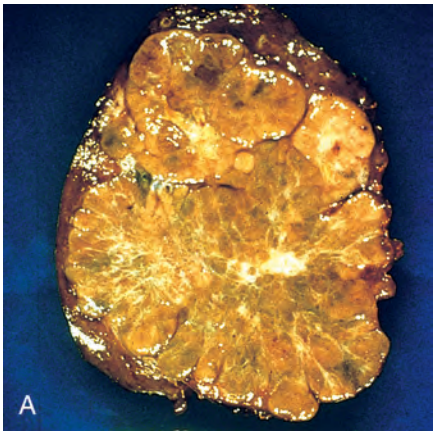
cancer, permeating widely and sometimes involving the entire liver. All three patterns may cause liver enlargement. The diffusely infiltrative tumor may blend so imperceptibly into a background of cirrhosis that it might not be apparent by imaging, even though most of the liver is replaced. HCCs may be pale compared to surrounding liver or they may have a variegated appearance reflecting different differentiation states (white when there is abundant stroma, yellow when fatty change predominates, green when well-differentiated malignant hepatocytes make abundant bile).

Intrahepatic metastases, by either vascular invasion or direct extension, become more likely once tumors reach 3 cm in size. These metastases are usually small, satellite tumor nodules around the larger, primary mass. The vascular route is also the most likely route for extrahepatic metastasis, especially by the hepatic venous system. Hematogenous metastases, especially to the lung, tend to occur late in the disease. Occasionally, long, snakelike masses of tumor invade the portal vein (causing portal hypertension) or inferior vena cava. The latter can even extend into the right side of the heart. Lymph node metastases are less common routes of extrahepatic spread. If venous invasion is identified in HCC-bearing explanted livers at the time of transplantation, tumor recurrence is likely to occur in the transplanted liver due to seeding of circulating tumor cells in the transplant recipient. Such lesions may appear months after the operation.

HCCs range from well-differentiated to highly anaplastic lesions. The better differentiated HCCs are comprised of cells that look much like normal hepatocytes and grow in structures that are distortions of normal: thickened trabecular structures (recapitulating liver cell plates) or pseudoglandular structures that are poorly formed, ectatic bile canaliculi (Fig. 18-56).

A distinctive variant of HCC is **fibrolamellar carcinoma**, constituting less than 5% of HCCs. 85% occur under the age of 35 years and without gender predilection or identifiable predisposing conditions. It usually presents as single large, hard "scirrhous" tumor with fibrous bands coursing through it. Microscopically, they are composed of well-differentiated cells rich in mitochondria (oncocytes) growing in nests or cords separated by parallel lamellae of dense collagen bundles (hence the name) (Fig. 18-59).



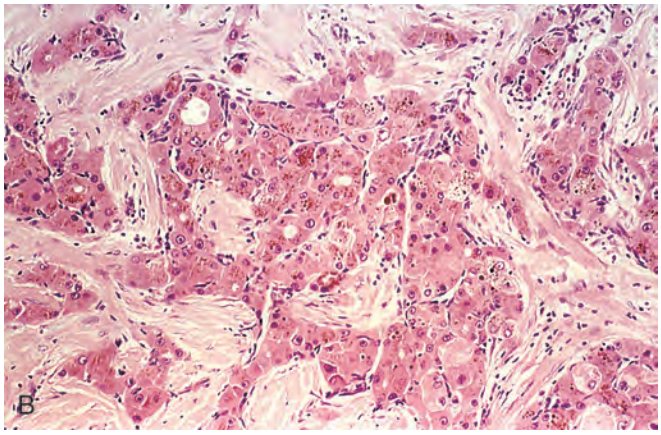


Figure 18-59 Fibrolamellar carcinoma. **A,** Resected specimen showing a well demarcated nodule. **B,** Microscopic view showing nests and cords of malignant-appearing, oncocytic hepatocytes separated by dense bundles of collagen.

Clinical Features. The clinical manifestations of HCC are seldom characteristic and, in the Western population, often are masked by those related to the underlying cirrhosis or chronic hepatitis. In areas of high incidence such as tropical Africa, in particular where aflatoxin exposure is common, patients usually have no clinical history of liver disease, although cirrhosis may be detected at autopsy. In both populations most patients have ill-defined upper abdominal pain, malaise, fatigue, weight loss, and sometimes awareness of hepatomegaly or an abdominal mass or abdominal fullness. Jaundice, fever, and gastrointestinal or esophageal variceal bleeding are inconstant findings.

Laboratory studies may be helpful but are rarely conclusive. Rising or elevated levels of *serum α-fetoprotein* are found in 50% of persons with advanced HCC. However, it is insensitive as a screening test for premalignant or early lesions as these usually do not produce particularly high levels of the protein.

Most valuable for detection of small tumors are imaging studies: ultrasonography to identify distinctive nodules of all kinds, and computed tomography and magnetic resonance imaging with vascular/contrast studies. The increasing arterialization in the process of conversion from high grade dysplastic nodule to early HCC and then to fully developed HCC, form the basis of diagnostic imaging. HCC, even when small, has such characteristic vascular changes that imaging can be diagnostic.

The natural course of HCC involves the progressive enlargement of the primary mass until it disturbs hepatic function or metastasizes to the lungs or to other sites. Death usually occurs from (1) cachexia, (2) gastrointestinal or esophageal variceal bleeding, (3) liver failure with hepatic coma, or, rarely, (4) rupture of the tumor with fatal hemorrhage. The 5-year survival of large tumors is dismal, the majority of patients dying within the first 2 years.

With implementation of screening procedures and advances in imaging, the detection of HCCs less than 2 cm in diameter has increased in countries where such facilities are available. These small tumors can be removed surgically or ablated (e.g., through embolization or with microwave radiation or freezing) with good outcomes. Radiofrequency ablation is used for local control of large tumors, and chemoembolization can also be used.