THYROID CANCER

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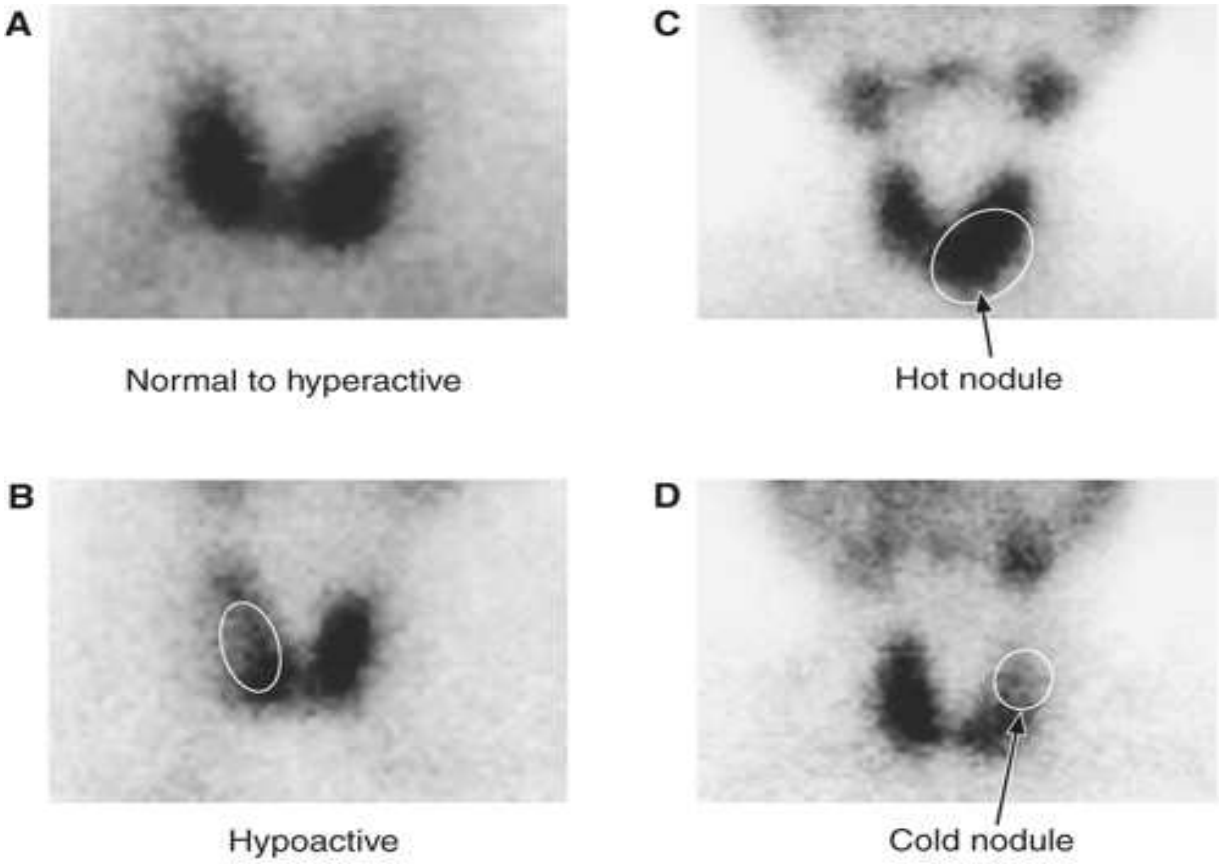
Thyroid development

- Arises from floor of primitive pharynx, descends into neck.
- Connected to tongue by thyroglossal duct. May persist as pyramidal lobe of thyroid (in 50% of patients).
- Foramen cecum (floor of mouth) is remnant of thyroglossal duct.
- Most common site of ectopic thyroid tissue is the tongue.

Thyroid nodules

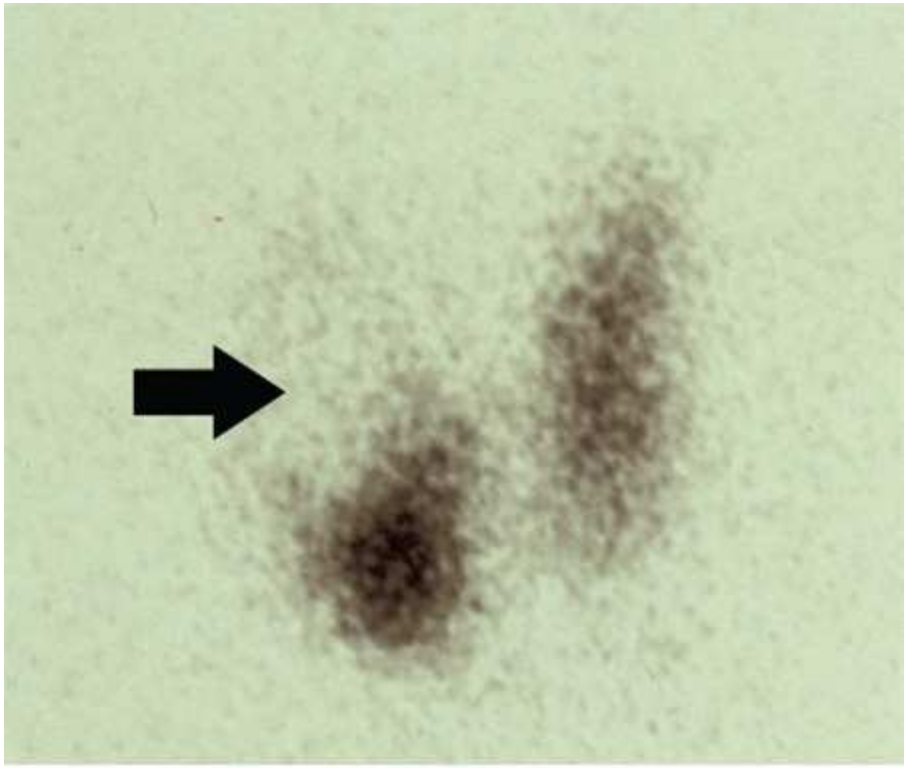


Source: Molina PE: *Endocrine Physiology*, 2nd Edition:
http://www.accessmedicine.com

Images courtesy of Dr. Luis Linares, Memorial Medical Center, New Orleans, LA

Fig. 8-29 Accessed 02/01/2010

Solitary nodule



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Thyroid scan showing a "cold" nodule in the right superior pole of the thyroid.

Fig. 31-1 Accessed 08/01/2010

The solitary nodule

- Usually painless
- May represent the only thyroid gland present
- May also represent the portion of intra-thoracic thyroid in the neck.
- Solitary nodule present in 1-10% of population.
- Four times more common in women
- 1% malignant
- BUT, 10% of “cold” nodules are malignant
- Nodules <1 cm in size are generally benign
- Nodules >4 cm in size are generally malignant

The solitary nodule

- Younger patients, men, and history of radiation to the head and neck are factors associated with increased incidence of thyroid malignancy (up to 35%).
- Malignancy more frequent in Chinese.
- Thyroid suppression to induce resolution of nodule is not particularly useful.
- Fine needle aspiration accuracy 70-97%. CT scan more sensitive if medullary carcinoma.
- Isotope scanning may identify autonomously functioning nodule.

Diagnostic strategy

- Fine needle aspiration is the first step.
- If the aspirate is benign, measure TSH.
- If TSH elevated, measure anti-TPO and follow observed nodule serially.
- If TSH normal, follow observed nodule serially.
- If TSH low, perform radioisotope scan.
- If the nodule is hot and not the only tissue present, proceed to radioiodine ablation.
- If the nodule is cold, follow serially.
- Nodules <1cm diameter may be followed with yearly ultrasonography.

Diagnostic strategy

- If the fine needle aspiration is inadequate or non-diagnostic, it must be repeated.
- If the fine needle aspiration is diagnostic of medullary thyroid carcinoma, obtain RET genetic testing.
- If no RET mutation and no suspicion of multiple endocrine neoplasia (MEN), proceed to surgery.
- If RET mutated or there is suspicion of MEN, measure VMA, metanephrine, PTH, and test RET in kindred.
- Proceed to surgery.

Diagnostic strategy

- If the fine needle aspiration is suspicious or diagnostic for thyroid carcinoma, proceed to surgery.
- Measure iCa^{2+} (ionized) preoperatively.
- Total thyroidectomy is the preferred approach in the US.
- Patients with papillary carcinoma frequently have involvement of lateral neck regions IV, III, V, and II.
- Parathyroid glands should be preserved in the dissection.

Adenoma

- Discrete, solitary mass derived from follicular epithelium
- Vast majority of adenomas are nonfunctional
- 20% of non-functioning adenomas have RAS or PIK3CA mutations or bear a PAX-PPARG fusion gene (t(2;3)(q13;p25)).
- A small subset cause clinically apparent thyrotoxicosis ("toxic adenoma")
- Hormone production in functional adenomas is independent of TSH stimulation.
- TSHR and the α-subunit of G_s (GNAS) gain of function mutations are found in toxic adenomas

Adenoma

- Well-defined capsule separates the solitary adenoma from surrounding thyroid parenchyma
- Bulges from the cut surface and compresses the adjacent thyroid. The color ranges from gray-white to red-brown
- The constituent cells often form uniform appearing follicles that contain colloid.
- Growth pattern differs from adjacent normal thyroid
- Abnormal nuclei do not necessarily indicate malignancy.

Adenoma

- Hürthle cell or oxyphil change may be present.
- Hüthle cell adenoma behaves as does a follicular adenoma.
- The integrity of the capsule distinguishes this from carcinoma.
- Extensive mitotic activity, necrosis, or cellularity is unusual in an adenoma and may suggest the follicular variant of papillary carcinoma
- Rare to find fusions

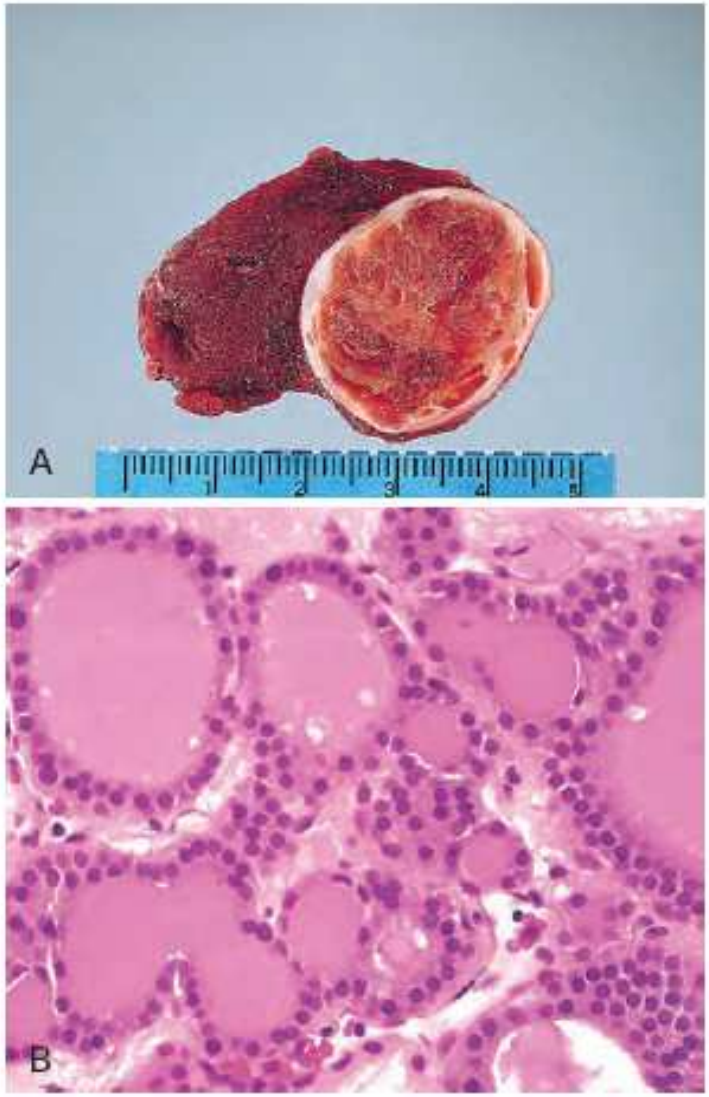


Figure 24-16 Follicular adenoma of the thyroid. **A,** A solitary, well-circumscribed nodule is seen. **B,** The photomicrograph shows well-differentiated follicles resembling normal thyroid parenchyma.

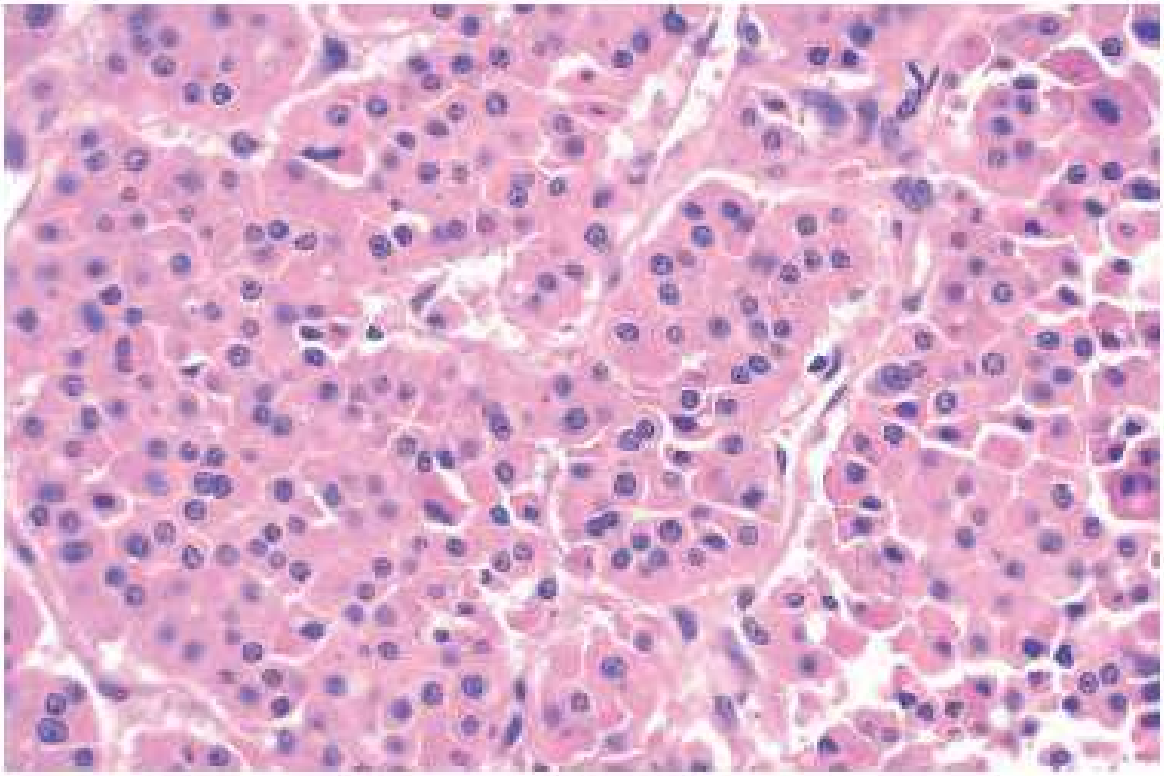


Figure 24-17 Hürthle cell (oxyphil) adenoma. A high-power view showing that the tumor is composed of cells with abundant eosinophilic cytoplasm and small regular nuclei. (Courtesy Dr. Mary Sunday, Duke University, Durham, N.C.)

Adenocarcinoma

- Patients <20 years old have a higher expression of proteins involved in iodine metabolism.
- Proliferative rates of normal thyroid tissue decrease with age.
- Relative to normal thyroid, thyroid cancer is characterized by reduced Na^{+}-I^{-} transporter expression.
- Iodine deficiency may predispose to follicular carcinoma
- Female predominance if thyroid cancer occurs in early and mid-adult years

Adenocarcinoma

- Genetic alterations in the three follicular cell–derived malignancies are in growth factor receptor signaling pathways
- Somatic testing is recommended for patients with differentiated thyroid carcinoma that is locally recurrent, advanced, or metastatic
- OR is not amenable to radioactive iodine therapy
- AS WELL as patients with anaplastic thyroid carcinoma
- RET/PEC rearrangement (disrupt TSH action) more common in young
- BRAF mutation more common in adults
- Associated with invasion, extension, metastasis.
- Mortality rates increase at 45yo (women: perimenopause age 50).
- Peak again over 60yo.

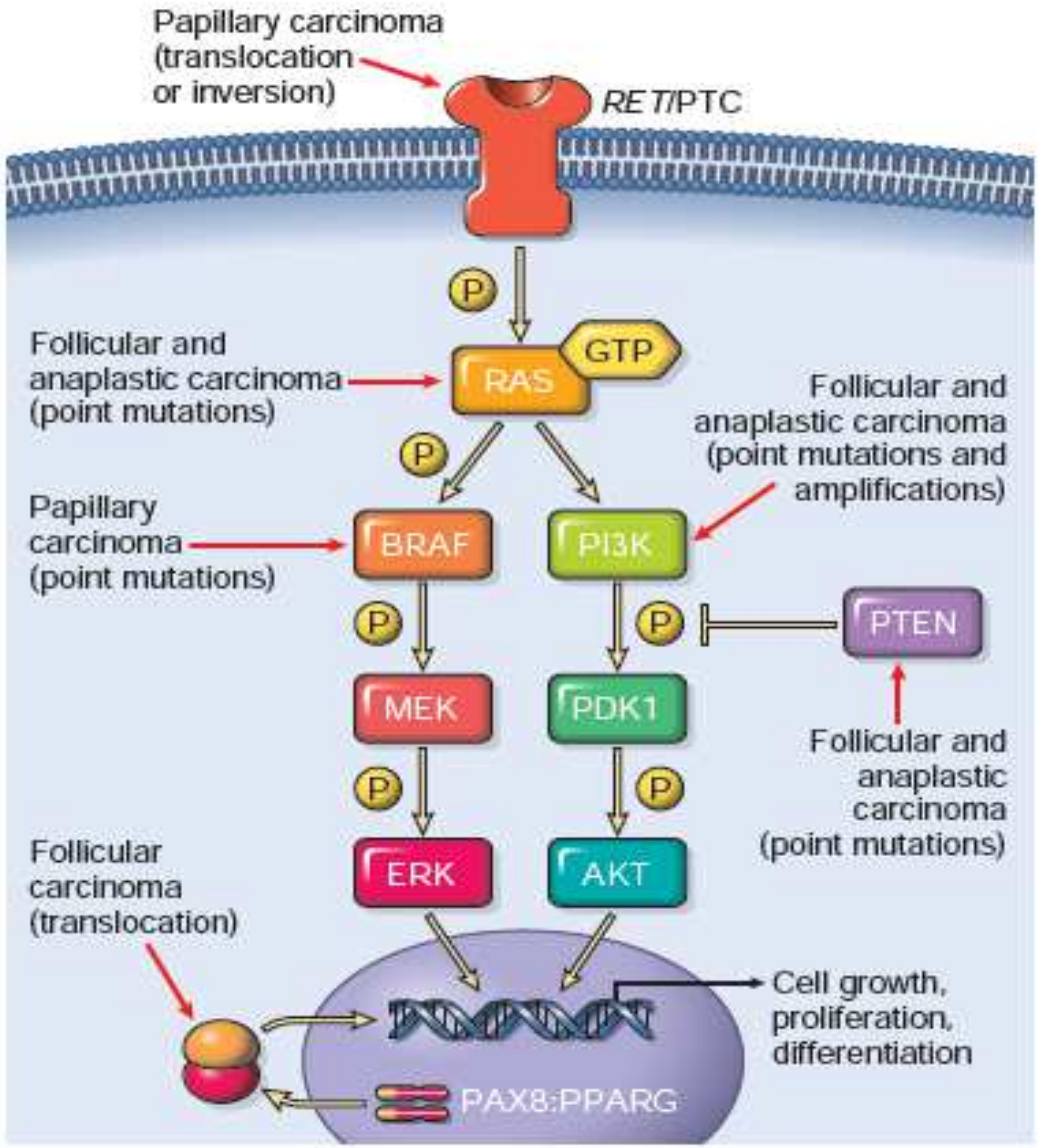


Figure 24-18 Genetic alterations in follicular cell-derived malignancies of the thyroid gland.

Papillary carcinoma

- >85% of thyroid cancers.
- 25-50 years of age
- Single nodules that move freely with the thyroid gland during swallowing
- First manifestation may be a mass in a cervical lymph node.
- Hoarseness, dysphagia, cough, or dyspnea suggests advanced disease
- 4% of patients present with metastases.
- 10% RET mutation
- Fusion partners common

Papillary carcinoma

- May be solitary or multifocal.
- Some tumors are well circumscribed and even encapsulated
- Others infiltrate the adjacent parenchyma and have ill-defined margins.
- The tumors may contain areas of fibrosis and calcification and are often cystic.
- The cut surface sometimes reveals papillary foci.

Papillary carcinoma

- Contain complex branching papillae having a dense fibrovascular stalk covered by a single to multiple layers of cuboidal epithelial cells.
- Generally, the epithelium covering the papillae consists of well-differentiated, uniform, orderly cuboidal cells

Papillary carcinoma

- Pathognomonic are groundglass or Orphan Annie eye nuclei,
- With invaginations of the cytoplasm that give the appearance of intranuclear inclusions (“pseudo-inclusions”) or intranuclear grooves.
- Psammoma bodies are concentrically calcified bodies within the core of the papillae.
- Rarely found in other thyroid neoplasms

Papillary carcinoma

- The follicular variant of papillary carcinoma is the most common
- Has the characteristic nuclear features of papillary carcinoma and an almost totally follicular architecture.
- A lower frequency of RET/PTC rearrangements; a lower frequency and different spectrum of BRAF mutations; and a significantly higher frequency of RAS mutations
- If well encapsulated, behaves as does a follicular carcinoma

Papillary carcinoma

- The tall-cell variant
- Occur in older individuals
- Higher frequencies of vascular invasion, extrathyroidal extension, and cervical and distant metastases
- Tall columnar cells with intensely eosinophilic cytoplasm lining the papillary structures.
- Up to 100% have BRAF mutations
- Often have RET/PTC translocations as well.
- Aggressive

Papillary carcinoma

- The diffuse sclerosing variant of papillary carcinoma occurs in younger individuals, including children.
- The tumor has a prominent papillary growth pattern intermixed with solid areas containing nests of squamous metaplasia.
- Fibrosis is extensive.
- Lymphocytic infiltrates are prominent.
- Lymph node metastases common.
- Lack BRAF mutation
- 50% have RET/PTC translocation
- Aggressive

Papillary carcinoma

- Columnar variant
- Columnar cells with nuclear pseudostratification, scant cytoplasm and absent or minimal nuclear features of papillary thyroid carcinoma
- Up to 70% in women
- 55% with lymph node metastases
- 33% with BRAF mutation
- Aggressive
- Papillary microcarcinoma
- Papillary carcinoma less <1 cm
- Usually incidental
- May be precursors of typical papillary carcinoma

Papillary carcinoma

- If encapsulated, 80-95% survival rate.
- 5-20% may recur
- Thyroidectomy followed by ^{131}Iodine ablation of residual tissue.
- Thyroxine administration improves survival.
- Follow with measurement of serum thyroglobulin to detect disease recurrence.

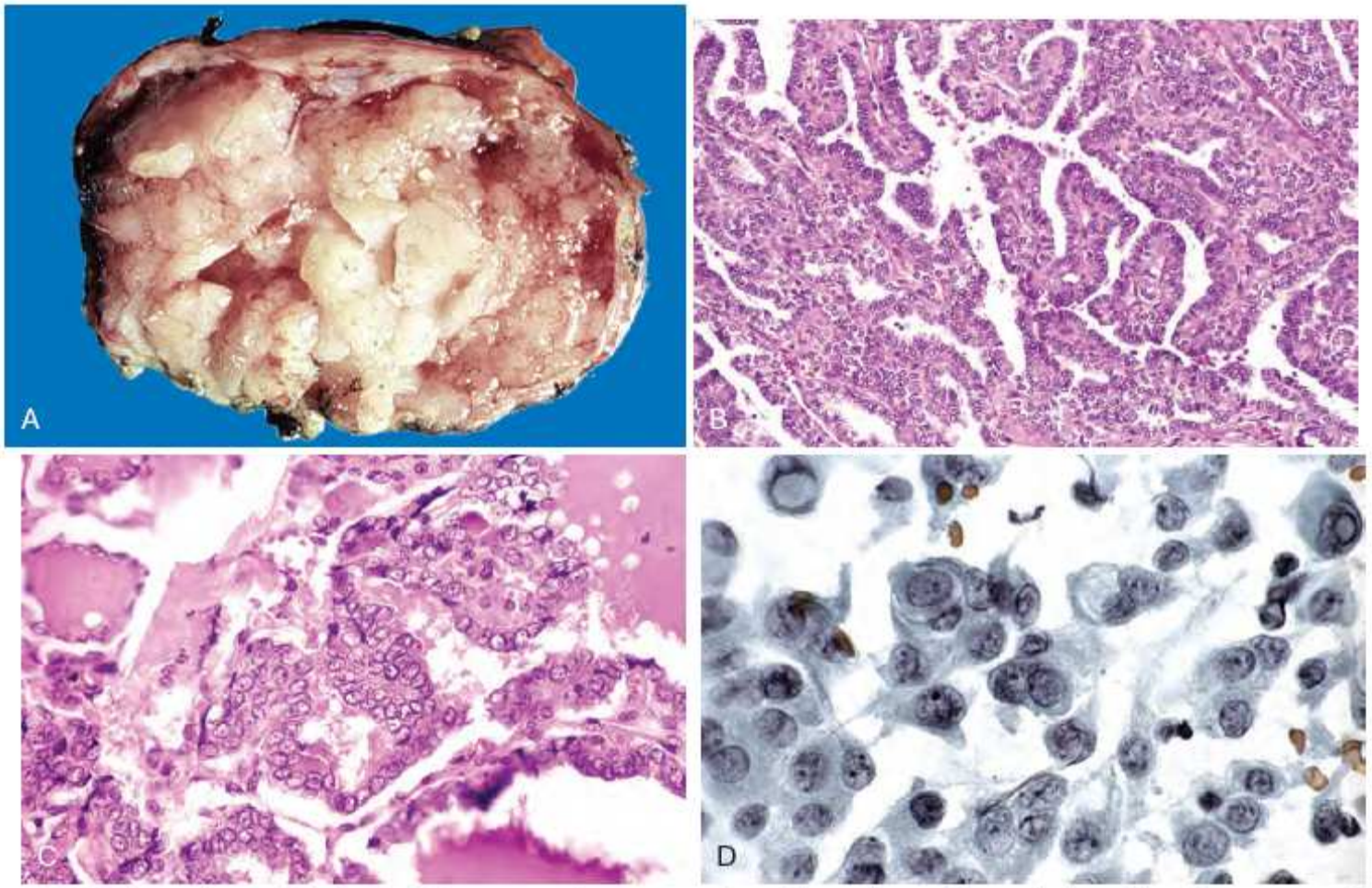


Figure 24-19 Papillary carcinoma of the thyroid. **A,** The macroscopic appearance of a papillary carcinoma with grossly discernible papillary structures. **B,** This particular example contains well-formed papillae. **C,** High power shows cells with characteristic empty-appearing nuclei, sometimes called "Orphan Annie eye" nucle. **D,** Cells obtained by fine-needle aspiration of a papillary carcinoma. Characteristic intranuclear inclusions are visible in some of the aspirated cells.

Papillary carcinoma

Branching papillae with fibrovascular core. Nuclei show ground-glass appearance. Psammoma body is characteristic. If one sees a psammoma body in what otherwise appears to be a follicular or medullary carcinoma, reconsider the diagnosis.

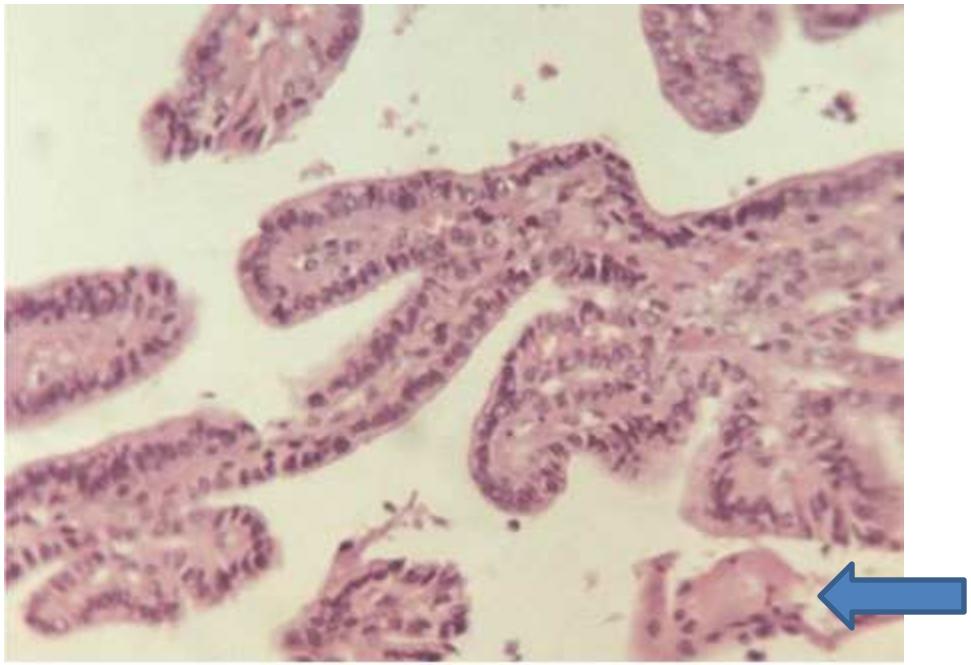


Fig. 31-2 Accessed 08/01/2010

Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Follicular carcinoma

- 5-10% of thyroid malignancies.
- Women 3:1
- 40-60 years old
- Up to 50% have RAS or PI_3K/AKT pathway mutations.
- Up to 50% have t(2;3)(q13;p25)
- Fusion gene of PAX8 and the peroxisome proliferator-activated receptor gene (PPARG),
- Noted in 10% of follicular adenomas

Follicular carcinoma

- Single nodule
- May be sharply demarcated from surrounding tissue
- Gray to tan to pink on cut section and may be somewhat translucent due to the presence of large, colloid-filled follicles.
- Fairly uniform cells forming small follicles containing colloid with back to back apposition of glands.
- Abnormal nuclei
- Extension beyond capsule
- Lymph node metastases are uncommon
- .

Follicular carcinoma

- Vascular dissemination common.
- From 16-33% of patients present with metastases.
- 80-95% survival rates if treated while confined to gland.
- Thyroidectomy followed by ^{131}Iodine ablation of residual tissue has replaced neck dissection.
- Thyroxine administration improves survival.
- Follow with measurement of serum thyroglobulin to detect disease recurrence.

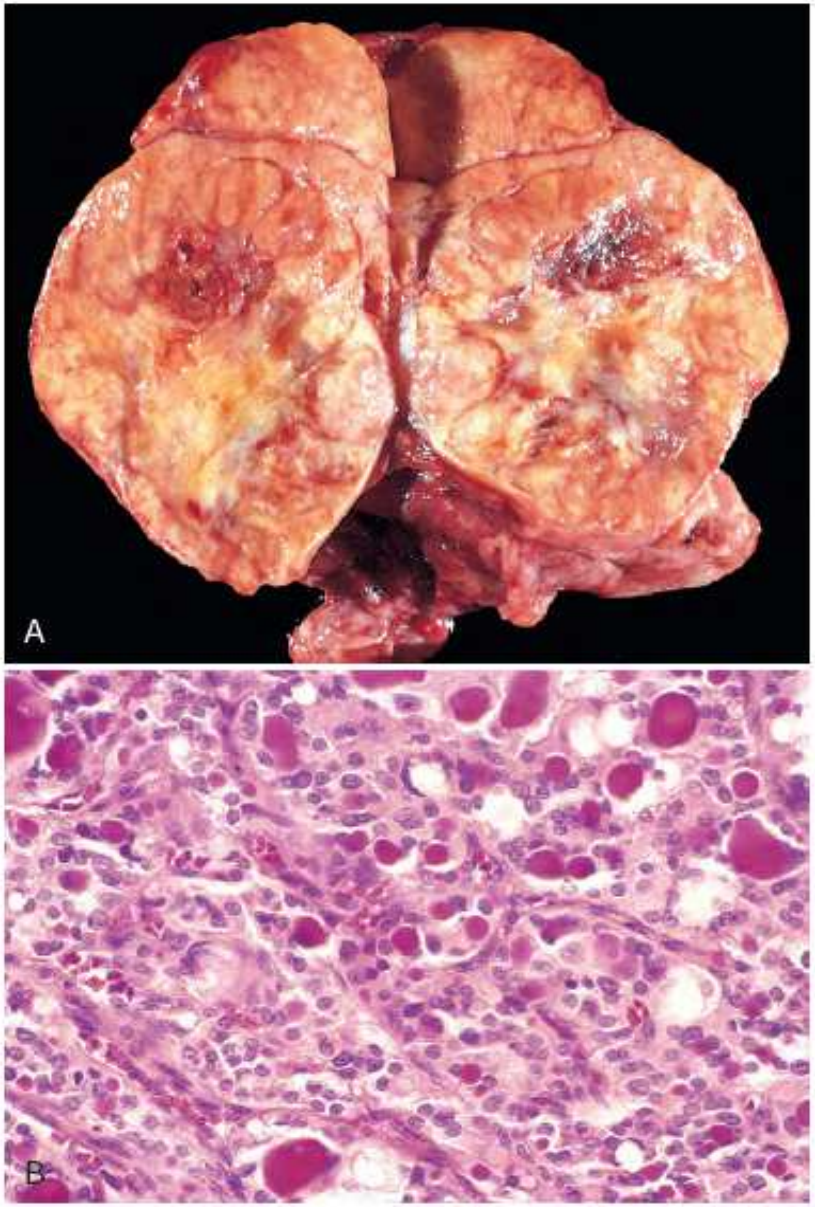


Figure 24-20 Follicular carcinoma. **A,** Cut surface of a follicular carcinoma with substantial replacement of the lobe of the thyroid. The tumor has a light-tan appearance and contains small foci of hemorrhage. **B,** A few of the glandular lumens contain recognizable colloid.

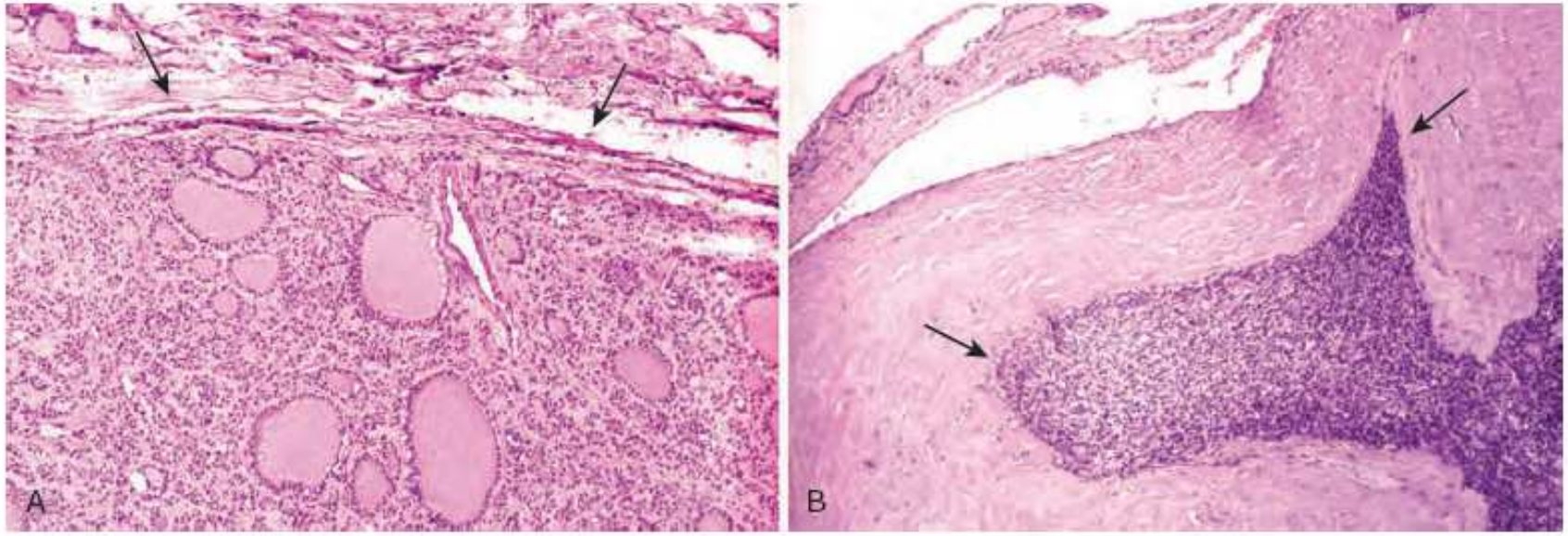
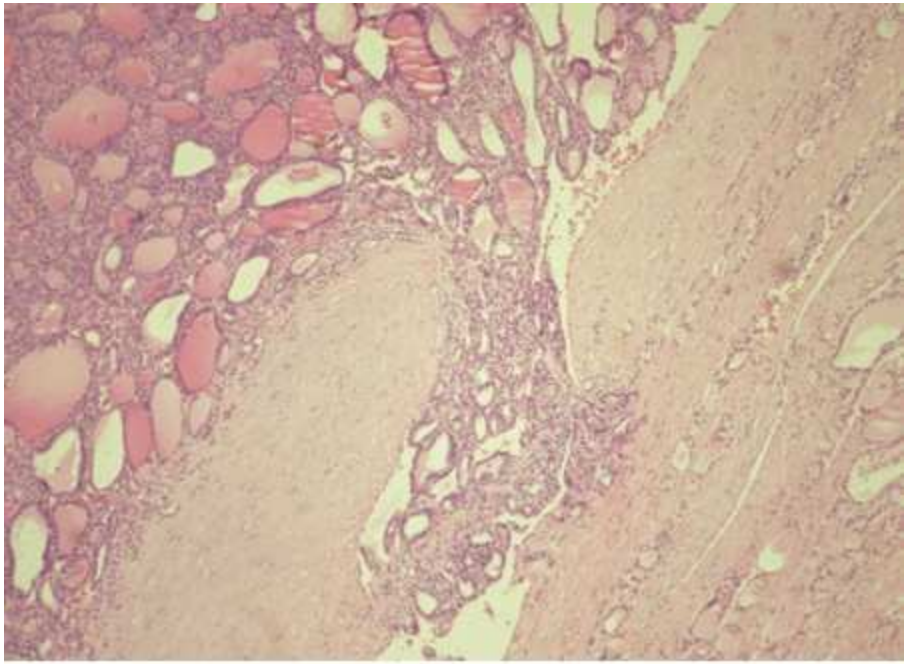


Figure 24-21 Capsular integrity in follicular neoplasms. In adenomas (**A**), a fibrous capsule, usually thin but occasionally more prominent, circumferentially surrounds the neoplastic follicles and no capsular invasion is seen *(arrows)*; compressed normal thyroid parenchyma is usually present external to the capsule *(top of the panel)*. In contrast, follicular carcinomas demonstrate capsular invasion (**B,** *arrows*) that may be minimal, as in this case, or widespread. The presence of vascular invasion is another feature of follicular carcinomas.

Follicular carcinoma



Histology of follicular carcinoma at the site at which the cancer invades the capsule of the nodule. Capsular and vascular invasion of nodules in a lesion that contains cells with the features of follicular neoplasm is follicular carcinoma by definition.

Fig. 31-3 Accessed 08/01/2010

Anaplastic carcinoma

- Present as rapidly enlarging bulky mass with involvement of surrounding structures and with lung metastases
- May represent dedifferentiation of papillary or follicular carcinoma
- 4-% have BRAF mutations
- Additional mutations are of TP53 and β-catenin
- 65 years of age
- Highly aggressive (up to 100% mortality within 1 year)

Anaplastic carcinoma

- Histopathology
- Anaplastic cells:
- Pleomorphic giant cells and occasional osteoclast-like multinucleate giant cells;
- Spindle cells with a sarcomatous appearance;
- Mixed spindle and giant cells.
- Cytokeratin positive staining
- Thyroglobulin negative staining

Medullary carcinoma

- 3-5% of all thyroid carcinomas.
- Neuroendocrine tumor of parafollicular C cells.
- 30% associated with MEN 2A and 2B.
- Bilateral or multicentric
- Germline RET mutations
- Sporadic cancers occur at 40-50 years of age
- Single nodules
- 50% present with regional lymphadenopathy.
- Somatic testing including TMB or somatic RET fusions is also recommended for patients who are RET germline wild-type or germline unknown with recurrent, persistent locoregional, or distant metastatic disease

Medullary carcinoma

- Usually presents as neck mass.
- The tumor tissue is firm, pale gray to tan, and infiltrative.
- Polygonal to spindle-shaped cells, which may form nests, trabeculae, and even follicles.
- More anaplastic cells may be found.
- Acellular amyloid deposits derived from calcitonin polypeptides are present in the stroma in many cases

Medullary carcinoma

- Presence of multicentric C-cell hyperplasia in the surrounding thyroid parenchyma in familial cases.
- Stain positively for calcitonin.
- Neurosecretory granules demonstrable on electron microscopy

Medullary carcinoma

- In some instances, the initial manifestations are those of a paraneoplastic syndrome caused by the secretion of vasoactive intestinal peptide (VIP) or Cushing syndrome due to ACTH
- Hypocalcemia is not a prominent feature
- Median survival 3-4 months if metastatic.

Medullary carcinoma

- Thyroidectomy and central node dissection treatment of choice.
- ETV6 common fusion partners
- NTREK3 common fusion partners
- Iodine refractory tumors and symptomatic, use VEGFR inhibitor (Selpercatinib)
- TKI (Cabozantanib) prolongs survival in metastatic disease.
- Blocks MET, VEGFR2, RET and KIT

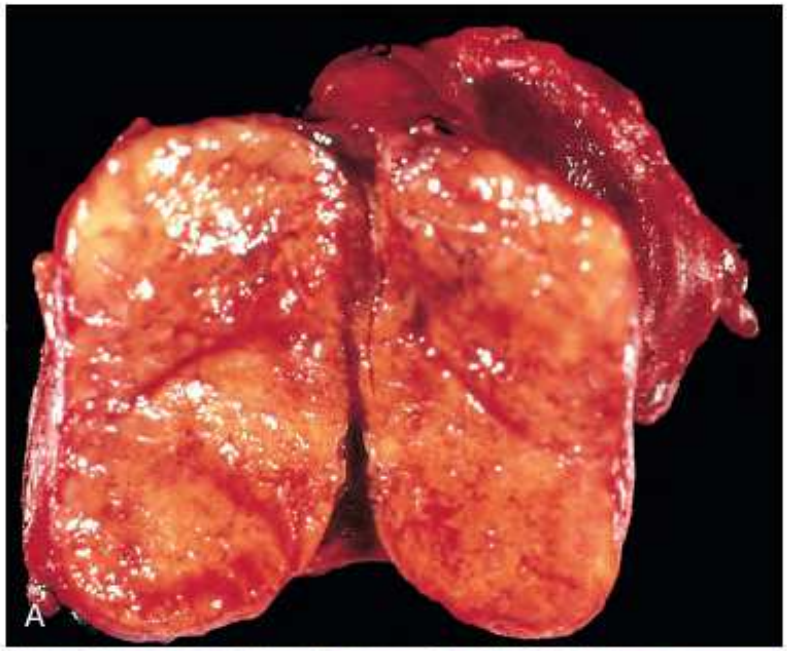
Medullary carcinoma

- Calcitonin produced in parafollicular cells.
- Diminshes bone resorption of Calcium.
- Secreted in response to rising serum Calcium level.
- Calcitonin (>100 pg/ml)and CEA elevated in serum.
- Calcitonin >1000 pg/ml associated with distant metastases.

Table 25.3 Contrasting features of main histologic types of thyroid carcinoma.

	FEATURE	PAPILLARY CARCINOMA	FOLLICULAR CARCINOMA	MEDULLARY CARCINOMA	ANAPLASTIC CARCINOMA
1.	*Frequency*	75-80%	10-20%	5%	5%
2.	*Age*	All ages	Middle to old age	Middle to old age; familial too	Old age
3.	*Female/male ratio*	3:1	2.5:1	1:1	1.5:1
4.	*Relation to radiation*	Maximum	Present	None	Present
5.	*Genetic alterations*	*RET* gene over-expression, *NTRK* gene rearrangement	*RAS* mutation, *PAX-PPAR γ1* fusion	*RET* point mutation	*p53* loss, β-catenin mutation
6.	*Cell of origin*	Follicular	Follicular	Parafollicular	Follicular
7.	*Gross*	Small, multifocal	Moderate size, nodular	Moderate size	Invasive growth
8.	*Pathognomonic* microscopy	Nuclear features, papillary pattern	Vascular and capsular invasion	Solid nests, amyloid stroma	Undifferentiated, spindle-shaped, giant cells
9.	*Regional metastases*	Common	Rare	Common	Common
10.	*Distant metastases*	Rare	Common	Rare	Common
11.	*10-year survival*	80-95%	50-70%	60-70%	5-10% (median survival about 2 months)

Mohan, H, Textbook of Pathology, 7th ed., Health Science Publishers. New Delhi. 2015.



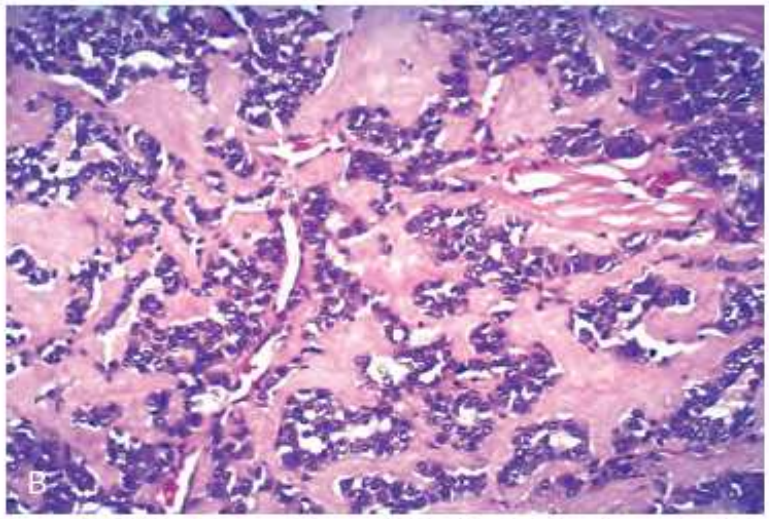
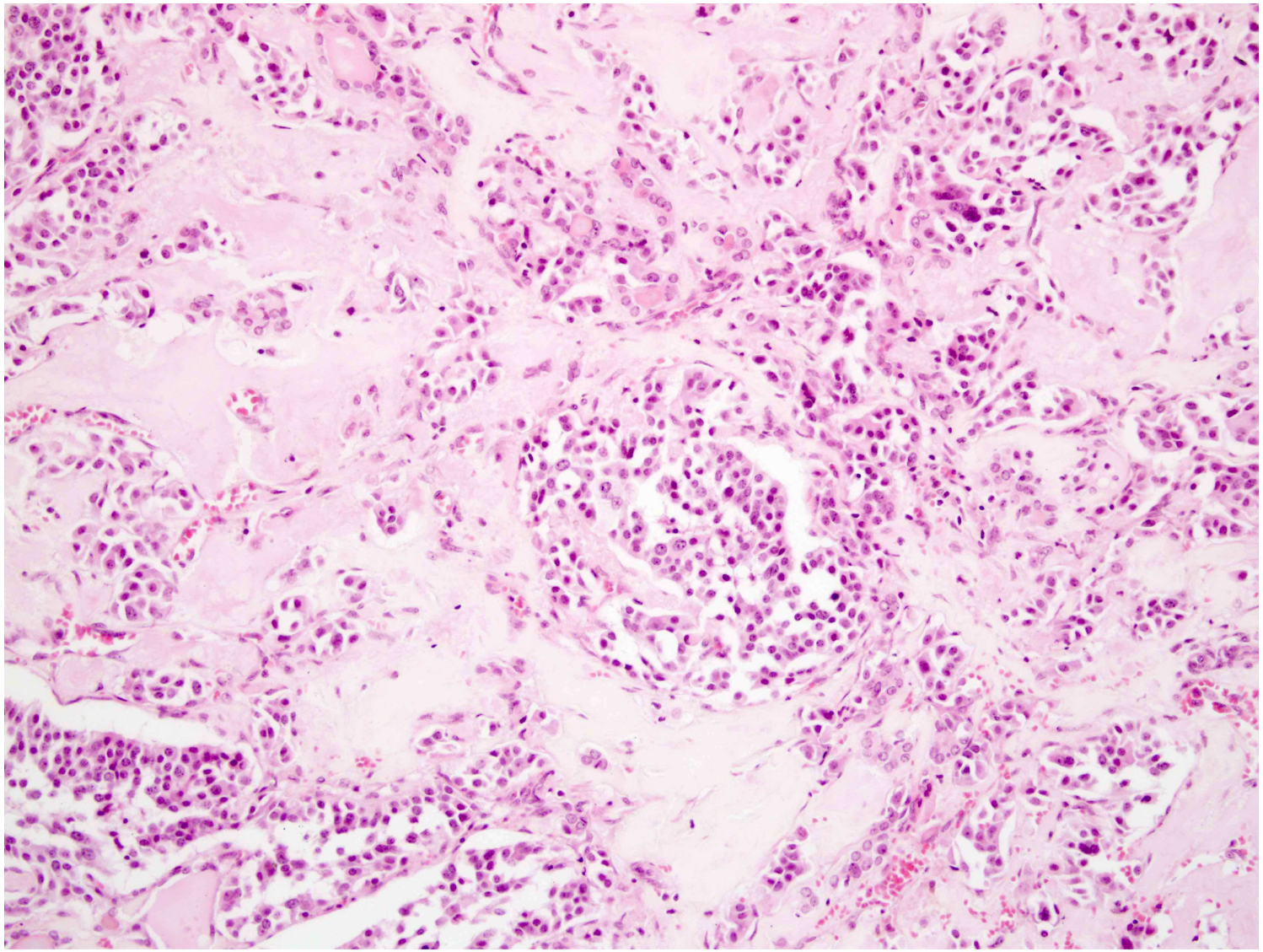


Figure 24-22 Medullary carcinoma of thyroid. **A,** These tumors typically show a solid pattern of growth and do not have connective tissue capsules. **B,** Histology demonstrates abundant deposition of amyloid, visible here as homogeneous extracellular material, derived from calcitonin molecules secreted by the neoplastic cells. (**A,** Courtesy Dr. Joseph Corson, Brigham and Women's Hospital, Boston, Mass.)

Medullary carcinoma



Background of amyloid (x200)

Therapy

- Thyroidectomy with removal of lymph nodes adjacent to thyroid (central compartment neck dissection)
- Thyroid hormone replacement initiated prior to surgery
- Radioiodine therapy (I^{131}) is administered following thyroidectomy for T3 and T4 tumors
- For spread to lymph nodes or distant sites

Therapy

- Unresectable or borderline resectable anaplastic thyroid carcinoma
- Attempt to shrink the tumor to permit resection
- Dabrafenib and trametinib for BRAF V600E mutations
- Addition of pembrolizumab associated with 11 median month survival
- Selpercatinib or pralsetinib for RET gene fusion–positive tumors
- Larotrectinib or entrectinib for patients with NTRK gene fusion–positive tumors
- In resectable disease, neoadjuvant trametinib and dabrafenib associated with median 63 month survival