A. The Thyroid Gland

NEOPLASTIC LESIONS

Classification

The primary tumors of the thyroid gland, grouped according to the line of differentiation, include the following.

Tumors of Thyroid Follicular Epithelium

- Follicular adenoma, including Hurthle cell adenoma
- Follicular carcinoma, including Hurthle cell carcinoma
- Papillary carcinoma
TABLE 44–1. Immunohistochemical Staining Profile of the Various Thyroid Neoplasms

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Cytokeratin</th>
<th>Pan-neuroendocrine Markers (such as synaptophysin, chromogranin)</th>
<th>Thyroglobulin</th>
<th>Calcitonin</th>
<th>Thyroid Transcription Factor 1</th>
<th>Other Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary carcinoma; follicular adenoma-carcinoma; poorly differentiated thyroid carcinoma; columnar cell carcinoma</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Carinoembryonic antigen (CEA); S-100 sustentacular cells may be present in hereditary form</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Mixed follicular-parafollicular carcinoma</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Anaplastic carcinoma</td>
<td>Variable (positive in ~50% of cases)</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Usually negative</td>
<td></td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>Variable (usually negative, but sometimes positive)</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Carcinoma showing thymus-like element (CASTLE)</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Leukocyte common antigen and other lymphoid markers' CBS</td>
</tr>
<tr>
<td>Intrathyroid parathyroid tumor</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Parathyroid hormone· S-100· sustentacular cells; CEA</td>
</tr>
<tr>
<td>Paraganglioma</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

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Tumors are shown in Table 44–1.2–5 Histological profiles of the more common thyroid neoplasms are required for a definitive classification. The immunohistochemical staining findings are important but not always diagnostic. Nonetheless, in some circumstances, immunohistochemical studies are indispensable for a definitive classification. Immunohistochemical studies can sometimes be used to establish a diagnosis when morphologic assessment alone is ineffective. In some cases, the diagnosis can be readily made on morphologic assessment alone. Nonetheless, in some circumstances, especially with medullary carcinoma or unusual-looking tumors, immunohistochemical studies are required for a definitive classification. The immunohistochemical profiles of the more common thyroid tumors are shown in Table 44–1.2–5

General Considerations

PATHOGENESIS

Some risk factors for development of thyroid cancer have been identified; radiation exposure is the best documented factor. External radiation was once popularly used to treat patients with a variety of benign disorders of the head and neck region, such as acne, tinea capitis, cervical tuberculous lymphadenitis, and thyromegaly; such patients have an increased chance of developing thyroid cancer. Cancer patients treated with radiation have been shown to have an excess of thyroid cancer compared with control subjects. Survivors of the Hiroshima atomic bomb have a high risk for development of thyroid cancer; persons who were younger than 10 years when they were exposed have an excess relative risk of 9.46. The Chernobyl nuclear accident in 1986 provides further evidence of the importance of radiation in thyroid carcinogenesis; in some exposed areas, the incidence of thyroid cancer in children increased from 0.5 per million per year to 96.4 per million per year. The clinicopathologic features of the Chernobyl accident–associated thyroid cancers are listed in Table 44–2.

Iodine deficiency and endemic goiter are associated with an increased risk of thyroid carcinoma and angiosarcoma. It has been postulated that the risk may result from prolonged stimulation of the thyroid tissues by thyroid-stimulating hormone.8 Hashimoto’s thyroiditis and lymphocytic thyroiditis are associated with an increased risk for malignant lymphoma. In addition, sclerosing mucoepidermoid carcinoma with eosinophilia almost always arises in a setting of fibrosing Hashimoto’s thyroiditis. Hashimoto’s thyroiditis may slightly increase the risk for development of papillary carcinoma.9

<table>
<thead>
<tr>
<th>TABLE 44–2. Features of Chernobyl Nuclear Accident–Associated Thyroid Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is caused by exposure to radioactive iodine fallout; the accident occurred on April 26, 1986. Most cases are papillary carcinomas (90%). The papillary carcinomas often show a follicular, solid, or mixed follicular-papillary pattern, contrasting with the typical papillary pattern seen in sporadic papillary carcinomas in children. The incidence of thyroid cancer in areas around Chernobyl has increased 6–500-fold compared with previous years, depending on the distance from the accident site. The greatest number of cases occur in areas where the thyroid radiation dose is &gt;0.5 gy. The tumors show greater aggressiveness at presentation, such as extrathyroidal extension, venous invasion, and lymph node metastasis. Thus, treatment often entails total thyroidectomy and lymph node dissection. Lymphocytic thyroiditis and antithyroid peroxidase antibody are more common than in sporadic cases. Age at diagnosis is usually &lt;14 years, which is younger than for the sporadic thyroid cancers in children not related to a nuclear accident. The time interval between the nuclear accident and the diagnosis of thyroid cancer is ~6–7 years. Subjects younger than 5 years or in utero at the time of the nuclear accident account for the majority of cases. Papillary carcinomas occurring in this setting show a much higher frequency of RET/PTC (especially RET/PTC1) gene rearrangement compared with sporadic cases.</td>
</tr>
</tbody>
</table>

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Thyroid cancer can occur as a component of some heritable syndromes. Medullary carcinoma is a key component of multiple endocrine neoplasia type 2 (MEN 2) or familial medullary thyroid carcinoma. Thyroid adenoma or carcinoma sometimes occurs as a component of MEN type 1 (MEN 1). Some patients with familial adenomatous polyposis develop thyroid cancer, most commonly papillary carcinoma of the cribriform-morular variant (so-called familial adenomatous polyposis–associated thyroid carcinoma). Thyroid tumors also constitute a component of Cowden’s disease and may include follicular adenoma, follicular carcinoma, and papillary carcinoma. There are also less well defined familial nonmedullary thyroid cancer syndromes.

**GRADING AND STAGING**

The TNM staging is the most widely used staging system for thyroid cancer (Table 44–3). There are no universally accepted grading systems for thyroid cancers, although the histologic grade may be implied from the histologic type (e.g., low grade for papillary carcinoma and high grade for anaplastic carcinoma).

### TABLE 44–3. Staging of Thyroid Tumors

**TNM Staging**

- **Primary Tumor (T)**
  - TX: Primary tumor cannot be assessed
  - T0: No evidence of primary tumor
  - T1: Tumors ≤ 1 cm, limited to the thyroid
  - T2: Tumor 1–4 cm, limited to the thyroid
  - T3: Tumor >4 cm, limited to the thyroid
  - T4: Tumor of any size extending beyond thyroid capsule

- **Lymph Node (N)**
  - NX: Regional lymph nodes cannot be assessed
  - N0: No regional lymph node metastasis
  - N1a: Metastasis in ipsilateral cervical lymph nodes
  - N1b: Metastasis in bilateral, midline or contralateral cervical, or upper mediastinal lymph nodes

- **Distant Metastasis (M)**
  - MX: Presence of distant metastasis cannot be assessed
  - M0: No distant metastasis
  - M1: Distant metastasis

**Stage Grouping**

- **Papillary or Follicular Carcinoma**
  - Stage <45 y ≥45 y
    - I: Any T, any N, M0
    - II: Any T, any N, M1
    - III: Any T, N0, M0
    - IV: Any T, any N, M1

- **Medullary Carcinoma**
  - Stage TNM status
    - I: T1, N0, M0
    - II: T2, N0, M0
    - III: Any T, N1, M0
    - IV: Any T, any N, M1

- **Anaplastic Carcinoma**
  - All cases are stage IV (i.e., any T, any N, any M)

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THERAPY

The mainstay of therapy for thyroid tumors is surgical excision, and the extent of surgery depends on the tumor type. For thyroid carcinomas that can be eradicated. Thyroxine is also commonly given postoperatively to suppress thyroid-stimulating hormone activity in the hope of reducing tumor recurrence. External radiation therapy and chemotherapy are often reserved for uncontrollable disease or highly aggressive tumors.

TABLE 44–4. Diagnostic Categories from Fine-Needle Aspiration Cytology of the Thyroid

<table>
<thead>
<tr>
<th>Cytologic Diagnosis</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate for diagnosis</td>
<td>With the exception of cyst (which can be hypocellular, with only macrophages being identified), the minimal criterion for adequacy of a specimen is the presence of 5–6 groups of thyroid follicular epithelium with &gt;10 cells per group.</td>
</tr>
<tr>
<td>Benign, e.g., nodular goiter, cyst, Hashimoto’s thyroiditis</td>
<td>Nodular goiter can usually be recognized by features such as abundant thick colloid, low cellularity, large follicles, and honeycombed arrangement of nuclei in the epithelial fragments.</td>
</tr>
<tr>
<td>Follicular lesion</td>
<td>It is not possible to make a distinction between cellular adenomatoid nodule and follicular neoplasm. In such situations, the descriptive term follicular lesion is applicable.</td>
</tr>
<tr>
<td>Follicular neoplasm</td>
<td>It is not possible to make a distinction between follicular carcinoma and follicular adenoma on the basis of fine-needle aspiration cytology.</td>
</tr>
<tr>
<td>Suspicious of malignancy</td>
<td>A diagnosis of &quot;suspicious of malignancy&quot; is justified if there are cytologic features suggestive of but not diagnostic of malignancy.</td>
</tr>
<tr>
<td>Malignant neoplasm, e.g., papillary carcinoma, medullary carcinoma, anaplastic carcinoma, lymphoma</td>
<td>Papillary carcinoma, medullary carcinoma, anaplastic carcinoma, and malignant lymphoma can often be diagnosed on the basis of fine-needle aspiration samples because they exhibit distinctive cytologic and sometimes architectural features. Immunohistochemical studies on the aspirate smears or cell blocks prepared from the aspirated materials are particularly helpful in supporting a diagnosis of medullary carcinoma or lymphoma. The cytologic diagnosis for triage, patients with a diagnosis of tumor or who are suspected of having tumor can be selected for early operation. Those shown on cytologic assessment to have non-neoplastic lesions (such as cyst or colloid nodule) can be followed up; repeated fine-needle aspiration may be required during follow-up to rule out a missed neoplasm.</td>
</tr>
</tbody>
</table>

Core Needle Biopsy

Core needle biopsy is performed in some centers either as the sole procedure or as a complementary procedure to fine-needle aspiration for the initial investigation of thyroid nodules. The procedure is more traumatic than fine-needle aspiration, but the yield is generally higher, permitting more accurate diagnoses to be made in some cases.
Surgical Excision

Surgical excision is the standard treatment of thyroid tumors, providing ample tissue for histologic examination and special studies. It is most important to sample the specimen adequately so that an accurate diagnosis can be reached and all prognostic information can be provided. Sampling is most critical for encapsulated follicular neoplasm because a diagnosis of follicular carcinoma can be missed owing to the focal nature of the invasive foci. Some authors recommend a minimum of 10 blocks. Others recommend at least five blocks initially, with five or more additional blocks being taken if the tumor is found to be cellular on initial histologic examination. Most blocks should be taken from the peripheral portions of the tumor, including the interface with the normal thyroid, rather than from the central portion. For optimal assessment of the capsule in all histologic sections, radial cuts are made to produce wedge-shaped pieces, like cutting slices of an orange.

Intraoperative Frozen Section

Diagnosis of thyroid tumors is usually not difficult on frozen sections; the greatest difficulty lies in the distinction between follicular adenoma and follicular carcinoma because the invasive component is often focal and thus not seen in random frozen sections. Touch preparations form an important adjunct at intraoperative assessment and are particularly helpful for recognizing the characteristic nuclear features of papillary carcinoma and medullary carcinoma.

The role of intraoperative frozen section has much diminished in recent years because of the widespread use of fine-needle aspiration cytology for preoperative screening or diagnosis. It is currently used mostly when fine-needle aspiration findings are suggestive of malignancy or are inconclusive. Intraoperative frozen section is of limited use and cost-effectiveness for follicular neoplasms because of the high deferral rate ("follicular neoplasm; defer diagnosis to permanent sections"). After frozen section is performed, the remaining tissue should be fixed and further sampled for histologic examination.

Follicular Adenoma

Clinical Considerations

Presentation

Follicular adenoma occurs most commonly in adult women aged 20 to 50 years, although no age or sex is exempt. Most patients present with a painless thyroid nodule ("cold" nodule on iodine scan). Rare tumors show increased iodine uptake ("hot" nodules) and may be associated with hyperthyroidism. Follicular adenomas are benign and are adequately treated by lobectomy.

FIGURE 44-1. Follicular adenoma. The tumor is enveloped by a thin fibrous capsule. There is no capsular or vascular invasion.

FIGURE 44-2. Follicular adenoma. A. This tumor is composed of small follicles lined by cells with uniform dark nuclei. B. This tumor shows a trabecular to microfollicular growth pattern and comprises cells with mildly atypical nuclei.
Macroscopic Findings
Follicular adenomas are almost invariably soli-
tary. They are round or oval and are enveloped in a
fibrous capsule, which is often thin. The cut surface
shows homogeneous tan-brown fleshy tumor, some-
times with a glistening quality. Secondary changes
such as hemorrhage and cystic degeneration may be
present. Hurthle cell adenomas are typically mahog-
any brown.

DIAGNOSTIC CONSIDERATIONS

Microscopic Findings
Follicular adenoma is typically enclosed in a fi-
brous capsule of variable thickness, often with com-
pression of the surrounding thyroid tissue (Fig.
44–1). It can show a wide spectrum of architectural
features, but a follicular pattern is most common.

The lining cells often have uniform, dark, round nu-
clei, although occasional enlarged hyperchromatic
nuclei can be interspersed (Fig. 44–2).

The many histologic variants of follicular ade-
noma are listed in Table 44–5 (Figs. 44–3 to 44–10).
By definition, capsular or vascular invasion must be
absent; if invasion is found, the tumor has to be
diagnosed as follicular carcinoma.23,56 The nature
of hyalinizing trabecular adenoma has been most
controversial. The hyalinizing trabecular pattern is
not specific for follicular adenoma; it can be ob-
served in papillary carcinoma and follicular carci-
noma as well as focally in various thyroid lesions,
such as colloid nodule and thyroiditis.57–59 Some in-
vestigators consider hyalinizing trabecular adenoma
to represent a peculiar variant of papillary carci-
noma because of merging with typical papillary
carcinoma in some cases, similarities in cytologic

TABLE 44–5. Variants of Follicular Adenoma

<table>
<thead>
<tr>
<th>Variant*</th>
<th>Defining Morphologic Features</th>
<th>Entity for Which the Variant May be Mistaken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrofollicular</td>
<td>Most follicles in the neoplasm are large.</td>
<td>Nodular goiter</td>
</tr>
<tr>
<td>Microfollicular</td>
<td>Most follicles in the neoplasm are small.</td>
<td>Poorly differentiated (insular) carcinoma</td>
</tr>
<tr>
<td>Trabecular (embryonal)</td>
<td>The tumor cells form straight trabeculae separated by a delicate vasculature.</td>
<td>Poorly differentiated (insular) carcinoma, Medullary carcinoma</td>
</tr>
</tbody>
</table>
|Hyalinizing trabecular | The tumor forms wavy trabeculae with inter-

persed microcystic spaces representing abortive follicle formation. The elongated tumor cells are aligned per-

pendicularly in the trabeculae. The nuclei are often grooved and show pseudoinclu-
sions. Unique cytoplasmic yellow bodies are present. | Papillary carcinoma, Paraganglioma, Medullary carcinoma |

Lumpy hyaline material is interspersed throughout the tumor. Calcified colloid may be present. | |

Table continues on following page

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TABLE 44–5. Variants of Follicular Adenoma (Continued)

<table>
<thead>
<tr>
<th>Variant*</th>
<th>Defining Morphologic Features</th>
<th>Entity for Which the Variant May Be Mistaken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurthle cell</td>
<td>Follicular neoplasm; most tumor cells have abundant oxyphilic cytoplasm because of accumulation of mitochondria. Nuclei are often distinct. Some nuclei can be grooved. The tumor often shows a microlaticular or trabecular pattern of growth.</td>
<td>Medullary carcinoma, oxyphilic variant Papillary carcinoma, oxyphilic variant</td>
</tr>
<tr>
<td>Clear cell</td>
<td>Follicular neoplasm; the tumor cells possess clear cytoplasm because of ballooning of mitochondria, accumulation of lipid or glycogen, or deposition of intracellular thyroglobulin. The clear cytoplasm often retains a finely reticulated or granular quality, instead of being water-clear.</td>
<td>Other primary thyroid neoplasms with clear cell change Metastatic renal cell carcinoma Intrathyroid parathyroid neoplasm</td>
</tr>
<tr>
<td>Signet ring cell</td>
<td>The tumor cells exhibit discrete cytoplasmic vacuoles that displace the nuclei to one side. The cytoplasmic vacuoles are thyroglobulin immunoreactive and often show the staining properties of mucosubstances. They correspond structurally to intracellular lumina lined by microvilli. Signet ring cell changes can be focal or diffuse, and this pattern may merge into microcystic spaces filled with extracellular mucin.</td>
<td>Metastatic adenocarcinoma</td>
</tr>
<tr>
<td>Mucinous</td>
<td>The tumor shows abundant extracellular basophilic mucinous material, often accompanied by a microcystic or reticular growth pattern in the follicular epithelium. Some tumor cells may exhibit signet ring appearance.</td>
<td>Metastatic adenocarcinoma</td>
</tr>
<tr>
<td>Follicular adenoma with papillary hyperplasia (papillary variant of follicular adenoma)</td>
<td>The tumor is encapsulated and partially cystic. It is composed of papillae and follicles lined by cells with uniform, round, and hyperchromatic nuclei regularly aligned at the base.</td>
<td>Papillary carcinoma</td>
</tr>
<tr>
<td>Hot adenoma (toxic adenoma)</td>
<td>Follicular adenoma producing symptoms of hyperthyroidism. On histologic examination, the follicles often show papillary infoldings, similar to the follicles seen in Graves' disease.</td>
<td>—</td>
</tr>
<tr>
<td>Adenolipoma</td>
<td>Follicular adenoma accompanied by a stroma containing adipose cells</td>
<td>—</td>
</tr>
<tr>
<td>Follicular adenoma with bizarre nuclei</td>
<td>An otherwise typical follicular adenoma with interspersed huge monstrous cells</td>
<td>Follicular carcinoma Anaplastic carcinoma</td>
</tr>
<tr>
<td>Atypical adenoma</td>
<td>Follicular neoplasm shows generalized nuclear atypia, giant cells, or unusual histologic patterns (such as spindle cell fascicles) but lacks vascular and capsular invasion after thorough sampling. It pursues a benign course.</td>
<td>Follicular carcinoma Anaplastic carcinoma</td>
</tr>
</tbody>
</table>

*All tumors have to be assessed for vascular or capsular invasion, which, if present, is indicative of a diagnosis of follicular carcinoma.

features, and similarities in immunohistochi-}
Follicular adenoma, clear cell variant. The clear cytoplasm is not water-clear but retains a finely reticulated quality.

Immunohistochemistry

Follicular adenomas are immunoreactive for cytokeratin and thyroglobulin but not for calcitonin and pan-neuroendocrine markers. Hyalinizing trabecular adenoma is peculiar in that it often shows an unusual cell membrane pattern of staining for Ki-67.

Molecular Biology

Mutations in the ras gene are found in some follicular adenomas, at a frequency lower than in follicular carcinomas.62, 63 Hemizygous deletion of the Cowden disease gene, PTEN, is found in 26% of follicular adenomas.64 Activating mutations of the genes coding for the thyrotropin receptor and α-subunit of the stimulatory G protein have been detected in some follicular adenomas, especially the hyperfunctioning ones.62, 65–70

Differential Diagnosis

COLLOID (ADENOMATOID) NODULE. It can be difficult to distinguish between follicular adenoma and adenomatoid nodule (hypercellular colloid nodule); the distinction is sometimes arbitrary. In general, adenomatoid nodules are multiple, lack a well-defined fibrous capsule, and are composed of follicles morphologically similar to those in the surrounding thyroid tissue.

PAPILLARY CARCINOMA. Pale or clear nuclei are not uncommonly encountered in follicular ade-
FIGURE 44–8. Follicular adenoma with papillary hyperplasia, so-called papillary adenoma. A. The tumor is surrounded by a well-defined fibrous capsule. Arborizing papillae are present. B. In contrast to papillary carcinoma, the tumor cells have regularly aligned, basal, dark-staining nuclei.

FIGURE 44–7. Follicular adenoma, mucinous variant. Interacellular pools of mucin are evident.

FIGURE 44–9. Follicular adenoma, adenolipoma variant.

FIGURE 44–10. Atypical follicular adenoma. Many tumor cells have enlarged hyperchromatic nuclei.

Intrathyroid Parathyroid Tumor. Parathyroid adenoma can sometimes arise within the thyroid gland and thus can be mistaken for microfollicular adenoma, clear cell follicular adenoma, or Hurthle cell adenoma. The presence of clear cells is a most useful clue that the tumor in question might be of parathyroid origin. The diagnosis can be confirmed by the clinical information (hypercalcemia) and positive immunostaining for parathyroid hormone.
TABLE 44–6. Comparison Between Papillary and Follicular Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Papillary Carcinoma</th>
<th>Follicular Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>&gt;70% of thyroid cancers</td>
<td>&lt;20% of thyroid cancers</td>
</tr>
<tr>
<td>Age</td>
<td>Wide age range (mean, 43 y)</td>
<td>Minimally invasive type: mean, 48 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Widely invasive type: mean, 55 y</td>
</tr>
<tr>
<td>Presentation</td>
<td>Slow-growing thyroid mass; cervical lymphadenopathy; incidental finding</td>
<td>Slow-growing thyroid mass; fast-growing thyroid mass (less common); distant metastasis (such as bone)</td>
</tr>
<tr>
<td>Multifocal disease</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Clinical behavior</td>
<td>Tumor is locally invasive; typically spreads by lymphatic route to lymph nodes (1–40%). Distant metastasis (such as to lungs) is rare. The tumor is indolent; the cancer-related mortality is only 6.5%—often confined to older patients with extensive extrathyroid disease or distant metastases.</td>
<td>Tumor spreads predominantly by bloodstream; bone is the predilection site. Lymph node metastasis is uncommon. The cumulative mortality rates of the minimally invasive and widely invasive types are 3% and 32%, respectively.</td>
</tr>
<tr>
<td>Basis of diagnosis</td>
<td>Diagnosis is mostly based on the nuclear characteristics (crowded, ground-glass, grooved nuclei) with pseudo-inclusions, and demonstration of invasion is not required for the diagnosis. Therefore, this tumor is diagnosable by fine-needle aspiration cytology.</td>
<td>A follicular neoplasm demonstrating vascular or capsular invasion, and nuclear features of papillary carcinoma, and vascular or capsular invasion, and nuclear features of papillary carcinoma.</td>
</tr>
<tr>
<td>Genetic basis</td>
<td>Overexpression of RET proto-oncogene due to fusion with PTC1, PTC2, or PTC3 gene, or overexpression of NTRK1 gene due to fusion with other genes such as TPM3</td>
<td>Somatic mutation of ras oncogene in ~50% of cases, most commonly involving codon 61 (CAK → CGA (Gln → Arg). t(2;3)(p13 5) resulting in PAX8-PPARγ fusion is found in ~20% of cases.</td>
</tr>
</tbody>
</table>

Follicular Carcinoma

CLINICAL CONSIDERATIONS

Presentation

Follicular carcinoma is a malignant thyroid neoplasm showing follicular cell differentiation but lacking the diagnostic features of papillary carcinoma. It generally occurs in patients with a mean age higher than that of those with follicular adenoma. It usually manifests as a solitary thyroid mass or, less commonly, as a metastatic tumor, in particular in bone. The main mode of spread is hematogenous (predilection sites are bone and lung) rather than lymphatic. The differences in clinicopathologic and biologic features between follicular carcinoma and papillary carcinoma are listed in Table 44–6.

Macroscopic Findings and Major Subtypes of Follicular Carcinoma

Follicular carcinoma is categorized into minimally invasive and widely invasive types, which show different clinical outcome (Table 44–7). The minimally invasive type is more common.

Minimally invasive carcinomas are macroscopically indistinguishable from follicular adenoma, although the capsule tends to be thicker. Vascular or capsular invasion is identified only on histologic assessment (Fig. 44–12). The prognosis is excellent, and thus treatment can be conservative. The less common widely invasive follicular carcinoma shows obvious invasion of the adjacent thyroid parenchyma (Fig. 44–13). The tumor can extend into the perithyroid tissues, and plugging of blood vessels by tumor may also be evident. There is a significant risk of distant metastasis, and the prognosis is much worse than for minimally invasive follicular carcinoma. Of note, many cases reported in the literature as "widely invasive follicular carcinomas" are now reclassifiable as poorly differentiated thyroid carcinomas.
MICROSCOPIC FINDINGS

Follicular carcinomas are often surrounded by a thick, dense fibrous capsule, although some widely invasive follicular carcinomas may not have a fibrous capsule (see Figs. 44–12 and 44–13). The tumors comprise cuboid cells forming closely packed follicles, trabeculae, or solid sheets. The follicles are mostly small, but large follicles can also be present. The tumor cells often have uniform, dark-staining or pale-staining, round nuclei, but significant nuclear atypia can be observed in some cases (Fig. 44–14). The cytoplasm is eosinophilic, oxyphilic, or clear. Mitotic figures range from being scanty to easily found. Secondary changes such as hemorrhage, hemosiderin deposition, sclerosis, edema, necrosis, and cystic change are not uncommon. The tumors may show variant histologic features like those listed for follicular adenomas.\( ^{31, 34, 90–93} \) (see Table 44–5).

The only feature that distinguishes a follicular carcinoma from a follicular adenoma is the presence of vascular or capsular invasion.\( ^{1} \) Strict criteria must be applied in the assessment of invasion.\( ^{94–98} \) The histologic features that should heighten the suspicion for follicular carcinoma are listed in Table 44–8, but they are by themselves insufficient for a diagnosis of malignancy.

To qualify for vascular invasion, the following two criteria must be satisfied: 24

- Involved blood vessels have to be located within or outside the fibrous capsule.
- The intravascular polypoid tumor plug has to be covered by endothelium; if it is not endothelialized, it must be associated with thrombus formation (Fig. 44–15; see also Fig. 44–12).

DIAGNOSTIC CONSIDERATIONS

Follicular carcinomas are often surrounded by a thick, dense fibrous capsule, although some widely invasive follicular carcinomas may not have a fibrous capsule (see Figs. 44–12 and 44–13). The tumors comprise cuboid cells forming closely packed follicles, trabeculae, or solid sheets. The follicles are mostly small, but large follicles can also be present. The tumor cells often have uniform, dark-staining or pale-staining, round nuclei, but significant nuclear atypia can be observed in some cases (Fig. 44–14). The cytoplasm is eosinophilic, oxyphilic, or clear. Mitotic figures range from being scanty to easily found. Secondary changes such as hemorrhage, hemosiderin deposition, sclerosis, edema, necrosis, and cystic change are not uncommon. The tumors may show variant histologic features like those listed for follicular adenomas.\(^{31, 34, 90–93}\) (see Table 44–5).

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---

**TABLE 44–7. Categories of Follicular Carcinoma**

<table>
<thead>
<tr>
<th>Minimally Invasive</th>
<th>Widely Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Tumor shows obvious invasion of adjacent thyroid tissue.</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Younger (mean, ~48 y)</td>
</tr>
<tr>
<td><strong>Metastases</strong></td>
<td>Regional lymph node or distant metastasis is rare and occurs late if it does.</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Excellent prognosis. The long-term mortality is only 3%–5%.</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Curable by lobectomy or subtotal thyroidectomy, with or without suppressive dose of thyroxine.</td>
</tr>
</tbody>
</table>

**FIGURE 44–12.** Follicular carcinoma, minimally invasive type. The tumor is typically surrounded by a thick fibrous capsule. Vascular invasion is present (upper field).

**FIGURE 44–13.** Follicular carcinoma, widely invasive type. There is frank invasion of the thyroid tissue in the form of multiple cellular tumor nodules. The upper field shows vascular invasion.
An invasive bud frequently pushes into the fibrous capsule and then into a capsular blood vessel lumen (Fig. 44–16). Mere bulging of follicles against the thin-walled capsular vessels is not sufficient for a designation of vascular invasion (Fig. 44–17). Retraction spaces around tumor islands should not be mistaken for vascular invasion, and they can be recognized by the lack of endothelial lining. The presence of ragged clusters of nonendothelialized tumor within blood vessels does not count for vascular invasion. This is believed to result from artifactual dislodgment of tumor during sectioning of the specimen. Intravascular endothelial hyperplasia occurring in capsular blood vessels should also not be mistaken for vascular invasion; the intravascular polypoid plug is formed by plump spindly endothelial cells and pericytes instead of follicular epithelial cells (Fig. 44–18).

To qualify for capsular invasion, there must be complete transgression of the fibrous capsule by tumor. That is, the tumor bud must have extended beyond an imaginary line drawn through the exter-

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**TABLE 44–8. Key Points and Caveats in Diagnosis of Follicular Adenoma and Carcinoma**

There is a tendency to overdiagnose follicular carcinoma. To qualify for follicular carcinoma, the following criteria must be satisfied:

- Follicular neoplasm lacking nuclear features of papillary carcinoma
- Capsular or vascular invasion, which must be unequivocal

Histologic features in a follicular neoplasm warranting more careful sampling to look for invasion (these features are not diagnostic of carcinoma per se):

- Thick fibrous capsule
- High cellularity, i.e., tumors that are predominantly solid, trabecular, or microfollicular
- Diffuse nuclear atypia (as opposed to presence of occasional bizarre cells)
- Readily identifiable mitotic figures
- Perpendicularly aligned neoplastic follicles or mushroom-shaped tumor bud in fibrous capsule
- Hürthle cell neoplasm (~35% of all Hürthle cell neoplasms are malignant, a percentage higher than that of non–Hürthle cell neoplasms)

Do not mistake capsular rupture associated with prior fine-needle aspiration as true capsular invasion. Capsular rupture can be recognized by the following features:

- Tumor buds within fibrous capsule (at most one or two sites) are tiny and lack a "mushroom" contour.
- Tumor buds are associated with blood, chronic inflammatory cells, and hemosiderin deposit.
- Tumor cells often have a degenerated appearance.
- Hemorrhagic track (with or without reparative features) is often identifiable in the vicinity.

If prominent delicate fibrovascular septa are present, consider the alternative possibilities:

- Medullary carcinoma
- Intra-thyroid parathyroid neoplasm
- Paraganglioma

If a Hürthle cell neoplasm appears unusual, it may represent oxyphilic variant of the following tumors:

- Medullary carcinoma
- Intra-thyroid parathyroid neoplasm
- Papillary carcinoma

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FIGURE 44–15. Follicular carcinoma showing vascular invasion. A. A tumor plug projects into a capsular blood vessel, and it is clothed by endothelium. B. The intravascular tumor plug has a jagged outline and is not clothed by endothelium. However, this satisfies the criterion for vascular invasion because there is associated fibrin thrombus (left field).

FIGURE 44–16. Follicular carcinoma. The tumor (lower field) extends into the fibrous capsule and then projects into a vascular lumen in the capsule.

FIGURE 44–17. Follicular adenoma. Bulging of tumor against blood vessels within the tumor proper does not constitute vascular invasion.

FIGURE 44–18. Follicular adenoma with intravascular endothelial hyperplasia in the capsule mimicking vascular invasion. A. Cellular proliferation is seen in the capsular blood vessel (upper field). B. Closer examination reveals that the intravascular proliferation consists of small blood vessels and not tumor cells.
Thyroid and Parathyroid
17

ual contour of the capsule (Fig. 44–19). The invasive bud may be “naked” (without a fibrous capsule) or clothed by a thinner, newly formed fibrous capsule24, 71, 78, 100 (Fig. 44–19). A tumor bud that shows incomplete penetration of the capsule despite examination of multiple levels of the tissue block can be disregarded. Follicles entrapped in the capsule by a sclerotic process are often aligned parallel to the fibers of the capsule (Fig. 44–20), whereas follicles oriented perpendicular to the fibers or forming a mushroom-shaped bud are more indicative of an active invasive process, mandating examination of multiple levels and multiple blocks for more definite evidence of capsular invasion (Fig. 44–21). Fine-needle aspiration can result in capsular rupture, mimicking capsular invasion; see Table 44–8 for features supportive of this interpretation101 (Fig. 44–22).

Hu¨ rthle Cell Carcinoma

Hu¨ rthle cell carcinoma is a variant of follicular carcinoma characterized by mitochondria-rich cells,75 although some investigators consider it to be a distinct entity.45 There is new evidence that the pattern of chromosome allelic alteration in Hu¨ rthle cell carcinomas differs from that of conventional follicular carcinomas.102 On gross evaluation, the tumor is bright brown. A size of 4 cm or larger is strongly correlated with malignancy.103 On histologic examination, the tumor shows a trabecular, microfollicular, diffuse, or rarely papillary growth pattern. The tumor cells possess abundant brightly eosinophilic granular cytoplasm, which can exhibit partial to complete clearing as a result of ballooning of the mitochondria (Fig.

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The nuclei are round or sometimes grooved. The chromatin is granular to coarse, and nucleoli are often prominent. Some degree of nuclear pleomorphism is common. The colloid can undergo calcification and thus may be mistaken for psammoma bodies. Hürthle cell neoplasms are particularly prone to infarction after fine-needle aspiration. Some previous studies have proposed aggressive treatment for all Hürthle cell neoplasms, irrespective of whether invasion could be demonstrated histologically, on the basis of the belief that all were potentially malignant. However, many later studies have challenged this misconception and shown that the behavior of Hürthle cell neoplasms can be accurately predicted by histologic features (i.e., whether there is vascular or capsular invasion, as in follicular neoplasms). Only those showing invasion are diagnosed as carcinoma (see Fig. 44–15). Such tumors can recur locally, metastasize to regional lymph nodes, or show distant metastasis (especially to bone and lungs). However, with stratification by the extent of invasion, the differences are obliterated. It has been suggested that the presence of a solid or trabecular pattern in more than 75% of the tumor area identifies a poorly differentiated subgroup with worse prognosis—30% died of disease or were alive with recurrent disease, compared with a 2.5% mortality rate for the non–poorly differentiated subgroup.

The overall mortality rate of Hürthle cell carcinomas is 30% to 70%. Compared with conventional follicular carcinomas, Hürthle cell carcinomas take up radioactive iodine less satisfactorily; they show a higher frequency of extrathyroidal extension, local recurrence, and metastasis to lymph nodes, and the survival rate is lower. However, with stratification by the extent of invasion, the differences are obliterated. It has been suggested that the presence of a solid or trabecular pattern in more than 75% of the tumor area identifies a poorly differentiated subgroup with worse prognosis—30% died of disease or were alive with recurrent disease, compared with a 2.5% mortality rate for the non–poorly differentiated subgroup.
Immunohistochemistry

Follicular carcinoma is immunoreactive for cytokeratin and thyroglobulin but not for pan-neuroendocrine markers. Immunochemical studies are rarely required for diagnosis of this tumor with the exception of two scenarios:

- Unusual-looking thyroid neoplasm—thyroglobulin immunoreactivity confirms the presence of thyroid follicular cell differentiation and is helpful for distinction from medullary carcinoma.

- Metastatic neoplasm suspected to represent metastatic follicular carcinoma—thyroglobulin immunoreactivity confirms the thyroid origin of the carcinoma.

Molecular Biology and Special Studies

Clonal chromosome abnormalities, such as non-disjunctional chromosome loss and deletions in 3p25 → pter, are common in follicular carcinomas. Comparative genomic hybridization studies reveal frequent DNA copy number changes; loss of chromosome 22 is associated with the widely invasive type and old age at presentation. Molecular studies show frequent loss of heterozygosity on chromosomes 3p (86%), 17p (72%), and 1q (57%); 17p change is correlated with mortality. A high frequency of activating point mutations in the family of ras genes is found in follicular carcinomas, although similar mutations can also be found in some follicular adenomas. N-ras mutation is found in 50% of follicular carcinomas, most commonly involving codon 61 with CGA → CAA (Gln → Arg); this mutation is observed in approximately 25% of anaplastic carcinomas but not in papillary carcinomas. H-ras codon 12 mutation is found in 33% of follicular carcinomas. Alteration in the TP53 gene is uncommon, but its presence is associated with an increased risk of metastasis. Recently, t(2;3)(q13;p25), which results in fusion of peroxisome proliferator-activated receptor gamma 1 (PPARγ1) gene with peroxisome proliferator-activated receptor gamma 1 (PPARγ1) gene, has been shown to be a characteristic genetic aberration of follicular carcinoma. The fusion transcript is detected in 5 of 8 follicular carcinomas, but not in 20 follicular adenomas, 10 papillary carcinomas and 10 cases of follicular adenoma. DNA ploidy analysis also fails to distinguish follicular carcinoma from follicular adenoma.

HASHIMOTO’S THYROIDITIS AND DYSHORMONOGENESIS. In Hashimoto’s thyroiditis or dyshormonogenetic goiter, multiple cellular hyperplastic nodules can be present, raising a concern for follicular carcinoma. However, vascular invasion is not found, and the different cellular nodules often exhibit different cellularity and follicle size.

MEDULLARY CARCINOMA. Some variants of medullary carcinoma can mimic follicular or Hurthle cell carcinoma. The presence of prominent delicate fibrovascular septa should always raise the possibility of medullary carcinoma. If there is any uncertainty about the diagnosis, immunohistochemical studies should be performed.

PAPILLARY CARCINOMA. Some follicular carcinomas may show nuclear clearing, mimicking papillary carcinomas. However, this phenomenon is often confined to the central portion of the tumor, where there is delayed fixation. Hurthle cell carcinomas can show nuclear grooving, but this is often a focal phenomenon and other cytologic features of papillary carcinoma are lacking.

PROGNOSTIC CONSIDERATIONS

The most important prognostic factors for follicular carcinoma are age, degree of invasiveness, and presence or absence of distant metastasis.

AGE. The prognosis is excellent for patients younger than 30 to 40 years.

MINIMALLY INVASIVE VERSUS WIDELY INVASIVE TYPE. The prognosis of the widely invasive follicular carcinoma is much worse than that of the minimally invasive type (see Table 44–7). Tumor invasion of the soft tissues of the neck is associated with a particularly unfavorable prognosis.

METASTASIS. Distant metastasis at presentation is a highly unfavorable prognostic factor.

SEX. Some studies have shown the male sex to be associated with a worse outcome.

HISTOLOGIC TYPE OR PATTERN. As a group, Hurthle cell carcinomas have a worse prognosis than that of conventional follicular carcinomas. Presence of a solid or trabecular pattern in more than 25% of the tumor area is associated with a worse prognosis.

References 44, 71, 78, 82, 100, 111, 123, 155, 156.

References 44, 71, 81, 100, 111, 123, 156–158.
**Tumor Size.** Some studies have reported a large tumor (>4 cm) to be associated with a worse prognosis.79, 102, 122, 137, 138

**Vascular Invasion.** Follicular carcinomas showing capsular invasion alone in the absence of vascular invasion have a negligible risk of metastasis.91, 121, 154, 155

**E-Cadherin Expression.** Lack of E-cadherin expression is reported to be an unfavorable prognostic factor.160

**DNA Aneuploidy.** Whereas some studies suggest that aneuploid follicular carcinomas are more aggressive, other studies have not been able to confirm this observation.150, 151, 161

**p53 Aberration.** Presence of p53 aberration may confer an increased chance of metastasis.124, 135

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**Papillary Carcinoma**

**CLINICAL CONSIDERATIONS**

**Presentation**

Papillary carcinoma can occur in patients of any age, including children. The mean age is 43 years, and there is a female predilection162–165 (see Table 44–6). The patients usually present with a thyroid mass or cervical lymph node metastasis. Small papillary carcinoma can also be discovered incidentally in thyroid glands excised for various reasons (latent papillary carcinoma).106, 107

**Macroscopic Findings**

The macroscopic appearances of papillary carcinoma are highly variable, mirroring the myriad histologic patterns that this tumor can assume. The classic examples exhibit firm to hard white-tan tumors with invasive borders. The tumor often has a granular quality on the cut surface due to the presence of papillae. The presence of psammoma bodies can impart a gritty sensation on cutting of the tumor. Tumors with a predominantly follicular architecture are often tan-brown and fleshy, similar to follicular neoplasms. Some tumors can be encapsulated. Cystic change can occur.

**DIAGNOSTIC CONSIDERATIONS**

**Microscopic Findings**

Papillary carcinoma is defined as a malignant epithelial tumor showing evidence of follicular cell differentiation, typically with papillary and follicular structures as well as characteristic nuclear changes.5, 104, 105 The diagnosis is based on the nuclear characteristics, which include large size, pallor, ground-glass appearance, irregular outline, deep grooves, and pseudoinclusions169–172 (Fig. 44–24).
Papillary carcinomas are usually infiltrative, but some may be circumscribed or even encapsulated (Fig. 44–25). The papillae are usually arborizing, with delicate fibrovascular cores (Fig. 44–26A; see also Fig. 44–25). However, the papillae can be broad, with the cores being formed by fibrocellular, edematous, or hyalinized tissue, which may contain foamy macrophages, adipose cells, or small neoplastic follicles. Microcystic and papillary structures comprising cellular tufts are sometimes formed. Follicles are frequently present. They vary in size and contour but are commonly elongated or irregularly shaped and contain dark-staining colloid. Some follicles can be large and markedly distended with colloid. Intrafollicular hemorrhage is common. There is commonly an abundant sclerotic stroma, and desmoplastic stroma is often confined to the invasive fronts (Fig. 44–27; see also Fig. 44–25). The stroma commonly shows patchy infiltration of lymphocytes, plasma cells, and macrophages. Psammoma bodies are found in the stroma of the papillae, in the fibrous stroma, or among the tumor cells in about 50% of cases; they are virtually pathognomonic of papillary thyroid carcinoma (Fig. 44–26A). Multinucleated histiocytes with deeply eosinophilic cytoplasm can be found in the luminal space of some follicles and papillae in approximately 50% of cases and can aid in the diagnosis of papillary carcinoma because they are extremely rare in other thyroid lesions or tumors (see Fig. 44–24C).

There is commonly an abundant sclerotic stroma, and desmoplastic stroma is often confined to the invasive fronts (Fig. 44–27; see also Fig. 44–25). The stroma commonly shows patchy infiltration of lymphocytes, plasma cells, and macrophages. Psammoma bodies are found in the stroma of the papillae, in the fibrous stroma, or among the tumor cells in about 50% of cases; they are virtually pathognomonic of papillary thyroid carcinoma (Fig. 44–26A). Multinucleated histiocytes with deeply eosinophilic cytoplasm can be found in the luminal space of some follicles and papillae in approximately 50% of cases and can aid in the diagnosis of papillary carcinoma because they are extremely rare in other thyroid lesions or tumors (see Fig. 44–24C).

The nuclei of papillary carcinoma are characteristically large, crowded, ovoid, ground-glass (“Orphan Annie” eye), and grooved and contain small distinct nucleoli (see Fig. 44–24). Nuclear pseudoinclusions may be identified in a small proportion of tumor cells (see Fig. 44–24C). Mitotic figures are usually sparse. In some papillary carcinomas, the typical nuclear features may not be well developed, and thus the diagnosis of papillary carcinoma would have to depend on the architectural features and on the identification of foci showing more typical nuclear features (Fig. 44–28).

The neoplastic cells are cuboid, polygonal, columnar, flattened, dome shaped, or hobnailed. The cytoplasm is lightly eosinophilic to amphophilic, but it can be oxyphilic or clear. Cytoplasmic mucin can be demonstrated by histochemical stains in a proportion of cases. Focal squamous differentiation is common, and such foci usually do not exhibit the characteristic nuclear features of papillary carcinoma (Fig. 44–29).

Many variants of papillary carcinoma have been recognized, but only some are of prognostic signifi-
cancer. They are listed in Table 44–9 (Figs. 44–30 to 44–42).

**Latent Papillary Carcinoma**

Latent papillary carcinomas are cancers incidentally found in thyroidectomy specimens or at autopsy. In autopsy series, they are found in approximately 5% to 10% of cases, but the frequency ranges from as high as 46% in Finland to as low as 1.2% in Switzerland. Latent papillary carcinomas usually appear after puberty, and the prevalence does not show a significant increase with age thereafter. A small proportion of cases can show regional lymph node metastasis, but the deposits are often microscopic and probably remain dormant even without excision. The lack of female predominance in latent papillary carcinomas and the dissociation between the prevalence rates of latent and clinical thyroid carcinomas suggest that most latent papillary carcinomas remain dormant and do not grow to become clinically apparent tumors. Because latent papillary carcinomas are innocuous, no additional therapy is required.

Latent papillary carcinomas are almost always tiny and commonly show a predominantly follicular architecture. Most cases exhibit an invasive stellate contour and sclerosis; others comprise a circumscribed or encapsulated collection of neoplastic follicles without intratumoral sclerosis. (Figs. 44–43 and 44–44).

**Immunohistochemistry**

The immunohistochemical profile of papillary carcinoma is listed in Table 44–1. The staining for
TABLE 44–9. Variants of Papillary Carcinoma

<table>
<thead>
<tr>
<th>Variant*</th>
<th>Defining Morphologic Features</th>
<th>Entity for Which the Variant May Be Mistaken</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular variant</td>
<td>Composed exclusively or almost exclusively of follicles</td>
<td>Follicular adenoma</td>
<td>No prognostic implications</td>
</tr>
<tr>
<td></td>
<td>The follicles are often elongated and irregularly shaped, with abortive papillae.</td>
<td>Follicular carcinoma</td>
<td>No prognostic implications</td>
</tr>
<tr>
<td></td>
<td>The colloid is often dark staining.</td>
<td></td>
<td>No prognostic implications</td>
</tr>
<tr>
<td>Encapsulated variant</td>
<td>Tumor with a distinct fibrous capsule</td>
<td>Follicular adenoma</td>
<td>Highly favorable prognostic no tumor relapse after nodulectomy or lobectomy</td>
</tr>
<tr>
<td></td>
<td>Capillary or vascular invasion may or may not be present.</td>
<td>Follicular carcinoma</td>
<td>Highly favorable prognostic no tumor relapse after treatment</td>
</tr>
<tr>
<td>Cystic variant</td>
<td>Prominent cyst formation</td>
<td>Cystic degeneration of colloid nodule</td>
<td>No prognostic implications</td>
</tr>
<tr>
<td></td>
<td>There may or may not be neoplastic papillae projecting into the cystic space.</td>
<td></td>
<td>No prognostic implications</td>
</tr>
<tr>
<td>Encapsulated follicular</td>
<td>Encapsulated tumor composed exclusively or almost exclusively of follicles</td>
<td>Follicular adenoma</td>
<td>No prognostic implications</td>
</tr>
<tr>
<td>variant</td>
<td></td>
<td>Follicular carcinoma</td>
<td>No prognostic implications</td>
</tr>
<tr>
<td>Diffuse sclerosing variant</td>
<td>Diffuse extensive involvement of one or both lobes without forming a gross tumor nodule</td>
<td>Thyroiditis, especially because of the diffuse nature of the process and frequent presence of circulating antithyroid antibodies</td>
<td>Some studies have reported this variant to be more aggressive, with frequent lymph node and sometimes distant metastases, but outcome is still favorable because of the young age of patients (favorable prognostic factor). Some studies have not shown this variant to exhibit a high metastatic rate.</td>
</tr>
<tr>
<td></td>
<td>Thyroid parenchyma shows sclerosis and lymphoid infiltration. Tumor islands are often small and dispersed, with many lying within lymphatic spaces. Tumor commonly shows squamous metaplasia and prominent psammoma body formation.</td>
<td></td>
<td>No prognostic implications</td>
</tr>
<tr>
<td>Diffuse follicular variant</td>
<td>Diffuse involvement of the entire thyroid without formation of discrete tumor nodules, and composed entirely of follicles</td>
<td>Coflloid goiter</td>
<td>More aggressive, with frequent lymph node and distant metastases, but outcome is still favorable because of the young age of patients (favorable prognostic factor) and good response to radioactive iodine therapy.</td>
</tr>
<tr>
<td>Macropholicular variant</td>
<td>Presence of many large follicles, mimicking colloid nodule</td>
<td>Nodular goiter</td>
<td>No prognostic implications</td>
</tr>
<tr>
<td>Tall cell variant</td>
<td>&gt;50% of tumor cells with a height of more than twice the breadth</td>
<td>Columnar cell carcinoma</td>
<td>As a group, tall cell variant is more aggressive than conventional papillary carcinoma, with larger tumors, more frequent extrathyroidal extension, higher recurrence rate, and higher mortality (reported 9%–25%). For intrathyroidal tumors occurring in young patients, however, the prognosis appears to be similar to that of conventional papillary carcinoma.</td>
</tr>
<tr>
<td>Oxyphil cell variant</td>
<td>&gt;50% of tumor cells with abundant oxyphilic cytoplasm</td>
<td>Hürthle cell adenoma or carcinoma</td>
<td>No prognostic implications</td>
</tr>
<tr>
<td>Solid variant</td>
<td>&gt;50% of tumor showing a solid growth pattern</td>
<td>Poorly differentiated (insular) carcinoma</td>
<td>No prognostic implications</td>
</tr>
</tbody>
</table>

Table continued on following page
thyroglobulin is patchy, and it is often absent in areas of squamous differentiation. The main application of immunohistochemical staining is in confirmation of the thyroid origin of metastatic carcinoma, such as cystic metastasis of papillary thyroid carcinoma in a cervical lymph node. Although staining for high-molecular-weight cytokeratin or cytokeratin 19 has been suggested to be of value in supporting a diagnosis of papillary carcinoma versus benign thyroid lesions in difficult cases,244–247 the results are not consistent enough for routine application.

**Cytogenetics and Molecular Biology**

The key molecular change in papillary carcinoma involves activation of the proto-oncogene RET or **NTRK1** by intrachromosome inversion or chromosome translocation.248–250 Constitutive activation of RET (a receptor tyrosine kinase) occurs through fu-

### TABLE 44–9. Variants of Papillary Carcinoma Continued

<table>
<thead>
<tr>
<th>Variant*</th>
<th>Defining Morphologic Features</th>
<th>Entity for Which the Variant May Be Mistaken</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trabecular variant</td>
<td>&gt;5% of tumor showing a trabecular growth pattern</td>
<td>Follicular adenoma or carcinoma, trabecular (embryonal) type</td>
<td>Some studies have shown this variant to have a less favorable outcome.</td>
</tr>
<tr>
<td>Cribiform-morular variant</td>
<td>An intricate admixture of cribiform structures, closely packed small follicles, papillae, and squamoid islands (morulas); Collid is usually scanty or absent. Some tumor cells in the monora contain nuclei with a lightly eosinophilic homogenous appearance caused by biotin accumulation. The tumor cell nuclei are often more hyperchromatic and pseudostatified compared with classic papillary carcinoma.</td>
<td>Columnar cell carcinoma</td>
<td>Familial adenomatous polyposis should be excluded because the papillary carcinomas associated with the syndrome commonly exhibit histologic features of this variant. By itself, the variant has no prognostic implications.</td>
</tr>
<tr>
<td>Variant with nodular fasciitis-like stroma</td>
<td>Presence of abundant nodular fasciitis-like reactive stroma; The papillary carcinoma component can be masked by the stromal component or shows peculiar architectural features reminiscent of fibrocystic disease or phyllodes tumor of the breast.</td>
<td>Nodular fasciitis Fibromatosis Benign mesenchymal neoplasm</td>
<td>No prognostic implications</td>
</tr>
<tr>
<td>Warthin tumor–like variant</td>
<td>Presence of broad papillae covered by oehophilic neoplastic cells, with the cores being packed with lymphoid cells, reminiscent of Warthin tumor of salivary gland</td>
<td>Hashimoto’s thyroiditis</td>
<td>No prognostic implications</td>
</tr>
<tr>
<td>Papillary microcarcinoma</td>
<td>Small tumor, &lt;1 cm</td>
<td>Multifocal fibrous thyroiditis Hyperplastic adenomatoid nodule</td>
<td>Highly favorable prognosis Virtually all patients remain well on long-term follow-up. The rare patients who have an unfavorable outcome are those with lymphadenopathy &gt;3 cm and a nonencapsulated type of primary lesion.</td>
</tr>
<tr>
<td>Dedifferentiated papillary carcinoma</td>
<td>Papillary carcinoma accompanied by an anaplastic carcinoma or poorly differentiated thyroid carcinoma, indicating transformation to a higher-grade neoplasm</td>
<td>—</td>
<td>High mortality rate</td>
</tr>
</tbody>
</table>

* All variants show the typical nuclear characteristics of papillary carcinoma, at least in some areas of the tumor.
FIGURE 44–31. Papillary carcinoma, encapsulated follicular variant. A. The encapsulated tumor is composed exclusively of follicles, rendering distinction from follicular adenoma or follicular carcinoma difficult. The clues to diagnosis are dark-staining colloid, elongated follicles, and presence of abortive papillae. B. The follicles are lined by cells with crowded, pale, and grooved nuclei, compatible with papillary carcinoma.

FIGURE 44–32. Papillary carcinoma, cystic variant. A. The cyst has a fibrous wall lined by attenuated epithelium and can potentially be mistaken for cystic degeneration of colloid nodule. B. In the wall, there are occasional follicles lined by cells with active- looking and crowded nuclei. C. Focally, short papillae lined by cells exhibiting features of papillary carcinoma are identified, permitting the correct diagnosis to be made.

The RET/PTC translocation occurs in approximately 30% to 40% of papillary carcinomas, but the frequency is higher in children and young patients, Chernobyl accident–associated tumors, and patients who received external radiation during child-

sion of the RET gene with a gene commonly expressed in thyroid epithelial cells, such as PTC1 through inv(10)(p11.2q21), PTC2 through t(10;17) (q11.2;q23), and PTC3 through cytogenetically undetectable paracentric inversion within 10q11.2.271–277
FIGURE 44–33. Papillary carcinoma, diffuse sclerosing variant. A. The thyroid gland shows sclerosis and chronic inflammation, mimicking thyroiditis. However, linear scratches on the slide suggest the presence of calcified psammoma bodies. B. Hiding within the gland are islands of papillary carcinoma. A psammoma body is seen in the left lower field.

FIGURE 44–34. Papillary carcinoma, diffuse follicular variant. A. The neoplasm shows extensive involvement of the thyroid without discrete nodular formation or sclerosis and thus can be mistaken for a diffuse goiter, especially because some follicles are large. B. Careful examination of the smaller follicles reveals cytologic features of papillary carcinoma.

FIGURE 44–35. Papillary carcinoma, tall cell variant. A. The neoplastic cells are tall columnar and exhibit oncocytic cytoplasmic features. The nuclear features are no different from those of conventional papillary carcinoma. B. In this unusual example, the cells show cytoplasmic clearing.
Activation of the NTRK1 gene product (a receptor for nerve growth factor) occurs through fusion with widely expressed “housekeeping” genes, such as TPM3 (tropomyosin gene), TPR, and TAG.268, 280, 281, 285, 297–299

### Differential Diagnosis

The main criteria and problems in diagnosis of papillary carcinoma are listed in Table 44–10.300 Some immunohistochemical markers, such as expression of high-molecular-weight cytokeratin (34βE12, cytokeratin 19, vimentin, mesothelium-associated antibody HBME-1, Leu-7 (CD57), CD15 (Leu-M1), or CD44, and loss of expression of thyroid peroxidase or retinoblastoma protein have been reported to be of value in distin-
FIGURE 44–40. Papillary carcinoma, variant with nodular fasciitis–like stroma. A. The interaction of the abundant fibrocellular stroma with the papillary carcinoma results in a peculiar pattern mimicking sclerosing adenosis of the breast. B. The stroma comprises loose fascicles of active-looking myofibroblasts, mimicking nodular fasciitis or fibromatoses.

FIGURE 44–41. Papillary carcinoma, Warthin tumor–like variant. The resemblance to Warthin tumor of the salivary gland is striking. The neoplastic cells show oncocytic change.

FIGURE 44–42. Papillary carcinoma, dedifferentiated variant. Papillary carcinoma component is shown on the left; the anaplastic carcinoma comprising pleomorphic spindly cells is shown on the right.

FIGURE 44–43. Latent papillary carcinoma as an incidental finding. A. Near the central field, there is a collection of small follicles representing latent papillary carcinoma. It is not accompanied by a sclerotic stroma. B. The follicles are lined by cells with large pale nuclei lacking polarity (left field), characteristic of papillary carcinoma. Note the abrupt difference in nuclear features compared with the adjoining normal follicles (right field).
Distinguishing papillary carcinoma from benign thyroid lesions and other thyroid tumors, but so far none of these markers is reliable enough to aid in routine diagnosis of papillary carcinoma. Future studies are required to determine whether overexpression of RET by in situ hybridization or immunohistochemistry can aid in the diagnosis of papillary carcinoma. Currently, morphologic assessment remains the gold standard in rendering a diagnosis of papillary carcinoma.

**COLLOID NODULE.** In contrast to papillary carcinoma, the papillae found in colloid or adenomatoid nodules are often broad, with small follicles in the loose core. The cells are usually columnar, with dark round nuclei regularly aligned at the base of the cells. In some colloid or adenomatoid nodules, there can be collections of follicles with pale or clear nuclei, raising a concern for papillary carcinoma. However, a diagnosis of papillary carcinoma (follicular variant) should not be made unless there are totally convincing nuclear features (see Figs. 44–24 and 44–31 and Table 44–10). The neoplastic follicles of papillary carcinoma should show an abrupt change from the surrounding benign follicles, often accompanied by enlargement of the nuclei (see Fig. 44–43). In contrast, the atypical follicles of adenomatoid nodule typically show gradual transition with the surrounding benign follicles.

**FOLLICULAR ADENOMA WITH PAPILLARY HYPERPLASIA.** Distinguishing features from papillary carcinoma are the same as those for colloid nodule.

**FOLLICULAR ADENOMA.** Some follicular adenomas may have some pale or clear nuclei, raising the possibility of follicular variant of papillary carcinoma. The nuclear clearing is often artifactual because of delayed fixation, with “blowing up” of the nuclei (see Fig. 44–11). Convincing nuclear features must be present in rendering a diagnosis of papillary carcinoma in an encapsulated follicular neoplasm because there is no harm in missing an encapsulated papillary carcinoma, which has an excellent prognosis (see Table 44–9).

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**TABLE 44–10. Key Points and Caveats in Diagnosis of Papillary Carcinoma**

<table>
<thead>
<tr>
<th>Diagnostic criteria for papillary carcinoma are based on a constellation of features, no single one of which is pathognomonic. For a noninvasive tumor, the diagnostic label &quot;papillary carcinoma&quot; should be applied only when the typical cytologic features are well developed.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic criteria</strong></td>
</tr>
<tr>
<td>• Cytologic features: ovoid nuclei that are crowded, without polarization, clear or pale, and grooved, with or without pseudoinclusions</td>
</tr>
<tr>
<td>• Demonstration of vascular or capsular invasion is not required</td>
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<tr>
<td><strong>Strong supporting feature, if present</strong></td>
</tr>
<tr>
<td>• Psammoma bodies</td>
</tr>
<tr>
<td><strong>Other supporting histologic features</strong></td>
</tr>
<tr>
<td>• Papillae (including abortive papillae)</td>
</tr>
<tr>
<td>• Follicles that are elongated or irregularly shaped</td>
</tr>
<tr>
<td>• Dark-staining colloid</td>
</tr>
<tr>
<td>• Multinucleated histiocytes in lumina of follicles or papillae</td>
</tr>
<tr>
<td><strong>Deceptively &quot;benign&quot; patterns warranting serious consideration of the possibility of papillary carcinoma:</strong></td>
</tr>
<tr>
<td>• &quot;Colloid nodule&quot; with delicate papillary budding in some follicles, or psammoma bodies, or many clear nuclei (papillary carcinoma, macrofollicular variant)</td>
</tr>
<tr>
<td>• Hashimoto’s or lymphocytic thyroiditis-like picture, but with many “knife marks” on the histologic section due to presence of psammoma bodies (diffuse sclerosing variant of papillary carcinoma)</td>
</tr>
<tr>
<td>• &quot;Follicular adenoma&quot; with many elongated follicles and dark-staining colloid or abortive papillae (papillary carcinoma, encapsulated follicular variant)</td>
</tr>
<tr>
<td>• &quot;Degenerate cyst,&quot; but with occasional small papillary tufts projecting into the lumen or some follicles in the fibrous wall lined by cells with high nuclear-to-cytoplasmic ratio (cystic variant of papillary carcinoma)</td>
</tr>
<tr>
<td>• Spindle cell proliferation resembling nodular fasciitis or fibromatosis (papillary carcinoma variant with exuberant nodular fasciitis–like stroma)</td>
</tr>
</tbody>
</table>
**COLUMNAR CELL CARCINOMA**. See later.

**MEDULLARY CARCINOMA WITH PSEUDOPAPILLARY PATTERN**. See later.

**PROGNOSTIC CONSIDERATIONS**

Papillary carcinoma is an indolent neoplasm. According to a long-term follow-up study from the Mayo Clinic, the cancer-related mortality is only 6.5%.164 The tumor is locally invasive and has a propensity to metastasize to regional lymph nodes, but distant metastasis is uncommon and often late (< 10%).73, 192, 193, 316.

The most significant prognostic factors are age, stage, and tumor size. To aid in prediction of outcome and selection of therapy, a number of parameters (such as age, metastasis, extent of primary cancer, and tumor size) are taken into consideration to divide patients into low-risk and high-risk groups.127-129 The low-risk group has an excellent prognosis, and conservative therapy can be considered. The high-risk group has a worse outcome, and thus more aggressive therapy is required.

**AGE.** Young age is an important favorable prognostic factor. Few patients younger than 40 years die of papillary carcinoma.164, 165, 241, 321–329

**SEX.** The male sex is often associated with a worse prognosis.226, 323, 325, 326, 329–332

**TUMOR SIZE.** Risk of death from papillary carcinoma increases with the size of the primary tumor.164 Microcarcinomas (<1 to 1.5 cm) have an excellent prognosis, whereas tumors larger than 4 cm fare worse.76, 164, 241, 325, 333

**TUMOR STAGE.** Extrathyroidal extension worsens the prognosis, which is even worse when there is invasion of the esophagus or trachea.164, 325, 327, 334, 335 Presence of distant metastasis is a highly unfavorable prognostic feature.164 Papillary carcinoma is unique among carcinomas in that most studies have not found lymph node metastasis to be of prognostic significance.*

**TUMOR ENCAPSULATION.** Encapsulated papillary carcinomas have an excellent prognosis. There is no recurrence after excision of the tumor.72, 192, 196

**HISTOLOGIC VARIANTS.** The prognostic significance of the variants is listed in Table 44–9.340

**COMPLETENESS OF EXCISION.** Incomplete tumor excision increases the probability of recurrence.318, 341

**HISTOLOGIC FEATURES.** The histologic features shown in some studies to be associated with a worse prognosis are marked cellular atypia (multilayered cells with marked variation in cellular and nuclear size and shape, uneven distribution of chromatin) and trabecular growth pattern.27, 302, 332, 342 (Fig. 44–45). High tumor grade (grade 2), as defined by the presence of marked nuclear atypia, tumor necrosis, or vascular invasion, has been reported to be associated with a worse prognosis.130, 343

**STROMAL REACTION.** Chronic thyroiditis in the background thyroid tissue and stromal bone formation have been reported to be favorable prognostic factors.77, 324

**VASCULAR INVASION.** Invasion of sizable blood vessels is an unfavorable prognostic factor.77, 302

**IMMUNOHISTOCHEMICAL FEATURES.** High density of S-100 protein–positive histiocytes is a favorable prognostic factor.339 The features associated with a worse prognosis are Leu-M1 positivity, epithelial membrane antigen positivity, p53 protein immunoreactivity, lack of E-cadherin expression, and low-level expression of retinoblastoma protein.340, 343, 347-348

**TUMOR ANGIogenesis.** Whereas some studies have suggested that a high microvessel count (intratumoral microvessel count as highlighted by immunostaining for vascular markers) correlates with a worse prognosis, other studies cannot confirm this finding.349–351

**DNA PloidY.** Multiploidy or aneuploidy is an unfavorable prognostic factor.178, 352

**N-ras MUTATION.** N-ras mutation at codon 61, which is uncommon, is associated with a more aggressive behavior.353

**Poorly Differentiated Thyroid Carcinoma**

**CLINICAL CONSIDERATIONS**

**Presentation**

Poorly differentiated thyroid carcinoma shows histologic and biologic features intermediate between differentiated thyroid carcinomas and anaplastic carcinomas.342, 354–355 It retains sufficient dif-
Thyroid and Parathyroid

Differentiation to form small follicular structures and to produce thyroglobulin, but it lacks the usual morphologic characteristics of papillary and follicular carcinoma. An alternative designation of "primordial cell carcinoma" has also been proposed in view of the cytoarchitectural resemblance to the fetal thyroid.

Poorly differentiated carcinomas can arise de novo or transform from differentiated thyroid carcinomas, either after repeated recurrences or with the two components being discovered simultaneously at diagnosis. They can further transform to anaplastic carcinoma.

The tumor predominantly affects middle-aged and elderly adults, with a mean age of 54 years. Women are more commonly affected than men (male-to-female ratio = 1:2). Most patients present with an enlarging thyroid mass, and there may be a preceding history of long-standing goiter. Rare patients present with bone metastasis. The disease is often locally advanced at presentation, with extrathyroidal extension in more than 50% of cases. Lymph node and distant metastases are already present at presentation in approximately 40% and approximately 30% of cases, respectively.

Macroscopic Findings

The tumor is partially encapsulated or frankly invasive. It is often large, with a mean size of 4.7 cm. The cut surface is solid, firm, and fleshy, often punctuated by areas of necrosis and hemorrhage.

Diagnostic Considerations

Microscopic Findings

Insular carcinoma typically grows in the form of large solid nests (insulae) decorated with variable numbers of small abortive follicles (Fig. 44–46). It is common to observe retraction artifacts around the tumor islands. The frequent presence of coagulative necrosis results in a characteristic "peritheliomatous" appearance. The tumor can also form diffuse sheets, trabeculae, festoons, and papillae (Fig. 44–47). Vascular invasion is common. Some cases may show transition with typical papillary carcinoma or follicular carcinoma. The tumor cells are relatively small, with uniform round, hyperchromatic nuclei, indistinct nucleoli and scanty cytoplasm. Some mitotic figures can often be identified.

There is a morphologic range of poorly differentiated thyroid carcinomas that do not fit the histologic description of insular carcinoma. They are composed of large cells growing in a trabecular, cribriform, solid, or focally follicular pattern (Fig. 44–48).

Immunohistochemistry

Poorly differentiated thyroid carcinoma is immunoreactive for cytokeratin, thyroglobulin, and thyroid transcription factor 1. The positive staining for thyroglobulin may be confined to the abortive follicles and isolated cells in the form of paranuclear globules. There is reduced expression of the cyclin-dependent kinase inhibitor p27 and a higher Ki-67 index compared with differentiated thyroid carcinomas. Positive staining for Bcl-2 is common (84%), contrasting with the infrequent positive staining in anaplastic carcinomas (14%).

Molecular Biology

Approximately half of the cases of poorly differentiated thyroid carcinomas show immunoreactivity for p53 protein, whereas this feature is uncommon in well-differentiated thyroid carcinomas but common in anaplastic carcinomas. Thus, it appears that TP53 gene mutation may play a role in the genesis of some cases. The finding of point mutations in the ras oncogene in a proportion of cases suggests...
FIGURE 44–47. Insular carcinoma. A. A “peritheliomatous” pattern results from degeneration and necrosis of tumor away from the blood vessels. B. A festooning pattern is also common. C. A papillary pattern is occasionally observed.

FIGURE 44–48. Poorly differentiated carcinoma. A. In insular carcinoma, the tumor cells are typically small and monotonous, with fairly uniform dark-staining nuclei. Some mitotic figures can often be identified. Note the focal differentiation into small follicles. B. In this poorly differentiated thyroid carcinoma, the right lower field shows cytologic features characteristic of insular carcinoma. In the left upper field, the cells are slightly larger and more pleomorphic, with brisk mitotic activity. This component is still a form of poorly differentiated rather than anaplastic carcinoma because there is organoid arrangement of the tumor cells and immunoreactivity for thyroglobulin.
a relationship with follicular carcinoma in such cases.8, 365

**Differential Diagnosis**

**MEDULLARY CARCINOMA.** Insular carcinoma may mimic medullary carcinoma as a result of the growth pattern and amyloid-like sclerosis. The distinction can be readily made by immunostaining for thyroglobulin and calcitonin (see Table 44–1).

**ANAPLASTIC THYROID CARCINOMA.** Poorly differentiated carcinoma lacks the prominent nuclear pleomorphism and frequent mitoses of anaplastic carcinoma and furthermore shows abortive follicles and thyroglobulin immunoreactivity.

**SOLID VARIANT OF PAPILLARY CARCINOMA.** See Table 44–9.

**PROGNOSTIC CONSIDERATIONS**

Recurrence or metastasis develops in approximately 60% of cases after treatment.8, 54, 354 In contrast to the rapidly fatal course of anaplastic carcinoma, poorly differentiated carcinoma causes death after several years (mean survival, 3.9 years). The long-term survival rate is around 40%.8, 354–356, 365 Death is often attributable to metastasis rather than to uncontrollable local disease. The treatment usually consists of total thyroidectomy, radioactive iodine, and suppressive thyroxine.254 Radiotherapy and chemotherapy may also be considered in view of the unfavorable prognosis. Poor prognostic factors include advanced age, large tumor size, extrathyroidal extension, lymph node metastasis, and presence of an anaplastic carcinoma component.238 Whether the presence of a minor component of poorly differentiated carcinoma worsens the prognosis of an otherwise typical differentiated thyroid carcinoma remains controversial.238, 347–348 The outcome will probably be worsened if the poorly differentiated carcinoma component is found in the invasive portions of the tumor but not if the component is confined to an encapsulated tumor.

**Anaplastic (Undifferentiated) Carcinoma**

**CLINICAL CONSIDERATIONS**

**Presentation**

Anaplastic carcinoma is predominantly a disease of older adults with a mean age of 67 years; there is a slight female predominance.238, 370–372 The patients present with a rapidly enlarging thyroid mass or metastatic tumor in cervical lymph nodes or distant sites. The mass lesion is frequently accompanied by hoarseness, dysphagia, and dyspnea. Some patients have a history of a long-standing goiter or well-differentiated thyroid carcinoma.238, 354, 370, 372, 374 Squamous cell carcinoma and carcinosarcoma can be considered variants of anaplastic carcinoma.
FIGURE 44–50. Anaplastic carcinoma. A. This tumor is composed of ovoid and plump spindly cells with significant nuclear pleomorphism. Many tumor cells possess multiple large nucleoli. B. This tumor is composed of spindly cells with distinct nucleoli.

FIGURE 44–51. Anaplastic carcinoma. This tumor shows cellular dehiscence and interstitial hemorrhage, mimicking angiosarcoma.

FIGURE 44–52. Anaplastic carcinoma. A highly characteristic feature is obliteration of the wall and lumen of large blood vessels by tumor cells.

FIGURE 44–53. Anaplastic carcinoma. A. A component of Hürthle cell neoplasm (left field) is found in this anaplastic carcinoma. B. At the interface between the two components, there are highly atypical Hürthle cells that merge into the anaplastic carcinoma, suggesting transformation of Hürthle cell neoplasm into anaplastic carcinoma.

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**Immunohistochemistry**

In anaplastic carcinoma, epithelial markers cannot be consistently demonstrated, except in areas of squamous differentiation. Cytokeratin is positive in only approximately half of the cases, whereas epithelial membrane antigen is positive in only 33% to 55%. Vimentin is positive in 50% to 100% but has no diagnostic value. Thyroglobulin and thyroid transcription factor 1 are negative in the anaplastic carcinoma component, but immunostaining for these markers can sometimes highlight the preexisting differentiated thyroid carcinoma component if it is present. Calcitonin is negative. Focal immunoreactivity for factor VIII–related antigen has been reported, possibly indicating focal divergent endothelial differentiation.

**Molecular Biology**

Aberrations in the p53 pathways have been implicated in the transformation of differentiated thyroid carcinoma to anaplastic carcinoma. The anaplastic carcinoma component commonly shows strong immunoreactivity for p53 protein, whereas the differentiated thyroid carcinoma component is negative. The ß-catenin gene commonly shows somatic mutations in anaplastic carcinoma and may thus play a key role in the development of this tumor type.

**Differential Diagnosis**

The main pitfalls in diagnosis of anaplastic carcinoma are listed in Table 44–12.

<table>
<thead>
<tr>
<th>Variant*</th>
<th>Defining Morphologic Features</th>
<th>Entity for Which the Variant May Be Mistaken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiomatoid variant</td>
<td>Presence of irregular cleftlike tumor cell–lined spaces mimicking vascular spaces</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Osteoclastic variant</td>
<td>Reactive osteoclastic giant cells are interpersed in an otherwise typical anaplastic carcinoma</td>
<td>Giant cell tumor of larynx (thyroid cartilage)</td>
</tr>
<tr>
<td>Paucicellular variant</td>
<td>Low-cellularity tumor with large areas of sclerosis and infarction. A sprinkling of lymphocytes is often present. Focally, spindly tumor cells with mild to moderate nuclear atypia can be identified. These spindle cells also obliterate the wall and lumina of blood vessels.</td>
<td>Riedel's thyroiditis</td>
</tr>
<tr>
<td>Lymphoepithelioma-like variant</td>
<td>Irregular infiltrative islands and sheets of synoviated-appearing pleomorphic tumor cells, heavily intermingled with lymphocytes and plasma cells</td>
<td>CASTLE</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Identical to squamous cell carcinoma occurring in other sites</td>
<td>CASTLE</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>Squamous cell carcinoma with areas of mucin production</td>
<td>—</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>Anaplastic carcinoma accompanied by a sarcomatous component with muscle, fat, cartilage, or bone differentiation</td>
<td>—</td>
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</table>

* None of these variants has clinical or prognostic significance.
metastatic carcinoma, although metastatic carcinoma should be suspected if the bulk of the tumor lies within lymphovascular spaces. The presence of a component of differentiated thyroid carcinoma strongly favors the diagnosis of anaplastic carcinoma.

**Parathyroid Carcinoma.** Parathyroid carcinoma presenting as a thyroid mass is not uncommonly misdiagnosed as anaplastic thyroid carcinoma. The distinction is important because parathyroid carcinoma is a much more indolent neoplasm. Histologic clues to the correct diagnosis are presence of clear cells, mixture of cell types, paucity of mitotic figures, and prominent delicate vasculature.

**Riedel’s Thyroiditis.** The paucicellular variant of anaplastic carcinoma can be mistaken for Riedel’s thyroiditis, which has a favorable prognosis. Features favoring the diagnosis of a paucicellular variant of anaplastic carcinoma are presence of infarction, cytologic atypia (albeit focal and often subtle), vascular occlusion by spindle cells, discrete interface with the adjacent tissue, and cytokeratin immunoreactivity.

**Angiosarcoma.** See later.

**Solid Variant of Papillary Carcinoma.** The solid variant of papillary carcinoma can be distinguished from anaplastic carcinoma by the typical nuclear features, lack of bizarre cells, and paucity of mitotic figures.

**Poorly Differentiated Thyroid Carcinoma.** Poorly differentiated thyroid carcinoma usually shows definite cellular organization into islands with microfollicles, relatively small cells, fairly uniform nuclei, lack of bizarre cells, and thyroglobulin immunoreactivity.

**Thymic and Related Tumors.** See later.

**Prognostic Considerations**

Anaplastic carcinoma is inoperable in about half of the cases because of extensive local disease. Regional lymph node and distant metastases (mostly lungs, sometimes bones) are common. The cause of death...
Thyroid and Parathyroid

is usually upper airway obstruction from extensive local disease or a combination of the effects of local and metastatic disease. The median survival is only 3 to 4 months, and the 5-year survival rate is 5% to 10%. The rare patients who can achieve a cure usually have relatively small (<5 cm) tumors confined to the thyroid gland and have been treated with aggressive local intervention. Unfavorable prognostic factors for anaplastic carcinoma include large tumor size (>6 cm), extension of tumor beyond the neck, old age at diagnosis, male gender, and dyspnea as a presenting symptom.

Columnar Cell Carcinoma

CLINICAL AND PROGNOSTIC CONSIDERATIONS

Although columnar cell carcinoma was originally reported as an aggressive neoplasm, studies have shown that aggressive behavior is observed only in the frankly invasive tumors. For invasive tumors, there is slight male predilection and the mean age is 55.6 years. There is a high frequency of regional lymph node and distant metastases. The mortality rate, which is at least 75%, is high. In contrast, for encapsulated tumors, there is marked female predominance and patients are younger (mean, 42.7 years). Most patients remain well on follow-up.

There are divergent views on the nature of columnar cell carcinoma: a distinct tumor type versus a variant of thyroid carcinoma. In fact, occasional cases show merging with tall cell papillary carcinoma. There is also some morphologic overlap with the cribriform-morular variant of papillary carcinoma and familial adenomatous polyposis–associated thyroid carcinoma.

DIAGNOSTIC CONSIDERATIONS

Microscopic Findings

Columnar cell carcinoma shows heterogeneous growth patterns, including papillary, complex glandular, cribriform, and solid. The cells are tall columnar and characteristically show marked nuclear pseudostratification and hyperchromasia, reminiscent of colorectal adenocarcinoma or endometrioid adenocarcinoma (Fig. 44–56). Subnuclear vacuoles and diffuse cytoplasmic clearing can sometimes oc-

<table>
<thead>
<tr>
<th>TABLE 44–12. Main Pitfalls in Diagnosis of Anaplastic Thyroid Carcinoma</th>
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<tbody>
<tr>
<td><strong>Main Diagnostic Pitfall</strong></td>
</tr>
<tr>
<td>Benign lesions mimicking anaplastic thyroid carcinoma</td>
</tr>
<tr>
<td>Low-grade malignant tumors mimicking anaplastic thyroid carcinoma</td>
</tr>
<tr>
<td>Anaplastic thyroid carcinoma variant potentially misdiagnosed as benign or low-grade malignant lesions</td>
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FIGURE 44–56. Columnar cell carcinoma. A. Complex tubulopapillary structures characteristic of the growth pattern of this tumor. B. The lining cells are markedly pseudostratified cells and possess chromatin-rich nuclei.
cur. Short fascicles of spindle cells can also be present. The follicular epithelial nature of the tumor is evidenced by thyroglobulin immunoreactivity.

**Differential Diagnosis**

Columnar cell carcinoma can be distinguished from tall cell papillary carcinoma by the features of taller cells, striking nuclear pseudostratification, nuclear hyperchromasia, and lack of oxyphilic change.

**Mucoepidermoid Carcinoma**

**CLINICAL AND PROGNOSTIC CONSIDERATIONS**

This is a rare tumor showing female predominance. The mean age is 37.9 years. The patients present with a thyroid mass. Lymph node metastasis is common (60%), but distant metastasis is rare (13%). This is a low-grade malignant neoplasm; most patients remain well after treatment.

The nature of mucoepidermoid carcinoma is controversial: origin from ultimobranchial body, origin from thyroglossal duct, or merely a metaplastic variant of papillary carcinoma. In some cases, a component of conventional papillary carcinoma can be identified.

**DIAGNOSTIC CONSIDERATIONS**

The tumor comprises tumor cell islands that infiltrate a sclerotic stroma. The tumor cells are squa-moid to squamous, and there are interspersed mucin-secreting cells (Fig. 44–57 A). In areas, a cribriform pattern with elongated lumina containing colloid-like material can be found. The nuclei are hyperchromatic or pale; nuclear pleomorphism is mild to moderate (Fig. 44–57 B). Comedo-type necrosis or psammoma bodies can sometimes be found. The tumor usually does not show immunoreactivity for thyroglobulin while the papillary carcinoma component, if present, is immunoreactive for thyroglobulin.

**Sclerosing Mucoepidermoid Carcinoma with Eosinophilia**

**CLINICAL AND PROGNOSTIC CONSIDERATIONS**

Sclerosing mucoepidermoid carcinoma with eosinophilia is a low-grade malignant neoplasm that usually arises in a background of fibrosing Hashimoto’s thyroiditis. It affects adults with a mean age of 55 years, and there is a marked female predominance. Regional or distant metastases are uncommon, and the outcome is generally favorable.

**DIAGNOSTIC CONSIDERATIONS**

**Microscopic Findings and Immunohistochemistry**

Sclerosing mucoepidermoid carcinoma with eosinophilia is typically infiltrative, and there may be extrathyroidal extension. Anastomosing cords and nests of tumor cells are associated with a sclerotic stroma infiltrated by eosinophils. The tumor cells are polygonal, with mild to moderate nuclear pleomorphism and distinct nucleoli. There can sometimes be foci of squamous differentiation and small pools of mucus (Fig. 44–58). Tumor cell dehiscence may produce a pseudovascular appearance. The tumor cells are immunoreactive for cytokeratin but not for thyroglobulin and calcitonin.

**Differential Diagnosis**

The most important reasons to recognize sclerosing mucoepidermoid carcinoma with eosinophilia are not to mistake it for the vastly more aggressive anaplastic or squamous carcinomas of the thyroid on the one hand and not to misdiagnose it as be-

---

**FIGURE 44–57.** Mucoepidermoid carcinoma. A. Irregular islands of tumor infiltrate a desmoplastic stroma. Multiple mucin-containing cystic spaces are interspersed within the tumor islands. B. The tumor cells often have bland-looking and pale-staining nuclei.
nign squamous metaplasia on the other. In contrast to anaplastic or squamous cell carcinoma, the growth pattern is more diffuse with formation of cords or large islands; nuclear atypia is generally not striking, and the inflammatory component is usually eosinophilic rather than neutrophilic.

Mucinous Carcinoma

Primary mucinous carcinoma of the thyroid is extremely rare; only four cases have been reported in the literature.448–451 It is histologically identical to colloid carcinoma of other sites, except that thyroglobulin is usually positive.

Medullary Thyroid Carcinoma

CLINICAL CONSIDERATIONS

Presentation

Medullary thyroid carcinoma is a malignant neoplasm exhibiting parafollicular C cell differentiation.452 The patients are mostly adults with slight female predominance.453–464 Most patients present with a thyroid mass or cervical lymphadenopathy.465 Some patients may have diarrhea or, more rarely, Cushing’s syndrome.454, 466 The stage distribution at presentation is as follows: stage I, 21%; stage II, 21%; stage III, 47%; and stage IV, 12%.467 In some centers, routine screening of the calcitonin level in patients with nodular thyroid disease allows early diagnosis of unsuspected sporadic medullary thyroid carcinoma.468–470

Approximately 20% to 30% of medullary carcinomas are heritable (autosomal dominant with high penetrance).453, 455 The tumor often appears at an earlier age, multicentrically and bilaterally, and on a background of C cell hyperplasia448–451, 474–475 (Table 44–13). Germline mutation in the RET gene is the underlying molecular event.452–464 Thyroidectomy is usually performed for the mutant RET gene carriers identified through screening of family members, and the medullary carcinomas diagnosed in such circumstances are often small and at an early stage.

Macroscopic Findings

Medullary carcinoma has a predilection for the middle third of the lateral lobe, where normal C cells are most prevalent.465 It is infiltrative, circumscribed, or encapsulated(465, 471 (Fig. 44–59). It is firm and grayish white, tan, or reddish brown. Hemorrhage and necrosis can be seen in larger tumors.472

DIAGNOSTIC CONSIDERATIONS

Microscopic Findings

Medullary carcinoma typically grows in the form of sheets, packets, or irregular islands tra-
### TABLE 44–13. Sporadic and Hereditary Forms of Medullary Thyroid Carcinoma (MTC)

<table>
<thead>
<tr>
<th></th>
<th>Sporadic MTC</th>
<th>Hereditary MTC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age at diagnosis</strong></td>
<td>44–50 y</td>
<td>29–43 y</td>
</tr>
<tr>
<td><strong>Sex ratio</strong></td>
<td>Male-female 1:1.4</td>
<td>Male-Female 1:1.1</td>
</tr>
<tr>
<td><strong>Other components of the syndrome</strong></td>
<td>Nil</td>
<td>Pheochromocytoma, Parathyroid hyperplasia</td>
</tr>
<tr>
<td><strong>Germline mutation in RET proto-oncogene</strong></td>
<td>Nil</td>
<td>Mutation involving exon 10, 11, 13, or 14</td>
</tr>
<tr>
<td><strong>Bilaterality and C cell hyperplasia in the background</strong></td>
<td>Uncommon</td>
<td>Frequent</td>
</tr>
<tr>
<td><strong>Metastases at diagnosis</strong></td>
<td>Lymph node: 40%–50%, Distant: 12%</td>
<td>Lymph node: 10%–20%, Distant: 0%</td>
</tr>
<tr>
<td><strong>Tumor-related mortality</strong></td>
<td>~30%</td>
<td>Lymph node: 14%, Distant: 0%–3%</td>
</tr>
</tbody>
</table>

**MEN**: multiple endocrine neoplasia.

Weidner (SAUNM) LEFT INTERACTIVE
versed by delicate fibrovascular septa (Fig. 44–60). On occasion, a trabecular, pseudopapillary, whorled, rosette, tubular, microglandular, or cribriform pattern can be observed. Cellular dehiscence and interstitial edema are common (Fig. 44–61A). The tumor cells are polygonal or spindly. Their round or oval nuclei exhibit finely stippled chromatin and indistinct nucleoli. The nuclei often appear uniform, with occasional interspersed larger hyperchromatic nuclei (Fig. 44–61B). The cytoplasm is finely granular. Cytoplasmic mucin is demonstrable in some tumor cells in up to 50% of cases (Fig. 44–62).

Amyloid, in the form of globules or massive deposits, is found in 80% to 85% of cases (Fig. 44–63). It may show calcification or foreign body giant cell reaction. In microcarcinomas, amyloid is less common, being found in 27% of cases (Fig. 44–64).

Many histologic variants of medullary carcinoma have been recognized, but most are of no prognostic importance (Fig. 44–65; Table 44–14). It is usually not too difficult to render a correct diagnosis for such variants because a component of conventional medullary carcinoma can often be identified on careful search (Fig. 44–66A). Immunohistochemistry

A diagnosis of medullary carcinoma should always be confirmed by immunohistochemistry. Almost all cases are immunoreactive for calcitonin, and a low percentage of positive cells is correlated with a more aggressive behavior (Fig. 44–66B). If the staining is equivocal or difficult to interpret, immunostaining with a pan-neuroendocrine marker such as chromogranin can readily confirm the diagnosis (Fig. 44–66B). Carcinoembryonic antigen is positive in 88% to 100% of cases; this is a highly useful diagnostic marker for poorly differentiated or small cell medullary carcinoma, when calcitonin may be negative.
TABLE 44–14. Variants of Medullary Thyroid Carcinoma

<table>
<thead>
<tr>
<th>Variant*</th>
<th>Defining Morphologic Features</th>
<th>Entities for Which the Variant May Be Mistaken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glandular-follicular</td>
<td>Presence of glandular or follicular structures which may contain eosinophilic secretion in the lumina. The cytoplasm toward the luminal aspect is often more deeply eosinophilic due to polarization of neurosecretory granules.</td>
<td>Follicular adenoma or carcinoma</td>
</tr>
<tr>
<td>Papillary</td>
<td>Presence of pseudopapillae due to cellular dehiscence, and only rarely are there true papillary formations.</td>
<td>Papillary carcinoma</td>
</tr>
<tr>
<td>Oxyphilic</td>
<td>Tumor cells with abundant eosinophilic granular cytoplasm due to accumulation of mitochondria. The cytoplasm toward the luminal aspect is often more deeply eosinophilic due to polarization of neurosecretory granules.</td>
<td>Hürthle cell neoplasm</td>
</tr>
<tr>
<td>Clear cell</td>
<td>Presence of tumor cells with water-clear cytoplasm</td>
<td>Other clear cell tumors</td>
</tr>
<tr>
<td>Spindle cell</td>
<td>Presence of spindle tumor cells arranged in fascicles or whorls</td>
<td>Mesenchymal tumors</td>
</tr>
<tr>
<td>Pigmented</td>
<td>Presence of brown melanin pigment in some tumor cells</td>
<td>—</td>
</tr>
<tr>
<td>Squamous</td>
<td>Presence of squamous differentiation</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Small cell</td>
<td>Tumor composed predominantly of small cells, often with nuclear molding, resembling small cell carcinoma of lung</td>
<td>Malignant lymphoma</td>
</tr>
<tr>
<td>Giant cell (anaplastic)</td>
<td>Presence of large cells with bizarre and pleomorphic nuclei, but mitotic figures are rare</td>
<td>Anaplastic carcinoma</td>
</tr>
<tr>
<td>Neuroblastoma-like</td>
<td>Presence of fibrillary matrix or rosettes, resembling neuroblastoma</td>
<td>Malignant lymphoma</td>
</tr>
<tr>
<td>Carcinoid-like</td>
<td>Histologic features resembling intestinal carcinoid, with tumor islands, trabeculae, or glands separated by fibrohyaline stroma</td>
<td>Metastatic carcinoid</td>
</tr>
<tr>
<td>Hyalinizing trabecular adenoma-like</td>
<td>Waxy trabeculae of tumor cells, which merge into abundant extracellular hyaline material, mimicking hyalinizing trabecular adenoma</td>
<td>Hyalinizing trabecular adenoma</td>
</tr>
<tr>
<td>Paraganglioma-like</td>
<td>Tumor forming packets delineated by a delicate vasculature</td>
<td>Paraganglioma</td>
</tr>
</tbody>
</table>

* The listed variants have no clinical or prognostic significance, except the small cell type, which is more aggressive. The prognostic implication of the giant cell variant is still unsettled.
S-100 protein–positive sustentacular cells are usually absent, except in the setting of multiple endocrine neoplasia or familial medullary carcinoma, when 62.5% of cases can show a population of sustentacular cells.531 The hereditary form of medullary carcinoma typically arises in a background of C cell hyperplasia, which has been classified into a diffuse type and a nodular type. However, there are no universally accepted criteria for the diffuse type of C cell hyperplasia, and a similar degree of C cell proliferation can be seen in normal subjects, around various types of thyroid tumors, and in thyrotoxicosis509–510 (Fig. 44–67). The nodular type of C cell hyperplasia is defined as “complete obliteration of follicular space by C cells with production of solid intrafollicular aggregates,” but distinction from a minute medullary carcinoma or intrathyroid spread of medullary carcinoma can be difficult.508 (Fig. 44–68).

**Molecular Biology**

The RET proto-oncogene on chromosome 10q11 plays a key role in the genesis of medullary carcinoma. The RET gene, which comprises 21 exons, encodes a receptor tyrosine kinase with a cysteine-rich extramembrane domain, a transmembrane domain, and an intracellular tyrosine kinase component. Germline mutations of RET are found in patients with MEN 2 or familial medullary thyroid carcinoma. The mutations result in constitutive activation of the receptor owing to dimerization or alteration in the tyrosine kinase substrate specificity.522, 523 In MEN 2A, the mutations involve the cysteine-rich region of the extracellular domain, resulting in substitution of cysteine by another amino acid, the most common being TGC → GCC (Cys → Arg) at codon 634.513, 514 The sites of mutation are more varied in familial medullary thyroid carcinoma.513–515 Molecular study is currently the most reliable way to diagnose the hereditary form of medullary thyroid carcinoma—germline mutation in RET can be conveniently demonstrated on DNA extracted from peripheral blood leukocytes or paraffin-embedded nontumor tissues. After exons 10, 11, and 16 are amplified by the polymerase chain reaction, mutation screening can be performed by the single-stranded conformation polymorphism or heteroduplex technique; the site of mutation can be confirmed by DNA sequencing or restriction endonuclease cleavage. If the patient is confirmed to show germline mutation in RET, all family members should be screened to detect carriers of the RET mutation, who should be counseled, offered thyroidectomy, and closely followed up.516–518

In sporadic medullary carcinomas, somatic mutations in RET are found in 26% to 69% of cases, most commonly involving codon 918 of exon 16 (ATG → ACC).514, 519–522

**Differential Diagnosis**

**POORLY DIFFERENTIATED (INSULAR) THYROID CARCINOMA.** See earlier.

**HYALINIZING TRABECULAR ADENOMA.** Hyalinizing trabecular adenoma can mimic medullary carcinoma architecturally, but long wavy trabeculae are most uncommon in medullary carcinoma, and the nuclear features (nuclear grooves, nuclear pseudoinclusions, perinucleolar haloes) are also different.

**PARAGANGLIOMA.** There is significant morphologic overlap between paraganglioma and medullary carcinoma, such as packeting pattern, rich vascularity, and granular cytoplasm. Paraganglioma differs in being negative for cytokeratin, calcitonin, and carciinoembryonic antigen.

**METASTATIC NEUROENDOCRINE CARCINOMA.** Metastatic neuroendocrine carcinoma (carcinoïd and atypical carcinoid) from the bronchus or intraabdominal sites can present initially as thyroid tumor and is often misdiagnosed as medullary carcinoma.532 The neuroendocrine carcinoma forms nests, ribbons, islands, rosettes, and sheets traversed by delicate fibrovascular stroma. Clues to the diagnosis are predominantly interstitial growth, multiple tumor foci, absence of C cell hyperplasia, presence of peculiar protrusions into thyroid follicles in the form of subepithelial cell balls, and lack of amyloid. The tumor cells lack immunoreactivity for calcitonin and carciinoembryonic antigen.

**HURTHLE CELL NEOPLASM.** Medullary carcinoma with oncocytic change is not uncommonly misdiagnosed as Hurthle cell neoplasm. The most helpful clue is the presence of the delicate fibrovascular septa; identification of areas of conventional medullary carcinoma is also helpful.

**ANAPLASTIC CARCINOMA.** Bizarre and highly atypical cells may occur in an otherwise typical medullary carcinoma; this tumor can be distin-
FIGURE 44–65. Variants of medullary carcinoma. A. Glandular-follicular variant, which can potentially be mistaken for a follicular neoplasm. B. Papillary variant comprising pseudopapillae produced by cellular dehiscence. The tumor cells lack the typical nuclear features of papillary carcinoma. C. Oncocytic variant, which can be mistaken for Hürthle cell follicular neoplasm. D. Clear cell variant. E. Spindle cell variant, which may be mistaken for a mesenchymal neoplasm. F. Small cell variant. G. Giant cell variant.
guished from anaplastic carcinoma by the presence of many bland-looking cells among the bizarre cells and the paucity of mitotic figures.

**Parathyroid Neoplasm.** See later.

**Prognostic Considerations**

The tumor tends to spread by lymphatics to lymph nodes of the neck (one third to two thirds) and upper mediastinum. Local recurrence develops in about one third of cases after treatment. Late in the course, the tumor may metastasize to other sites, such as lungs, liver, adrenal, and bone, although distant metastasis is already present in 8% of patients at presentation. Patients may still survive for many years despite the presence of distant metastases. The 5-year, 10-year, and 15-year survival rates are 65% to 87%, 51% to 78%, and 65%, respectively, indicating that this tumor is indolent and not rapidly lethal. However, there is still an excess mortality 10 years after a diagnosis of medullary carcinoma. Because medullary carcinoma is not radiosensitive, adequate surgical clearance (total thyroidectomy) is the mainstay of primary treatment.

Tumor stage is the single most important prognostic factor on multivariate analysis. Stage of disease. Extrathyroidal extension is associated with a high risk of recurrence, disease progression, and worsened survival. Presence of lymph node metastasis at diagnosis greatly worsens the prognosis, with 10-year survival dropping from 86% to 95% (node negative) to 46% to 55% (node positive). Distant metastasis is associated with a poor survival.

**Age.** Older patients (>50 to 60 years) have a worse outcome. Some studies have shown the female sex to be associated with a better prognosis, but this factor loses prognostic significance on multivariate analysis according to some series.

**Medullary Carcinoma of MEN 2.** MEN 2A–associated medullary carcinoma has a better prognosis than the sporadic variety does; MEN 2B–associated medullary carcinoma is associated with a worse prognosis. Nonetheless, this factor is apparently not significant after multivariate analysis according to one study.

**Tumor Size.** Small tumors less than 1 cm have an excellent prognosis. Unfavorable outcome in microcarcinomas is virtually confined to patients who are symptomatic (such as palpable microcarcinoma, diarrhea, or metastatic disease at presentation).

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*References 455, 465, 493, 524, 526, 529, 530.

*References 453, 455, 465, 473, 493, 524, 526, 528.
Endocrine System

**BIOCHEMICAL CURE.** Achievement of biochemical cure predicts good survival (98% at 10 years versus 71% for those not achieving biochemical cure).\(^5\)\(^2\)\(^5\), \(^5\)\(^3\)\(^0\)

**HISTOLOGIC FEATURES.** Features associated with a worse prognosis include high mitotic count (more than 1 mitotic figure per 25 high-power fields), coagulative necrosis, absence of amyloid, and small cell variant.\(^4\)\(^7\)\(^4\), \(^4\)\(^7\)\(^5\), \(^4\)\(^8\)\(^6\), \(^5\)\(^2\)\(^6\), \(^5\)\(^3\)\(^3\), \(^5\)\(^2\)\(^7\), \(^5\)\(^3\)\(^3\) (Fig. 44–69).

**IMMUNOHISTOCHEMICAL FEATURES.** Calcitonin-poor medullary carcinomas fare worse than calcitonin-rich tumors.\(^5\)\(^3\)\(^4\)–\(^5\)\(^3\)\(^6\). The calcitonin content of the tumor may decrease at relapse. Strong expression of CD15/Leu-M1 is correlated with a higher risk of local recurrence and tumor mortality.\(^5\)\(^3\)\(^7\), \(^5\)\(^3\)\(^8\). Low expression of chromogranin B or Bcl-2 is associated with a more aggressive course.\(^5\)\(^3\)\(^9\), \(^5\)\(^4\)

**N-MYC EXPRESSION.** Increased expression of N-myc has been reported to be an unfavorable prognostic factor.\(^5\)\(^4\)

**TUMOR ANGIOGENESIS.** A high microvessel count is associated with a poorer prognosis.\(^5\)\(^4\)

**DNA PLOIDY.** Aneuploid tumors behave more aggressively than diploid ones do.\(^5\)\(^4\), \(^5\)\(^2\), \(^5\)\(^4\), \(^5\)\(^4\)

**Collision Tumor**

Collision tumors are neoplasms comprising two components: medullary carcinoma and a carcinoma of follicular cell derivation (follicular carcinoma or papillary carcinoma).\(^5\)\(^4\)–\(^5\)\(^5\)\(^2\). The two components can be intermingled, contiguous, or separate. Most probably represent coincidental occurrence of two neoplasms in proximity.

**Mixed Follicular-Parafollicular Carcinoma**

**CLINICAL CONSIDERATIONS**

Mixed follicular-parafollicular carcinoma, also known as differentiated carcinoma of intermediate type, is an uncommon tumor of the thyroid comprising closely intermingled follicular and parafollicular cells. The follicular cells secrete thyroglobulin, and the parafollicular cells secrete calcitonin or other hormone products such as somatostatin and neurotensin; on occasion, both hormone products can be produced by the same cell.\(^5\)\(^3\)\(^0\)–\(^5\)\(^3\)\(^5\). The patients have a median age of 48 years. They present with a thyroid nodule, and lymph node involvement is common (~75%). The mean size of the tumor is 3.7 cm.\(^5\)\(^6\)

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**FIGURE 44–68.** C cell hyperplasia, nodular type, associated with MEN 2A. A. Small nodular clusters of cells are found among the follicles, sometimes obliterating their lumina. B. A corresponding field stained for calcitonin clearly delineates the hyperplastic C cells.

**FIGURE 44–69.** Medullary carcinoma showing “aggressive” histologic features, such as diffuse cellular atypia, coagulative necrosis, and mitotic figures.

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DIAGNOSTIC CONSIDERATIONS

Microscopic Findings

Mixed follicular-parafollicular carcinomas are often completely or partially encapsulated. They show solid, nested, or cribriform growth with intermingled follicles. It is important not to mistake entrapped thyroid follicles in a conventional medullary carcinoma for a mixed follicular-parafollicular carcinoma. Cytologic comparison of the cells lining the follicles with those of the surrounding follicles is most helpful. The most definitive evidence of follicular differentiation is identification of follicles in metastatic deposits. Amyloid is occasionally present. On ultrastructural examination, neurosecretory granules, follicular cells, cells with intermediate features, and indifferent cells are identified.

Immunohistochemistry

Thyroglobulin immunoreactivity is characteristically seen in the follicular and cribriform areas and sometimes in the solid component; calcitonin immunoreactivity is most conspicuous in the solid areas (Fig. 44–71). Rare cells with dual hormone production can be identified in some cases.

Differential Diagnosis

This tumor histologically mimics the less well differentiated examples of follicular carcinoma or insular carcinoma. Immunohistochemical confirmation is therefore essential for diagnosis. However, the possibilities of entrapped benign follicles and diffusion of thyroglobulin from surrounding thyroid tissue have to be excluded.

Molecular Biology

Although it has been thought that mixed follicular-parafollicular carcinoma results from an uncommitted stem cell capable of differentiating toward both follicular cells and C cells, molecular studies have failed to confirm such a hypothesis. Studies of gene mutation, allelic loss, and clonal composition on microdissected tumor tissue show that the follicular and parafollicular components belong to different clones. Furthermore, the follicular component is often oligoclonal or polyclonal.

PROGNOSTIC CONSIDERATIONS

Mixed follicular-parafollicular carcinomas spread by both the lymphatic and hematogenous routes and are more aggressive than differentiated thyroid carcinomas. In the series of 18 patients reported by Ljungberg, 6 developed metastasis, and 4 died of the tumor 1 month to 15 years after surgery. According to the review of Papotti and colleagues, 56% of patients (N = 25) were alive with disease or dead of disease up to 10 years after diagnosis. The results contrast with those of otherwise typical med-
Endocrine System

**FIGURE 44–72.** Spindle epithelial tumor with thymus-like element. A. The tumor forms lobules demarcated by sclerotic septa, reminiscent of the architectural features of thymoma. B. Compact and reticulated fascicles of spindly cells merge imperceptibly into tubulopapillary epithelial structures (right field). This tumor type shows cytoarchitectural resemblance to synovial sarcoma.

**TABLE 44–15.** Clinicopathologic Features of Thymic and Related Branchial Pouch Tumors in the Thyroid

<table>
<thead>
<tr>
<th></th>
<th>Ectopic Thymoma</th>
<th>Spindle Epithelial Tumor with Thymus-like Element (SETTLE)</th>
<th>Carcinoma Showing Thymus-like Element (CASTLE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Middle age</td>
<td>Children and young adults, with a mean age of 18 y</td>
<td>Middle and old age, with a mean age of 49 y</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>F &gt; M</td>
<td>M &gt; F</td>
<td>M ≤ F</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Thyroid mass</td>
<td>Thyroid mass</td>
<td>Thyroid mass, with or without cervical node enlargement</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>Encapsulated tumor with jigsaw puzzle–type lobulation, composed of a variable admixture of pale-staining plump epithelial cells and small lymphocytes</td>
<td>The tumor is demarcated into incomplete lobules by sclerotic stroma. It is highly cellular, with compact interlacing to reticulated fascicles of spindle cells merging imperceptibly into epithelial structures that can be in the form of cords, tubules, or papillae. The spindle cells possess elongated bland-looking nuclei with fine chromatin; mitosis is infrequent. In some cases, discrete glandular structures lined by mucinous or respiratory-type epithelium are found. Lymphocytes are sparse or absent.</td>
<td>The tumor usually involves the lower pole of the thyroid and invades in pushing fronts. Variably sized, often smooth-contoured lobules of tumor cells are demarcated by desmoplastic fibrous stroma. The tumor cells have indistinct cell borders, vesicular nuclei, and prominent nucleoli or show a squamous or squamoid appearance. The tumor cells and fibrous septa show scanty to heavy infiltration by lymphocytes and plasma cells.</td>
</tr>
<tr>
<td><strong>Immunohistochemistry</strong></td>
<td>Epithelial component is cytokeratin positive, lymphoid component comprises mostly immature T cells (TdT–).</td>
<td>Both glandular and spindle cell components are cytokeratin positive. CD5 negative.</td>
<td>Cytokeratin and CD5 positive</td>
</tr>
<tr>
<td><strong>Clinical behavior</strong></td>
<td>Benign in all reported cases</td>
<td>Behavior is unpredictable, but a significant proportion of patients develop delayed distant metastasis (~70% with long-term follow-up), especially to the lungs. Even in the presence of metastasis, this indolent tumor can pursue a protracted course for many years before killing the patient.</td>
<td>Extrathyroidal extension is common. Regional lymph node metastasis occurs in about half of the cases. The tumor is indolent; most patients enjoy long survivals after surgery or radiation therapy, although occasional cases can pursue a more aggressive course.</td>
</tr>
</tbody>
</table>
ullary carcinoma shown on immunohistochemical staining to be thyroglobulin positive, which has a prognosis similar to or better than that of conventional medullary carcinoma.561

Thymic and Related Branchial Pouch Tumors of the Thyroid

CLINICAL CONSIDERATIONS

The occasional presence of sequestered thymic tissue or branchial pouch remnants in the thyroid gland may explain the occurrence of ectopic thymic tumors in the thyroid. These rare tumors include ectopic thymoma, spindle epithelial tumor with thymus-like element (SETTLE), and carcinoma showing thymus-like element (CASTLE); their clinicopathologic features are summarized in Table 44–15 (Figs. 44–72 to 44–74).562–581

DIAGNOSTIC CONSIDERATIONS

Ectopic thymoma is histologically identical to the mediastinal counterpart. For CASTLE, the morphologic features and expression of CD5 (a lymphocyte-associated marker commonly expressed in thymic carcinomas but not in neothymic carcinomas) strongly suggest that this is an intrathyroid thymic carcinoma.582–584 The histogenesis of SETTLE currently remains elusive.581

The most important reason for recognizing this group of neoplasms is that they are benign to low-grade malignant and should not be mistaken for lymphoma or the vastly more aggressive anaplastic carcinoma. Follicular dendritic cell tumor can also potentially be misdiagnosed as CASTLE.585

Intrathyroid Parathyroid Tumor

Because the parathyroid glands are close to or are embedded in the thyroid gland, parathyroid adenoma or carcinoma can occur as primary thyroid tumor.586, 587 These tumors are not uncommonly misdiagnosed as follicular adenoma, follicular carcinoma, or anaplastic carcinoma (Fig. 44–75A). A parathyroid origin should be suspected when there are clear cells, prominent delicate vasculature, and regimentation of nuclei along the vascular septa. The diagnosis can be confirmed by immunostaining for parathyroid hormone (Fig. 44–75B).

Malignant Lymphoma

CLINICAL CONSIDERATIONS

Presentation

Primary lymphoma of the thyroid accounts for approximately 5% of all thyroid cancers.588 It affects mostly adults, and there is a female predominance (male-to-female ratio = 1:2.5).589–590 Hashimoto's
thyroiditis and lymphocytic thyroiditis are recognized predisposing factors. Some patients present with a rapidly enlarging thyroid mass, which may be accompanied by dysphagia or hoarseness, simulating the presentation of anaplastic carcinoma. Others present with gradual enlargement of the thyroid gland or a slow-growing thyroid nodule. The tumor can be confined to the thyroid or show extrathyroidal extension. Regional lymph nodes are sometimes involved.

**Macroscopic Findings**

The lymphoma forms a noncircumscribed rubbery to soft mass in one or both lobes of the thyroid. The cut surfaces are slightly bulging, fleshy, light tan, and often homogeneous, with or without necrosis and hemorrhage. The size ranges from less than 1 cm to 19.5 cm.592, 600

**DIAGNOSTIC CONSIDERATIONS**

**Histologic Types**

Hodgkin’s lymphoma of the thyroid is extremely rare. Among non-Hodgkin’s lymphomas, diffuse large B cell lymphoma and extranodal marginal zone B cell lymphomas of mucosa-associated lymphoid tissue (MALT) type constitute almost all cases.589, 596, 599, 602 Exceptional examples of follicular lymphoma, intravascular lymphomatosis, and T cell lymphomas have been reported.599, 603–607

**Extranodal Marginal Zone B Cell Lymphoma of MALT Type**

The histologic features of extranodal marginal zone B cell lymphoma involving the thyroid are similar to those of this lymphoma type occurring elsewhere. Within the diffuse lymphomatous infiltrate, some reactive lymphoid follicles are often interspersed (Fig. 44–76A). The lymphoma cells are small to medium sized, resembling small lymphocytes, centrocytes, or monocyteoid B cells; the cellular composition is often mixed. Plasma cells, often in groups, are commonly found among the lymphoma cells. Invasion of the thyroid follicles by lymphoma cells results in formation of lymphoepithelial lesions and plugging of the follicular lumina by lymphoma cells589, 590, 608 (Fig. 44–77; see also Fig. 44–76B). Colonization of the reactive lymphoid follicles can result in a pattern reminiscent of follicular lymphoma (see Fig. 44–76C).590, 608, 609 Immunohistochemical staining shows expression of B markers; CD5, CD10, CD23, and cyclin D1 are negative.590, 607 Monotypic immunoglobulin can be demonstrated in the plasma cells in approximately 30% of cases.608, 609

**Diffuse Large B Cell Lymphoma With or Without a Component of Extranodal Marginal Zone B Cell Lymphoma**

Diffuse large B cell lymphoma accounts for more than 60% of all thyroid lymphomas. In some cases, there is a component of extranodal marginal zone B cell lymphoma, suggesting transformation from it.590, 591, 593, 599, 611, 612 The lymphomatous growth effaces the architecture of the thyroid tissue (Fig. 44–78A). The lymphoma cells are large, with round vesicular nuclei, distinct nucleoli, and a moderate amount of amphophilic cytoplasm that may sometimes be plasmacytoid (Fig. 44–78B). Mitotic figures and apoptotic bodies are common. Invasion of the thyroid epithelium to produce lymphoepithelial lesions is common, whereas plugging of follicular lumina by lymphoma cells is much less frequent.590, 592, 596, 597 Vascular invasion can sometimes be identified590, 602 (Fig. 44–78C). Immunohistochemical analysis shows positive staining for leukocyte common antigen and B markers.

**Differential Diagnosis**

**Hashimoto’s Thyroiditis.** When Hashimoto’s thyroiditis shows florid chronic inflammatory cell infiltrate, it can be difficult to tell whether there is superimposed extranodal marginal zone B cell lymphoma.
Thyroid and Parathyroid

FIGURE 44–76. Extranodal marginal zone B cell lymphoma of the thyroid. A. An intense lymphoid infiltrate characterizes lymphoma. B. The infiltrate comprises centrocyte-like cells with irregular nuclei, plasma cells, and plasmacytoid cells. The lymphoid cells infiltrate into the thyroid follicles (lymphoepithelial lesions) and characteristically plug up the lumina of the follicles. C. The preexisting reactive lymphoid follicles are colonized by monotonous-appearing lymphoma cells, resulting in a resemblance to follicular lymphoma.

FIGURE 44–77. Extranodal marginal zone B cell lymphoma of the thyroid. A. The lymphoma cells show prominent infiltration and expansion of the thyroid follicles to produce lymphoepithelial lesions (right field). B. Cytokeratin immunostaining of a corresponding field clearly shows follicular destruction and expansion by the neoplastic infiltrate.

Phoma. A dense lymphoid infiltrate, broad bands of centrocyte-like cells or clear cells, and prominent lymphoepithelial lesions are histologic features strongly favoring a diagnosis of lymphoma, which can be further supported by immunohistochemical studies to demonstrate sheets of B cells, aberrant coexpression of CD43, or light chain restriction.

Anaplastic Carcinoma. Features favoring a diagnosis of lymphoma are lack of cellular cohesion, plasmacytoid cytoplasm, presence of lymphoepithelial lesions, and plugging of follicular lumina by tumor cells. The diagnosis can be readily confirmed by immunohistochemical studies (see Table 44–1).
PROGNOSTIC CONSIDERATIONS

The 5-year survival rate for thyroid lymphoma is 50% to 79%.* The most important prognostic factors are tumor stage and histologic type.

**TUMOR STAGE.** Stage II E or higher is associated with a much worse prognosis than is stage I E disease; almost all mortalities are confined to the stage II E and higher group. Most studies have also shown extrathyroidal extension to worsen the prognosis, with a 5-year survival of 40% compared with 85% for intrathyroidal tumor.

**HISTOLOGIC TYPE.** Although some studies have not found the histologic type to correlate with prognosis, other studies have shown the prognosis of extranodal marginal zone B cell lymphoma of MALT type to be much superior to that of diffuse large B cell lymphoma. According to the series from the Armed Forces Institute of Pathology, none of 30 patients with pure extranodal marginal zone B cell lymphoma died of lymphoma, whereas 20 (26%) of 77 patients with a diffuse large B cell lymphoma component died of the disease. There is no difference in outcome for diffuse large B cell lymphoma with or without an identifiable component of extranodal marginal zone B cell lymphoma, similar to the findings in other mucosal sites such as the stomach, although conflicting results are reported by Skacel and coworkers.

**AGE.** Advanced age (older than 60 to 65 years) has been shown in some studies to be associated with a worse prognosis.

**TUMOR SIZE.** A large tumor (>10 cm) is reported to be associated with a worse prognosis according to some but not all studies.

**VASCULAR INVAsION.** Vascular invasion is associated with a worse prognosis.

**HISTOLOGIC FEATURES.** High mitotic count and high apoptotic count are associated with a worse prognosis. Tumor necrosis is associated with a worse prognosis according to one study but not another.

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**Plasmacytoma of the Thyroid**

Plasmacytoma of the thyroid is uncommon, and the prognosis is excellent (Table 44–16). The neoplastic infiltrate comprises a monotonous population of mature-looking, immature-looking, pleomorphic, or plasmablastic plasma cells. It has been suggested that thyroid plasmacytoma may represent an ex-

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*References 589–591, 593, 600, 611, 614, 615.
Thyroid and Parathyroid

### Extramarginal Zone B Cell Lymphoma

**TABLE 44–16. Comparison Between Plasmacytoma and Malignant Lymphoma of Thyroid**

<table>
<thead>
<tr>
<th></th>
<th>Plasmacytoma</th>
<th>Malignant Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>Slight male predominance (male-female 1.4:1)</td>
<td>Female predominance (male-female 1.2:5)</td>
</tr>
<tr>
<td><strong>Age (mean)</strong></td>
<td>58 y</td>
<td>62 y</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Usually slowly growing thyroid mass</td>
<td>Rapidly or slowly growing thyroid mass</td>
</tr>
<tr>
<td><strong>5-year survival</strong></td>
<td>More favorable: 85%</td>
<td>Less favorable: overall - 60%, but much more favorable for extranodal marginal zone B cell lymphoma of MALT type</td>
</tr>
</tbody>
</table>

### Langerhans Cell Histiocytosis (Histiocytosis X)

**Clinical and Prognostic Considerations**

The thyroid gland can be involved by Langerhans cell histiocytosis as the sole lesion or as part of disseminated disease. The patients show a wide age range (median, 37 years), and there is no sex predilection.623–628 The disease presents either as an incidental finding in the thyroid removed for other reasons or at autopsy or as a large thyroid. The prognosis is excellent for disease limited to the thyroid but poor for patients with disseminated disease.

**Diagnostic Considerations**

The thyroid is infiltrated by Langerhans cells in a patchy or extensive pattern, and there can be extrathyroidal extension. The Langerhans cells possess grooved or highly contorted nuclei, thin nuclear membrane, delicate chromatin, and moderate amount of eosinophilic cytoplasm. They can infiltrate and destroy the thyroid follicular epithelium. There are variable numbers of admixed eosinophils, sometimes with formation of eosinophil abscesses. The diagnosis should be confirmed by positive immunostaining for S-100 protein and CD1a.

### Angiosarcoma

**Clinical and Prognostic Considerations**

**Presentation**

Angiosarcoma of the thyroid is extremely aggressive, and metastatic spread is common, such as to the lung, pleura, lymph node, adrenal, gastrointestinal tract, and bone.629 The median survival is only 3.5 months, and the rare survivors all have small tumors lacking extrathyroidal extension.630

**Macroscopic Findings**

The tumor is usually solitary and infiltrative, with a fleshy gray-tan appearance punctuated by areas of necrosis and hemorrhage. There can be a central cavity filled with coagulated or fluid blood.629

**Diagnostic Considerations**

Microscopic Findings

Angiosarcomas of the thyroid are often poorly differentiated. The tumors grow in solid sheets and irregular anastomosing channels that contain blood. The tumor cells often exhibit significant nuclear pleomorphism; some of them have cytoplasmic vacuolation. Some cases can show epithelioid morphologic features, with polygonal tumor cells and abundant eosinophilic hyaline cytoplasm.630–632 (Fig. 44–79).

**Immunohistochemistry**

A diagnosis of angiosarcoma has to be substantiated by positive immunohistochemical staining for?
endothelial markers, such as factor VIII–related antigen, CD31, and CD34. Some cases exhibit immunoreactivity for cytokeratin.

Differential Diagnosis

Because anaplastic carcinoma can exhibit angiosarcoma-like morphologic features focally (angioma-toid carcinoma), distinction between anaplastic carcinoma and pure angiosarcoma can be difficult. The distinction is not too important from a clinical point of view, however, because both are highly aggressive neoplasms with similar survival figures.

Fine-needle aspiration changes such as reactive vascular proliferation or pseudoangiosarcomatous change in the damaged thyroid follicular epithelium can mimic angiosarcoma.

Sclerosing mucoepidermoid carcinoma with eosinophilia can exhibit a pseudoangiomatous pattern, focally mimicking angiosarcoma.

Solitary Fibrous Tumor

Solitary fibrous tumor can rarely occur as a primary thyroid tumor. All patients have remained well after surgical excision.

The histologic features are identical to those of the pleural counterpart. The tumor is well circumscribed, although some thyroid follicles can be entrapped in the periphery. It shows alternating hypercellular and hypocellular areas, with haphazardly distributed bland-looking spindly or stellate cells intimately intermingled with delicate to thick collagen fibers (Fig. 44–80). A pericytomatous vascular pattern is common. The tumor cells are immunoreactive for CD34 but are negative for cytokeratin and S-100 protein.

Other Mesenchymal Tumors

Smooth muscle tumors of the thyroid gland are rare, and most are malignant. Leiomyomas are encapsulated and confined to the thyroid gland, with no cellular atypia, necrosis, or mitotic activity. Leiomyosarcomas often affect older patients and are often larger. On histologic examination, they exhibit cellular pleomorphism, mitotic activity, necrosis, hemorrhage, invasive growth, and extrathyroidal extension. The diagnosis has to be confirmed by immunohistochemical or ultrastructural studies, especially for distinction from anaplastic carcinoma. These tumors are aggressive; most patients die within 2 years. Metastases to the lungs and other sites develop early in the course of disease.

Rare mesenchymal tumors reported to occur in the thyroid include hemangioma, lymphangioma, peripheral nerve sheath tumors, fibrosarcoma, liposarcoma, chondrosarcoma, osteosarcoma, and follicular dendritic cell sarcoma.

Paraganglioma

CLINICAL CONSIDERATIONS

Rarely, paragangliomas can occur within the thyroid gland, probably from the inferior laryngeal paraganglia. There is a female predominance, and most patients are aged between 40 and 60 years. The patients present with a neck mass. The tumors are circumscribed or can extend into the adjacent larynx or trachea. All patients have remained well after surgical excision.

DIAGNOSTIC CONSIDERATIONS

The tumors usually have a size of approximately 2 cm. Alveolar packets of ovoid cells with finely granular cytoplasm are surrounded by an inconspicuous layer of sustentacular cells (Fig. 44–81; see Table 44–1). The stroma is typically richly vascularized.
ized. Tumors with enlarged, hyperchromatic, or bizarre nuclei can potentially be misdiagnosed as a malignant neoplasm. Other major differential diagnoses are medullary carcinoma and hyalinizing trabecular adenoma.

Teratoma

CLINICAL AND PROGNOSTIC CONSIDERATIONS

There are two distinct age peaks for the occurrence of thyroid teratomas. The first and higher peak is in the newborn period to the age of 2 years; the second smaller peak is in older children and adults, mostly between the ages of 20 and 50 years. These tumors are more common in females than in males. Most patients present with a large thyroid or neck mass, which may be accompanied by respiratory difficulties.

Thyroid teratomas occurring before the age of 2 years usually pursue a benign course after surgical excision, although some patients may die of respiratory obstruction. Thyroid teratomas occurring in adults are more likely to be malignant, with local recurrence, cervical lymph node metastasis, and pulmonary metastasis. Nonetheless, long-term survival is possible with aggressive treatment including chemotherapy and surgery.

Diagnostic Considerations

The teratomas are most often immature, although some may be of the mature type. Tissues from the various germ layers are present, and neuroectodermal tissue may be prominent. The presence of neural tissue provides a strong point against the differential diagnosis of anaplastic carcinoma.

Tumors occurring in neonates and infants are often immature (grade 1 or 2), but they are sometimes mature. Those occurring in adults most often show grade 3 immaturity (“malignant”).

Metastatic Malignant Neoplasms in Thyroid

Because the thyroid gland is rich in blood vessels and lymphatics, it is not infrequently involved by metastatic cancer in patients with carcinoma, most commonly due to pulmonary carcinoma (usually adenocarcinoma), breast carcinoma, malignant melanoma, and renal cell carcinoma. The metastatic deposits are often small and asymptomatic and are associated with obvious widespread metastatic tumor elsewhere.

Renal cell carcinoma can metastasize to the thyroid gland as the initial manifestation of the tumor or as the first evidence of relapse many years after resection of the renal primary. It can potentially be misdiagnosed as primary clear cell tumor of the thyroid, but it can be recognized by the presence of multiple tumor nodules, distinct cell membranes, water-clear cytoplasm, sinusoidal vascular pattern, fresh hemorrhage in the glandular lumina, and negative immunostaining for thyroglobulin.

**TABLE 44–17. Contents of the Final Surgical Pathology Report**

*Specimen type/operation procedure*
- Diagnosis
- Histologic type, and variant if applicable
- Histologic grade, if relevant
- Other tumor features
  - Tumor location (right lobe, left lobe, isthmus)
  - Tumor size
  - Solitary or multicentric
  - Encapsulated or nonencapsulated
  - Capsular invasion (absent, present, extensive)
  - Vascular invasion (absent, present, extensive)
  - Extrathyroidal extension (structures invaded, if applicable)
- Mitotic activity
- Surgical margins: free, close to surgical margin (specify distance), or margin involved (specify site)
- Non-neoplastic thyroid: normal, nodular goiter, lymphocytic thyroiditis, Hashimoto’s thyroiditis, atrophy, fibrosis
- Lymph nodes
  - Number of lymph nodes found, and their location (level)
  - Number of involved lymph nodes
  - Size of largest metastatic deposit
  - Presence or absence of extracapsular extension

In the surgical pathology report of thyroid excision specimens for tumors, it is important to include all information relevant for staging and prognostication in addition to the diagnosis.

**NON-NEOPLASTIC LESIONS**

Incidental and Insignificant Findings in the Thyroid Gland

Skeletal muscle fibers may be intermingled with the thyroid follicles in the region beneath the thyroid capsule. Adipose cells and hyaline cartilage rest are occasionally found incidentally in the thyroid gland. Ectopic parathyroid tissue, ectopic thymic tissue, and ectopic salivary gland tissue can also sometimes be found within the thyroid. Rarely, there can be columnar ciliated epithelium replacing part of the follicular epithelium. The thyroid follicular epithelium can also undergo squamous metaplasia or oncocytic metaplasia.
Crystals are commonly found in the colloid of the thyroid follicles. They are most commonly seen in nodular goiters, but they can be seen in various non-neoplastic and neoplastic lesions of the thyroid. The crystals vary in geometric shapes and are most often composed of calcium oxalate.672–674

Solid cell nests, common incidental findings in the thyroid, are often detected at low-magnification scanning as a blue-staining cellular focus.671, 675–679 They appear as a small collection of solid epithelial islands resembling transitional epithelium (Fig. 44–82). Some islands can show cystic change and contain mucinous substance. The epithelial cells possess oval grooved nuclei. The solid cell nests are believed to be remnants of ultimobranchial bodies, and many scattered C cells are associated with these nests.508, 677

Palpation granuloma (palpation thyroiditis) is a common incidental finding of no consequence and is believed to result from the mechanical trauma of palpation.680 One or two thyroid follicles appear to have ruptured and are replaced by histiocytes and multinucleated histiocytes. They are not associated with fibrous scarring.

Cysts
The most common cyst of the thyroid gland is degenerate cyst resulting from cystic degeneration of nodular goiter. Cystic degeneration can also occur in various thyroid tumors, such as follicular adenoma. The cystic variant of papillary carcinoma is characterized by the presence of a prominent cystic component lined by neoplastic cells.

Thyroglossal duct cyst represents cystic dilatation of the persistent thyroglossal duct. The patient usually present in the first 3 decades of life with a swelling in the midline of the neck that typically moves upward with swallowing. The cyst is usually situated below the hyoid bone but above the thyroid isthmus. When it is complicated by infection, there can be tenderness and pain. Histologic examination shows the cyst to be lined by respiratory or stratified squamous epithelium. The wall consists of fibrous tissue, which may be infiltrated by chronic inflammatory cells. Mucous glands can be present in the wall. Some thyroid follicles are often seen in this setting.671–673, 681–683

Multiple branchial cleft–like cysts are rarely found in association with Hashimoto’s thyroiditis. The cysts are lined by squamous or respiratory epithelium and are surrounded by a band of dense lymphoid infiltrate.684 Postulated pathogenetic mechanisms include metaplastic and cystic change of the thyroid follicles in the setting of thyroiditis and origin from developmental rests.684, 685

Thyroid Tissue in the Lateral Neck
LATERAL ABERRANT THYROID
Thyroid tissue occurring in the lateral neck separate from the thyroid gland has often been referred to as lateral aberrant thyroid. This can occur in several circumstances: 1) sequestered nodule in nodular goiter; the nodule may still be connected by a narrow strand of tissue to the main gland; 2) regrowth of thyroid tissue that has been implanted in the soft tissues of the neck from prior surgery; and 3) sequestered thyroid tissue involved by Hashimoto’s thyroiditis or Graves’ disease. It is most important, however, to rule out the possibility of metastatic thyroid carcinoma (most commonly papillary carcinoma) in cervical lymph nodes.

FIGURE 44–82. Solid cell nest of the thyroid. A. Small, blue-staining islands of epithelium are disposed in a stellate configuration among the thyroid follicles. Occasional epithelial islands show cyst formation with secretion. B. The epithelial cells resemble transitional epithelium, and nuclear grooves are common.
THYROID INCLUSIONS IN CERVICAL LYMPH NODE

Benign thyroid follicles can rarely occur in cervical lymph nodes. Nonetheless, this belief is not universally accepted; some investigators consider all thyroid tissues within lymph nodes to represent metastasis from clinically undetected thyroid carcinoma. Because the distinction between benign thyroid inclusions and metastasis from an occult thyroid carcinoma can be extremely difficult owing to the almost normal histologic appearances of some thyroid carcinomas, strict criteria must be used in the diagnosis of benign thyroid inclusions:

- They consist of only a small conglomerate of thyroid follicles.
- They are limited to the periphery of one or two lymph nodes.
- Nuclear features of papillary carcinoma are lacking, that is, nuclei are not enlarged, with fine chromatin and inconspicuous nucleoli.
- Psammoma bodies are absent.
- There is lack of a desmoplastic reaction.

METASTATIC THYROID CARCINOMA IN CERVICAL LYMPH NODE

Papillary carcinoma commonly metastasizes to lymph nodes, whereas follicular carcinoma rarely does. Cervical lymph node metastasis is sometimes the first clinical manifestation of an occult papillary thyroid carcinoma—the thyroid primary is almost always located on the ipsilateral side. The node can be cystic or show sudden enlargement because of hemorrhage. On histologic examination, a diagnosis of metastatic papillary thyroid carcinoma can be obvious because of presence of recognizable lymph node tissue and papillary carcinoma. However, in some cases, the cyst wall is formed by dense fibrous tissue with scanty lymphoid tissue underneath and lined by attenuated nondescript cells, and thus it may be mistaken for a branchial cyst (Fig. 44–83). Careful search may be required to uncover small papillae projecting into the lumen or some elongated follicles in the wall, with the cells exhibiting the typical nuclear features of papillary carcinoma (Fig. 44–83, C). A diagnosis can be readily confirmed by positive immunostaining for thyroglobulin.

MIMICKER OF METASTATIC THYROID CARCINOMA IN CERVICAL LYMPH NODE

A sequestered thyroid nodule involved by florid Hashimoto’s thyroiditis can potentially be mistaken for metastatic thyroid carcinoma in lymph node because the lymphoplasmacytic infiltrate with germinal center formation imparts a lymph node-like appearance and the thyroid follicles can exhibit nuclear atypia or pallor. However, subcapsular sinuses, a hallmark of lymph node, are lacking.

FIGURE 44–83. Cystic metastasis of papillary thyroid carcinoma in lymph node. A. This cyst excised from the lateral neck can be mistaken for a developmental cyst because of its innocuous appearance. The wall is formed by fibrous tissue with only focal lining by attenuated epithelium. B. In areas, more plump and slightly pseudostratified epithelial cells are seen lining the cyst. C. On careful search, a small focus with papillary structures is found, clinching the diagnosis of metastatic papillary carcinoma.
Thyroiditis

ACUTE THYROIDITIS

Acute thyroiditis is rare. It is caused by bacterial infection, such as Staphylococcus, Streptococcus pyogenes, and Haemophilus influenzae. The patients are often immunosuppressed, or there is a regional infective focus, such as phlegmon sinus fistula. They present with painful swelling of the thyroid and fever. Histologic examination shows polymorph in filtration associated with destruction of the thyroid follicles.

INFECTIOUS GRANULOMATOUS THYROIDITIS

Granulomatous inflammation can be produced in the thyroid by some infective processes, such as tuberculosis, actinomycosis, and fungal infection. The patients are often immunocompromised. Granulomas with or without caseation are found in the thyroid, although they can be poorly formed in immunocompromised hosts. The main differential diagnoses are sarcoidosis and de Quervain’s thyroiditis.

DE QUERVAIN’S THYROIDITIS (SUBACUTE GRANULOMATOUS THYROIDITIS)

de Quervain’s thyroiditis is thought to be caused by viral infection, although no specific virus has been incriminated. The main features are summarized in Table 44–18. In contrast to the randomly distributed granulomas in infectious granulomatous thyroiditis, the granulomas in de Quervain’s thyroiditis are centered around residual colloid (Fig. 44–84).

<table>
<thead>
<tr>
<th>TABLE 44–18. Major Types of Thyroiditis</th>
</tr>
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<tbody>
<tr>
<td><strong>Hashimoto’s Thyroiditis</strong></td>
</tr>
<tr>
<td><strong>Nature of disease process</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
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<tr>
<td><strong>Presentation</strong></td>
</tr>
<tr>
<td><strong>Pattern of involvement of the thyroid gland</strong></td>
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<tr>
<td><strong>Antithyroid antibodies in serum</strong></td>
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<td><strong>Major histologic features</strong></td>
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<tr>
<td><strong>Clinical outcome</strong></td>
</tr>
</tbody>
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HASHIMOTO’S THYROIDITIS

Clinical Considerations

Hashimoto’s thyroiditis, also known as struma lymphomatosa, is the prototype of autoimmune thyroiditis. The salient clinical features are summarized in Table 44–18.689–691 There is an increased risk for development of malignant lymphoma and papillary carcinoma. The thyroid is usually symmetrically enlarged, with a firm or rubbery consistency. The cut surface is tan or tan-brown, with a homogeneous or vaguely lobulated appearance.

Diagnostic Considerations

On histologic examination, there is heavy infiltration of the interstitium and some thyroid follicles by lymphocytes and plasma cells. Reactive lymphoid follicles are often present. There is loss of thyroid follicles, and the remaining ones are often small. The thyroid follicular epithelium shows extensive oncocytic (Hürthle cell) change and can have enlarged or pale nuclei (Fig. 44–85). Those examples with heavy lymphoplasmacytic infiltration can be difficult to distinguish from extranodal marginal zone B cell lymphoma or plasmacytoma arising in Hashimoto’s thyroiditis; see the relevant sections for distinguishing features.

Nodular Hashimoto’s thyroiditis refers to the presence of superimposed nodules comprising closely packed small follicles or trabeculae, most of which are lined by Hürthle cells (Fig. 44–86). The multiplicity of nodules and the frequent presence of isolated pleomorphic nuclei can potentially lead to an erroneous diagnosis of Hürthle cell carcinoma. Vascular invasion is absent, however.

The fibrosing variant accounts for 12.5% of all cases of Hashimoto’s thyroiditis. It is defined by the presence of broad bands of dense hyaline fibrous tissue occupying more than one third of the thyroid gland, separating islands of thyroid parenchyma exhibiting typical histologic features of Hashimoto’s thyroiditis (oxyphilic change, follicular cell damage, and lymphoid infiltration)692 (Fig. 44–87). Squamous metaplasia in the thyroid follicles is common. Clinically, the thyroid gland feels firm or hard, and pressure symptoms can be present. The antithyroid antibody titers are often high. Clinical evidence of hypothyroidism is present in approximately 50% of cases.

LYMPHOCYTIC THYROIDITIS AND PAINLESS THYROIDITIS

The term lymphocytic thyroiditis is often applied when there is diffuse or multifocal lymphoplasmacytic infiltration in the absence of oncocytic change in the thyroid follicular epithelium. There is no significant atrophy of the thyroid follicles. However, during the active phase, there can be follicular destruction and hyperplastic change in the follicles.
The disease is believed to have an autoimmune basis. The clinical counterpart is variously known as painless thyroiditis, silent thyroiditis, juvenile thyroiditis, or postpartum thyroiditis, depending on the clinical scenario. In most patients, there is transient hyperthyroidism followed by hypothyroidism and spontaneous evolution. Some patients present with thyroid swelling. The entire clinical course usually lasts less than 1 year. Only rarely do the patients eventually become hypothyroid.

**RIEDEL'S THYROIDITIS**

The main features of Riedel’s thyroiditis are summarized in Table 44–18 (Fig. 44–88). The clinical impression is usually that of thyroid cancer because of the presence of a stony hard thyroid mass. Riedel’s thyroiditis is rare; for unknown reasons, its incidence has decreased dramatically during the past few decades. Although steroid treatment may sometimes be effective, surgical excision is usually required to relieve the pressure symptoms and to exclude malignancy. The most important differential diagnosis is paucicellular variant of anaplastic carcinoma because of marked differences in outcome (see “Anaplastic Carcinoma”). Riedel’s thyroiditis can also be distinguished from fibrosing Hashimoto’s thyroiditis by the features of extrathyroidal extension of the fibroproliferative process, presence of phlebitis, and relatively normal surviving thyroid tissue. Riedel’s thyroiditis can also be distinguished from fibrosing Hashimoto’s thyroiditis by the features of extrathyroidal extension of the fibroproliferative process, presence of phlebitis, and relatively normal surviving thyroid tissue.

**FOCAL LYMPHOCYTIC THYROIDITIS**

(FOCAL LYMPHOCYTIC THYROIDITIS)

Focal lymphoid infiltration in the thyroid gland is a fairly common incidental finding in thyroidectomy specimens and at autopsy. This is also a common finding in the vicinity of various thyroid tumors, especially papillary carcinoma. The lymphoid cells tend to be localized to the interlobular areas, with little evidence of destruction of thyroid follicles. The pathogenesis is unknown, but the lesion is probably of no consequence.

**MULTIFOCAL FIBROSING THYROIDITIS**

Multifocal fibrosing thyroiditis is a peculiar form of thyroiditis characterized by many microscopic foci of stellate cellular fibrosis with some entrapped thyroid follicles, mimicking the low-magnification architecture of papillary microcarcinoma. The pathogenesis is not known.

**Graves’ Disease**

**CLINICAL CONSIDERATIONS**

Graves’ disease is the most common cause of hyperthyroidism. It is an organ-specific autoimmune disease produced by thyroid-stimulating antibodies...
thyrotropin receptor antibody, which stimulates hormone production, and thyroid growth—stimulating immunoglobulin, which promotes parenchymal hyperplasia.

Graves’ disease mostly affects adults in their 20s and 30s with a marked female predominance. The patients present with hyperthyroidism, diffuse swelling of the thyroid gland, and exophthalmos.

**DIAGNOSTIC CONSIDERATIONS**

Thyroid gland involved by Graves’ disease is typically diffusely and symmetrically enlarged, with a meaty quality on the cut surface. An accentuated lobular architecture is evident histologically. The follicles are mostly medium sized. The lining columnar cells form papillary projections into the luminal spaces, with some lumina appearing star shaped (Fig. 44–89). The nuclei often show some variation in size, and some can appear pale. Colloid is scanty, pale, and scalloped. There is a patchy light lymphoid infiltrate in the interstitium.

The typical histologic features are now rarely seen in surgical pathology practice because the patients have been treated with drugs to control the hyperthyroidism before the operation. With such treatment, the follicles show greater variation in size, and some follicles may appear involuted. The follicular epithelium becomes less tall, and colloid can often be seen. Nonetheless, the hyperplastic appearance with papillary infoldings is often still evident in focal areas.

**Nodular Goiter**

**CLINICAL CONSIDERATIONS**

Presentation

Nodular goiter is the most common thyroid lesion encountered in surgical pathology practice. It is characterized by nodule formation in the thyroid, with hyperplastic as well as involuted areas.

The endemic form (endemic goiter) is due to iodine deficiency in the diet or water and hence a low production of thyroid hormones, leading to compensatory increase in thyroid-stimulating hormone, which stimulates the thyroid follicles to undergo hyperplasia (parenchymatous goiter). Subsequently, some follicles undergo involution with massive accumulation of colloid (diffuse colloid goiter), and nodule formation supervenes. The sporadic form of nodular goiter is of unknown pathogenesis.

The patients usually present with an enlarged multinodular thyroid gland, which may be accompanied by compression symptoms. Extension into the mediastinum can occur, producing additional symptoms related to the mediastinal location. There can be pain and sudden enlargement of the thyroid gland due to hemorrhage. Some patients present with a solitary thyroid mass, but additional nodules are often evident on ultrasound examination. Most patients are euthyroid, but rare patients may have hyperthyroidism (toxic nodular goiter).

**Macroscopic Findings**

The thyroid gland is enlarged, sometimes to an enormous size. The external contour is often distorted. There are multiple nodules, which often lack fibrous capsules (Fig. 44–90A). The nodules exhibit variable appearances ranging from colloid-rich with brown color and glistening quality to solid, tan, and fleshy. Secondary changes such as fibrosis, hemorrhage, cystic degeneration, and calcification are common. In some cases, there is an apparently solitary nodule surrounded by a thin capsule, making distinction from follicular neoplasm difficult (Fig. 44–90B). Careful examination of the background thyroid often reveals multiple vague nodules with a colloid-rich quality.

**DIAGNOSTIC CONSIDERATIONS**

**Microscopic Findings**

In most cases, multiple, variably sized nodules are evident. The different nodules often exhibit different degrees of cellularity and variations in follicle size (Fig. 44–91).

The typical nodule comprises large follicles lined by regular low cuboidal epithelium and distended with colloid (colloid nodule) (Fig. 44–92). There are frequently some broad papillae projecting into the large follicles, so-called Sanderson polsters (Fig. 44–93). In contrast to papillary carcinoma, the papillae have broad edematous cores and are lined by columnar cells with dark round nuclei regularly aligned at the base of the cells. Smaller “daughter” follicles are present in the cores of these papillae. Hemosiderin-laden macrophages are commonly found within the follicular lumina or in the interstitium, providing evidence of prior hemorrhage. Patchy fibrosis and calcification are common (Fig. 44–94A). Some areas may undergo infarction, with only “ghost” follicles being identifiable. There can be
interspersed cysts comprising a fibrous wall with or without lining by attenuated epithelium (Fig. 44–94B). The lining epithelium and entrapped follicles in the fibrous wall may show reactive atypia or squamous metaplasia. In some cysts, collections of residual large follicles project into the cyst lumen.

Some nodules can be highly cellular, being composed of small follicles and trabeculae (Fig. 44–95; see also Fig. 44–92C). The nuclei of the thyroid epithelial cells appear uniform or atypical. Oncocytic, clear cell, and signet ring change can occur. There can also be areas resembling hyalinizing trabecular adenoma.57 These cellular nodules (adenomatoid nodules) can be difficult to distinguish from follicular neoplasm or even insular carcinoma. When the follicles exhibit large pale nuclei, the additional differential diagnosis of papillary carcinoma may be raised; these follicles show gradual transition with the normal or benign follicles, and they lack the sharp demarcation from the non-neoplastic follicles as seen in papillary carcinoma.

**Differential Diagnosis**

**FOLLICULAR ADENOMA.** The distinction between nodular goiter presenting as a solitary nodule and follicular adenoma can be difficult and sometimes arbitrary. The distinction is not critical, however, as long as there is no capsular or vascular invasion. In general, an adenoma is solitary, is completely enveloped by a fibrous capsule, is expansile and produces a compression effect on the surrounding tissues, and shows cytoarchitectural features dissimilar from the surrounding parenchyma. **FOLLICULAR CARCINOMA.** See earlier. **PAPILLARY CARCINOMA.** See earlier. **INSULAR CARCINOMA.** See earlier. **DYSHORMONOGENESIS.** For young patients not living in areas of endemic goiter and presenting with large multinodular goiter, the possibility of dyshormonogenesis should be entertained.

**FIGURE 44–90.** Nodular goiter. A. In this case, multiple nodules with a glistening colloid (gelatinous) quality are evident. B. In this case, the nodule is apparently solitary and enveloped by a thin capsule. It has a variegated appearance with colloidlike areas, small cysts, hemorrhagic areas, fibrosis, and calcification.

**FIGURE 44–91.** Nodular goiter. Multiple nodules with variable cellularity and follicle sizes are seen. A. In this case, most follicles are large. B. In this case, there are large as well as small follicles.
Dyshormonogenetic Goiter

**CLINICAL CONSIDERATIONS**

Dyshormonogenesis is a form of familial goiter caused by genetic enzyme defects in thyroid hormone synthesis. The patients usually present with congenital hypothyroidism or early-onset goiter. However, some patients may not present until middle age. The enlarged multinodular thyroid can weigh up to 600 g. There can be a slightly increased risk for thyroid carcinoma.

**DIAGNOSTIC CONSIDERATIONS**

**Microscopic Findings**

The most salient feature of dyshormonogenetic goiter is the presence of highly cellular nodules ex-
FIGURE 44–94. Nodular goiter. A. Nodular goiter showing patchy fibrosis, with infiltration of histiocytes and chronic inflammatory cells. B. Cystic degeneration in nodular goiter. The cyst has a fibrous wall lined by attenuated epithelium.

FIGURE 44–95. Nodular goiter with cellular nodules (adenomatoid nodules). A. The follicles are small, and distinction from follicular neoplasm can be difficult. B. A solid appearance can also be produced.

FIGURE 44–96. Dyshormonogenesis. A. A multinodular pattern is evident. B. The follicles are often small with no or scanty colloid. There are interspersed cells with large hyperchromatic nuclei.
hibiting a variety of architectural features (Fig. 44–96A). The nodules can show a microfollicular, trabecular, solid, papillary, insular, or mixed growth pattern. Follicles, when present, are small and frequently devoid of colloid. There are commonly interspersed cells with large hyperchromatic nuclei or vesicular nuclei. Cells with hyperchromatic pleomorphic nuclei are most commonly found in the interstitial tissue in association with streaming of follicles. There is often prominent fibrosis between the nodules. Because of the presence of multiple highly cellular nodules, cellular atypia, and pseudoinfiltrative pattern created by the fibrosis, dyshormonogenetic goiter can be mistaken for follicular carcinoma.706

**Differential Diagnosis**

**FOLLICULAR CARCINOMA.** In contrast to follicular carcinoma, the different nodules exhibit different degrees of cellularity and architectural features, and genuine vascular invasion is lacking.707

**NODULAR GOITER.** In contrast to nodular goiter, there is scanty colloid, less degenerative change, presence of prominent nuclear atypia, and absence of normal interstitial tissue.706

**THYROID TREATED WITH RADIOACTIVE IODINE.** The thyroid glands in patients treated with radioactive iodine can be indistinguishable from dyshormonogenetic goiter histologically. The clinical history is essential for making the distinction.

**Fine-Needle Aspiration–Associated Changes in the Thyroid Gland**

Fine-needle aspiration of the thyroid gland can lead to a variety of histologic changes, some mundane and some potentially causing diagnostic problems.101, 106

**TISSUE INJURY**

In the track of the needle pass, a linear hemorrhagic track or an irregularly shaped hematoma is formed (Fig. 44–97A). The thyroid follicles in the vicinity can undergo partial disruption or necrosis.

**REPARATIVE CHANGE**

Organization of the hematoma and damaged tissue leads to granulation tissue formation, chronic inflammatory cell infiltration, hemosiderin deposition, and subsequently fibrous scarring.

**TISSUE INJURY OR REPAIR-ASSOCIATED REACTIVE CHANGES THAT MAY LEAD TO A MISDIAGNOSIS OF MALIGNANCY**

The stromal reparative reaction to the trauma of fine-needle aspiration can be exuberant. Active-looking plump spindly myofibroblasts are admixed with thin-walled blood vessels, histiocytes, and hemosiderin (Fig. 44–97B). The lesion can be mistaken for Kaposi’s sarcoma or other sarcomas; the term post–fine-needle aspiration spindle cell nodule has also been applied to this lesion.708

Tumor infarction complicating fine-needle aspiration can be accompanied by exuberant fibrogranulation tissue that begins in the peripheral zone and gradually extends inward. This reparative process can potentially be mistaken for anaplastic carcinoma, attributable to the poorly defined contour of the lesion and reactive atypia of the spindly cells (Fig. 44–98).

Organization of the fine-needle aspiration–associated hematoma can result in an exuberant, Masson tumor–like reaction, which can potentially be mistaken for angiosarcoma.709

The follicles around the areas of tissue injury or infarction can exhibit reactive atypia, such as nuclear enlargement and prominent nucleoli, and can potentially be mistaken for high-grade carcinoma. These reactive follicles can show anastomosis and intrafol-
licular hemorrhage, resulting in an angiosarcoma-like appearance106, 709, 710 (Fig. 44–99).

TUMOR IMPLANTATION IN NEEDLE TRACK
At the site of needle puncture of the fibrous capsule of a thyroid neoplasm, some tumor islands can herniate into the capsule. This phenomenon (capsular rupture) can potentially lead to an erroneous interpretation of capsular invasion (see Fig. 44–22 and Table 44–8).

TUMOR INFARCTION
Among the various types of thyroid tumors, Hurthle cell tumor is particularly prone to undergo infarction after fine-needle aspiration, probably because of the high energy requirements of the mitochondria-rich tumor cells104 (Fig. 44–100). Papillary carcinoma also occasionally undergoes infarction after fine-needle aspiration (see Fig. 44–98). It can be difficult to arrive at a definitive diagnosis in the excision specimen if the tumor shows complete infarction.

Amyloid Goiter
The thyroid gland is a common site for deposition of amyloid in systemic amyloidosis, but this usually does not result in enlargement of the thyroid or clinical symptoms. However, on occasion, amyloid deposits are so extensive that the patients present with a nontender, rapidly enlarging neck mass, which may be associated with dysphagia, dyspnea, and hoarseness. There is usually no clinical or biochemical evidence of thyroid dysfunction.711, 712

On histologic examination, amyloid is deposited between and around the follicles, accompanied by
atrophy of the follicles (Fig. 44–101). Amyloid is also deposited in the blood vessel walls. Adipose cells are commonly interspersed within the amyloid. The amyloid can be of AA or AL type.

Black Thyroid

Black thyroid is an uncommon but dramatic condition caused by administration of minocycline, a form of tetracycline. There are no clinical symptoms. On gross evaluation, the thyroid is black. On histologic examination, the follicular cells contain fine, dark brown granules, and ultrastructural analysis shows the pigment to be located in lysosomes (Fig. 44–102). The pigment is currently believed to result from oxidative interaction between thyroid peroxidase and the drug; it resembles neuromelanin in histochemical properties. Of interest, when a tumor arises in a black thyroid, the tumor is often nonpigmented.

Uncommon Lesions of the Thyroid Gland

Exceptional examples of Rosai-Dorfman disease, macropolakia, extramedullary hematopoiesis, and inflammatory pseudotumor (plasma cell granuloma) have been reported in the thyroid.

B. The Parathyroid Gland

NEOPLASTIC LESIONS

Classification

Few tumor types are known to affect the parathyroid gland, and they include the following:

- Parathyroid adenoma
  - Typical
  - Variants
    - Lipoadenoma
    - Papillary variant
    - Water-clear variant
    - Follicular variant
    - Oxyphil variant
  - Parathyroid carcinoma (functional or nonfunctional)
- Parathyroid neoplasm of uncertain malignant potential

General Considerations

PATHOGENESIS

Parathyroid adenomas and carcinomas usually occur sporadically, but they can sometimes occur as a component of multiple endocrine neoplasia (MEN 1 and MEN 2) or familial idiopathic hyperparathyroidism. Radiation to the head and neck region has also been implicated as a possible etiologic factor of parathyroid adenoma. Parathyroid carcinoma can occasionally supervene on parathyroid adenoma or parathyroid hyperplasia.
Endocrine System

HYPERPARATHYROIDISM AS THE MAIN CLINICAL MANIFESTATION OF PARATHYROID NEOPLASMS

Parathyroid neoplasms typically present with features of hyperparathyroidism, although some patients are asymptomatic. There are three forms of hyperparathyroidism: primary, secondary, and tertiary. Only the primary and tertiary forms are associated with hyperparathyroidism and its related complications, such as polyuria and polydipsia, muscle weakness, renal stone, and mental disturbance, but all three forms can be associated with hyperparathyroid bone disease manifesting as bone pain or fracture.738, 739, 740

Primary Hyperparathyroidism

Primary hyperparathyroidism is defined as overproduction of parathyroid hormone as a result of an intrinsic abnormality of the parathyroid glands. In more than 85% of cases, the underlying pathologic process is a parathyroid neoplasm. The remaining cases result from primary parathyroid hyperplasia, which can be sporadic or syndromic (Table 44–19).

Secondary Hyperparathyroidism

Secondary hyperparathyroidism is defined as compensatory hyperplasia of parathyroid glands with overproduction of parathyroid hormone due to hypocalcemia. As a result, the serum calcium concentration is often normalized. Nonetheless, the parathyroid hormone can stimulate bone resorption, resulting in parathyroid bone disease. Underlying disorders include chronic renal failure (the most common), malabsorption, vitamin D deficiency, and renal tubular acidosis.

Tertiary Hyperparathyroidism

Tertiary hyperparathyroidism is defined as autonomous parathyroid hyperfunction supervening on secondary hyperparathyroidism. As a result, the serum calcium concentration is elevated. The autonomous parathyroid hyperfunction is most often caused by nodular hyperplasia; it is only uncommonly due to superimposed parathyroid adenoma or carcinoma.

Parathyroid Adenoma

CLINICAL CONSIDERATIONS

Presentation

Parathyroid adenoma is the most common cause of primary hyperparathyroidism (> 85%).749, 750 It occurs in patients with a mean age of 56 to 62 years. Women are more commonly affected than men. Approximately 50% of patients are asymptomatic, being incidentally found to have hypercalcemia on routine blood chemistry.750, 751 Others present with renal stone (30%) or parathyroid bone disease (20%), but simultaneous renal and skeletal disease is extremely rare.740–742 Surgical excision of the single involved parathyroid gland is curative.749, 756

Although parathyroid adenoma typically involves a single gland, occasionally two of the four glands are simultaneously involved (double adenoma) on both sides or on the same side of the neck.752

TABLE 44–19. Syndromes Associated with Hyperparathyroidism

<table>
<thead>
<tr>
<th>MEN 1</th>
<th>MEN 2A</th>
<th>Familial Isolated Hyperparathyroidism</th>
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</thead>
<tbody>
<tr>
<td>Endocrine organ disease</td>
<td>Parathyroid hyperplasia or neoplasm</td>
<td>Parathyroid hyperplasia or neoplasm</td>
</tr>
<tr>
<td></td>
<td>Thyroid nodule or follicular adenoma</td>
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<tr>
<td></td>
<td>Adrenal nodule or adenoma</td>
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<tr>
<td></td>
<td>Parathyroid hyperplasia or neoplasm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thyroid medullary carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phaeochromocytoma</td>
<td></td>
</tr>
<tr>
<td>Other clinical features</td>
<td>Facial angiofibromas</td>
<td>Lichen amyloidosis (some cases)</td>
</tr>
<tr>
<td></td>
<td>Collagenomas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple lipomas</td>
<td></td>
</tr>
<tr>
<td>Natural history of hyperparathyroidism</td>
<td>Hyperparathyroidism is commonly the first presentation. Serum calcium level tends to be lower than that of parathyroid adenoma, but incidence of renal or bone involvement is similar.</td>
<td>Hyperparathyroidism occurs in 20%–30% of cases and is usually mild and asymptomatic.</td>
</tr>
<tr>
<td>Genetic basis</td>
<td>Germline mutation in MEN1 locus on chromosome 11q13</td>
<td>Germline gain-of-function mutation in RET proto-oncogene on chromosome 10q11</td>
</tr>
</tbody>
</table>

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These patients are often symptomatic and have a significantly higher parathyroid hormone level and tumor weight than with solitary adenoma. Because distinction from asymmetric primary hyperplasia of the parathyroid glands can be difficult, strict criteria must be applied for its diagnosis:

- Two enlarged parathyroid glands are confirmed histologically to be hypercellular.
- The remaining parathyroid glands are confirmed intraoperatively to be normal (preferably confirmed histologically by biopsy).
- No clinical evidence or family history of multiple endocrine neoplasia or familial hyperparathyroidism is found.
- Permanent cure of hypercalcemia is achieved by excision of the two enlarged glands alone.

Parathyroid adenomas can sometimes cause problems in their localization because of occurrence in ectopic locations, such as the mediastinum, thyroid, or esophagus. When they occur within the thyroid gland, they can potentially be mistaken for thyroid follicular adenoma or medullary carcinoma.

**Macroscopic Findings**

Parathyroid adenomas usually weigh less than 1 g, with size ranging from less than 1 cm to several centimeters. The degree of hypercalcemia is generally correlated with the weight of the tumor. Parathyroid adenoma forms a solitary circumscribed nodule, which is usually soft and orange-brown or reddish yellow to mahogany brown. Hemorrhage or cystic degeneration can sometimes be seen. The unaffected parathyroid glands are normal in size or small.

**DIAGNOSTIC CONSIDERATIONS**

**Microscopic Findings**

Parathyroid adenomas are typically well circumscribed and solitary, although exceptionally they may be multinodular. A thin rim of compressed parathyroid tissue can be present at the periphery. In contrast to the normal parathyroid gland, interspersed adipose cells are absent or scanty.

The tumor cells form solid sheets, cords, acini, follicles, and microcysts traversed by a delicate capillary or sinusoidal network. They are polygonal, and the cytoplasm can be clear, eosinophilic, or oxyphilic. The nuclei are usually dark, round, and uniform, but there can be interspersed nuclei that are large, hyperchromatic, or even bizarre (Fig. 44–105). The nuclei also show a tendency to be polarized toward the vascular aspect of the cells. Vague nodular foci are sometimes seen within the tumor.

Fibrosis, hemorrhage, infarction, or cystic change can occur, but there should not be coagulative tumor necrosis; if it is present, coagulative tumor ne-
crosis strongly suggests parathyroid carcinoma. Rare cases show a lymphoid infiltrate in the peripheral portion in the form of lymphoid follicles or in the parenchyma in the form of isolated cells. Rarely, intrafollicular or interstitial amyloid can be found (Fig. 44–107). The morphologic variants are listed in Table 44–20 (Figs. 44–107 to 44–109).

**Immunohistochemistry**

The tumor cells of parathyroid adenoma are immunoreactive for cytokeratin, pan-neuroendocrine markers (such as synaptophysin, chromogranin, and neurofilament), and parathyroid hormone. The Ki-67 proliferative index is low (0.5% to 5.1%, with a mean of 2% to 3%), but the nodular foci may show a higher index.

Immunohistochemical staining for parathyroid hormone is rarely required for diagnostic purposes, except when there are difficulties in distinction from a thyroid follicular adenoma or when the tumor occurs in an ectopic location.

**Molecular Biology and Genetics**

Molecular evidence of monoclonality can be demonstrated in most parathyroid adenomas by use of X-linked restriction fragment length polymorphism studies. Furthermore, some cases exhibit tumor-specific DNA alterations in the parathyroid hormone gene.
TABLE 44–20. Morphologic Variants of Parathyroid Adenoma

<table>
<thead>
<tr>
<th>Variant</th>
<th>Major Pathologic Findings</th>
<th>Potential Diagnostic Pitfall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoadenoma</td>
<td>Often large size; chief and oxyphil cells are intermingled with many mature adipose cells, which occupy 20%–90% of the tissue area; loose fibromyxoid stroma can be present in some cases</td>
<td>Without information on the gross appearance (circumscribed and large), it can be mistaken histologically for normal parathyroid adenoma</td>
</tr>
<tr>
<td>Papillary</td>
<td>Prominent papillary pattern</td>
<td>May be mistaken for papillary thyroid carcinoma</td>
</tr>
<tr>
<td>Water-clear cell</td>
<td>Composed of tumor cells with clear cytoplasm and distinct cell membranes</td>
<td>May be mistaken for follicular thyroid neoplasm</td>
</tr>
<tr>
<td>Follicular</td>
<td>Prominent follicular-acinar pattern</td>
<td>May be mistaken for follicular thyroid neoplasm</td>
</tr>
<tr>
<td>Oxyphilic</td>
<td>Composed entirely of oxyphilic cells with abundant eosinophilic granular cytoplasm</td>
<td>May be mistaken for Hürthle cell neoplasms of thyroid</td>
</tr>
</tbody>
</table>

FIGURE 44–107. Parathyroid adenoma, oxyphilic type. A. The tumor cells form trabeculae and acini. Amyloid is found in the lumina of the acini. B. This example shows a diffuse growth pattern. In contrast to Hürthle (oxyphilic) cells of the thyroid, the cell membranes are typically distinct.
On cytogenetic analysis, rare cases of parathyroid adenoma show pericentric inversion of chromosome 11, which results in translocation of the cyclin D1 (PRAD1) gene with the parathyroid hormone gene, causing overexpression of cyclin D1 and hence increased cellular proliferation.796, 799, 800, 801 Immuno-histochemical expression of cyclin D1 occurs at a higher frequency (−25% of cases), suggesting deregulation of cyclin D1 by mechanisms other than pericentric chromosome inversion in such cases.796, 802 The MEN 1–associated MEN1 gene shows somatic mutation in 10% to 25% of sporadic parathyroid adenomas.803, 804 Chromosome abnormalities identified by comparative genomic hybridization include loss of 11p, 11q, 1p, and 1q and gain of 16p and 19p.805

**Differential Diagnosis**

**PRIMARY OR SECONDARY PARATHYROID HYPERPLASIA.** In parathyroid hyperplasia, all the parathyroid glands should be enlarged, although they are unevenly enlarged in some cases. Not uncommonly, the individual enlarged glands have a multinodular appearance.

**PARATHYROID CARCINOMA.** See subsequent section.

**THYROID FOLLICULAR ADENOMA.** When the parathyroid tumor is inside the thyroid gland and shows a microfollicular pattern, it can be mistaken for a follicular adenoma. Parathyroid adenoma is immunoreactive for parathyroid hormone, whereas thyroid follicular adenoma is immunoreactive for thyroglobulin.

**OXYPHIL CELL NODULE.** Oxyphil cell nodules are a common incidental finding in the parathyroid gland, especially in an older subject. They are small and commonly multifocal (Fig. 44-110).

**Intraoperative Frozen Section Diagnosis of Parathyroid Adenoma**

Intraoperative frozen section evaluation of patients presenting with hyperparathyroidism aims to achieve the following806, 807:

- Confirm that the tissue removed for examination indeed represents parathyroid tissue, not lymph node, thyroid, or ectopic thymus.
- Determine whether the abnormal parathyroid tissue represents parathyroid adenoma (removal of the diseased gland alone is sufficient), parathyroid hyperplasia (removal of 3.5 glands is required), or parathyroid carcinoma (en bloc radical excision is required).749, 756

The gland should be measured, weighed, and examined histologically. It is usually easy to confirm that the excised tissue is parathyroid gland on histologic examination, except that a small biopsy specimen of lymph node may occasionally be misinterpreted as parathyroid tissue because of artifactual spaces created by freezing that mimic adipose cells.808 A parathyroid gland with few or no interspersed adipose cells is supportive of a diagnosis of “hypercellular parathyroid gland, consistent with parathyroid adenoma or hyperplasia” (Table 44-21). Some investigators consider lipid staining (Sudan II or IV, oil red O) on frozen sections or imprint smears to be helpful in identifying an abnormal parathyroid gland797, 809–812 because the normal parathyroid cells contain abundant intracytoplasmic lipid droplets, whereas the hyperplastic or adenomatous cells are often devoid of intracytoplasmic lipid. An exception is the oxyphil cell, which always contains no or scanty intracytoplasmic lipid droplets.770 Adenomatous or hyperplastic glands may occasionally contain intracytoplasmic lipid, albeit weakly and focally.813–816

After it is confirmed that the parathyroid gland is hypercellular, the next step is to determine whether it represents an adenoma or hyperplastic process. Although a compressed rim of normal parathyroid gland is characteristic of parathyroid adenoma, it is not always found and it can be mimicked by the compressed intervening parenchyma in multinodular parathyroid hyperplasia.817, 818 The most reliable way to make the distinction is by de-

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**TABLE 44–21. Features Indicative of a Hypercellular (Neoplastic or Hyperplastic) Parathyroid Gland**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight: single gland weighing</td>
<td>&gt;100 mg (normal weight, &lt;30 mg)</td>
</tr>
<tr>
<td>Adipose cells in gland: few or absent</td>
<td>(on average, &lt;17% of a normal parathyroid gland is composed of adipose cells)</td>
</tr>
<tr>
<td>Intracytoplasmic lipid droplets</td>
<td>absent or scanty</td>
</tr>
</tbody>
</table>

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terminating the status of the other parathyroid glands. If they are all normal in size or small, a diagnosis of adenoma is favored. If all are enlarged, a diagnosis of parathyroid hyperplasia is favored. Simple inspection is not reliable because some hyperplastic processes affect the glands unequally; it is preferable to take an incisional biopsy specimen of one or more glands for histologic confirmation to ascertain whether they are normal-suppressed or hyperplastic.

Intraoperative assay of the parathyroid hormone level is an alternative way for guiding the extent of surgery, taking advantage of the fact that the hormone has a short half-life. If preoperative imaging studies can identify an enlarged parathyroid gland, a more limited unilateral procedure can be performed in place of bilateral neck exploration. Approximately 15 minutes after removal of the enlarged gland, a serum sample is taken for parathyroid hormone assay. A significant drop in the hormone level (≥50%) suggests successful removal of the hypersecreting tissue, and thus cure is reasonably ensured. The other parathyroid glands have to be explored for hyperplasia if the parathyroid hormone level remains elevated after removal of one enlarged gland.

**Parathyroid Carcinoma**

**Clinical Considerations**

**Presentation**

Parathyroid carcinomas are rare, constituting only about 2% of all parathyroid neoplasms. Compared with parathyroid adenomas, the patients with parathyroid carcinoma have a lower mean age (45 to 54 years), there is no sex predilection, and virtually all patients are symptomatic because of the high serum calcium level (3.5 to 4 mmol/L). Only rare tumors are nonfunctional.* The clues for recognizing the malignant nature of a parathyroid neoplasm are listed in Table 44–22.

**Macroscopic Findings**

The carcinomas are usually hard because of the presence of fibrous trabeculae. The size ranges from 1 cm to several centimeters. They are often much larger than parathyroid adenomas, with an average weight of 12 g (versus less than 1 g for parathyroid adenoma). They can be circumscribed or invasive. Necrosis and calcification can be present.

**Diagnostic Considerations**

**Microscopic Findings**

The tumor shows frank invasive features or is surrounded by a thick fibrous capsule (Fig. 44–111). It comprises polygonal cells forming solid sheets, trabeculae, acini, and packets. In some

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*The clinical clues actually reflect a large tumor or a tumor with invasive properties.

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**TABLE 44–22. Clues for Recognizing Parathyroid Carcinoma Versus Parathyroid Adenoma**

<table>
<thead>
<tr>
<th>Clinical Clues*</th>
<th>Clues at Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High serum calcium level (≥3.5 mmol/L or 14 mg/dL)</td>
<td>Firm consistency</td>
</tr>
<tr>
<td>Simultaneous parathyroid bone disease and renal stone (found in ~40%)</td>
<td>Thick capsule</td>
</tr>
<tr>
<td>Palpable neck mass (found in ~40%)</td>
<td>Adherence and invasion to adjacent organs, e.g., thyroid, muscle, nerve, esophagus</td>
</tr>
<tr>
<td>Vocal cord paralysis</td>
<td>Presence of metastasis</td>
</tr>
</tbody>
</table>

*References 731, 736, 752–754, 767, 823–833.

---

**FIGURE 44–111. Parathyroid carcinoma. A.** The tumor shows frank infiltration into the surrounding fibrofatty tissue. **B.** In this example, the tumor grows in the form of irregular infiltrative islands. The stroma is desmoplastic.
cases, the nuclei are uniform and bland-looking, with or without interspersed large hyperchromatic or bizarre nuclei731 (Fig. 44–112). In other cases, the nuclei are overtly pleomorphic (Fig. 44–112C). Nucleoli are sometimes prominent.835 The cytoplasm is clear, lightly eosinophilic, or oxyphilic.834, 836, 837 On occasion, monotonous small cells with high nuclear-to-cytoplasmic ratio can dominate (Fig. 44–113). Coagulative necrosis can be present.835

The features for diagnosing parathyroid carcinoma are outlined in Table 44–23.838 Stringent criteria must be used in the assessment of capsular or vascular invasion, similar to those applied for follicular neoplasms of the thyroid. Broad fibrous septa
traversing the tumor must be accompanied by ex-
pansil nodules before they are considered signifi-
cant to distinguish them from the focal scarring due
to previous hemorrhage or surgery (Fig. 44–114).
Although mitotic figures have been emphasized as
being the single most important criterion of malig-
nancy, they are now recognized as being signifi-
cant only when they are present in considerable
numbers (see Fig. 44–112B). Conversely, some carcinomas may show no or few mitotic fig-
ures. 

**Immunohistochemistry**

The tumor cells of parathyroid carcinoma are
immunoreactive for cytokeratin, pan-neuroendocrine
markers, and parathyroid hormone. Immunostaining
for parathyroid hormone is most helpful for con-
firming a diagnosis of nonfunctioning or ectopic
parathyroid carcinoma.

**Molecular Biology**

In most parathyroid carcinomas, allelic loss of
the retinoblastoma (RB) tumor suppressor gene is
found. On immunohistochemical staining, lack of immunoreactivity for the RB protein occurs in 20% to 88% of cases. Cyclin D1 overex-
pression is also common (91% of cases). There
is commonly reduced expression of the cyclin-de-
pendent kinase inhibitor protein p27 (mean labeling
index of 14% versus 57% for parathyroid ade-
noma).

**Differential Diagnosis**

The main problem in diagnosis of parathyroid
carcinoma is to recognize its malignant nature. The
difficulty lies in the fact that some apparently bland-
looking tumors may declare themselves to be malig-
nant by subsequent recurrence or metastasis. In
some cases, the malignant nature of the tumor is
obvious by virtue of the frankly invasive growth,
significant cellular pleomorphism, and frequent mi-
toses. However, in other cases, it is essential to con-
sider a number of features to render a diagnosis of
malignancy (see Table 44–23).

Immunostaining for the proliferation marker Ki-67 can sometimes be helpful because the index is higher in parathyroid carcinoma than in ade-
noma. Nonetheless, it cannot be used as the sole criterion because there is overlap in the counts
between adenomas and carcinomas. Whereas a high Ki-67 index (>5%) suggests a diagnosis of car-
cinoma, a low index does not exclude this possibil-
ity.
ity. The role of flow cytometric analysis of DNA in the diagnosis of parathyroid carcinoma remains controversial.845–848 A study employing a static DNA fluorometric method has reported a high nuclear DNA content and aneuploidy to favor a diagnosis of parathyroid carcinoma over parathyroid adenoma.849 When there are some but inconclusive features associated with malignancy, the designation “parathyroid neoplasm of uncertain malignant potential” or “atypical parathyroid adenoma” can be applied.850 Follow-up with regular monitoring of the serum calcium level will be helpful for such patients. Firm data on the outcome of these cases are lacking.

PROGNOSTIC CONSIDERATIONS

General Behavior
Parathyroid carcinoma generally pursues an indolent clinical course. It can invade contiguous structures, particularly the thyroid.754, 841, 853 Surgery is the mainstay of treatment. Local recurrence develops in approximately one third of patients, usually within 3 years; this occurrence may be reduced by postoperative radiotherapy.856 About one third of patients develop metastasis, usually relatively late in the course; the favored sites are regional lymph nodes of the neck and mediastinum, lungs, liver, and bones. The relapse usually manifests as recurrent hypercalcemia, and symptomatic control or even occasionally cure can still be achieved by further operations.8 The 5-year and 10-year survival rates are 60% and 40%, respectively. Death is usually caused by metabolic complications of hypercalcemia rather than by organ replacement by tumor.752–754, 823, 828, 830, 831

Prognostic Factors

Data on prognostic factors of parathyroid carcinoma are limited. Adequate en bloc excision (removal of the tumor, adjacent thyroid lobe, paratracheal soft tissues and lymph nodes, and ipsilateral thymus) on recognition of the malignant nature of the tumor at the initial operation offers the best chance of cure.824, 827, 833, 852 Nonfunctioning parathyroid carcinomas appear to behave more aggressively than functioning ones.823 The triad of macronucleoli, more than 5 mitoses per 50 high-power fields, and necrosis is correlated with a more aggressive outcome. High nuclear DNA content is correlated with a less favorable survival.835

Contents of the Final Surgical Pathology Report

The checklist of contents of the final report of parathyroid carcinoma excision specimens is listed in Table 44–24.

### TABLE 44–24. Contents of the Final Report: Parathyroid Excision Specimens

<table>
<thead>
<tr>
<th>Specimen type/operation procedure</th>
<th>Diagnosis</th>
<th>Histologic diagnosis</th>
<th>Other tumor features</th>
<th>Tumor location</th>
<th>Tumor size</th>
<th>Encapsulated or nonencapsulated</th>
<th>Capsular invasion (absent, present, extensive)</th>
<th>Vascular invasion (absent, present, extensive)</th>
<th>Tissues or structures invaded by the carcinoma</th>
<th>Mitotic count</th>
<th>Immunohistochemical expression of RB, cyclin D1, p27 (optional)</th>
<th>Surgical margins: free, close to surgical margin, or margin involved (specify site)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-neoplastic parathyroid: normal, diffuse hyperplasia, nodular hyperplasia</td>
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<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Number of lymph nodes found, and their location (level)</td>
<td>Number of involved lymph nodes</td>
<td>Size of largest metastatic deposit</td>
<td>Presence or absence of extracapsular extension</td>
<td></td>
<td></td>
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</tbody>
</table>

NON-NEOPLASTIC LESIONS

Primary Parathyroid Chief Cell Hyperplasia

CLINICAL CONSIDERATIONS

Primary parathyroid chief cell hyperplasia is a de novo hyperplastic process involving all the parathyroid glands, producing the clinical features of primary hyperparathyroidism.727, 734, 741, 854 Approximately 80% of cases are sporadic; the other cases occur as a component of MEN 1, MEN 2, familial isolated hyperparathyroidism, or hyperparathyroidism–jaw tumor syndrome. The condition is more common in females than in males. Treatment consists of subtotal parathyroidectomy (removal of 3.5 glands); the remaining gland is sometimes autotransplanted in the forearm.

DIAGNOSTIC CONSIDERATIONS

Although all parathyroid glands are involved, they may be unevenly enlarged, with some glands apparently having a “normal size” and hence leading to a misdiagnosis of parathyroid neoplasms. The combined weight of the parathyroid glands ranges from less than 1 g to 10 g.

In primary chief cell hyperplasia, the parathyroid glands are hypercellular, with marked reduction in interposed adipose cells. The proliferated parathyroid cells include predominantly chief cells, but water-clear cells and oxyphil cells are often present. The parathyroid cells show a solid, trabecular, follicular, or cordlike growth. In areas, it is common to see the characteristic palisading of the nuclei.
along the vascular septa. The pathologic process is initially diffuse, but with time, nodules will supervene on the background of diffuse hyperplasia. The various nodules often show different cellular compositions and different patterns of cellular organization.

Primary Water-Clear Cell Hyperplasia

CLINICAL CONSIDERATIONS

Water-clear cell hyperplasia is a rare form of primary parathyroid hyperplasia. It shows no familial incidence or association with multiple endocrine neoplasia. Of interest, for unknown reasons, this entity has virtually disappeared in the past few decades.\(^{737, 738, 855, 856}\)

The condition occurs mostly in older adults, but any age can be affected. It is slightly more common in males than in females. The patients present with features of primary hyperparathyroidism. In general, the hypercalcemia is more severe than in chief cell hyperplasia.

DIAGNOSTIC CONSIDERATIONS

In water-clear cell hyperplasia, the parathyroid glands are usually markedly enlarged; the combined weight of the gland is frequently above 10 g. The upper glands are often larger than the lower ones. On histologic examination, the hyperplastic parathyroid cells are large and possess water-clear cytoplasm. They form solid sheets and acini.

Secondary Parathyroid Hyperplasia

CLINICAL CONSIDERATIONS

Secondary parathyroid hyperplasia is a hyperplastic condition of the parathyroid glands in response to hypocalcemia or hyperphosphatemia. The most common cause is chronic renal failure. The patients present with features of secondary hyperparathyroidism (mostly with parathyroid bone disease) or tertiary hyperparathyroidism (mostly with complications of hypercalcemia). Treatment consists of subtotal parathyroidectomy.

DIAGNOSTIC CONSIDERATIONS

There is uniform or uneven enlargement of all parathyroid glands, indistinguishable from that seen in primary parathyroid hyperplasia. A multinodular pattern is seen in the majority of cases. The proliferation involves chief cells, clear cells, and oxyphil cells, which are arranged in sheets, trabeculae, or acini (Fig. 44–115). There can be fibrous bands.

**FIGURE 44–115.** Secondary parathyroid hyperplasia in chronic renal failure. A. The enlarged parathyroid gland is converted into multiple hyperplastic nodules. B. The nodules show different cell compositions. This field may give a false impression of an adenoma surrounded by compressed residual parathyroid tissue. C. The nodules often show a mixture of cell types.
around the nodules, hemosiderin deposition, and cystic change. Calcification can be present.

**Parathyroid Cyst**

Parathyroid cyst manifests clinically as a mass lesion or hypercalcemia, but it can also be an incidental finding. Its size can range from a few millimeters to 10 cm. The wall is thin and translucent. A diagnosis can be made by fine-needle aspiration, either by identification of parathyroid cells or by demonstration of elevated levels of parathyroid hormone in the cystic fluid. On histologic examination, it is often lined by attenuated parathyroid cells and surrounded by islands of normal, hyperplastic, or adenomatous parathyroid tissue (Fig. 44–116). That is, some cases represent cystic change of a parathyroid adenoma and are thus associated with hypercalcemia.

**Periparathyroid Salivary Heterotopia–Cyst Unit**

An uncommon lesion occurring in a periparathyroid location is the salivary heterotopia–cyst unit. It is usually small, measuring 1 to 6 mm, comprising small lobules of salivary acini and cysts. The cysts are lined by flattened, ciliated, or columnar cells, without parathyroid cell lining. The salivary heterotopia–cyst unit has been postulated to be of third branchial pouch derivation.

**Amyloidosis**

The parathyroid glands can be involved in systemic amyloidosis. The glands are enlarged and histologically show deposition of amyloid in blood vessel walls and the interstitium. When there is abundant amyloid deposition, parenchymal cells may be lost, leading to the development of mild hypocalcemia.

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