on prognosis and may be microscopic or macroscopic (visible on computed tomography [CT] scans). Most large tumors have microscopic vascular invasion, so full staging can usually be made only after surgical resection. Stage III disease contains a mixture of lymph node–positive and–negative tumors. Stage III patients with positive lymph node disease have a poor prognosis, and few patients survive 1 year. The prognosis of stage IV is poor after either resection or transplantation, and 1-year survival is rare.

New Directions Consensus is needed on staging. These systems will soon be refined or upended by proteomics.

APPROACH TO THE PATIENT: Hepatocellular Carcinoma

HISTORY AND PHYSICAL

The history is important in evaluating putative predisposing factors, including a history of hepatitis or jaundice, blood transfusion, or use of intravenous drugs. A family history of HCC or hepatitis should be sought and a detailed social history taken to include job descriptions for industrial exposure to possible carcinogenic drugs as well as contraceptive hormones. Physical examination should include assessing stigmata of underlying liver disease such as jaundice, ascites, peripheral edema, spider nevi, palmar erythema, and weight loss. Evaluation of the abdomen for hepatic size, masses or ascites, hepatic nodularity and tenderness, and splenomegaly is needed, as is assessment of overall performance status and psychosocial evaluation.

SEROLOGIC ASSAYS

AFP is a serum tumor marker for HCC; however, it is only increased in approximately one-half of U.S. patients. The lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) assay is thought to be more specific. The other widely used assay is that for des-γ-carboxy prothrombin (DCP), a protein induced by vitamin K absence (PIVKA-2). This protein is increased in as many as 80% of HCC patients but may also be elevated in patients with vitamin K deficiency; it is always elevated after warfarin use. It may also predict for portal vein invasion. Both AFP-L3 and DCP are U.S. Food and Drug Administration (FDA) approved. Many other assays have been developed, such as glypican-3, but none have greater aggregate sensitivity and specificity. In a patient presenting with either a new hepatic mass or other indications of recent hepatic decompensation, carcinoembryonic antigen (CEA), vitamin B_{12}, AFP, ferritin, PIVKA-2, and antimitochondrial antibody should be measured, and standard liver function tests should be performed, including prothrombin time (PT), partial thromboplastin time (PTT), albumin, transaminases, γ-glutamyl transpeptidase, and alkaline phosphatase. γ-Glutamyl transpeptidase and alkaline phosphatase may be particularly important in the 50% of HCC patients who have low AFP levels. Decreases in platelet count and white blood cell count may reflect portal hypertension and associated hypersplenism. Hepatitis A, B, and C serology should be measured. If HBV or HCV serology is positive, quantitative measurements of HBV DNA or HCV RNA are needed.

New Directions Newer biomarkers are being evaluated, especially tissue- and serum-based genomics profiling. Newer plasma biomarkers include glypican-3, osteopontin, insulin-like growth factor I, and vascular endothelial growth factor. However, they are still in process of validation. Furthermore, the commercial availability of kits for isolating circulating tumor cells is permitting the molecular profiling of HCCs without the need for further tissue biopsy.

RADIOLOGY

An ultrasound examination of the liver is an excellent screening tool. The two characteristic vascular abnormalities are hypervascularity of the tumor mass (neovascularization or abnormal tumor-feeding arterial vessels) and thrombosis by tumor invasion of otherwise normal portal veins. To determine tumor size and extent and the presence of portal vein invasion accurately, a helical/triphasic CT scan of the abdomen and pelvis, with fast-contrast bolus technique, should be performed to detect the vascular lesions typical of HCC. Portal vein invasion is normally detected as an obstruction and expansion of the vessel. A chest CT is used to exclude metastases. Magnetic resonance imaging (MRI) can also provide detailed information, especially with the newer contrast agents. Ethiodol (Lipiodol) is an ethiodized oil emulsion retained by liver tumors that can be delivered by hepatic artery injection (5–15 mL) for CT imaging 1 week later. For small tumors, Ethiodol injection is very helpful before biopsy because the histologic presence of the dye constitutes proof that the needle biopsied the mass under suspicion. A prospective comparison of triphasic CT, gadolinium-enhanced MRI, ultrasound, and fluorodeoxyglucose positron emission tomography (FDG-PET) showed similar results for CT, MRI, and ultrasound; PET imaging appears to be positive in only a subset of HCC patients. Abdominal CT versus MRI/CT uses a faster single breath-hold, is less complex, and is less dependent on patient cooperation. MRI requires a longer examination, and ascites can cause artifacts, but MRI is better able to distinguish dysplastic or regenerative nodules from HCC. Imaging criteria have been developed for HCC that do not require biopsy proof, as they have >90% specificity. The criteria include nodules >1 cm with arterial enhancement and portal venous washout and, for small tumors, specified growth rates on two scans performed less than 6 months apart (Organ Procurement and Transplant Network). Nevertheless, explant pathology after liver transplant for HCC has shown that ~20% of patients diagnosed without biopsy did not actually have a tumor.

New Directions The altered tumor vascularity that is a consequence of molecularly targeted therapies is the basis for newer imaging techniques including contrast-enhanced ultrasound (CEUS) and dynamic MRI.

PATHOLOGIC DIAGNOSIS

Histologic proof of the presence of HCC is obtained through a core liver biopsy of the liver mass under ultrasound guidance, as well as random biopsy of the underlying liver. Bleeding risk is increased compared to other cancers because (1) the tumors are hypervascular and (2) patients often have thrombocytopenia and decreased liver-dependent clotting factors. Bleeding risk is further increased in the presence of ascites. Tracking of tumor has an uncommon problem. Fine-needle aspirates can provide sufficient material for diagnosis of cancer, but core biopsies are preferred. Tissue architecture allows the distinction between HCC and adenocarcinoma. Laparoscopic approaches can also be used. For patients suspected of having portal vein involvement, a core biopsy of the portal vein may be performed safely. If positive, this is regarded as an exclusion criterion for transplantation for HCC.

New Directions Immunohistochemistry has become mainstream. Prognostic subgroupings are being defined based on growth signaling pathway proteins and genotyping strategies, including a prognostically significant five-gene profile score. Furthermore, molecular profiling of the underlying liver has provided evidence for a "field-effect" of cirrhosis in generating recurrent or new HCCs after primary resection. In addition, characteristics of HCC stem cells have been identified and include EpCAM, CD44, and CD90 expression, which may form the basis of stem cell therapeutic targeting strategies.

SCREENING HIGH-RISK POPULATIONS

There are two goals of screening, both in patients at increased risk for developing HCC, such as those with cirrhosis. The first goal is to detect smaller tumors that are potentially curable by ablation. The second goal is to enhance survival, compared with patients who were not diagnosed by surveillance. Evidence from Taiwan has shown a survival advantage to population screening in HBV-positive patients, and other evidence has shown its efficacy in diagnosis for HCV. Prospective studies in