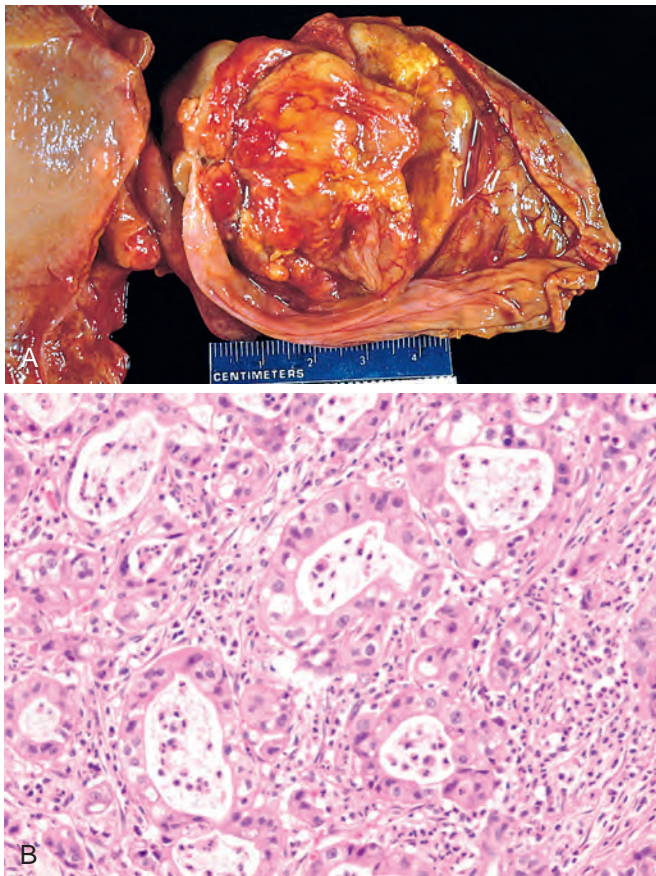


of chromatin remodeling genes such as *PBRM1* and *MLL3* in up to a quarter of cases. These could potentially provide targets for therapy.

## MORPHOLOGY

Carcinomas of the gallbladder show two patterns of growth: **infiltrating** and **exophytic**. The infiltrating pattern is more common and usually appears as a poorly defined area of diffuse mural thickening and induration. Deep ulceration can cause direct penetration into the liver or fistula formation to adjacent viscera into which the neoplasm has grown. These tumors are scirrhous and have a very firm consistency. The exophytic pattern grows into the lumen as an irregular, cauliflower mass, but at the same time invades the underlying wall (Fig. 18-65A).

**Most carcinomas of the gallbladder are adenocarcinomas.** Some of the carcinomas are papillary in architecture and are well to moderately differentiated; others are infiltrative and poorly differentiated to undifferentiated (Fig. 18-65B). About 5% are squamous cell carcinomas or have adenosquamous differentiation. A minority may show carcinoid or a variety of mesenchymal features (carcinosarcoma). Papillary tumors generally have a better prognosis than other tumors. By the time these neoplasms are discovered, most have invaded the liver centrifugally, and many have extended to the cystic duct and adjacent bile ducts and portal-hepatic lymph nodes. The peritoneum, gastrointestinal tract, and lungs are common sites of seeding.



**Figure 18-65** Gallbladder adenocarcinoma. **A**, The opened gallbladder contains a large, exophytic tumor that virtually fills the lumen. **B**, Malignant glands are seen infiltrating a densely fibrotic gallbladder wall.

It is not uncommon to find preneoplastic (dysplastic) lesions in the epithelium adjacent to invasive cancer, or in gallbladders with long-standing cholelithiasis. These are nearly always flat dysplasias, with varying grades of cellular atypia, including carcinoma-in-situ. Although polypoid adenomas of the gallbladder have been reported, these are uncommon precursors to invasive adenocarcinomas, and harbor distinct genetic alterations.

**Clinical Features.** Preoperative diagnosis of carcinoma of the gallbladder is the exception rather than the rule, occurring in fewer than 20% of patients. Presenting symptoms are insidious and typically indistinguishable from those associated with cholelithiasis: abdominal pain, jaundice, anorexia, and nausea and vomiting. Early detection of the tumor may be possible in patients who develop a palpable gallbladder and acute cholecystitis before extension of the tumor into adjacent structures, or when the carcinoma is an incidental finding during a cholecystectomy for symptomatic gallstones. Surgical resection, often including adjacent liver, is the only effective treatment, when possible, but chemotherapy regimens are also used.

## KEY CONCEPTS

### Diseases of the Gallbladder

- Gallbladder diseases include cholelithiasis and acute and chronic cholecystitis and gall bladder cancer.
- Gallstones are common in Western countries. The great majority are cholesterol stones. Pigmented stones containing bilirubin and calcium are most common in Asian countries.
- Risk factors for the development of cholesterol stones are advancing age, female gender, estrogen use, obesity, and heredity.
- Cholecystitis almost always occurs in association with cholelithiasis, although in about 10% of cases it occurs in the absence of gallstones. Gall stones are also a risk factor for gall bladder cancer.
- Acute calculous cholecystitis is the most common reason for emergency cholecystectomy.
- Gall bladder cancers are associated with gall stones in the vast majority of cases. Typically they are detected late because of non specific symptoms and hence carry a poor prognosis.

## SUGGESTED READINGS

### Mechanisms of Liver Injury and Repair

Gouw ASW, Clouston AD, These ND: Ductular reactions in human livers: diversity at the interface. *Hepatology* 54:1853, 2011. [A review of ductular reactions, the stem cell response of human livers in all liver diseases, that are related to mechanisms of regeneration, fibrogenesis and neoplasia.]

Kocabayoglu P, Friedman SL: Cellular basis of hepatic fibrosis and its role in inflammation and cancer. *Front Biosci (Schol Ed)* 5:217, 2013. [Interweaving what is known about hepatic stellate cells and other myofibroblastic cells of the liver with inflammatory, fibrosing, and neoplastic disease processes.]

Iwaisako K, Brenner DA, Kisseleva T: What's new in liver fibrosis? The origin of myofibroblasts in liver fibrosis. *J Gastroenterol Hepatol* 27(Suppl 2):65, 2012.