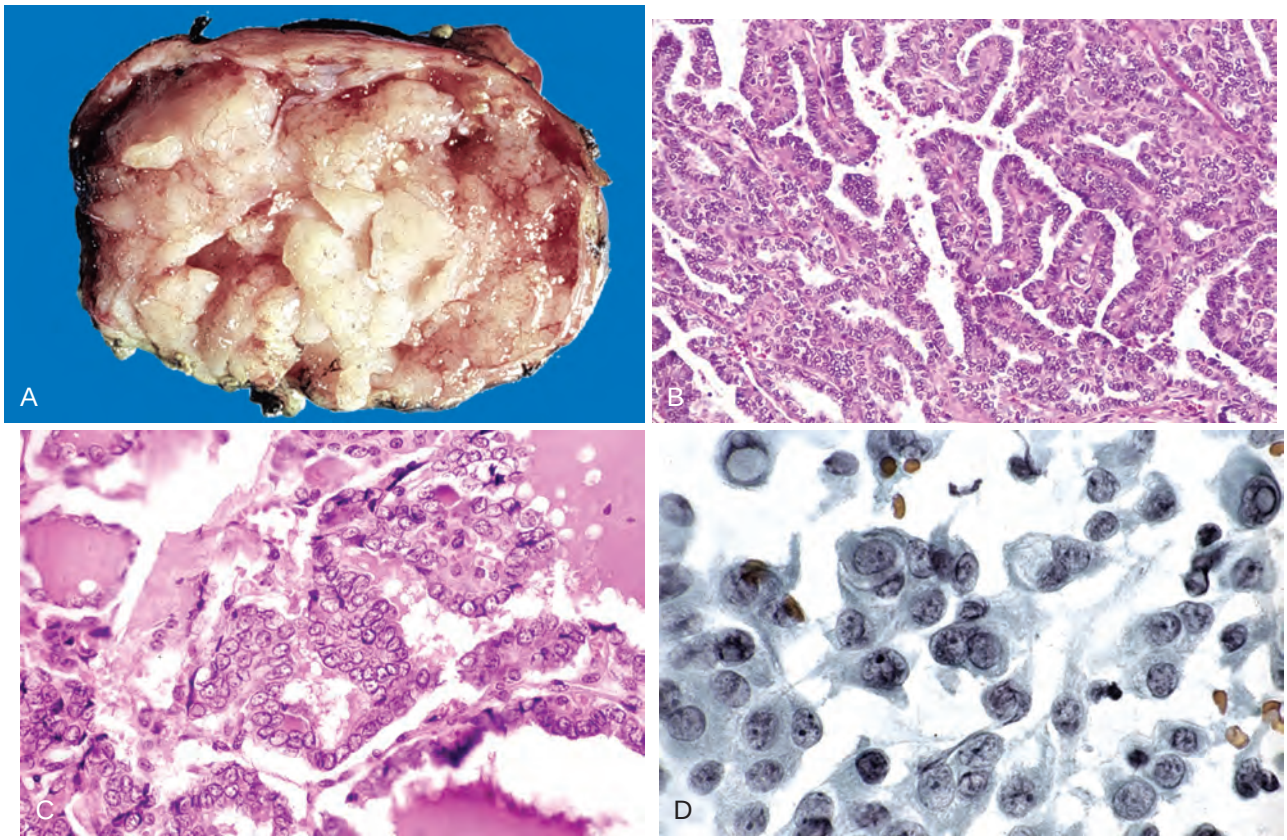

Figure 24-19 Papillary carcinoma of the thyroid. **A,** The macroscopic appearance of a papillary carcinoma with grossly discernible papillary structures. **B,** This particular example contains well-formed papillae. **C,** High power shows cells with characteristic empty-appearing nuclei, sometimes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

MORPHOLOGY

Papillary carcinomas may be solitary or multifocal. Some tumors are well circumscribed and even encapsulated; others infiltrate the adjacent parenchyma and have ill-defined margins. The tumors may contain areas of fibrosis and calcification and are often cystic. The cut surface sometimes reveals papillary foci that point to the diagnosis. The microscopic hallmarks of papillary neoplasms include the following (Fig. 24-19):

- Papillary carcinomas may contain branching **papillae** having a fibrovascular stalk covered by a single to multiple layers of cuboidal epithelial cells. In most neoplasms, the epithelium covering the papillae consists of well-differentiated, uniform, orderly cuboidal cells, but at the other extreme are those with fairly anaplastic epithelium showing considerable variation in cell and nuclear morphology. When present, the papillae of papillary carcinoma differ from those seen in areas of hyperplasia in being more complex and having dense fibrovascular cores.
- The nuclei of papillary carcinoma cells contain finely dispersed chromatin, which imparts an **optically clear** or **empty** appearance, giving rise to the designation **ground-glass** or **Orphan Annie eye nuclei**. In addition, invaginations of the cytoplasm may give the appearance of intranuclear inclusions ("pseudo-inclusions") or intranuclear grooves. **The diagnosis of papillary carcinoma can be made based on these nuclear features,** even in the absence of papillary architecture.
- Concentrically calcified structures termed **psammoma bodies** are often present, usually within the cores of papillae. These structures are almost never found in follicular and medullary carcinomas, and so, when present in fine-needle aspiration material, they are a strong indication that the lesion is a papillary carcinoma.
- Foci of lymphatic invasion by tumor are often present, but involvement of blood vessels is relatively uncommon, particularly in smaller lesions. Metastases to adjacent cervical lymph nodes occur in up to half of cases.

There are over a dozen histologic variants of papillary carcinoma that can mimic other thyroid lesions or harbor distinct prognostic implications; most are beyond the scope of this book. The most common variant, and the one most liable to misdiagnosis, is the **follicular variant,** which has the characteristic nuclear features of papillary carcinoma and an almost totally follicular architecture. Follicular variant papillary carcinomas can be either encapsulated or poorly circumscribed and infiltrative. The encapsulated follicular variant of papillary carcinoma has a generally favorable prognosis, while the poorly circumscribed and infiltrative lesions need to be treated more aggressively. The genetic alterations in the follicular variant, especially the encapsulated tumors, demonstrate several distinctions from conventional papillary carcinomas, including a lower frequency of *RET/PTC* rearrangements, a lower frequency and different spectrum of *BRAF* mutations, and a significantly higher frequency of *RAS* mutations. When considered in conjunction with their higher propensity for angioinvasion and lower