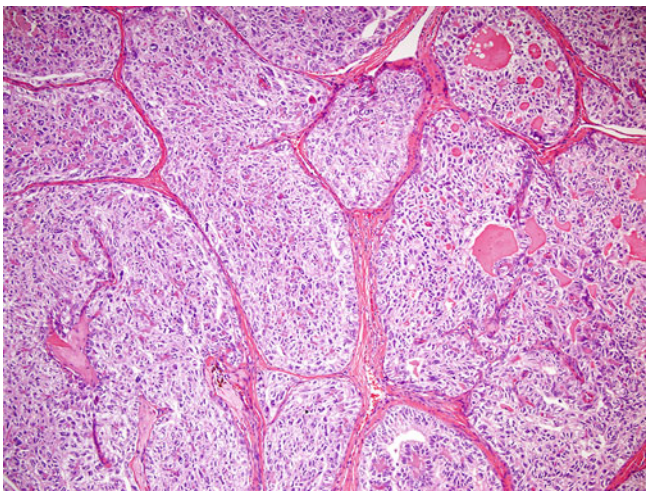

Fig. 5.51 Solid variant of papillary thyroid carcinoma. The solid variant of PTC has a solid growth pattern, as demonstrated in this image; however, a trabecular growth pattern also may be seen. The tumor cells are in solid sheets or nests or trabeculae, and psammoma bodies and fibrosis may be seen in some cases. These tumors generally lack a fibrous capsule and necrosis, and have few mitoses. A thyroid tumor with solid growth, prominent mitotic activity, and necrosis more likely would be classified as a poorly differentiated carcinoma

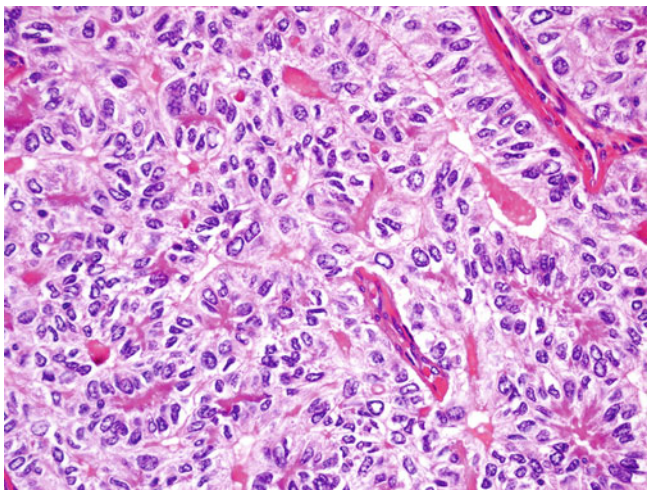

Fig. 5.52 Solid variant of papillary thyroid carcinoma. The solid variant of PTC has a solid growth pattern and nuclear features of PTC. This tumor is more common in children, particularly those exposed to radiation [57]. The solid variant was the most common PTC in Belarus children after the Chernobyl disaster [57]. This variant is associated with *BRAF* mutation, but the radiation-associated tumors have a low incidence of *BRAF* mutation and commonly have *RET/PTC* rearrangements [58]. The pediatric post-Chernobyl PTCs were associated with *RET/PTC1* and *RET/PTC3* rearrangements. *RET/PTC1* occurs with classic and diffuse sclerosing PTCs and *RET/PTC3* with the solid/follicular variant [59]. These tumors occur in young children and have a high frequency of solid growth, an equal female-to-male ratio, a short latency, intraglandular spread, and capsular and soft tissue invasion and metastases [57, 60]

Tall Cell Variant of PTC

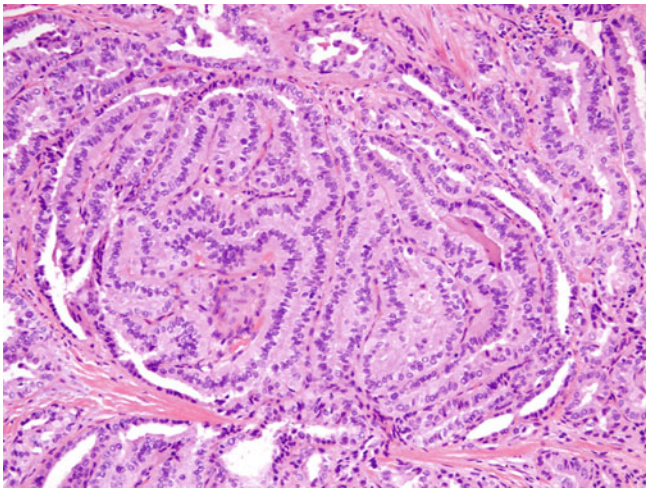

Fig. 5.53 Tall cell variant of papillary thyroid carcinoma. The tall cell variant of PTC is characterized by cells twice as tall as they are wide and by nuclear features of PTC [61]. Tall cell PTC, described in 1976 by Hawk and Hazard [62], is aggressive and occurs more often in males and elderly people. These tumors often are large (>6 cm) and have aggressive features of extrathyroid extension, vascular invasion, metastases, and shorter disease-free survival than that of classic PTC [63, 64]. Up to 20–25 % of patients with this tumor die from the disease [64]. Recent studies suggest it may not be the histologic subtype of the tumor that is prognostic but other factors, such as tumor size, age, and extrathyroid extension, among others. A study of 62 tall cell and 83 classic PTCs without extrathyroid extension found no difference between tall cell and classical PTC with regard to age, gender, size, risk stratification, type of therapy, or length of follow-up, but found the tall cell variant without extrathyroid extension more aggressive than classic PTC without extrathyroid extension, independent of age, gender, or tumor size [65]

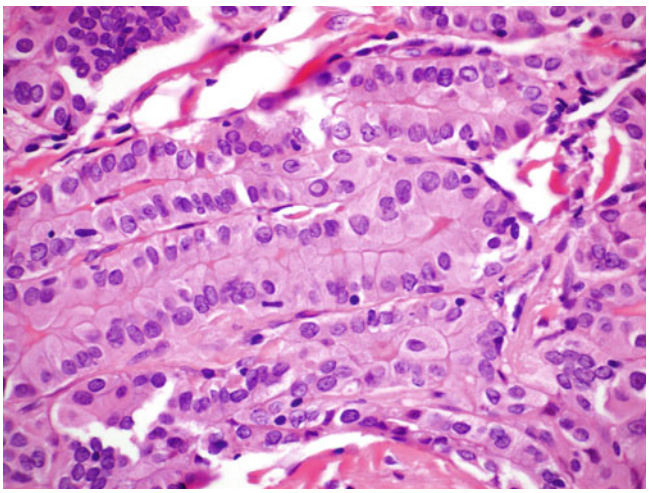

Fig. 5.54 Tall cell variant of papillary thyroid carcinoma. The papillary structures in tall cell PTC are lined by cells with abundant eosinophilic cytoplasm, basally oriented nuclei, and nuclear features of PTC. The tumor cells are at least twice as tall as they are wide. It has been proposed that the tall cell variant be diagnosed if the tumor is composed of 50 % or more of tall cells that have a height at least twice the width, eosinophilic cytoplasm, and nuclear features of PTC [61]. Regardless of the exact proportion of tall cells or whether they are twice or three times as tall as wide, this entity reportedly is underdiagnosed [61]. This is important because this tumor accounts for 20 % of incurable fludeoxyglucose positron emission tomography–positive thyroid carcinomas refractory to radioactive iodine therapy [61]

Columnar Variant of PTC

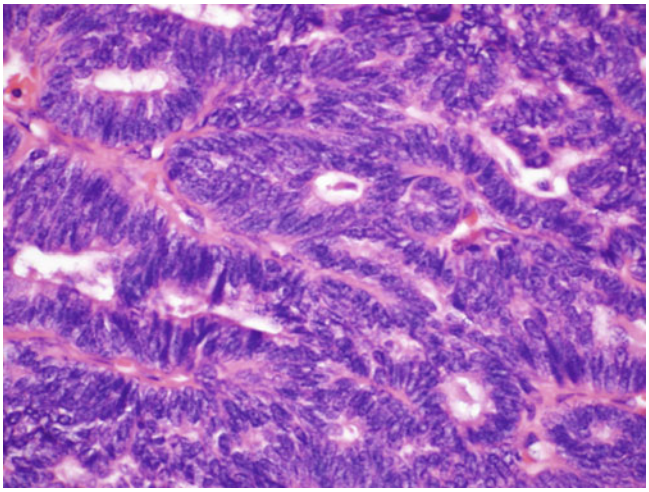

Fig. 5.55 Columnar variant of papillary thyroid carcinoma. The columnar variant of PTC is a rare, aggressive tumor that occurs over a wide age range, metastasizes widely, and does not respond to radioactive iodine or chemotherapy [66]. This tumor has a prominent papillary architecture and elongated cells with nuclear stratification and scant cytoplasm. The tumor appears basophilic and histologically resembles endometrial or colon cancer. Others may have more cytoplasmic clearing, similar to secretory endometrium. Solid growth with spindle cells and follicular and microfollicular growth may be seen [67, 68]. Tumors may have both tall cell and columnar features [69, 70]. The prognosis for encapsulated tumors is better than that of highly invasive unencapsulated tumors [68]. The columnar variant may be a distinct morphologic type of PTC but not necessarily a distinct clinical subtype, as the behavior may be associated with clinical stage and extrathyroid invasion rather than the morphologic subtype [71]. This variant of PTC has a high proliferation index with MIB1 [72, 73]

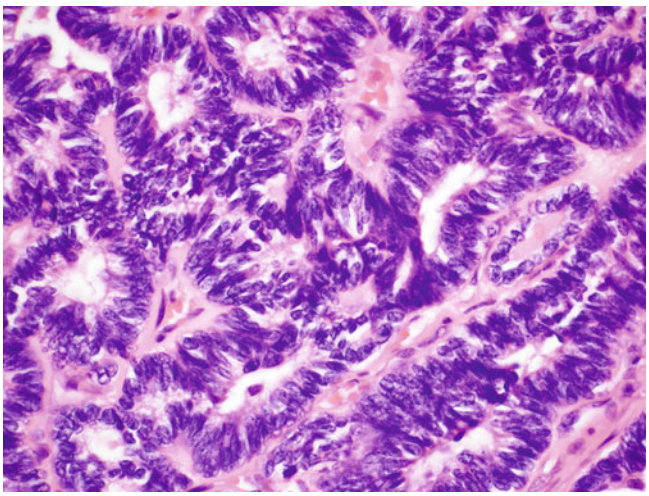

Fig. 5.56 Columnar variant of papillary thyroid carcinoma. This image of the columnar variant of PTC shows a focally microfollicular growth pattern, prominent nuclear stratification, and scant cytoplasm. The cells are twice as tall as they are wide, but unlike the tall cell variant of PTC, the columnar cells are more elongated than tall cells and show prominent nuclear stratification. Psammoma bodies usually are not seen. Although colloid may be seen, it is not prominent. These tumors often show angiolymphatic invasion, extrathyroid extension, and nodal and distant metastases. The mortality rate is high. The columnar variant of PTC is positive for TTF1, estrogen and progesterone receptor, and **β**-catenin (membranous); is negative for carcinoembryonic antigen and calcitonin; and may stain for CDX2, although reports are variable [73–75]

Hobnail Variant of PTC

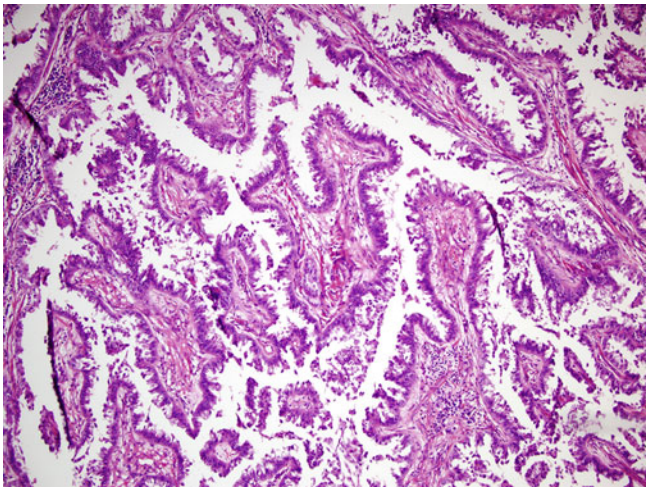

Fig. 5.57 Hobnail variant of papillary thyroid carcinoma. Hobnail PTC is a rare, recently described aggressive variant of PTC that has prominent hobnail (micropapillary) features. The tumor is composed of prominent papillae that lack fibrovascular cores, follicles with little colloid, and clusters of atypical cells with increased nuclear-to-cytoplasmic ratios and apical nuclei that appear hobnailed [76]. In the original eight cases from the Mayo Clinic, six were in women aged 28–78 years (mean, 58 years) [76]. The tumors were 1–4 cm (mean, 2.5 cm) and often multifocal. Four of the eight patients died of disease, and two were alive with disease [76]. In a subsequent series of 24 cases, 18 of 24 were women aged 28–78 years (mean, 57 years), the average follow-up was 106 months (range, 4–274 months), and tumor sizes ranged from 1 to 5.8 cm (mean, 3 cm) [77]. Of the 24 cases, 12 had <30 % and 12 had >30 % hobnail component. Six of the 12 with >30 % hobnail component died of disease, and 3 were alive with extensive disease with a mean follow-up of 32 months. Of the 12 with <30 % hobnail component, 2 died of disease [77]. These tumors are aggressive, particularly if >30 % of the tumor is hobnail; however, even in those with less hobnail component, aggressive behavior may occur [77]

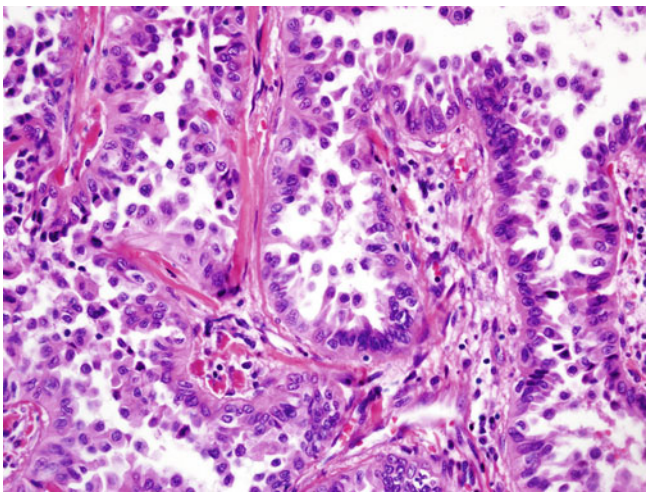

Fig. 5.58 Hobnail variant of papillary thyroid carcinoma. The cells lining the papillae and follicles in this hobnail variant of PTC show loss of polarity with apically placed nuclei and clusters of atypical cells. The papillae lack fibrovascular cores and follicular structures that, when present, lack colloid. The papillary structures vary in size and are lined by atypical cells with increased nuclear-to-cytoplasmic ratios and apical nuclei producing a surface bulge (hobnail) [76]. These tumors are positive for thyroglobulin, TTF1, HBME-1, p53, **β**-catenin (membranous), and E-cadherin [76]. Mitotic figures are common, and the Ki67 proliferative index is 2–20 % (mean, 10 %) [76]. *BRAF* mutation is present in 57 % of cases [76]

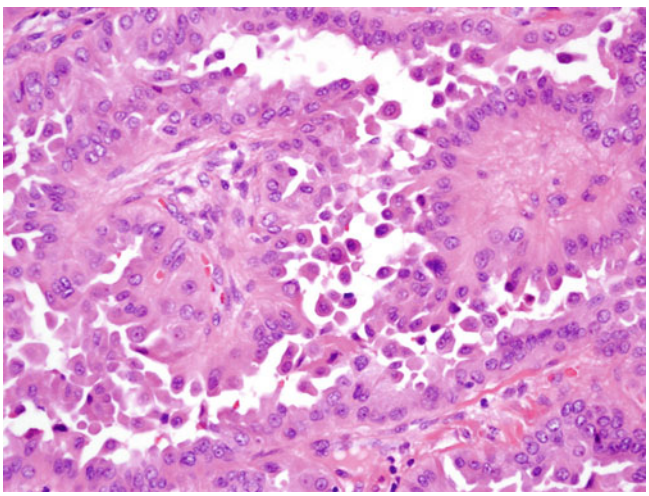

Fig. 5.59 Hobnail variant of papillary thyroid carcinoma. Hobnail PTC with prominent hobnail features, with papillae without fibrovascular cores lined by atypical epithelial cells with loss of polarity and apical nuclei, giving the tumor a hobnail (micropapillary) appearance. An intranuclear pink hole is identified in the center of the photomicrograph. The tumor cells also show a loss of cohesiveness. These tumors metastasize to the lymph nodes, liver, lung, bone, brain, muscle, and pancreas [76]. The metastases appear histologically similar to the primary tumor

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