the basis of cirrhosis, although both adenomas and HCCs are intensely vascular on the CT arterial phase and both can exhibit hemorrhage (40% of adenomas). However, adenomas have smooth, well-defined edges, and enhance homogeneously, especially in the portal venous phase on delayed images, when HCCs no longer enhance. FNHs exhibit a characteristic central scar that is hypovascular on the arterial-phase and hypervascular on the delayed-phase CT images. MRI is even more sensitive in depicting the characteristic central scar of FNH.

112 Pancreatic Cancer

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Pancreatic cancer is the fourth leading cause of cancer death in the United States and is associated with a poor prognosis. Endocrine tumors affecting the pancreas are discussed in Chap. 113. Infiltrating ductal adenocarcinomas, the subject of this Chapter, account for the vast majority of cases and arise most frequently in the head of pancreas. At the time of diagnosis, 85–90% of patients have inoperable or metastatic disease, which is reflected in the 5-year survival rate of only 6% for all stages combined. An improved 5-year survival of up to 24% may be achieved when the tumor is detected at an early stage and when complete surgical resection is accomplished.

EPIDEMIOLOGY

Pancreatic cancer represents 3% of all newly diagnosed malignancies in the United States. The most common age group at diagnosis is 65–84 years for both sexes. Pancreatic cancer was estimated to have been diagnosed in approximately 45,220 patients and accounted for approximately 38,460 deaths in 2013. Although survival rates have almost doubled over the past 35 years for this disease, overall survival remains low.

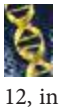
GLOBAL CONSIDERATIONS

An estimated 278,684 cases of pancreatic cancer occur annually worldwide (the thirteenth most common cancer globally), with up to 60% of these cases diagnosed in more developed countries. It remains the eighth most common cause of cancer death in men and the ninth most common in women. The incidence is highest in the United States and western Europe and lowest in parts of Africa and South Central Asia. However, increasing rates of obesity, diabetes, and tobacco use in addition to access to diagnostic radiology in the developing world are likely to increase incidence rates in these countries. In this situation, consideration of the cost implications of adoption of current treatment paradigms in resource-constrained environments will be necessary. Primary prevention such as limiting tobacco use and avoiding obesity may be more cost effective than improvements in treatment of preexisting disease.

RISK FACTORS

Cigarette smoking may be the cause of up to 20–25% of all pancreatic cancers and is the most common environmental risk factor for this disease. A longstanding history of type 1 or type 2 diabetes also appears to be a risk factor; however, diabetes may also occur in association with pancreatic cancer, possibly confounding this interpretation. Other risk factors may include obesity, chronic pancreatitis, and ABO blood group status. Alcohol does not appear to be a risk factor unless excess consumption gives rise to chronic pancreatitis.

GENETIC AND MOLECULAR CONSIDERATIONS



Pancreatic cancer is associated with a number of well-defined molecular hallmarks. The four genes most commonly mutated or inactivated in pancreatic cancer are *KRAS* (predominantly codon 12, in 60–75% of pancreatic cancers), the tumor-suppressor genes *p16* (deleted in 95% of tumors), *p53* (inactivated or mutated in 50–70% of tumors), and *SMAD4* (deleted in 55% of tumors). The pancreatic cancer precursor lesion pancreatic intraepithelial neoplasia (PanIN) acquires these genetic abnormalities in a progressive manner associated with increasing dysplasia; initial *KRAS* mutations are followed by *p16* loss and finally *p53* and *SMAD4* alterations. *SMAD4* gene inactivation is associated with a pattern of widespread metastatic disease in advanced-stage patients and poorer survival in patients with surgically resected pancreatic adenocarcinoma.

Up to 16% of pancreatic cancers may be inherited. Germline mutations in the following genes are associated with a significantly increased risk of pancreatic cancer and other cancers: (1) *STK11* gene (Peutz-Jeghers syndrome), which carries a 132-fold increased lifetime risk of pancreatic cancer above the general population; (2) *BRCA2* (increased risk of breast, ovarian, and pancreatic cancer); (3) *p16/CDKN2A* (familial atypical multiple mole melanoma), which carries an increased risk of melanoma and pancreatic cancer; (4) *PALB2*, which confers an increased risk of breast and pancreatic cancer; (5) *hMLH1* and *MSH2* (Lynch syndrome), which carries an increased risk of colon and pancreatic cancer; and (6) *ATM* (ataxia-telangiectasia), which carries an increased risk of breast cancer, lymphoma, and pancreatic cancer. Familial pancreatitis and an increased risk of pancreatic cancer are associated with mutations of the *PRSS1* (serine protease 1) gene. However, for most familial pancreatic syndromes, the underlying genetic cause remains unexplained. The absolute number of affected first-degree relatives is also correlated with increased cancer risk, and patients with at least two first-degree relatives with pancreatic cancer should be considered to have familial pancreatic cancer until proven otherwise.

The desmoplastic stroma surrounding pancreatic adenocarcinoma functions as a mechanical barrier to chemotherapy and secretes compounds essential for tumor progression and metastasis. Key mediators of these functions include the activated pancreatic stellate cell and the glycoprotein SPARC (secreted protein acidic and rich in cysteine), which is expressed in 80% of pancreatic ductal adenocarcinomas. Targeting this extracellular environment has become increasingly important in the treatment of advanced disease.

SCREENING AND PRECURSOR LESIONS

Screening is not routinely recommended because the incidence of pancreatic cancer in the general population is low (lifetime risk 1.3%), putative tumor markers such as carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) have insufficient sensitivity, and computed tomography (CT) has inadequate resolution to detect pancreatic dysplasia. Endoscopic ultrasound (EUS) is a more promising screening tool, and preclinical efforts are focused on identifying biomarkers that may detect pancreatic cancer at an early stage. Consensus practice recommendations based largely on expert opinion have chosen a threshold of greater than fivefold increased risk for developing pancreatic cancer to select individuals who may benefit from screening. This includes people with two or more first-degree relatives with pancreatic cancer, patients with Peutz-Jeghers syndrome, and *BRCA* 2, *p16*, and hereditary nonpolyposis colorectal cancer (HNPCC) mutation carriers with one or more affected first-degree relatives.

PanIN represents a spectrum of small (<5 mm) neoplastic but noninvasive precursor lesions of the pancreatic ductal epithelium demonstrating mild, moderate, or severe dysplasia (PanIN 1–3, respectively); however, not all PanIN lesions will progress to frank invasive malignancy. Cystic pancreatic tumors such as intraductal mucinous papillary neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) are increasingly detected radiologically and are frequently asymptomatic. Main duct IPMNs are more likely to occur in older persons and have higher malignant potential than branched duct IPMNs (invasive cancer in 45% vs 18% of resected lesions, respectively). In contrast, MCNs are solitary lesions of the distal pancreas that do not communicate with the duct system. MCNs have an almost exclusive female distribution (95%). The rate of invasive cancer in resected MCNs is lower (<18%) with increased rates associated with larger tumors or the presence of nodules.

CLINICAL FEATURES

Clinical Presentation Obstructive jaundice occurs frequently when the cancer is located in the head of the pancreas. This may be accompanied