hypoglycemia (insulinoma), Zollinger-Ellison syndrome (gastrinoma), hyperglycemia (glucagonoma), and diarrhea with electrolyte disturbances (VIPoma).

Diagnosis

Imaging of the pancreatobiliary system using ultrasound, CT, or magnetic resonance imaging (MRI) can identify lesions. However, small intrapancreatic, periampullary, and biliary system lesions causing pancreatobiliary obstruction may not be evident on imaging. If a malignancy is suspected, endoscopic ultrasound and endoscopic retrograde cholangiopancreatography are very useful tests. During these procedures, lesions can be visualized better, obstruction can be relieved by stent placement, and histologic confirmation can be obtained by biopsies, fine-needle aspirations, and bile duct brushings. Somatostatin-receptor scintigraphy can be helpful in localizing occult neuroendocrine tumors.

Treatment

Pancreatobiliary malignancies are some of the most difficult cancers to treat. Their anatomic locations make them poor candidates for resection: Pancreatic cancer frequently involves the celiac arterial axis and superior mesenteric artery, and biliary cancers can obstruct the entire biliary outflow (Klatskin tumors). Aggressive surgeries such as the Whipple procedure (pancreatoduodenectomy), radical cholecystectomy (resection of the gallbladder, porta hepatis, liver segments IV and V), and segmental liver resection with biliary tree reconstruction (for cholangiocarcinoma) can be attempted. However, the 5-year overall survival rate after pancreatic adenocarcinoma resection is less than 20%.

Recent studies with multiagent regimens such as a combination of 5-FU, irinotecan, and oxaliplatin, or combined gemcitabine and nab-paclitaxel, have demonstrated improved overall survival for metastatic pancreatic cancer. Gemcitabine with cisplatin has emerged as a standard for cholangiocarcinoma. Octreotide, a somatostatin analogue, is useful in the management of neuroendocrine tumors. Recent studies in neuroendocrine tumors have also shown improvement in outcomes with targeted agents such as everolimus and sunitinib. Palliation of symptoms is a large component of care. Opioid analgesics and celiac nerve plexus blocks for pain; biliary stents and percutaneous tubes for obstructive jaundice; palliative surgeries for gastric outlet and biliary obstruction; appetite stimulants such as olanzapine, megestrol, and dronabinol for anorexia; and supplemental pancreatic enzymes for malabsorption are all interventions that can improve patients' quality of life.

Prognosis

Pancreatobiliary malignancies have some of the worst outcomes; the 5-year overall survival rate remains less than 10%. Survival has not improved significantly over the last few decades, in contrast to several other cancers.

HEPATOCELLULAR CARCINOMA

Epidemiology

Hepatocellular carcinoma (HCC), or primary liver cancer, is a common disease around the world. It is the second most common cause of cancer-related death in men, worldwide.

Pathology

Most HCCs arise in the setting of underlying cirrhosis, with alcohol use, hepatitis B, and hepatitis C being the most common causes. Other diseases causing cirrhosis are also contributory, such as hemochromatosis, primary biliary cirrhosis, and α_1-antitrypsin deficiency. Cirrhosis involves chronic hepatocyte injury and ensuing cell regeneration, which provides the substrate for cancer development: inflammatory cytokine stress, constant cell cycling, and aberrant cell development and differentiation.

Clinical Presentation

HCC is frequently masked by the underlying liver disease. Abdominal distention from ascites, fatigue, muscle wasting, anorexia, and encephalopathy are features of cirrhosis. Acute hepatic decompensation or right upper quadrant pain may herald the development of HCC. HCC can also be an incidental finding during routine surveillance by screening ultrasound for patients with cirrhosis.

Diagnosis

HCC is one of those rare malignancies for which a diagnosis can be made without histologic confirmation. Nonhistologic criteria for diagnosis include underlying cirrhosis, elevated α-fetoprotein level (>400 ng/mL), and a characteristic appearance on contrast-enhanced CT or MRI (arterial enhancement and rapid washout). In the absence of underlying cirrhosis, a tissue diagnosis must be obtained. For patients with cirrhosis, a surveillance program incorporating regular measurements of α-fetoprotein and ultrasound imaging can detect early lesions.

Treatment

For small lesions, surgical resection can be curative. Preoperative assessment of liver function to ensure that the patient is an appropriate candidate for partial liver resection is critical. Liver transplantation is an option that can treat HCC as well as the underlying cirrhosis. Strict criteria, such as the Milan criteria (i.e., single tumor ≤5 cm, or up to three tumors each <3 cm, and no vascular invasion), are used to determine which patients are eligible for transplantation. For those who are ineligible for surgical approaches, radiofrequency ablation, transarterial chemoembolization, yttrium-90 embolization, and percutaneous ethanol injection can provide local control. Sorafenib, a multikinase inhibitor that targets RAF kinases (CRAF, BRAF), vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3), and other cell surface kinase receptors (PDGFR-β, KIT, FLT3, and RET), has been shown to improve clinical outcomes for metastatic disease.

Prognosis

The 5-year survival rate approaches 50% with complete surgical resection or liver transplantation. For advanced HCC, the median overall survival time with sorafenib therapy remains less than 1 year. It is important to note that prognosis in HCC is often determined by the severity of the underlying liver disease.