Neoplasms of the Thyroid

The solitary thyroid nodule is a palpably discrete swelling within an otherwise apparently normal thyroid gland. The estimated incidence of solitary palpable nodules in the adult population of the United States varies between 1% and 10%, although it is significantly higher in endemic goitrous regions. Single nodules are about four times more common in women than in men. The incidence of thyroid nodules increases throughout life.

From a clinical standpoint, the possibility of neoplastic disease is of major concern in patients who present with thyroid nodules. Fortunately, the overwhelming majority of solitary nodules of the thyroid prove to be localized, non-neoplastic conditions (e.g., nodular hyperplasia, simple cysts, or foci of thyroiditis) or benign neoplasms such as follicular adenomas. In fact, benign neoplasms outnumber thyroid carcinomas by a ratio of nearly 10:1. Carcinomas of the thyroid are thus uncommon, accounting for well under 1% of solitary thyroid nodules and representing about 15,000 new cancer cases each year. Moreover, as will be seen subsequently, most are indolent, permitting a 90% survival at 20 years. Several clinical criteria might provide a clue to the nature of a given thyroid nodule:

- **Solitary nodules**, in general, are more likely to be neoplastic than are multiple nodules.
- **Nodules in younger patients** are more likely to be neoplastic than are those in older patients.
- **Nodules in males** are more likely to be neoplastic than are those in females.
- A history of radiation treatment to the head and neck region is associated with an increased incidence of thyroid malignancy.
- **Nodules that take up radioactive iodine** in imaging studies (**hot nodules**) are more likely to be benign than malignant.

Such general trends and statistics, however, are of little significance in the evaluation of a given patient, in whom the timely recognition of a malignancy, however uncommon, can be life-saving. Ultimately, it is the morphologic evaluation of a given thyroid nodule, in the form of fine-needle aspiration biopsy and histologic study of surgically resected thyroid parenchyma, that provides the most definitive information about its nature. In the following sections, we consider the major thyroid neoplasms, including adenoma and carcinoma in its various forms.

**ADENOMAS**

Adenomas of the thyroid are typically discrete, solitary masses. With rare exception, they are derived from follicular epithelium and so might all be called **follicular adenomas**. A variety of terms have been proposed for classifying adenomas on the basis of degree of follicle formation and the colloid content of the follicles. Simple colloid adenomas (macrofollicular adenomas), a common form, resemble normal thyroid tissue; others recapitulate stages in the embryogenesis of the normal thyroid (fetal or microfollicular, embryonal or trabecular). There is limited utility in these classifications because mixed patterns are common, and most of these benign tumors are nonfunctional. Clinically, follicular adenomas can be difficult to distinguish from dominant nodules of follicular hyperplasia or from the less common follicular carcinomas. Numerous studies have
made it clear that adenomas are not forerunners of cancer except in rare instances. Although the vast majority of adenomas are nonfunctional, a small proportion produce thyroid hormones and cause clinically apparent thyrotoxicosis. Hormone production in functional adenomas ("toxic adenomas") occurs independent of TSH stimulation and represents another example of thyroid autonomy, analogous to toxic multinodular goiters.

Pathogenesis.

The TSH receptor signaling pathway plays an important role in the pathogenesis of toxic adenomas. Activating ("gain of function") somatic mutations in one of two components of this signaling system—most often the TSH receptor itself or the α-subunit of Gs—cause chronic overproduction of cAMP, generating cells that acquire a growth advantage (see Fig. 24-3). This results in clonal expansion of follicular epithelial cells that can autonomously produce thyroid hormone and cause symptoms of thyroid excess. Overall, mutations leading to constitutive activation of the cAMP pathway appear to be the cause of a proportion (10% to 75%) of autonomously functioning thyroid adenomas. However, the molecular pathogenesis of a significant proportion of thyroid tumors remains to be defined, especially the pathogenesis of nonfunctioning adenomas.

Morphology.

The typical thyroid adenoma is a solitary, spherical, encapsulated lesion that is well demarcated from the surrounding thyroid parenchyma (Fig. 24-14). Follicular adenomas average about 3 cm in diameter, but some are smaller and others are much larger (up to 10 cm in diameter). In freshly resected specimens, the adenoma bulges from the cut surface and compresses the adjacent thyroid. The color ranges from gray-white to red-brown, depending on the cellularity of the adenoma and its colloid content. The neoplastic cells are demarcated from the adjacent parenchyma by a well-defined, intact capsule. These features are important in making the distinction from multinodular goiters, which contain multiple nodules on their cut surface (even though the patient may present clinically with a solitary dominant nodule), produce less compression of the adjacent thyroid parenchyma, and lack a well-formed capsule. Areas of hemorrhage, fibrosis, calcification, and cystic change, similar to those encountered in multinodular goiters, are common in follicular adenomas, particularly within larger lesions.
Microscopically, the constituent cells often form uniform-appearing follicles that contain colloid (Fig. 24-15). The follicular growth pattern within the adenoma is usually quite distinct from the adjacent non-neoplastic thyroid. This is another feature distinguishing adenomas from multinodular goiters, in which nodular and uninvolved thyroid parenchyma may have similar growth patterns. The epithelial cells composing the follicular adenoma reveal little variation in cell and nuclear morphology. Mitotic figures are rare, and extensive mitotic activity warrants careful examination of the capsule to exclude follicular carcinoma. Similarly, papillary change is not a typical feature of adenomas and, if extensive, should raise the suspicion of an encapsulated papillary carcinoma (see below). Occasionally, the neoplastic cells acquire brightly eosinophilic granular cytoplasm (oxyphil or Hürthle cell change) (Fig. 24-16); the clinical presentation and behavior of a follicular adenoma with oxyphilia (Hürthle cell adenoma) is no different from that of a conventional adenoma. Other variants of follicular adenomas include extensive clear cell change of the cytoplasm (clear cell follicular adenoma) and adenomas with “signet-ring” features (signet-ring cell follicular adenoma). Similar to endocrine tumors at other anatomic sites, even benign follicular adenomas may, on occasion, exhibit focal nuclear pleomorphism, atypia, and prominent nucleoli (endocrine atypia); this by itself does not constitute a feature of malignancy. Infrequently, adenomas can demonstrate increased cellularity, more extensive variation in cellular size and nuclear morphology, and even mitotic activity. These adenomas have been called atypical follicular adenomas and warrant careful examination of the tumor capsule to exclude capsular and/or vascular invasion. The hallmark of all follicular adenomas is the presence of an intact, well-formed capsule encircling the tumor. Careful evaluation of the integrity of the capsule is therefore critical in distinguishing follicular adenomas from follicular carcinomas, which demonstrate capsular and/or vascular invasion (see below).
Clinical Features.

Many thyroid adenomas present as a unilateral painless mass, often discovered during a routine physical examination. Larger masses may produce local symptoms, such as difficulty in swallowing.

Most adenomas take up less radioactive iodine than does normal thyroid parenchyma. On radionuclide scanning, therefore, adenomas usually appear as cold nodules relative to the adjacent thyroid tissue. Up to 10% of cold nodules eventually prove to be malignant on histologic analysis. By contrast, malignancy is rare in hot nodules. In a minority of cases, adenomas may be hyperfunctional, producing signs and symptoms of hyperthyroidism (toxic adenomas). On radionuclide imaging, hyperfunctioning adenomas appear hot compared with the paranodular thyroid tissue, which is deprived of thyrotropin stimulation. Hot adenomas occasionally have some dependence on TSH and may be induced to regress by the administration of thyroid hormones, which suppress TSH secretion.

Other techniques used in the preoperative evaluation of suspected adenomas are ultrasonography and fine-needle aspiration biopsy. Owing to the need for evaluating capsular integrity, the definitive diagnosis of adenomas can be made only after careful histologic examination of the resected specimen. Suspected adenomas of the thyroid are therefore removed surgically to exclude malignancy. Thyroid adenomas, including atypical adenomas, have an excellent prognosis and do not recur or metastasize. About 20% of follicular adenomas have point mutations in the RAS family of oncogenes, which have also been identified in 30% to 40% of follicular carcinomas. This finding raises the possibility that some adenomas may progress to carcinomas.

OTHER BENIGN TUMORS
Solitary nodules of the thyroid gland may also prove to be cysts. The great preponderance of these lesions represent cystic degeneration of a follicular adenoma; the remainder probably arise in multinodular goiters. They are often filled with a brown, turbid fluid containing blood, hemosiderin pigment, and cell debris. Additional benign rarities include dermoid cysts, lipomas, hemangiomas, and teratomas (see mainly in infants).

**CARCINOMAS**

Carcinomas of the thyroid are relatively uncommon in the United States, accounting for about 1.5% of all cancers. Most cases occur in adults, although some forms, particularly papillary carcinomas, may present in childhood. A female predominance has been noted among patients who develop thyroid carcinoma in the early and middle adult years, perhaps related to the expression of estrogen receptors on neoplastic thyroid epithelium. In contrast, cases presenting in childhood and late adult life are distributed equally among males and females. Most thyroid carcinomas are well-differentiated lesions. The major subtypes of thyroid carcinoma and their relative frequencies include the following:

- Papillary carcinoma (75% to 85% of cases)
- Follicular carcinoma (10% to 20% of cases)
- Medullary carcinoma (5% of cases)
- Anaplastic carcinoma (<5% of cases)

Most thyroid carcinomas are derived from the follicular epithelium, except for medullary carcinomas; the latter are derived from the parafollicular or C cells. Because of the unique clinical and biologic features associated with each variant of thyroid carcinoma, these subtypes are described separately.

**Pathogenesis**

There are several factors, genetic and environmental, implicated in the pathogenesis of thyroid cancers.

**Genetic Factors.**

Genetic factors are important in both familial and nonfamilial ("sporadic") forms of thyroid cancer. Familial medullary cancers account for most inherited cases of thyroid cancer. Familial nonmedullary thyroid cancers (papillary and follicular variants) are very rare. Distinct genes are involved in the histologic variants of thyroid cancer.

**Follicular Thyroid Carcinomas.**

Approximately half of follicular thyroid carcinomas harbor mutations in the RAS family of oncogenes (HRAS, NRAS, and KRAS) (Chapter 7), NRAS mutations being the most common. Recently, a unique translocation has been described between PAX8, a paired homeobox gene that is important in thyroid development (see above), and the peroxisome proliferator-activated receptor
γ1 (PPARγ1), a nuclear hormone receptor implicated in terminal differentiation of cells. The PAX8-PPARγ1 fusion is present in approximately one-third of follicular thyroid carcinomas, specifically those cancers with a t(2;3)(q13;p25) translocation, which permits juxtaposition of portions of both genes. Follicular carcinomas appear to arise by at least two distinct and virtually nonoverlapping molecular pathways. Tumors carry either a RAS mutation or a PAX8-PPARγ1 fusion, and rarely are both genetic abnormalities present in the same case. Fewer than 10% of follicular adenomas harbor a PAX8-PPARγ1 fusion transcript, and this translocation has not been documented to date in other thyroid neoplasms.

Papillary Thyroid Carcinomas.

Like follicular thyroid carcinomas, papillary carcinomas also appear to arise by multiple distinct, nonoverlapping molecular pathways. One pathway involves rearrangements of the tyrosine kinase receptors RET or NTRK1 (neurotrophic tyrosine kinase receptor 1) and another involves activating mutations in the BRAF oncogene. A third pathway involves RAS mutations (10% to 20% of papillary carcinomas), suggesting that some of these cancers are related to follicular adenomas. RET, located on chromosome 10q11, and NTRK1, located on chromosome 1q21, belong to the family of receptor tyrosine kinases that transduce extracellular signals for cell growth and differentiation and exert many of their downstream effects through the ubiquitous MAP kinase signaling pathway (Chapter 7). Neither receptor is normally expressed on the surface of thyroid follicular cells. In papillary thyroid cancers, either a paracentric inversion of chromosome 10 or a reciprocal translocation between chromosomes 10 and 17 places the tyrosine kinase domain of RET under the transcriptional control of constitutively active genes on these two chromosomes. The novel fusion genes that are so formed are known as ret/PTC (ret/papillary thyroid carcinoma) and are present in approximately one-fifth of papillary thyroid cancers. The frequency of ret/PTC rearrangements is significantly higher in papillary cancers arising in children and in the backdrop of radiation exposure. Similarly, paracentric inversions or translocations of NTRK1 that constitutively activate its tyrosine kinase domain are present in 5% to 10% of papillary thyroid cancers. One-third to one-half of papillary thyroid carcinomas harbor an activating mutation in the BRAF gene, which encodes a signaling intermediary in the MAP kinase pathway. Since chromosomal rearrangements of the RET or NTRK1 genes and mutations of BRAF have redundant effects on the thyroid epithelium (recall that both mechanisms result in activation of the MAP kinase signaling pathway), papillary thyroid carcinomas demonstrate either one or the other molecular abnormality, but not both.

Medullary Thyroid Carcinomas.

Medullary carcinomas arise from the parafollicular C cells in the thyroid. Familial medullary thyroid carcinomas occur in multiple endocrine neoplasia type 2 (MEN-2, see below) and are associated with germ-line RET protooncogene mutations that affect residues in the cysteine-rich extracellular or the intracellular tyrosine kinase domains, leading to constitutive activation of the receptor. RET mutations are detectable in approximately 95% of families with MEN-2; in the remaining few cases, the mutations may arise in hard-to-detect promoter sequences or intronic sites. RET mutations are also seen in nonfamilial (sporadic) medullary thyroid cancers. Chromosomal
rearrangements involving RET, such as the ret/PTC translocations reported in papillary cancers, are not seen in medullary carcinomas.

**Anaplastic Carcinomas.**

These highly aggressive and lethal tumors can arise de novo or by "dedifferentiation" of a well-differentiated papillary or follicular carcinoma. Inactivating point mutations in the p53 tumor suppressor gene are rare in well-differentiated thyroid carcinomas but common in anaplastic tumors.  

**Environmental Factors.**

The major risk factor predisposing to thyroid cancer is exposure to ionizing radiation, particularly during the first two decades of life. In the past, radiation therapy was liberally employed in the treatment of a number of head and neck lesions in infants and children, including reactive tonsillar enlargement, acne, and tinea capitis. Up to 9% of people receiving such treatment during childhood have subsequently developed thyroid malignancies, usually several decades after exposure. The importance of radiation as a risk factor for thyroid carcinoma was highlighted by the increased incidence of papillary thyroid carcinomas in children in the Marshall Islands after atomic bomb testing and, more recently, by the dramatic rise in the incidence of pediatric thyroid carcinoma among children exposed to ionizing radiation after the Chernobyl nuclear disaster in the Ukraine in 1986. More than 400 cases of pediatric thyroid carcinoma have been observed in this region of Belarus between the time of the incident and the present, a number far in excess of the usual incidence for this area. More than half of the children lived in areas that had the highest radiation exposure.

Long-standing multinodular goiter has been suggested as a predisposing factor in some cases, since areas with iodine deficiency-related endemic goiter have a higher prevalence of follicular carcinomas. While most, if not all, thyroid lymphomas arise from pre-existing Hashimoto thyroiditis, there is no conclusive evidence to suggest that thyroiditis is associated with an increased risk of thyroid epithelial carcinomas.

**Papillary Carcinoma**

Papillary carcinomas are the most common form of thyroid cancer. They occur at any age but most often in the twenties to forties, and account for the majority of thyroid carcinomas associated with previous exposure to ionizing radiation.

**Morphology.**

Papillary carcinomas are solitary or multifocal lesions. Some tumors may be well-circumscribed and even encapsulated; others may infiltrate the adjacent parenchyma with ill-defined margins. The lesions may contain areas of fibrosis and calcification and are often cystic. On the cut surface, they may appear granular and may sometimes contain grossly discernible papillary foci. The definitive diagnosis of papillary carcinoma can be made only after microscopic examination. The characteristic hallmarks of papillary neoplasms include the following (Fig. 24-17):
Papillary carcinomas can contain branching papillae having a fibrovascular stalk covered by a single to multiple layers of cuboidal epithelial cells. In most neoplasms, the epithelium covering the papillae consists of well-differentiated, uniform, orderly, cuboidal cells, but at the other extreme are those with fairly anaplastic epithelium showing considerable variation in cell and nuclear morphology. When present, the papillae of papillary carcinoma differ from those seen in areas of hyperplasia. In contrast to hyperplastic papillary lesions, the neoplastic papillae are more complex and have dense fibrovascular cores.

The nuclei of papillary carcinoma cells contain finely dispersed chromatin, which imparts an optically clear or empty appearance, giving rise to the designation ground glass or Orphan Annie eye nuclei. In addition, invaginations of the cytoplasm may in cross-sections give the appearance of intranuclear inclusions ("pseudo-inclusions") or intranuclear grooves. As currently used, the diagnosis of papillary carcinoma is based on these nuclear features even in the absence of papillary architecture.

Concentrically calcified structures termed psammoma bodies are often present within the lesion, usually within the cores of papillae. These structures are almost never found in follicular and medullary carcinomas, and so, when present, they are a strong indication that the lesion is a papillary carcinoma. It is said that whenever a psammoma body is found within a lymph node or perithyroidal tissues, a hidden papillary carcinoma must be considered.

Foci of lymphatic invasion by tumor are often present, but involvement of blood vessels is relatively uncommon, particularly in smaller lesions. Metastases to adjacent cervical lymph nodes are estimated to occur in up to half the cases.

Figure 24-17  Papillary carcinoma of the thyroid. A, The macroscopic appearance of a papillary carcinoma with grossly discernible papillary structures. This particular example
contains well-formed papillae (B), lined by cells with characteristic empty-appearing nuclei, sometimes termed "Orphan Annie eye" nuclei (C). D, Cells obtained by fine-needle aspiration of a papillary carcinoma. Characteristic intranuclear inclusions are visible in some of the aspirated cells.

There are variant forms of papillary carcinoma that are important to recognize because they can resemble other lesions and have unique clinical features. The **encapsulated variant** constitutes about 10% of all papillary neoplasms. It is usually confined to the thyroid gland, is well encapsulated, and rarely presents with vascular or lymph node dissemination, and so it can easily be confused with a benign adenoma. In most cases, this variant has an excellent prognosis.

The **follicular variant** has the characteristic nuclei of papillary carcinoma but has an almost totally follicular architecture. Grossly, the tumor may be encapsulated, and focally, psammoma bodies may be seen. These follicular variants still behave biologically as usual papillary carcinomas as long as they meet the nuclear criteria for diagnosis of papillary cancers (see above). The true follicular carcinoma, in contrast, lacks these nuclear features, frequently demonstrates capsular and vascular invasion, and has a less favorable prognosis. A differential diagnosis of thyroid lesions with a follicular architecture is summarized in **Table 24-4**.

### Table 24-4 -- Thyroid Lesions with a Follicular Architecture

<table>
<thead>
<tr>
<th>Non-Neoplastic</th>
<th>Neoplastic</th>
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</thead>
<tbody>
<tr>
<td>Hyperplastic nodule in goiter</td>
<td>Follicular adenoma *</td>
</tr>
<tr>
<td></td>
<td>Follicular carcinoma *</td>
</tr>
<tr>
<td></td>
<td>Follicular variant of papillary carcinoma ?</td>
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</table>

* Differentiating follicular carcinoma from follicular adenoma requires histologic evidence of **capsular or blood vessel invasion**, or **documented metastasis**.

? The diagnosis of papillary carcinoma is rendered on the presence of **characteristic nuclear features**, irrespective of the presence or absence of papillae.

**A tall cell variant** is marked by tall columnar cells with intensely eosinophilic cytoplasm lining the papillary structures. Typically, the cells are at least twice as tall as they are wide (hence the eponym "tall cell" variant). These tumors tend to occur in older individuals and are usually large with prominent vascular invasion, extrathyroidal extension, and cervical and distant metastases. It has been recently demonstrated that more than half the tall cell variants harbor a **ret/PTC** translocation that confers greater mitogenic potential than the **ret/PTC** observed in usual papillary
thyroid cancers. The presence of this genetic abnormality might result in more aggressive behavior.

An unusual **diffuse sclerosing variant** of papillary carcinoma occurs in younger individuals, including children. These tumors do not present with a mass, but rather with a bilateral goiter. There is a characteristic "gritty" sensation to the cut surface of the lesion due to the presence of abundant psammoma bodies. The tumor demonstrates a prominent papillary growth pattern, intermixed with solid areas containing nests of squamous cells (squamous morules). The neoplastic cells exhibit classic nuclear features of a papillary neoplasm. As the name suggests, there is extensive, diffuse fibrosis throughout the thyroid gland, often associated with a prominent lymphocytic infiltrate, simulating Hashimoto thyroiditis. The neoplastic cells have a peculiar propensity to invade intrathyroidal lymphatic channels; hence, nodal metastases are present in almost all cases.

**Hyalinizing trabecular tumors**, a group that includes both adenomas and carcinomas, have recently been reconsidered as a variant of papillary carcinomas, based on the presence of ret/PTC gene rearrangements in 30% to 60% of these tumors. They are characterized by an "organoid" growth pattern, with nests and trabeculae of elongated tumor cells within a fibrovascular stroma; at first glance, the tumor may resemble an extra-adrenal paraganglioma (see below). Both intracellular and extracellular hyalinization are prominent and confer a pink hue on the tumor on low-power microscopic examination. The nuclear features resemble those seen in classic papillary carcinomas, and psammoma bodies may be present. Hyalinizing trabecular adenomas are well encapsulated, while carcinomas demonstrate capsular and/or vascular invasion.

**Clinical Course.**

Most papillary carcinomas present as asymptomatic thyroid nodules, but the first manifestation may be a mass in a cervical lymph node. Interestingly, the presence of isolated cervical nodal metastases does not appear to have a significant influence on the generally good prognosis of these lesions. The carcinoma, which is usually a single nodule, moves freely during swallowing and is not distinguishable from a benign nodule. Hoarseness, dysphagia, cough, or dyspnea suggests advanced disease. In a minority of patients, hematogenous metastases are present at the time of diagnosis, most commonly in the lung.

A variety of diagnostic tests have been employed to help separate benign from malignant thyroid nodules, including radionuclide scanning and fine-needle aspiration. Most papillary lesions are cold masses on scintiscans. Improvements in cytologic analysis have made fine-needle aspiration cytology a reliable test for distinguishing between benign and malignant nodules. The nuclear features are often nicely demonstrable in aspirated specimens.

Papillary thyroid cancers have an excellent prognosis, with a 10-year survival rate in excess of 95%. Five per cent to 20% of patients have local or regional recurrences, and 10% to 15% have distant metastases. The prognosis of a patient with papillary thyroid cancers is dependent on several factors including age (in general, the prognosis is less favorable among patients older than 40 years), the presence of extrathyroidal extension, and presence of distant metastases (stage).
Follicular Carcinoma

Follicular carcinomas are the second most common form of thyroid cancer, accounting for 10% to 20% of all thyroid cancers. They tend to present in women, and at an older age than do papillary carcinomas, with a peak incidence in the forties and fifties. The incidence of follicular carcinoma is increased in areas of dietary iodine deficiency, suggesting that in some cases, nodular goiter may predispose to the development of the neoplasm. The high frequency of RAS mutations in follicular adenomas and carcinomas suggests that the two may be related tumors.

Morphology.

Follicular carcinomas are single nodules that may be well circumscribed or widely infiltrative (Fig. 24-18). Sharply demarcated lesions may be exceedingly difficult to distinguish from follicular adenomas by gross examination. Larger lesions may penetrate the capsule and infiltrate well beyond the thyroid capsule into the adjacent neck. They are gray to tan to pink on cut section and, on occasion, are somewhat translucent when large, colloid-filled follicles are present. Degenerative changes, such as central fibrosis and foci of calcification, are sometimes present.

![Figure 24-18](image_url)

**Figure 24-18** Follicular carcinoma. 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.

Microscopically, most follicular carcinomas are composed of fairly uniform cells forming small follicles containing colloid, quite reminiscent of normal thyroid (Fig. 24-19). In other cases, follicular differentiation may be less apparent, and there may be nests or sheets of cells without colloid. Occasional tumors are dominated by cells with abundant granular, eosinophilic cytoplasm (Hürthle cells). Whatever the pattern, the nuclei lack the features typical of papillary carcinoma, and
psammoma bodies are not present. It is important to note the absence of these details because some papillary carcinomas may appear almost entirely follicular (see Table 24-4). Follicular lesions in which the nuclear features are typical of papillary carcinomas should be treated as papillary cancers. While nuclear features are helpful in distinguishing papillary from follicular neoplasms, they are of little value in distinguishing follicular adenomas from \textit{minimally invasive follicular carcinomas}. This distinction requires extensive histologic sampling of the tumor-capsule-thyroid interface to exclude capsular and/or vascular invasion (Fig. 24-20). The criterion for vascular invasion is applicable only to capsular vessels and vascular spaces beyond the capsule; \textit{the presence of tumor plugs within intratumoral blood vessels has little prognostic significance}. Unlike in papillary cancers, lymphatic spread is distinctly uncommon in follicular cancers.

\textbf{Figure 24-19} Follicular carcinoma of the thyroid. A few of the glandular lumens contain recognizable colloid.

\textbf{Figure 24-20} Capsular integrity in follicular neoplasms. Evaluating the integrity of the capsule is critical in distinguishing follicular adenomas from follicular carcinomas. In adenomas (A), a fibrous capsule, usually thin but occasionally more prominent, circumferentially surrounds the neoplastic follicles and \textit{no} capsular invasion is seen (arrowheads); compressed normal thyroid parenchyma is usually present external to the capsule (top of the panel). In contrast, follicular carcinomas demonstrate capsular invasion (B, arrow-heads) that may be minimal, as in this case, or widespread with extension into local structures of the neck. The presence of vascular
invasion is another feature of follicular carcinomas.

In contrast to minimally invasive follicular cancers, extensive invasion of adjacent thyroid parenchyma or extrathyroidal tissues makes the diagnosis of carcinoma obvious in widely invasive follicular carcinomas. Histologically, these cancers tend to have a greater proportion of solid or trabecular growth pattern, less evidence of follicular differentiation, and increased mitotic activity.

Clinical Course.

Follicular carcinomas present as slowly enlarging painless nodules. Most frequently, they are cold nodules on scintigrams, although in rare cases, the better-differentiated lesions may be hyperfunctional, take up radioactive iodine, and appear warm on scintiscan. Follicular carcinomas have little propensity for invading lymphatics; therefore, regional lymph nodes are rarely involved, but vascular invasion is common, with spread to bone, lungs, liver, and elsewhere. The prognosis is largely dependent on the extent of invasion and stage at presentation. Widely invasive follicular carcinomas not infrequently develop metastases, and up to half succumb to their disease within 10 years. This is in stark contrast to minimally invasive follicular carcinoma, which has a 10-year survival rate greater than 90%. Most follicular carcinomas are treated with total thyroidectomy followed by the administration of radioactive iodine, the rationale being that metastases are likely to take up the radioactive element, which can be used to identify and ablate such lesions. In addition, because any residual follicular carcinoma may respond to TSH stimulation, patients are usually treated with thyroid hormone after surgery to suppress endogenous TSH.

Medullary Carcinoma

Medullary carcinomas of the thyroid are neuroendocrine neoplasms derived from the parafollicular cells, or C cells, of the thyroid. The cells of medullary carcinomas, similar to normal C cells, secrete calcitonin, the measurement of which plays an important role in the diagnosis and postoperative follow-up of patients. In some instances, the tumor cells elaborate other polypeptide hormones, such as somatostatin, serotonin, and vasoactive intestinal peptide (VIP). The tumors arise sporadically in about 80% of cases. The remainder occurs in the setting of MEN syndrome 2A or 2B or as familial tumors without an associated MEN syndrome (familial medullary thyroid carcinoma, or FMTC; discussed later). Recall that activating point mutations in the RET protooncogene play an important role in the development of both familial and sporadic medullary carcinomas. Cases associated with MEN-2 occur in younger patients and may even arise during childhood. In contrast, sporadic medullary carcinomas as well as FMTC are lesions of adulthood, with a peak incidence in the forties and fifties.

Morphology.

Medullary carcinomas can arise as a solitary nodule or may present as multiple lesions involving both lobes of the thyroid. The sporadic neoplasms tend to originate in one lobe (Fig. 24-21). In
contrast, bilaterality and **multicentricity** are common in familial cases. Larger lesions often contain areas of necrosis and hemorrhage and may extend through the capsule of the thyroid. The tumor tissue is firm, pale gray to tan, and infiltrative. There may be foci of hemorrhage and necrosis in the larger lesions.

![Image](image.jpg)

**Figure 24-21** Medullary carcinoma of thyroid. These tumors typically show a solid pattern of growth and do not have connective tissue capsules. *(Courtesy of Dr. Joseph Corson, Brigham and Women's Hospital, Boston, MA.)*

Microscopically, medullary carcinomas are composed of polygonal to spindle-shaped cells, which may form nests, trabeculae, and even follicles. Small, more anaplastic cells are present in some tumors and may be the predominant cell type. Acellular amyloid deposits, derived from altered calcitonin molecules, are present in the adjacent stroma in many cases ([Fig. 24-22](#)). Calcitonin is readily demonstrable within the cytoplasm of the tumor cells as well as in the stromal amyloid by immunohistochemical methods. Electron microscopy reveals variable numbers of membrane-bound electron-dense granules within the cytoplasm of the neoplastic cells ([Fig. 24-23](#)). One of the peculiar features of familial medullary cancers is the presence of multicentric **C-cell hyperplasia** in the surrounding thyroid parenchyma, a feature that is usually absent in sporadic lesions. While the precise criteria for defining C-cell hyperplasia are not established, the presence of multiple prominent clusters of C cells scattered throughout the parenchyma should raise the specter of a familial tumor, even if that history is not explicitly present. Foci of C-cell hyperplasia are believed to represent the precursor lesions from which medullary carcinomas arise.
Clinical Course.

Sporadic cases of medullary carcinoma come to medical attention most often as a mass in the neck, sometimes associated with local effects such as dysphagia or hoarseness. In some instances, the initial manifestations are those of a paraneoplastic syndrome, caused by the secretion of a peptide hormone (e.g., diarrhea owing to the secretion of VIP). Notably, hypocalcemia is not a prominent feature, despite the presence of raised calcitonin levels. Screening of relatives for elevated calcitonin levels or RET mutations permits early detection of tumors in familial cases. As will be discussed later, all MEN-2 kindred carrying RET mutations are offered prophylactic thyroidectomy to preclude the development of medullary carcinomas, the major risk factor for poor outcome in these families. Sometimes, the only histologic finding in the resected thyroid of asymptomatic carriers is the presence of C-cell hyperplasia or small (<1 cm) "micromedullary" carcinomas. Recent studies have shown that specific RET mutations correlate
with the aggressiveness of medullary carcinomas and the propensity of MEN-2 patients to develop other coincident endocrine tumors. □ □

Anaplastic Carcinoma

Anaplastic carcinomas of the thyroid are undifferentiated tumors of the thyroid follicular epithelium. In striking contrast to the differentiated thyroid carcinomas, anaplastic carcinomas are aggressive tumors, with a mortality rate approaching 100%. These tumors account for fewer than 5% of all thyroid cancers. Patients with anaplastic carcinoma are older than those with other types of thyroid cancer, with a mean age of 65 years. About half of the patients have a history of multinodular goiter, whereas 20% of the patients with these tumors have a history of differentiated carcinoma, and another 20% to 30% have a concurrent differentiated thyroid tumor, frequently a papillary carcinoma. These findings have led to the proposal that anaplastic carcinoma develops by so-called dedifferentiation from more differentiated tumors as a result of one or more genetic changes, including the loss of the \( p53 \) tumor suppressor gene.

Morphology.

Microscopically, these neoplasms are composed of highly anaplastic cells, which may take one of several histologic patterns: (1) large, pleomorphic giant cells, including occasional osteoclast-like multinucleate giant cells; (2) spindle cells with a sarcomatous appearance; (3) mixed spindle and giant cells; and (4) small cells resembling those seen in small cell carcinomas arising at other sites. It is unlikely that a true small cell carcinoma exists in the thyroid, and a significant number of such "small cell" tumors have ultimately proven to be medullary carcinomas (discussed previously) or malignant lymphomas, which may also occur in the thyroid but have a much better prognosis. Foci of papillary or follicular differentiation may be present in some tumors, suggesting origin from a better differentiated carcinoma.

Clinical Course.

Anaplastic carcinomas usually present as a rapidly enlarging bulky neck mass. In most cases, the disease has already spread beyond the thyroid capsule into adjacent neck structures or has metastasized to the lungs at the time of presentation. Compression and invasion symptoms, such as dyspnea, dysphagia, hoarseness, and cough, are common. There is no effective therapy for anaplastic thyroid carcinoma, and the disease is almost uniformly fatal. Although metastases to distant sites are common, in most cases death occurs in less than 1 year as a result of aggressive growth and compromise of vital structures in the neck.