## GASTRIC CANCER

### Epidemiology

Gastric adenocarcinoma is one of the rare malignancies that has shown a remarkable decline in incidence and mortality in the United States over the 20th century. Much of this decline can be attributed to refrigeration, which obviated the use of food preservatives that harbor carcinogenic nitrites and nitrosamines. Improved hygiene and sanitation also lowered the prevalence of *Helicobacter pylori* infection, which is associated with gastric cancer. However, this disease remains common in Asian countries (China, Japan, and Korea), in the Middle East, and in Eastern Europe, placing it among the five most common cancers worldwide.

### Pathology

Traditionally, two main histologic subtypes exist: diffuse and intestinal. The diffuse type is associated with younger age, poor differentiation, signet ring cells, an increasing incidence, and a worse prognosis. Carriers of inactivating mutations in the E-cadherin gene (*CDH1*), such as those with hereditary diffuse gastric cancer syndrome, are prone to such cancers. The intestinal type is seen in older patients, is differentiated with a background of intestinal metaplasia, and has a declining incidence and a somewhat better prognosis. In many cases, however, this histologic distinction is not possible and does not alter management.

### Clinical Presentation

The classic triad is anemia, anorexia, and asthenia. Early satiety (linitis plastica), dysphagia (gastroesophageal junction or cardia tumors), epigastric pain, nausea, vomiting, and gastrointestinal bleeding are also commonly seen. Metastatic spread causing peritoneal carcinomatosis can lead to ascites.

### Diagnosis

Esophagogastroduodenoscopy is the preferred diagnostic test. Biopsies to confirm disease should follow, and then metastatic disease assessment by CT. If linitis plastica is suspected, blind biopsies may be needed, because overt mucosal lesions are often not evident. Screening endoscopy is recommended in high-incidence countries such as Japan.

### Treatment

Surgery remains the cornerstone of treatment for nonmetastatic disease. The extent of dissection is debated. In high-incidence countries such as Japan and Korea, extended surgery (D2 dissection) to remove the stomach, all surrounding lymph nodes, and the spleen is performed and is associated with clinical benefit. However, this benefit has not been seen in the Western population. For locally advanced disease, in addition to surgery, either perioperative chemotherapy with epirubicin, cisplatin, and 5-FU or postoperative chemoradiation with 5-FU is an acceptable approach. For metastatic disease, first- and second-line palliative chemotherapy can improve outcomes, including survival. For patients with HER2-overexpressing tumors, the addition of trastuzumab to chemotherapy further extends survival.

### Prognosis

Clinical outcomes depend on the stage at diagnosis. Early-stage cancer can be cured; 5-year survival rates are 65%, 40%, 15%, and 5% for stages I, II, III, and IV, respectively. Survival outcomes in Japan and Korea are better than in most Western countries; this disparity may be attributable to routine screening endoscopies or to differences in disease biology.

## PANCREATOBILIARY CANCERS

### Epidemiology

The incidence and mortality of pancreatic ductal adenocarcinoma are slowly but steadily increasing. It is the tenth most common cancer but the fourth leading cause of cancer-related death in the United States. Smoking and chronic pancreatitis are established clinical risk factors. Pancreatic cancer risk increases with inherited mutations in *BRCA1*, *BRCA2*, and *PALB2* and with familial syndromes such as the Peutz-Jeghers and Lynch syndromes. Pancreatic neuroendocrine tumors are uncommon malignancies that originate from the endocrine cells in the pancreas. They may be nonfunctional, or they may secrete hormones such as insulin (insulinoma), gastrin (gastrinoma), glucagon (glucagonoma), or vasoactive intestinal peptide (VIPoma).

Cholangiocarcinoma, defined as cancer arising from the biliary epithelium, comprises intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer. It is an uncommon malignancy. Established risk factors include conditions that cause chronic inflammation of the biliary system, such as primary sclerosing cholangitis, cholelithiasis, and infection with liver flukes (*Clonorchis*, *Opsithorcis*), and anatomic abnormalities of the biliary tree (e.g., Caroli's disease, choledochal cysts). Gallbladder cancer is particularly prevalent in Chile and northern India.

### Pathology

Pancreatic adenocarcinoma develops with an accumulation of mutations in the pancreatic duct epithelium; the affected genes are *KRAS*, followed by *CDKN2A (p16)*, *TP53*, *SMAD4 (DPC4)*, and others. Histologic progression occurs in various stages of pancreatic intraepithelial neoplasia, leading to invasive adenocarcinoma. Desmoplastic reaction—the production of abundant fibrotic stroma—is often seen in pancreatic cancer.

### Clinical Presentation

Painless jaundice is a frequent presenting symptom and is caused by biliary obstruction. Epigastric pain radiating through to the back and new-onset type 2 diabetes mellitus in an adult older 50 years of age without overt obesity-related risk factors should raise suspicion for pancreatic cancer. Constitutional symptoms include anorexia, unintentional weight loss, and malaise. Steatorrhea occurs because of exocrine pancreatic insufficiency. Venous thromboembolism, seen with various malignancies, is most associated with pancreatic cancer and can be a presenting feature. Gallbladder cancer is sometimes an incidental finding during the evaluation of histologic specimens after cholecystectomy, which is commonly performed for presumed cholelithiasis or cholecystitis. Secretory pancreatic neuroendocrine tumors can cause symptoms related to excess hormone production, including