Ductal adenocarcinoma is the most common primary malignant disease of the pancreas and periampullary region. It accounts for more than 75% of all nonendocrine tumors arising in this region, which includes the pancreas, the ampulla of Vater, the distal common bile duct, and the peripancreatic duodenum. Pancreatic adenocarcinoma is the most common of the periampullary neoplasms. In the United States, the annual incidence of pancreatic cancer is 9 cases per 100,000 population; it ranks eleventh among all cancers and ninth among nondermatologic cancers. It remains the most lethal cancer, with an overall 5-year survival rate of less than 3% and a death-to-incidence ratio of approximately 0.99. Because more than 28,000 persons in the United States are expected to die of pancreatic cancer in 2000, it is the fifth leading cause of cancer deaths in this country. This chapter largely focuses on pancreatic adenocarcinoma.

Ampullary, distal common bile duct, and duodenal adenocarcinomas are less common than pancreatic tumors. They account for 15 to 20% of all periampullary malignant diseases. Arising in the same region, they are associated with similar clinical presentations and management algorithms, but these tumors have different survival rates. These entities are discussed briefly in this chapter.

Epidemiology and Risk Factors

Demographic Patterns

The risk factors for pancreatic cancer have been well studied and are summarized in Table 5–1. From 1920 to 1978, the incidence rates of pancreatic cancer in the United States increased nearly threefold, and they subsequently have plateaued. In nearly all European countries, a similar increase has been observed, with incidence rates that continue to rise. A portion of this apparent increase may have resulted from misclassification of pancreatic cancers as other cancers, particularly gastric cancer, early in the 1900s. However, several subsequent analyses have indicated that part of the increase is real, despite confounding factors.2–4

Advancing age is a risk factor for pancreatic cancer, with 80% of cases occurring in patients 60 to 80 years of age. The gender distribution of pancreatic cancer has nearly equalized, and the incidence is slightly higher in males. Blacks have the highest worldwide risk of pancreatic cancer, a risk approximately 30 to 40% higher than that observed in whites.2

In population studies in the United States, pancreatic cancer occurs more frequently among Jews than among Roman Catholics or Protestants. A similar pattern is observed among Jews and non-Jews in Israel. Mormons in Utah have been reported to have a lower incidence of pancreatic and other smoking-related cancers. However, this decrease is also seen in non-Mormons living in Utah, a finding suggesting that environmental factors may play a significant role. Some evidence indicates that migrant status is a risk factor. Immigrants from Japan have a threefold higher risk of developing pancreatic cancer than do children born in the United States of Japanese immigrant parents and a 1.7-fold higher risk than whites in the United States.2

From a worldwide perspective, pancreatic cancer rates are highest in Western and industrialized countries and lowest in developing nations. An exception is noted in the Maoris, a Polynesian people native to New Zealand, who have incidence rates similar to those seen in developed countries.5

Host Factors

Host factors play an important role in the development of pancreatic cancer. The most striking examples are the six genetic syndromes associated with an increased risk of developing pancreatic cancer. These syndromes are hereditary nonpolyposis colorectal cancer (HNPCC), familial breast cancer associated with BRCA-2 mutations, Peutz-Jeghers syndrome, ataxia-telangiectasia syndrome, familial atypical multiple mole–melanoma syndrome (FAMMM), and hereditary pancreatitis. In addition to the genetic syndromes, pancreatic cancer has been noted to aggregate in families. Evidence from the National Familial Pancreas Tumor Registry (NFPTTR) at the Johns Hopkins Hospital in Baltimore indicates that members of families with two or more first-degree relatives affected by pancreatic cancer have at least a 16-fold increased risk of developing pancreatic cancer. This finding could be accounted for by a common nongenetic environmental exposure; however, evidence suggests that this observed familial aggregation has some genetic basis.6

Chronic pancreatitis, which is most commonly related to alcoholism, has been associated with an increased risk of developing pancreatic cancer. Although several studies...
Environmental Factors: Tobacco Diet Alcohol

Host Factors: Hereditary nonpolyposis colorectal cancer Diabetes Peptic ulcer surgery Tonsillectomy

A large body of evidence links cigarette smoking to pancreatic cancer. Nitrosamines and tobacco smoke have been shown to be carcinogenic for the pancreas in animal studies. In addition, human autopsy studies reveal hyperplastic changes with atypical nuclear patterns in the pancreatic ductal cells of smokers. Several prospective studies evaluating death from pancreatic cancer in smokers have demonstrated increased risk ratios ranging from 2 to 16. Some, but not all, studies demonstrated a dose-response relationship with either the number of cigarettes smoked or the duration of smoking.

Several reviews have examined the relationship of dietary factors to the development of pancreatic cancer. Despite conflicting data, some generalizations can be made. Pancreatic cancer appears to be associated with increased total energy intake, as well as increased intake of carbohydrate, cholesterol, meat, salt, dehydrated food, fried food, refined sugar, soybeans, and nitrosamines. Fat, beta carotene, and coffee are of unproven risk, whereas dietary fiber, vitamin C, fruits, vegetables, absence of preservatives, raw foods, pressure cooking, and microwave cooking may have a protective effect. Alcohol, coffee, and radiation exposure do not appear to be risk factors for the development of pancreatic cancer despite conflicting reports. When controlling for age, gender, smoking, socioeconomic status, and amount of alcohol consumed, three case-control studies from Europe failed to demonstrate an association between alcohol and pancreatic cancer. Despite past reports of increased risk of pancreatic cancer with coffee consumption, numerous subsequent reports have reported no association between the two. On the basis of these data, if an association exists, it is likely weak. The pancreas appears to be relatively insensitive to ionizing radiation, as demonstrated by studies evaluating the survivors of the bombings of Hiroshima and Nagasaki. These studies have shown no increased risk of pancreatic cancer.

### Risk Factors for Other Periampullary Cancers

Other periampullary cancers including distal common bile duct, ampullary, and duodenal cancers are less common and therefore are less well characterized in terms of risk factors. All are associated with increased age, with peak incidences in the 60- to 80-year range. Distal common bile duct cancers are associated with several known host factors in addition to advanced age. These include inflammatory bowel disease, sclerosing cholangitis, choledochal cysts, and intrahepatic or common bile duct stones. In addition, a geographic association has been noted for bile duct cancers, with clusters observed in some parts of the United States. Duodenal and ampullary cancers occur with increased frequency in patients with

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**Table 5–1. Epidemiology and Risk Factors**

<table>
<thead>
<tr>
<th>Increased Risk</th>
<th>Possible Risk</th>
<th>Unproven Risk</th>
<th>Decreased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Factors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advancing age</td>
<td>Geography</td>
<td>Socioeconomic status</td>
<td></td>
</tr>
<tr>
<td>Black race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jewish ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Host Factors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer</td>
<td>Diabetes</td>
<td>Peptic ulcer surgery</td>
<td></td>
</tr>
<tr>
<td>Familial breast cancer</td>
<td>Chronic pancreatitis</td>
<td>Cholecystectomy</td>
<td></td>
</tr>
<tr>
<td>Peutz-jeghers syndrome</td>
<td>Endocrine tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>Cystic fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial atypical multiple-mole melanoma</td>
<td>Sex hormones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>Pernicious anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Environmental Factors:</td>
<td>Diet</td>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td>Occupation</td>
<td>Coffee</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiation</td>
<td></td>
</tr>
</tbody>
</table>

hereditary polyposis syndromes including HNPCC, Peutz-Jeghers syndrome, familial adenomatous polyposis, and Gardner’s syndrome.

**PATHOLOGY**

Cancer of the pancreas and periampullary region can be broadly classified as primary, metastatic, or systemic. Primary cancers arise in the pancreas or other periampullary sites and can demonstrate either endocrine or nonendocrine differentiation. Ductal adenocarcinoma is by far the most common periampullary malignant disease. A careful analysis has yielded a large variety of histologic subtypes.

**Primary Solid Nonendocrine Epithelial Tumors**

*Ductal adenocarcinoma,* the most common primary pancreatic malignant disease, accounts for approximately 75% of all primary nonendocrine cancers. The head, neck, and uncinate process of the pancreas harbor 65% of all ductal carcinomas. In many cases, the tumor arises in close proximity to the genu (or knee) of the main pancreatic duct. An additional 15% of these tumors originate in the body and tail of the pancreas, whereas another 20% of lesions diffusely involve the gland. On gross section, ductal adenocarcinomas are white-yellow, poorly defined, firm masses that often obstruct the main pancreatic duct or common bile duct and lead to postobstructive dilatation.

Because of the tumor’s infiltrative nature, appreciating the true extent of neoplasm is often difficult intraoperatively. Microscopic analysis often demonstrates tumor extending beyond the grossly defined mass. On histologic analysis, ductal adenocarcinomas contain infiltrative glands of various shapes and sizes surrounded by an intense desmoplastic response (Fig. 5–1). The nuclei of the cells often show marked pleomorphism, hyperchromasia, loss of polarity, and prominent nucleoli. The epithelial cells often contain mucin and may form papillae and cribriform structures. These tumors frequently invade the vascular, lymphatic, and perineural spaces (Fig. 5–2). Such invasion is associated with a reduction in survival.

Ductal adenocarcinomas are typically aggressive tumors; most resected adenocarcinomas have already metastasized to regional lymph nodes. Moreover, these tumors may grow by direct extension to involve the common bile duct, duodenum, stomach, spleen, transverse mesocolon and colon, and adrenal glands. At the time of death, up to 80% of patients have liver metastases, 60% have peritoneal implants, 50 to 70% have metastases to the lungs or pleura, and 25% have metastases to the adrenal glands.

Increasing evidence suggests that pancreatic ductal adenocarcinoma has identifiable precursor lesions. In pancreata resected for pancreatic cancer, the epithelial cells adjacent to the tumor often show high-grade dysplasia or atypia (Fig. 5–3). Investigators have shown that papillary ductal lesions are three times more common in patients with pancreatic cancer than in normal pancreata. In addition, three-dimensional mapping techniques have demonstrated a stepwise transformation from mild to severe dysplasia in pancreatic duct lesions, and several cases have been reported in which ductal adenocarcinomas developed after the diagnosis of high-grade pancreatic intraepithelial neoplasia was made. Finally, ductal lesions display some of the same genetic changes as infiltrating carcinomas, specifically k-ras, p53, and p16 mutations, findings further supporting the existence of a precursor progression sequence.

Ductal adenocarcinomas of the pancreas, ampulla of Vater, distal common bile duct, and duodenum may be difficult to differentiate prior to microscopic evaluation. Histologically, the site of tumor origin is identified by (1)
looking for a component of carcinoma in situ in the pancreatic duct, ampulla of Vater, distal common bile duct, or duodenum and (2) determining where the tumor is centered (Fig. 5–4). It is important to differentiate these tumors because they have varying prognoses.

Adenosquamous carcinoma is a variant of adenocarcinoma with both glandular and squamous differentiation. It occurs more frequently in patients with a history of chemoradiation and has biologic behavior similar to that of ductal adenocarcinoma.

Giant cell carcinomas account for less than 5% of solid pancreatic malignant tumors. They arise with equal frequency in the head, body, and tail of the gland and are characterized grossly as large, hemorrhagic tumors. Microscopically, these tumors contain large, uninucleated or multinucleated tumor cells that are strikingly pleomorphic, with hyperchromatic, sharply angulated nuclei, prominent nucleoli, and bizarre mitotic figures. These tumors appear to be associated with a poorer prognosis than ductal cancers.

Acinar cell carcinomas have a distinct histologic appearance, typically larger (often greater than 10 cm), fleshy, often hemorrhagic, forming acini, and lacking a strong desmoplastic response. Immunohistochemical stains are often positive for trypsin, lipase, chymotrypsin, or amylase. In addition to biliary obstruction, up to 20% of patients with acinar cell cancers present with subcutaneous fat necrosis, an erythema nodosum–like rash, peripheral eosinophilia, and polyarthralgia. Patients with acinar cell cancers have a slightly better prognosis than do patients with the ductal counterparts of these tumors.

Pancreatoblastoma, or pancreatic cancer of infancy, occurs in children up to the age of 15 years. These tumors contain undifferentiated portions with back-to-back small cells in a syncytial growth pattern with eosinophilic cytoplasm and benign-appearing nuclei. The differentiated portions can demonstrate squamous, acinar, and endocrine differentiation. These tumors are uncommon and are associated with survival rates better than those seen in patients with ductal adenocarcinoma.

Primary Cystic Nonendocrine Epithelial Tumors

Cystic neoplasms account for fewer than 15% of cystic pancreatic lesions. However, these entities are important to recognize because their management is vastly different from that of nonneoplastic pancreatic cystic lesions including pseudocysts, congenital cysts, and retention cysts.

Serous cystic neoplasms, often called microcystic adenomas or glycogen-rich cystadenomas, vary in diameter and appear grossly as well-circumscribed, multiloculated cysts with watery, clear, or brown fluid. Simple cuboidal cells line the cyst, separated from one another by dense, fibrous bands (Fig. 5–5). These lesions are more common in women than in men. Most are benign, with only rare reports of metastases to lymph nodes.
Mucinous cystic neoplasms range from benign tumors with small cysts lined by a single layer of columnar epithelium to larger cysts associated with an infiltrating component. They, too, are more common in women. These tumors often harbor a dense stroma beneath the epithelial cells, similar to that seen in the ovary (Fig. 5–6). Microscopically, three different classes of mucinous neoplasms are seen: (1) mucinous cystadenomas, which contain a single layer of epithelium without atypia; (2) intermediate or borderline tumors, which may have cellular atypia and more complex architecture including papillae; and (3) mucinous cystadenocarcinoma, with invasion of epithelial cells into surrounding stroma. In contrast to serous cystic neoplasms, mucinous cystic neoplasms are precancerous lesions, and benign-appearing mucinous lesions may harbor small foci of invasive carcinoma. Therefore, all mucinous cystic neoplasms should be resected completely. Patients with resected mucinous cystadenocarcinoma are observed to have 5-year survival rates more than double those seen in patients with ductal pancreatic adenocarcinoma.

Intraductal papillary-mucinous neoplasms, also known as intraductal mucin-hypersecreting neoplasms, mucinous duct ectasia, and intraductal papillary neoplasms, contain columnar mucin-secreting cells with varying degrees of atypia that line papillary projections. These lesions reside within mucus-filled dilated pancreatic ducts and often diffusely involve the gland. They sometimes harbor k-ras mutations and may contain invasive carcinoma. Most patients have favorable outcomes after complete resection.

Solid and cystic papillary neoplasms, or Hamoudi’s tumors, occur most commonly in women aged 30 to 50 years. They are typically large tumors (5 to 15 cm) associated with cysts, hemorrhage, and necrosis. Microscopically, they contain solid, cystic, and papillary components. These lesions are typically benign, although metastases have been reported.

**Other Tumors**

Beyond the scope of this chapter are other uncommon tumors including malignant diseases metastatic to the pancreas, systemic malignancies, and mesenchymal tumors. The most common malignant diseases that metastasize to the pancreas are renal cell, breast, colorectal, small cell lung, and melanoma. Systemic malignant conditions involving the pancreas include leukemia and lymphoma. The benign and malignant mesenchymal tumors that affect the pancreas include leiomyosarcoma, liposarcoma, schwannoma, and malignant fibrous histiocytoma.

**Molecular Biology of Pancreatic Cancer**

Pancreatic cancer, like many other malignancies, is a disease of acquired and inherited mutations in cancer-causing genes. These cancer-causing genes can be divided into three broad categories: tumor suppressor genes, oncogenes, and DNA mismatch repair genes. Mutation in all three types of genes can accumulate to cause pancreatic adenocarcinoma. Most pancreatic cancers are multigenic. In an in-depth mutational analysis of 42 pancreatic cancers by Rozenblum and colleagues, all 42 tumors harbored k-ras mutations. Individual mutational frequencies of tumor suppressor genes p16, p53, DPC4, and BRCA2 were 82%, 76%, 53% and 10%, respectively.

**Tumor Suppressor Genes**

Tumor suppressor genes normally function to restrain cell proliferation. Loss of function of these genes by mutation, deletion, chromosome rearrangement, or mitotic recombination results in abnormally increased cell proliferation. At least five tumor suppressor genes are known to play a role in the development of pancreatic cancer (Table 5–2). In order of decreasing frequency of inactivation in pancreatic cancer, they are p16, p53, DPC4, BRCA2, and MKK4.

The p16 tumor suppressor gene, located on chromosome 9p, is inactivated in approximately 95% of pancreatic cancers. p16 is an important regulator of the cell cycle. The gene encodes for a protein that binds cyclin D-Cdk4 complexes. This subsequently inhibits the phosphorylation of a number of growth and regulatory pro-

| Table 5–2. Tumor Suppressor Genes in Pancreatic Cancer* |
|-------------|----------------|-------------|
| **Gene**    | **Chromosome Location** | **Frequency (%)** |
| p53         | 17p             | 75          |
| p16         | 9p              | 80          |
| DPC4        | 18q             | 50          |
| BRCA2       | 13q             | 4–7         |
| MKK4        | 7p              | 4           |

teins and leads to failure of cellular control and unchecked cellular proliferation.

The second most frequently inactivated tumor suppressor gene is p53, a well-characterized tumor suppressor that lies on chromosome 17p. It is inactivated in approximately 75% of all pancreatic cancers. Like p16, the p53 gene encodes for an important regulator of the cell cycle. The p53 gene product is a nuclear DNA binding protein that not only acts as a cell cycle check point but also serves to induce cell death (apoptosis). Therefore, mutations or deletions in the p53 gene lead to the loss of two important controls of cellular growth: the regulation of cellular proliferation and the induction of cell death.

The DPC4 gene on chromosome 18q is inactivated in approximately 50% of pancreatic cancers. The gene product of DPC4 appears to play a role in signal transduction involving the transforming growth factor-beta receptor. In contrast to p16 and p53, the inactivation of DPC4 appears to be relatively specific for pancreatic cancer.

The fourth major tumor suppressor gene known to be inactivated in pancreatic cancer is BRCA2, located on chromosome 13q. BRCA2 is inactivated in approximately 7% of pancreatic cancers. The BRCA2 mutation appears to be an inherited germline mutation as opposed to the acquired mutations commonly seen in p16, p53, and DPC4.

M KK4 (mitogen-activated protein kinase kinase 4), located on chromosome 17p, has been identified as a candidate tumor suppressor gene in pancreatic cancer. MKK4 plays a central role in the stress- and cytokine-induced signal transduction pathway involving mitogen-activated protein kinase (MAPK) proteins. Approximately 4% of pancreatic cancers appear to have mutations in MKK4.

### Oncogenes

Oncogenes are derived from normal cellular genes called proto-oncogenes that, when activated by a mutation or amplification, possess transforming properties. Activating point mutations in codons 12, 13, and 61 of the k-ras gene are common genetic alterations in pancreatic cancer. Mutations in k-ras are present in 80 to 100% of pancreatic cancers, and most are located at codon 12. k-ras mutations impair the intrinsic guanosine triphosphatase activity of its gene product and result in a protein that is constitutively active in signal transduction. Localization of these mutations to a single codon makes them relatively easy to detect and makes k-ras a potential target for molecular-based screening tests for pancreatic cancer.

### DNA Mismatch Repair Genes

DNA mismatch repair genes encode for proteins that correct many errors that normally occur when DNA is replicated. When these mismatch repair genes are dysfunctional, errors in DNA replication are not repaired. Mutations in DNA mismatch repair genes can lead to pancreatic cancer, as in the case of RER+ (replication error-positive) tumors. In RER+ tumors, mutations accumulate in normal simple repeated sequences located throughout the genome, known as “CA” repeats. This leads to well-defined molecular phenotype called “microsatellite instability.” An associated microscopic phenotype has poor differentiation, pushing borders, and a syncytial growth pattern. Microsatellite instability occurs in approximately 4% of pancreatic cancers.

### Familial Pancreatic Cancer

The familial aggregation of pancreatic cancer can be divided into two broad categories: those associated with known clinical syndromes and those without such an association. Six genetic syndromes have been associated with pancreatic cancer: hereditary pancreatitis, HNPCC, familial breast cancer, FAMMM, ataxia-telangiectasia, and Peutz-Jeghers syndrome. The mode of inheritance, gene, and chromosomal location are summarized in Table 5–3.

Pancreatic cancers also aggregate in families without known genetic syndromes. An analysis of the NFPT at the Johns Hopkins Hospital compared familial and sporadic cases of pancreatic cancer. The results suggest that familial aggregation has a genetic basis and is not due solely to a nongenetic environmental factor. In contrast to other familial cancers, familial cases were found to occur at a similar mean age as nonfamilial cases (65.8 years old).

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mode of Inheritance</th>
<th>Gene</th>
<th>Chromosome Locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary pancreatitis</td>
<td>AD</td>
<td>Cationic trypsinogen</td>
<td>7q35</td>
</tr>
<tr>
<td>HNPCC</td>
<td>AD</td>
<td>MSH2</td>
<td>2p</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MLH1</td>
<td>5p</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMS2</td>
<td>7p</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMS1</td>
<td>2q</td>
</tr>
<tr>
<td>Familial breast cancer</td>
<td>AD</td>
<td>BRCA2</td>
<td>13q</td>
</tr>
<tr>
<td>FAMMM</td>
<td>AD</td>
<td>p16</td>
<td>9p</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>AR</td>
<td>ATM</td>
<td>11q 22–23</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>AD</td>
<td>STK11</td>
<td>19p</td>
</tr>
</tbody>
</table>

AD = autosomal dominant, AR = autosomal recessive, FAMMM = familial atypical multiple-mole melanoma syndrome, HNPCC = hereditary nonpolyposis colorectal cancer.

years versus 65.2 years). In addition, familial cases had an increased proportion of second primary cancers (23.8% versus 18.9%), first-degree relatives with any cancer (28.2% versus 14.9%), second-degree relative with any cancer (27.2% versus 12.1%), and second-degree relatives with pancreatic cancer (3.7% versus 0.6%). Additionally, the NFPTR has gathered data concerning the prospective risk of pancreatic cancer in persons who have two or three affected first-degree relatives with the tumor. The risk is increased 16-fold with two affected first-degree relatives, and it is 33-fold with three affected first-degree relatives. Additional clinical and molecular data are needed to characterize familial pancreatic cancer better.

GROWTH FACTORS

Increasing evidence suggests that the overexpression of various polypeptide growth factors and their receptors may play a role in the development and biologic aggressiveness of pancreatic cancers. These factors act in an autocrine or paracrine fashion at or near their site of origin. They include epidermal growth factor, transforming growth factor-beta, fibroblast growth factors, and insulin and insulin-like growth factor.

CLINICOPATHOLOGIC STAGING

The most commonly used staging system for pancreatic adenocarcinoma is the Union Internationale Contre le Cancer (UICC) system, which is a tumor-node-metastasis (TNM)-based system (Table 5–4). The system allows stage classification by primary tumor extent (T), regional lymph node involvement (N), and the presence or absence of distant metastases (M), with determination of four stage groupings based on the TNM characteristics. A more complex staging system has been proposed by the Japan Pancreas Society (Table 5–5), including additional factors such as serosal invasion (S factor), retroperitoneal invasion (RP factor), and portal venous invasion (PV factor). Because of its cumbersome nature, this system has not gained common use.

DIAGNOSIS, IMAGING, AND STAGING

Clinical Presentation

Patients with pancreatic and other periampullary neoplasms often have vague symptoms early in the course of their disease. These symptoms often go unrecognized and lead to a delay in diagnosis. Approximately 65 to 75% of patients with pancreatic cancer come to medical attention when they develop obstructive jaundice secondary to obstruction of the intrapancreatic portion of the common bile duct. The jaundice is often associated with pruritus, acholic stools and dark urine. Despite the teaching that pancreatic carcinoma classically presents with painless jaundice, most patients experience pain as part of their presenting symptoms. Early in the course, the pain is often described as a vague upper abdominal, epigastric, or back discomfort. The pain can progress to unremitting epigastric pain radiating to the back. Weight loss and other constitutional symptoms including anorexia, fatigue, and change in bowel habits are seen in the majority of patients. Nausea and vomiting, usually as a result of early gastric outlet or duodenal obstruction, can occur frequently in this patient population and may be an ominous sign of locally advanced disease.

Occasionally, pancreatic cancer can present in an unusual manner. Asymptomatic patients may be found to have elevated liver function tests on routine laboratory screening. New-onset diabetes mellitus may be the first sign in approximately 10% of patients. Anemia secondary to gastrointestinal blood loss from erosion of the tumor into the duodenum is seen infrequently. Acute
Table 5–5. Japan Pancreas Society Stage Classification*

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>T</th>
<th>S</th>
<th>RP</th>
<th>PV</th>
<th>N</th>
<th>M</th>
<th>5-Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>S0</td>
<td>RP0</td>
<td>PV0</td>
<td>N0</td>
<td>M0</td>
<td>35–45%</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>S1</td>
<td>RP1</td>
<td>PV1</td>
<td>N1</td>
<td>M0</td>
<td>15–25%</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
<td>S2</td>
<td>RP2</td>
<td>PV2</td>
<td>N2</td>
<td>M0</td>
<td>5–15%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T4</td>
<td>S3</td>
<td>RP3</td>
<td>PV3</td>
<td>N3</td>
<td>M1</td>
<td>0–10%</td>
</tr>
</tbody>
</table>

Tumor (T)
- T1 = 0 to 2 cm
- T2 = 2.1 to 4 cm
- T3 = 4.1 to 6 cm
- T4 = >6.1 cm

Serosal invasion (S); Retroperitoneal invasion (RP); Portal venous invasion (PV)
- 0 = Absence of invasion
- 1 = Suspected invasion
- 2 = Definite invasion
- 3 = Severe invasion

Lymph nodes (N)
- N0 = No metastasis
- N1 = Primary lymph node group metastasis
- N2 = Secondary lymph node group metastasis
- N3 = Tertiary lymph node group metastasis

Distant metastasis (M)
- M0 = No distant metastasis
- M1 = Distant metastasis


Pancreatitis resulting from partial or complete obstruction of the pancreatic duct may be the first sign of a pancreatic neoplasm. It is therefore important to entertain the diagnosis of periampullary cancer in older patients presenting with acute pancreatitis and no obvious cause (i.e., no history of alcohol abuse and no biliary tract disease).

Although patients with pancreatic and distal common bile duct lesions are more likely to present with obstructive jaundice, those with ampullary and duodenal primary tumors are less likely to be jaundiced and are more likely to have signs of gastric outlet obstruction. Further, patients with lesions in the body and tail of the pancreas are more likely to have weight loss and abdominal pain, without jaundice. For this reason, left-sided pancreatic neoplasms are often diagnosed at a later stage and are associated with a poorer prognosis.

At the time of diagnosis, common findings on physical examination include jaundice, hepatomegaly, and a palpable gallbladder (Courvoisier’s gallbladder). Many patients have skin irritation resulting from the extreme pruritus and resultant scratching. Cachexia and muscle wasting are often signs of advanced disease. A search for metastatic disease should be undertaken during the physical examination. Such findings include a nodular liver, left supraclavicular adenopathy (Virchow’s node), periumbilical adenopathy (Sister Mary Joseph’s node), and pelvic metastases encircling the perirectal region (Blumer’s shelf).

In patients with cancers of the head of the pancreas or periampullary region, serum total and direct bilirubin, alkaline phosphatase, and gamma-glutamyl transpeptidase values are often markedly elevated, with associated mild elevations in the hepatic transaminases. Patients with pancreatic body and tail lesions often have normal laboratory values early in their course and only develop liver function test abnormalities later, a finding indicating diffuse metastatic disease with involvement of the porta hepatis. In patients with markedly elevated bilirubin levels, coagulation parameters should be checked. Decreased enterohepatic circulation of bile salts leads to malabsorption of fat-soluble vitamins and subsequent decreased hepatic production of vitamin K–dependent clotting factors. Hypoalbuminemia and normochromic anemia are often seen, reflections of poor nutritional status as a result of the underlying neoplastic process.

Considerable effort has been made to find serum markers for pancreatic cancer to facilitate early diagnosis. At present, the best available marker is the carbohydrate antigen 19-9 (CA 19-9). Serum levels of CA 19-9 are elevated to levels higher than normal (37 units/ml) in approximately 75% of patients with pancreatic cancer. CA 19-9 is also elevated in 10% of patients with benign conditions of the pancreas, liver, and bile ducts. A CA 19-9 level higher than the upper limit of normal has an accuracy of 80% in identifying patients with pancreatic cancer. Higher cutoff values increase the accuracy and specificity of the test, at the expense of decreasing the sensitivity. CA 19-9 as an independent test is not sufficiently sensitive or specific to warrant its use in population screening. In addition to diagnosis, CA 19-9 has been useful in following patients after resection of disease or during adjuvant and neoadjuvant regimens. Increasing levels of CA 19-9 reflect progression of disease, whereas
steady or declining levels suggest a stable tumor burden.55,56 Results of studies looking at other potential tumor markers including SPAN-1, CA-50, DUPAN-2, elastase 1, tissue polypeptide antigen, and tissue polypeptide-specific antigen have all been disappointing, with accuracy rates lower than those seen for CA 19-9. TIMP-1 (tissue inhibitor of metalloproteinase-1) has been shown by serial analysis of gene expression (SAGE) methodology to hold promise as an improved serum marker for pancreatic cancer.57

About 90% of pancreatic cancers contain mutations in the k-ras proto-oncogene. k-ras mutations have been detected from duodenal juice, pancreatic juice, stool and fine-needle aspirates of patients with proven pancreatic adenocarcinoma.58–60 Although this test is not commercially available, the use of such molecular genetic markers in the early diagnosis of pancreatic cancer may be crucial for earlier detection strategies.

Diagnostic Imaging

Diagnostic imaging modalities for patients with suspected periampullary neoplasms include ultrasonography, computed tomography (CT) scanning, magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and positron emission tomography (PET). With appropriate use of these studies, one should be able to arrive at the diagnosis of pancreatic cancer in more than 90% of patients presenting with the disease.

Standard transcutaneous abdominal ultrasound remains the most sensitive test for the detection of gallstones and is useful in demonstrating a dilated intrahepatic and extrahepatic biliary tree in cases of obstructive jaundice. Ultrasound examination can provide information about liver metastases, pancreatic masses, peripancreatic adenopathy, and ascites, but it depends on both the operator and the patient’s body habitus. Ultrasound scans reveal a pancreatic mass in 60 to 70% of patients with pancreatic cancer. However, the absence of a pancreatic mass on ultrasound scanning does not definitively rule out pancreatic cancer. If a pancreatic mass is identified, spiral CT is often indicated, because CT provides more complete and accurate imaging of the pancreatic head and surrounding structures. It has largely supplanted ultrasound as the initial diagnostic procedure of choice.

At present, high-quality spiral or helical CT is the single most useful staging modality.61 Pancreatic cancer usually appears as an area of enlargement in the pancreas, generally as a hypodense, focal lesion (Fig. 5–7). CT scanning provides useful information not only about tumor size but also about the extent of disease. Spread to the liver, peripancreatic lymph nodes, or retroperitoneal structures may be demonstrated. In addition, the CT scan can be used to evaluate major vessels adjacent to the pancreas (superior mesenteric artery and vein, portal vein, splenic vein, hepatic artery) for tumor invasion, encasement, or thrombosis (Fig. 5–8), to give useful information regarding resectability. Tumors smaller than 1 cm can be missed, and intrahepatic and extrahepatic ductal dilatation may be the only finding on spiral CT. Such a finding is suspicious for malignancy and should be followed up by cholangiography (ERCP, MRCP, or PTC).

Advances in MRI technology suggest that it may play an increasing role in pancreatic imaging. Ultrafast spin-echo MRI has been reported to be more sensitive than classic CT scanning, but because of motion artifacts, lack of bowel opacification, low spatial resolution, and low signal-to-noise ratio, MRI has not been shown to have a definitive advantage over modern CT scanning.61 MRCP holds promise as a noninvasive technique to image the biliary and pancreatic ductal systems in a fashion similar
to ERCP (Fig. 5–9). Likewise, magnetic resonance angiography (MRA) provides a noninvasive technique to evaluate major vascular involvement when CT is equivocal. Thus, MRI or MRCP has the potential to provide information about tumor size and extent, biliary and pancreatic ductal anatomy, and vascular involvement through a single, noninvasive procedure.

ERCP is a sensitive diagnostic test for pancreatic cancer, with sensitivities in the range of 90%. The finding of a long, irregular stricture in an otherwise normal pancreatic duct or a “double-duct sign” (cutoff of both the pancreatic and distal bile duct at the level of the genu of the pancreatic duct) with an appropriate history is nearly pathognomonic for pancreatic cancer (Fig. 5–10). However, with the current advances in CT and MRI technology, diagnostic ERCP is rarely necessary. ERCP or other forms of cholangiopancreatography should be considered in patients with common bile duct or pancreatic duct obstruction without the finding of a pancreatic mass on CT or MRI. ERCP can also be useful in distinguishing chronic pancreatitis from pancreatic cancer. Chronic pancreatitis is usually characterized by multiple focal stenoses of the pancreatic duct, with involvement of secondary and tertiary radicles, whereas pancreatic cancer is usually characterized by an abrupt cutoff of the pancreatic duct at a single location. Beyond its use in diagnosis, ERCP can be used therapeutically in patients with significant jaundice, because endoscopic stents (endoprosthesis) can be placed for decompression of the biliary tree.

PTC is another means of delineating biliary anatomy and can be accompanied by percutaneous biliary drainage (PBD) for relief of jaundice. When compared with ERCP and endoscopic drainage, PTC has the potential advantage of better defining proximal biliary anatomy and the level of biliary obstruction. However, PTC has several disadvantages, including its more invasive and traumatic nature, the risk of hemobilia, and the inability to visualize the pancreatic duct. In most cases, PTC or PBD is used only occasionally for patients with pancreatic or periampullary neoplasms and typically only after an unsuccessful ERCP.

The foregoing tests remain the mainstays of imaging in patients with suspected periampullary neoplasms. PET scanning, which uses the increased glucose metabolism of pancreatic cancer cells as the basis of imaging, has been evaluated as a tool for the diagnosis of periampullary neoplasms. At present, studies have failed to demonstrate a dramatic advantage over spiral CT scanning. PET scanning may be better able to distinguish between chronic pancreatitis and pancreatic cancer, and it may have some increased sensitivity for delineating metastatic disease.

Upper endoscopy is useful in the diagnosis of primary duodenal and ampullary neoplasms, because access by the endoscopic route allows for direct tumor visualization and acquisition of tissue by biopsy. In addition, upper endoscopy can evaluate the degree of duodenal invasion or narrowing by a periampullary lesion.

**Tissue Diagnosis**

The use of percutaneous pancreatic biopsy in the diagnostic evaluation of patients with suspected pancreatic...
neoplasms remains controversial. Biopsy under CT or ultrasonic guidance can be performed with nearly 100% specificity and 70 to 80% sensitivity in experienced hands.⁶³ Although a positive histologic diagnosis of malignancy is reliable, because of sampling error, malignancy cannot be ruled out with certainty when no malignant cells are found in the aspirate. Percutaneous biopsy can generally be performed safely, but rare complications including pancreatic fistula, pancreatitis, hemorrhage, abscess, and death have been reported. In addition, concerns exist regarding tumor dissemination resulting from capsular puncture of the neoplasm. Tumor seeding of the biopsy tract has been reported.⁶⁴

Currently percutaneous biopsy has no role in patients at low operative risk who are thought to have resectable disease. A negative biopsy in this group should not preclude exploration and resection and leaves no reason to perform a biopsy in this setting. Percutaneous biopsy should be performed in patients who are believed to be at prohibitively high operative risk and in patients whose tumors are believed to be unresectable because of locally advanced or metastatic disease. These patients may be candidates for palliative chemoradiation therapy, which cannot be performed without a tissue diagnosis. Further, percutaneous biopsy should be considered in patients whose presentation and workup are not suggestive of adenocarcinoma, but rather suggest more uncommon lesions including neuroendocrine tumors, pancreatic lymphomas, or tumors metastatic from another primary site, when such a diagnosis would dictate further management. Endoscopic access with biopsy or fine-needle aspiration (FNA) appears to be a more attractive means of obtaining a tissue diagnosis, when one is necessary. Such a practice may supersede percutaneous biopsy in the future.

**Preoperative Staging**

After making the diagnosis of periampullary cancer, the clinician should stage the tumor. In clinical practice, substantial overlap exists between diagnosis and staging. The studies used in the diagnostic workup of patients with periampullary cancer also aid in the staging or determination of resectability. Liver or peritoneal metastases and locally advanced cancers involving major vascular structures are the most common reasons precluding resection.

Spiral CT is not only the single most useful tool in the diagnosis of periampullary neoplasms, but it also serves as a major staging tool.⁶⁴ CT accurately detects liver metastases larger than 2 cm, but it frequently misses those smaller than 1 cm. CT is not highly accurate in determining retroperitoneal adenopathy or extension of tumor or in identifying peritoneal carcinomatosis in the absence of ascites. However, CT provides a great deal of information regarding local resectability. The preservation of fat planes around major peripancreatic vascular structures including the celiac axis, superior mesenteric vessels, and portal vein suggests no invasion of these structures by the tumor and is predictive of resectability.⁶⁵ Occlusion of the portal vein or superior mesenteric vessels and evidence of periportal collateral vessels indicate unresectable disease and preclude curative resection for lesions in the pancreatic head, neck, or uncinate process. For pancreatic body and tail lesions, the splenic vein is often compromised or occluded by tumor; however, this finding by itself is not a contraindication for resection.

Angiography was once the standard for the determination of vascular involvement by periampullary cancers. This method is now controversial; some studies have demonstrated that angiography enhances the reliability of CT, and other studies have shown that high-quality spiral CT can predict resectability better than angiography. Angiography is useful in diagnosing vascular invasion by tumor (Fig. 5–11) as well as vascular anomalies that may be clinically relevant (i.e., replaced right hepatic artery, stenosis of the celiac trunk). However, the experienced pancreatic surgeon should be able to identify these anomalies at the time of surgery. Pancreatic cancers, which infiltrate into surrounding tissues, are often associated with a desmoplastic response. The finding of venous encasement on an angiogram, often believed to represent tumor involvement of major venous structures, may instead be the result of this desmoplastic response. Angiography should be applied selectively when a question of vascular involvement on spiral CT exists. In addition, angiography is useful for patients in whom intraoperative assessment of major vessel involvement may be difficult, such as those who have undergone previous pancreatic or hepatobiliary surgery or those with a history of prior neoadjuvant chemoradiation therapy.

Endoscopic ultrasound (EUS) produces images of the pancreas using the wall of the stomach and duodenum.
as an acoustic window. The addition of EUS-guided FNA can also provide a tissue diagnosis in cases when one is desired.\textsuperscript{66} Although highly accurate in assessing the size and extent of the primary tumor (Fig. 5–12) and in detecting invasion of the portal and mesenteric vessels, EUS cannot reliably detect lymph node involvement or metastatic disease in the liver and must be used in combination with CT or MRI scans.

A further controversy in the management of patients with pancreatic and periamplullary tumors involves the role of staging laparoscopy. Staging laparoscopy can be performed safely on an outpatient basis using a 30-degree angled laparoscope to evaluate the peritoneal surfaces, the pericolic gutters, the hemidiaphragms, the pelvis, and the surface of the liver. Biopsies of peritoneal, liver, or omental nodules as well as enlarged lymph nodes can be performed. Experienced laparoscopists can perform a more extensive exploration including examination of the hilum of liver and the use of laparoscopic ultrasound to look for deep liver metastases and major vascular involvement.\textsuperscript{67–71} The rate of positive peritoneal findings in all patients with pancreatic cancer is reported to approach 20 to 25%. However, patients with lesions in the head of the pancreas have positive findings only 15 to 20% of the time, compared with those with body and tail lesions, in which the incidence of positive findings approaches 50%.\textsuperscript{72–74} Some clinicians are proponents of routine staging laparoscopy in all patients with potentially resectable pancreatic cancer. The rationale for routine laparoscopy is based on data suggesting that 20 to 40% of patients staged by other modalities including CT, MRI, ERCP, and EUS will have unexpected, small peritoneal or liver implants at the time of exploration. Proponents of this approach believe that nonoperative palliation in these patients is equivalent to operative palliation, and therefore, diagnostic laparoscopy spares many patients an unnecessary laparotomy. In contrast, other surgeons (including our group at Johns Hopkins) believe that patients with head of the pancreas lesions and resulting obstructive jaundice, gastric outlet obstruction, or tumor-related abdominal and back pain are best managed with surgical palliation including biliary-enteric bypass, gastrojejunostomy, and chemical splanchnecctomy of the celiac axis.\textsuperscript{75–80} Using this strategy, laparoscopy is unnecessary. In patients with body and tail lesions, the strategy differs. These patients have a high incidence of peritoneal metastases and do not usually require biliary or gastric bypass for relief of symptoms. Laparoscopy can spare these patients an unnecessary laparotomy, when either bile duct or gastric bypass has no therapeutic benefit.

**PALLIATIVE THERAPY**

**Nonoperative Palliation**

Despite a greater awareness of the disease and advances with imaging and diagnostic techniques, most patients with periamplullary adenocarcinoma have unresectable tumors at presentation. Only 15 to 20% of patients with pancreatic cancer have tumors that are resectable for cure at the time of presentation, because either metastatic disease or extensive local involvement precludes resection. Therefore, palliation of symptoms remains an important component in the management of this disease. Palliation of patients with periamplullary cancer is aimed at three major symptoms: obstructive jaundice, duodenal or gastric outlet obstruction, and tumor-associated pain.

Traditionally, surgery has offered the primary means for palliation of periamplullary carcinoma. Concomitant with advances and improvements in surgical therapy, some advances have been made in the nonoperative palliation of these symptoms.

Patients found to have distant metastases, unresectable local disease, or disseminated intra-abdominal tumors are appropriate candidates for nonoperative therapy. In addition, patients with debilitating disease in whom anesthesia and surgery are unsafe should be managed nonoperatively. Nonoperative palliation is not reliable for duodenal obstruction. Therefore, patients with symptomatic duodenal obstruction should be managed operatively with gastrojejunostomy whenever possible.\textsuperscript{81} Age alone is not a contraindication to surgical resection or palliation.\textsuperscript{82} In patients who are to be managed nonoperatively, a tissue diagnosis can be obtained by CT- or US-guided liver or pancreas biopsy, ERCP brushings, PTC brushings, or EUS-guided FNA.

**Biliary Obstruction**

Jaundice is present in most patients who have right-sided pancreatic cancer. If untreated, obstructive jaundice can
lead to progressive liver dysfunction, hepatic failure, and earlier death. In addition, the pruritus associated with biliary obstruction can be debilitating and refractory to medical therapy. Biliary decompression can be achieved by either endoscopic or percutaneous transhepatic techniques in nearly all patients who are not candidates for surgical intervention. Percutaneous and endoscopic palliation of obstructive jaundice can provide biliary tract decompression with lower early morbidity than open biliary bypass.83–86

The use of PBD was first reported in 1974 as an extension of diagnostic PTC.87 The procedure is now standardized and commonly performed. It is generally done using local anesthesia with intravenous sedation. Diagnostic cholangiography first defines the site of obstruction and serves as a guide for subsequent biliary drainage (Fig. 5–13). After accessing of the biliary tree, which is often easy to accomplish secondary to intrahepatic biliary dilatation, a guidewire is placed down the extrahepatic biliary tree, through the obstruction and into the duodenum. A small (normally No. 8 French) stent is then placed over the guidewire to stent the obstruction (Fig. 5–14). The small, stiff catheter can subsequently be exchanged for larger-diameter, softer tubes. A period of external drainage is usually allowed to minimize the risk of cholangitis. The stent can then be “internalized,” meaning turned off at the outside to allow all bile to flow into the duodenum. The internal-external biliary stents require maintenance, with catheter exchanges and upsizing every 3 months to prevent cholangitis and recurrent jaundice secondary to stent occlusion. The problem of late biliary obstruction resulting from stent occlusion may be improved by percutaneously placed self-expanding metallic endoprostheses, which have gained popularity because of their lower incidence of late occlusion.88 Overall, percutaneous external biliary drainage can be accomplished in nearly 100% of patients; however, the percentage of patients in whom complete internal drainage can be accomplished is lower.76 Complications of PTC or PBD include hemobilia, bile peritonitis, bile pleural effusion, cholangitis, pancreatitis, and acute cholecystitis.76,89

The endoscopic approach offers several distinct advantages over percutaneous methods.89 Endoscopic examination may reveal a periampullary tumor mass and can allow biopsy to provide a tissue diagnosis. In addition, a pancreatogram can be obtained, to provide information about the site of origin of the tumor. After endoscopic examination, a limited sphincterotomy is typically performed, and biliary cannulation is attempted. A guidewire is then manipulated proximal to the stricture, and an endoprosthesis is placed through the obstruction (Fig. 5–15). Endoprosthesis diameters typically are No. 7 to 10 French. The overall morbidity rate for endoscopic stent-
ing is less than 35%, but major procedure-related morbidity is seen in fewer than 10% of patients. Cholangitis, hyperamylasemia, and pancreatitis are the most common complications associated with this technique. As with percutaneous stents, endoscopic stents require planned removal and replacement every 3 to 6 months to prevent recurrent jaundice and cholangitis. Expandable metallic prostheses can also be placed by the endoscopic route.90 One prospective randomized trial and several other comparisons summarized in a 1992 review showed comparable success rates for the percutaneous and endoscopic approaches.78,91 However, the endoscopic approach has lower procedure-related morbidity and mortality, so it is the method of choice.

Four prospective randomized trials in the 1980s compared surgical biliary bypass with nonoperative biliary stenting and found that nonoperative methods of palliating obstructive jaundice had equal short-term efficacy with lower early morbidity and mortality.93-96 However, recurrent jaundice was seen in 17 to 38% of nonoperatively stented patients before they died,93-96 compared with fewer than 10% of patients in most series of operative biliary decompression.78,80

**Pain**

At the time of death, most patients with unresected pancreatic cancer experience significant pain. Unfortunately, the pain associated with pancreatic cancer is unremitting and incapacitating and is often poorly managed. The postulated causes of tumor-associated pain include tumor infiltration into the celiac plexus, pain associated with early satiety, gastroduodenal obstruction and gallbladder or biliary obstruction, increased parenchymal pressure caused by pancreatic duct obstruction, and pancreatic inflammation. The pain is not typically relieved by relief of gastric or biliary obstruction. Tumor-associated pain is best treated with long-acting oral or topical analgesics in appropriate doses.92 Poor pain control is often the result of inadequate dosing. Pain management specialists may be required to help manage this difficult problem. For pain intractable to typical narcotic regimens, several nonoperative palliative treatment modalities are available. These include CT-guided percutaneous celiac nerve block, external-beam radiation therapy, and thoracoscopic or endoscopic chemical splanchnicectomy.

**Duodenal Obstruction**

At the time of diagnosis, 30 to 50% of patients with pancreatic cancer complain of nausea and vomiting. However, actual mechanical obstruction of the duodenum occurs much less commonly.93 If this problem is not addressed at the time of initial palliation, between 10 and 15% of patients require gastrojejunostomy before they die, and an additional 15 to 20% die with symptoms of duodenal obstruction.75,78-79,83 Until recently, patients with malignant duodenal obstruction had few options besides surgical gastrojejunostomy or feeding tubes. Endoluminal approaches with biliary-type expandable metallic stents are being tested.94 Early results are based on small numbers of patients, and further assessment is necessary to determine the role of endoluminal stenting for malignant duodenal obstruction.

**Operative Palliation**

With accurate preoperative staging (short of laparoscopy), many tertiary centers report resectability rates for periampullary cancers ranging from 67 to 89%.74,80,95-97 The determination of resectability is one goal of surgical exploration in patients with periampullary adenocarcinoma.80 Palliative surgery is indicated in patients whose tumors are found to be unresectable at the time of laparotomy intended for curative resection and in patients considered good operative risks whose symptoms are not amenable to or well managed by current nonoperative palliative techniques.

**Obstructive Jaundice**

The most commonly performed surgical procedures for the relief of obstructive jaundice include hepaticojejunostomy or choledochojejunostomy, choledochooduodenostomy, and cholecystojejunostomy. Simple external drainage through a T-tube is not an option because it creates a high-output biliary fistula that leads to electrolyte abnormalities. Because of the proximity of the tumor to the anastomosis and the potential for duodenal obstruction, choledochooduodenostomy is associated with higher rates of recurrent jaundice and is generally avoided in malignant biliary obstruction. Likewise, although cholecystojejunostomy can be performed easily, it is not indicated in patients with tumors located less than 2 to 3 cm from
the cystic duct-common hepatic duct junction, for fear of cystic duct obstruction by tumor with resultant recurrent jaundice. Several studies comparing cholecystoenteric with choledochoenteric bypass suggested better long-term relief of jaundice with choledochoenteric bypass.\textsuperscript{75,78}

The favored technique is biliary-enteric bypass to the jejunum, performed as an end-to-side hepaticojejunostomy or choledochojejunostomy, with concomitant cholecystectomy (Fig. 5–16). Although clinical studies have failed to support an advantage with Roux-en-Y versus loop reconstruction, theoretic advantages exist to using a Roux-en-Y limb. They include easier management of biliary-anastomotic leaks, a lower rate of cholangitis, and improved mobility of the Roux limb to reach the hepatic hilum.\textsuperscript{98} In a current series from the Johns Hopkins Hospital using only choledochojejunostomy or hepaticojejunostomy, only 4% of operatively palliated patients had recurrent jaundice before they died.\textsuperscript{80}

**Pain**

At the time of operative palliation, chemical splanchnicectomy can be performed to alleviate the debilitating pain associated with pancreatic cancer. Intraoperative chemical splanchnicectomy was introduced by Copping and colleagues in 1969.\textsuperscript{99} In 1993, the first and only prospective, randomized trial comparing intraoperative chemical splanchnicectomy with placebo was performed.\textsuperscript{100} The procedure was performed by injecting 20 ml of 50% alcohol or saline placebo through a spinal needle on either side of the aorta at the level of the celiac plexus (Fig. 5–17). The mean pain scores as determined by a visual analog scale were lower in the group receiving the alcohol at all postoperative time points. These data support the use of chemical splanchnicectomy in all patients undergoing operative palliation for periampullary neoplasms.

**Duodenal Obstruction**

Since the 1970s, the natural history of duodenal obstruction in periampullary cancer has been extensively studied. As previously mentioned, for those patients without duodenal obstruction at presentation, 10 to 15% require gastrojejunostomy before they die, and an additional 15 to 20% die with symptoms of gastroduodenal obstruction.\textsuperscript{75,78,79,83} Despite these data, controversy remains re-

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**Figure 5–16.** The illustration depicts the anatomy after one method of palliative intervention. The biliary-enteric anastomosis is shown as a retrocolic end-to-side hepaticojejunostomy with a jejunal loop. A jejunojejunostomy was performed below the transverse mesocolon, to divert the enteric stream away from the biliary-enteric anastomosis. Also shown is a retrocolic gastrojejunostomy. (From Cameron, J.L.: Atlas of Surgery, vol. 1. Toronto, B.C. Decker, 1990, p. 427, with permission.)
RESECTIONAL THERAPY

Pancreaticoduodenectomy for Periampullary Tumors

Halsted performed the first successful resection of a periampullary tumor in 1898, and it involved local resection of an ampullary cancer.100 Codivilla performed the first unsuccessful en bloc resection of a periampullary cancer,101 whereas Kausch performed the first successful en bloc resection using a two-stage approach.102 Whipple and colleagues popularized the procedure in the 1930s and 1940s.103,104 Although early reports described pancreaticoduodenal resections that spared the pylorus, by the mid-1970s, the procedure was routinely performed with a distal gastrectomy. The concept of pylorus preservation was repopularized by Traverso and Longmire in 1978.105 Pylorus-preserving pancreaticoduodenectomy is now the favored procedure because the gastric reservoir and the pyloric mechanism are kept intact. Some investigators have cautioned that pylorus preservation may compromise anticancer therapy, but this has not been supported by our data.100,106 Distal gastrectomy is usually reserved for tumors involving the first portion of the duodenum, pylorus, or distal stomach or for patients with ischemia of the duodenal cuff after pylorus-preserving resection.

Operative Technique

The initial portion of the procedure is dedicated to the determination of resectability. The liver, visceral and peritoneal surfaces, and omentum are examined thoroughly for metastases not detected in the preoperative workup. An extensive Kocher maneuver is then performed, by elevating the duodenum and head of the pancreas out of the retroperitoneum, assessing the superior mesenteric vein and its branches, and palpating the superior mesenteric artery pulse in its retropancreatic position. The superior mesenteric vein is most easily identified during the extensive Kocher maneuver (Fig. 5–18). It can be seen running anterior to the third portion of the duodenum, often surrounded by adipose tissue with branches from both the uncinate process and the transverse mesocolon.107 By mobilizing the gallbladder out of the gallbladder fossa and following the cystic duct to its junction with the hepatic duct, the porta hepatis can be evaluated for tumor involvement. Early division of the common bile duct opens the plane to visualize the portal vein. If the tumor is localized to the periampullary region or head, neck, or uncinate process of the pancreas, with no evidence of distant metastatic disease or major vascular involvement, the surgeon then proceeds with resection. With experience, many tumors that initially appear unresectable on the basis of local extension can be successfully resected.108

Once the tumor is deemed resectable, the duodenum is divided approximately 2 cm distal to the pylorus by using a linear stapling device. Likewise, the jejunum just beyond the ligament of Treitz is cleared and divided. The jejunum and duodenum are then brought to the patient's...
right side, dorsal to the superior mesenteric vessels, to facilitate dissection of the uncinate process from the right lateral aspect of the superior mesenteric vein. The pancreatic neck is then divided with the electrocautery unit, and the remainder of the head and uncinate process of the pancreas are dissected from the major vessels.

Many options for restoring gastrointestinal continuity exist. The most common reconstructive technique anastomoses the pancreas first, followed by the bile duct and then the duodenum. The pancreatic anastomosis is most frequently performed as a pancreaticojejunostomy, in either an end-to-end or a end-to-side fashion. An alternative form of reconstruction is by pancreaticogastrostomy, which has been reported to decrease the incidence of postoperative pancreatic fistula formation. However, in the only prospective, randomized trial of pancreaticojejunostomy versus pancreaticogastrostomy, the pancreatic fistula rate was equivalent. Controversy regarding the optimal configuration of the pancreaticojejunostomy, the importance of duct-to-mucosa sutures, and the use of pancreatic duct stents is ongoing. The biliary anastomosis is typically performed as an end-to-side hepaticojejunostomy, 10 cm distal to the pancreatic anastomosis. Finally, the duodenojejunostomy is performed 10 to 20 cm downstream from the hepaticojejunostomy (Fig. 5–19).

Preoperative biliary stenting remains controversial. Multiple theoretic reasons to place preoperative biliary stents exist, including better definition of the level of obstruction, relief of jaundice and pruritus, increased ease in performing the biliary anastomosis, and the prevention of biliary sepsis. Current data indicate that routine preoperative biliary stenting is of no benefit and carries potential risk, including an increased risk of wound or infectious complications, as well as an increased risk of pancreatic fistula formation. Stenting should be used selectively in patients with obstructive jaundice who will have a substantial delay between initial presentation and definitive surgery, in patients with major hepatic or hematologic abnormalities, in patients having undergone previous biliary-bypass surgery, and in rare patients with primary suppurative cholangitis. The method of stenting, endoscopic versus percutaneous, should be chosen based on local expertise.

**Complications**

The operative mortality rate for pancreaticoduodenectomy is currently less than 3% in centers specializing in pancreatic surgery. Despite low mortality rates, the incidence of postoperative complications remains as high as 40 to 50%. The two leading causes of morbidity are early delayed gastric emptying and disruption or leak at the pancreatic anastomosis (pancreatic fistula). Delayed gastric emptying is seen in up to 20% of patients. Although not life-threatening and usually self-limited, this condition can result in markedly prolonged lengths of stay and increased hospital costs. The cause is likely multifactorial, and the standard treatment involves parenteral nutritional support and nasogastric decompression. Erythromycin, a motilin agonist, has been shown to improve gastric emptying after pancreaticoduodenectomy. Pancreatic fistula occurs in 10 to 15% of patients after pancreaticoduodenectomy. The morbidity resulting from a pancreatic leak is decreased by placing closed-suction drains near the pancreatic anastomosis, to create a controlled fistula and to reduce the risk of intra-abdominal collections. By definition, a pancreatic fistula occurs 7 or more days postoperatively, when the drain output contains milky, amylase-rich fluid in excess of 50 ml per day. In approximately 80% of patients, the pancreatic leak seals with parenteral nutrition, nothing-by-mouth status, and maintenance of the pancreatic drains.
Figure 5–19. Pylorus-preserving pancreaticoduodenectomy. Top left, The structures resected include the following: the duodenum (except for the initial 1 to 2 cm beyond the pylorus); the head, neck and uncinate process of the pancreas, with tumor (black); the gallbladder; and the distal extrahepatic biliary tree. Top right, The structures retained include the entire stomach, pylorus, proximal 1 to 2 cm of the duodenum, body and tail of the pancreas, proximal biliary tree, and jejunum distal to the ligament of Treitz. Bottom, The reconstruction is shown as a proximal end-to-end pancreaticojejunostomy, a hepaticojejunostomy decompressed with a percutaneous transhepatic catheter, and a distal duodenojejunostomy. (From Yeo, C.J., and Cameron, J.L.: The pancreas. In Hardy, J.D. [ed.]: Hardy’s Textbook of Surgery, 2nd ed. Philadelphia, J.B. Lippincott, 1988, p. 718, with permission.)

An additional 15% will require radiologic intervention for improved drainage. Five per cent may require reoperation for intra-abdominal sepsis. Other complications are less common and are summarized in Table 5–6.

Table 5–6. Complications in 650 Consecutive Pancreaticoduodenal Resections

<table>
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<th>Percentage of Patients (%)</th>
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<tr>
<td>Overall complications</td>
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<tr>
<td>Early delayed gastric emptying</td>
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<td>Pancreatic fistula</td>
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<td>Wound infection</td>
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<td>Intra-abdominal abscess</td>
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<td>Cholangitis</td>
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Prognostic Factors for Head of the Pancreas and Other Periampullary Cancers

The prognosis for patients with resected adenocarcinoma of the head, neck, or uncinate process of the pancreas is determined by multiple factors including tumor stage, biologic features, molecular genetics, perioperative factors, and the use of adjuvant chemoradiation. Other periampullary tumors including distal bile duct, ampullary, and duodenal adenocarcinomas are less common, and the prognostic factors in these cancers are not as well characterized as those for pancreatic cancers, but the overall 5-year survival rate is better. In an analysis of long-term survivors with resected periampullary adenocarcinoma, the site-specific 5-year actual survival rates were 15% for pancreatic cancer, 27% for distal bile duct cancer, 39% for ampullary cancer, and 59% for duodenal cancer (Fig. 5–20). In this series, well-differentiated tumors, negative resection margins, and negative nodal status were indicators of a better prognosis for all periampullary cancers.

For patients with pancreatic cancer, increasing clinicopathologic stage has been associated with worsening prognosis. In addition, tumor biologic features and molecular genetics play a role in overall prognosis. Allison and colleagues demonstrated that the DNA content of pancreatic cancers can be segregated into diploid and aneuploid tumors, and patients with diploid tumors fared significantly better than those with aneuploid tumors. Accumulating evidence suggests that mutations in tumor suppressor genes, oncogenes, and DNA mismatch repair genes also influence prognosis. Patients with tumors harboring p53 mutations have been shown to have a worse prognosis. As the number of tumor suppressor gene mutations increases, the risk of death from cancer appears to increase. In direct contrast, tumors with DNA mismatch repair mutations, so-called RER tumors,

been associated with an improved prognosis.\(^{47}\) This finding is similar to the improved progress seen in patients with HNPCC colorectal cancer, another group of tumors with mutations in DNA mismatch repair genes. In an analysis of 201 patients undergoing pancreaticoduodenectomy for pancreatic cancer, tumor diameter, lymph node status, and resection margin status were found to be important predictors of survival by univariate and multivariate analysis.\(^{30}\)

Various intraoperative and technical factors have been examined in relation to overall prognosis. Some investigators have suggested that extended retroperitoneal lymphadenectomy may improve survival. For example, Pedrazzoli and colleagues noted that patients with node-positive pancreatic cancer fared better after extended resection.\(^{119}\) The interim results of a prospective, randomized trial comparing pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy at Johns Hopkins (Fig. 5–21) suggested similar morbidity and mortality and no survival advantage for the extended lymphadenectomy group (Fig. 5–22).\(^{120}\) However, the survival data are not yet mature enough to draw strong conclusions. In many analyses, factors such as the type of pancreatectomy performed (pylorus-preserving versus classic), blood transfusions, and operative time were evaluated, but none of these factors were independent predictors of survival.\(^{50,121}\) Although single-institution experiences cannot consistently correlate intraoperative factors with long-term outcome, published data from large statewide registries have shown a relationship between hospital volume for pancreatic resection and perioperative mortality rates, length of hospital stay, hospital cost, and long-term outcome.\(^{122-125}\) These important studies suggest that regionalization of care will affect both the cost and the outcome for patients undergoing complex pancreatic procedures.

Another important prognostic factor for pancreatic
cancer is the use of postoperative adjuvant chemotherapy and radiation therapy. Such therapy has been shown to improve survival in most\textsuperscript{126–129} but not all analyses.\textsuperscript{130} In a 1997 study, a multidisciplinary group at the Johns Hopkins Hospital including surgeons, radiation oncologists, medical oncologists, and pathologists prospectively evaluated 174 patients with resected carcinoma of the head, neck, and uncinate process of the pancreas.\textsuperscript{121} This prospective study evaluated two different combined-modality adjuvant chemoradiation therapy regimens and found that adjuvant therapy significantly improved survival in a multivariate model. Based on these data and on earlier results from the Gastrointestinal Tumor Study Group (GITSG),\textsuperscript{126,127} standard 5-fluorouracil (5-FU)-based chemotheraphy and external-beam radiation therapy appear to be indicated after pancreaticoduodenectomy for pancreatic adenocarcinoma.

Bile duct cancers or cholangiocarcinomas are best classified as perihilar, distal, or intraductal. In a review of 294 patients with cholangiocarcinoma, 27% were distal or peripancreatic cholangiocarcinomas. The median survival was 22 months for distal bile duct tumors, with a 5-year survival of 28%.\textsuperscript{131} Surgical resection, negative microscopic margins, preoperative nutritional status, and absence of postoperative sepsis were the best predictors of improved outcome. Adjuvant chemoradiation did not appear to prolong survival; however, the use of postoperative therapy has not been well studied for these tumors.

Adenocarcinoma of the ampulla of Vater is the second most common peripancreatic malignancy. Compared with pancreatic cancer, cancer of the ampulla of Vater has a higher resectability rate and a better prognosis. In a series of 120 patients with resected ampullary cancer at the Johns Hopkins Hospital, the actuarial 5-year survival was 38%.\textsuperscript{132} Factors favorably influencing long-term outcome after resection included no perioperative blood transfusions, negative lymph node status, and well-differentiated or moderately differentiated tumors.

Of the peripancreatic neoplasms, adenocarcinoma of the duodenum is the least common, but it is associated with the best prognosis. In a series of 35 patients undergoing pancreaticoduodenectomy for duodenal cancer, the 5-year survival rate was 69%. Negative resection margins and tumors located in the first and second portion of the duodenum appeared to influence survival favorably by univariate analysis. Nodal status, tumor diameter, degree of differentiation, and the use of adjuvant chemoradiation did not influence survival.\textsuperscript{133}

As the population of the United States ages, increasing numbers of elderly patients may be considered for pancreaticoduodenal resection. Data from the Johns Hopkins Hospital demonstrate that pancreaticoduodenectomy for peripancreatic adenocarcinoma can be performed safely in selected octogenarians, with morbidity, mortality, and long-term survival rates (Fig. 5–23) comparable with those in younger patients. Age alone should not be a contraindication to potentially curative resection.\textsuperscript{82}

**Distal Pancreatectomy for Tumors of the Body and Tail**

A few patients with pancreatic cancer have tumors arising in the body and tail of the gland. Because these tumors do not obstruct the bile duct and cause early jaundice, the diagnosis of body and tail lesions is frequently delayed. As a result, tumors are often larger and more likely to have local extension or metastatic spread at the time of presentation, features that preclude resection. In addition to routine staging including abdominal CT, staging laparoscopy appears to have an important role in patients with body and tail tumors, because occult metastatic disease is present in the majority of these patients.

Should staging studies fail to reveal disseminated tumor or locally unresectable disease, curative resection should be attempted. The abdomen is first explored for evidence of metastatic disease as for pancreaticoduodenectomy. The ligament of Treitz should be carefully evaluated, because tumors of the body and tail often invade the fourth portion of the duodenum at the ligament. The gastrocolic ligament should be opened to allow complete assessment of the tumor’s proximity to the ligament of Treitz and the superior mesenteric vessels. Involvement of peripancreatic lymph nodes does not preclude resection, but it diminishes the likelihood of long-term survival.

If after careful exploration the tumor is thought to be resectable, the inferior surface of the pancreas is mobilized to assess retroperitoneal involvement. Although extensive involvement of the retroperitoneum precludes resection, involvement of the splenic vessels does not. Splenic preservation is not indicated in distal pancreatectomy for pancreatic cancer. The spleen is mobilized with early ligation of the splenic artery and short gastric vessels, to facilitate subsequent dissection of the pancreatic body and tail from the retroperitoneum (Fig. 5–24). If necessary, the inferior mesenteric vein can be taken without additional morbidity. The pancreas is then divided, to leave a 1- to 2-cm gross margin of normal parenchyma from the tumor. The pancreatic margin should be sent for frozen section and should be resected further, if necessary. Closure of the pancreatic margin can be performed with mattress sutures or with a linear stapler. A closed-suction drain is left near the pancreatic remnant

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**Figure 5–23.** Actuarial survival curves comparing patients 80 years of age or older undergoing pancreaticoduodenectomy for peripancreatic adenocarcinoma \((n = 41); \text{median survival}, 32 \text{months}; \text{5-year survival}, 19%) to those younger than 80 years \((n = 454); \text{median survival}, 20 \text{months}; \text{5-year survival} 27\% \text{P} = 0.77\). (From Sohn, T.A., Yeo, C.J., Cameron, J.L., et al.: Should pancreaticoduodenectomy be performed in octogenarians? J. Gastrointest. Surg., 2:207, 1998, with permission.)
Figure 5–24. Near the completion of a distal pancreatectomy and splenectomy for a tumor in the body of the pancreas. The spleen and tail of the pancreas have been mobilized out of the retroperitoneum. The pancreatic parenchyma is being divided with the electrocautery. (From Cameron, J.L.: Atlas of Surgery, vol. 1. Toronto, B.C. Decker, 1990, p. 27, with permission.)

Spleen
Tail of pancreas
Retroperitoneal bed
Superior mesenteric a.
Inferior pancreaticoduodenal v.and a.
Superior mesenteric v.
Tumor

...to control any leak from the oversewn pancreatic parenchyma and the divided main pancreatic duct.

If resection is not possible, several palliative maneuvers should be considered. Chemical splanchicectomy using alcohol has been shown to reduce or prevent the progression of pain and to reduce narcotic requirements for patients with unresected pancreatic head, neck, or uncinate cancers.76 If the tumor involves the ligament of Treitz, consideration should be given to palliative gastrojejunostomy to prevent late duodenal obstruction. Likewise, if the tumor appears to be extending toward the porta hepatitis, hepaticojejunostomy to prevent biliary obstruction should be considered. However, this procedure can be difficult in a nondilated biliary system. For this reason, cholecystectomy alone to prevent acute cholecystitis is currently favored, with subsequent placement of an endoprosthesis should obstructive jaundice occur.

The resectability rate for distal pancreatic adenocarcinoma was approximately 10% before routine laparoscopic staging. The routine use of staging laparoscopy detects metastatic disease and prevents unnecessary laparotomy. Overall, patients with resectable disease have a poor prognosis, with a median survival of 7 to 13 months and a 5-year survival of less than 10%.134–138 Tumor size, lymph node involvement, and surgical margins all appear to affect long-term survival. Data on the role of adjuvant therapy for these tumors are limited.

CHEMORADIATION THERAPY

The major obstacle to postresection cure of pancreatic adenocarcinoma appears to be the burden of remaining subclinical regional disease. This finding is confirmed by four observations: (1) the pattern of lymphatic involvement identified when regional staging is performed; (2) the patterns of failure observed after pancreaticoduodenectomy; (3) the impact of positive nodal and resection margin status on long-term survival; and (4) the reports of improved survival with radical or extended lymph node dissection during pancreatectomy. Radiation therapy and chemotherapy are the two mainstays for the management of this subclinical tumor burden.

Ionizing radiation in the form of external-beam radiation therapy, intraoperative radiation therapy, or brachytherapy is damaging to both normal tissue and tumor. Numerous studies of radiation therapy in pancreatic cancer have been reviewed.139 Similarly, the principles regarding the use of systemic chemotherapy are well known and include the delivery of the maximal tolerated dose in repeated cycles, at the time of least possible tumor burden, using combinations of maximally effective drugs. The combination of chemotherapy and radiation incorporates the benefits of each therapy alone. Radiation therapy deals with the tumor burden in the region from which the tumor was resected, whereas chemotherapy deals with microscopic systemic disease. The two also act synergistically, whereby the combined effects yield enhanced tumor killing beyond what would be seen with either modality alone.

Adjuvant Therapy

Early observations on combined-modality therapy with 5-FU and radiation for gastrointestinal malignant diseases...
were first presented by Moertel and colleagues. The benefit of 5-FU and radiation for pancreatic cancer was subsequently confirmed by the GITSG in 1985 and 1987. The first study was a prospective, randomized trial evaluating 5-FU-based chemotherapy and external-beam radiation after pancreatic resection for pancreatic cancer. The 22 patients in the control arm had a median survival of 11 months, compared with 21 months in the treatment arm ($P = .03$). This finding was confirmed in the second study by comparing 30 patients with historical controls and demonstrating a comparable 18-month median survival. Unfortunately, the slow accrual rates, the small sample sizes, and the lack of concurrent controls in the latter series weakened the data.

Bosset and colleagues evaluated radiation therapy alone in a prospective, randomized trial, showing a median survival of 23 months with external-beam radiation therapy alone. Similarly, Bakkevold and colleagues evaluated chemotherapy alone (5-FU, doxorubicin, and mitomycin C) and demonstrated improved survival. In a prospective trial at the Johns Hopkins Hospital, patients with pancreatic adenocarcinoma were offered three options after resection: (1) standard therapy with radiation to the tumor bed and intermittent bolus 5-FU therapy; (2) intensive therapy, with radiation to the tumor bed as well as prophylactic hepatic irradiation and continuous 5-FU infusion; and (3) no adjuvant therapy. By univariate analysis, patients who received either type of adjuvant therapy had a median survival of 19.5 months and a 2-year survival rate of 39% (Fig. 5–25), which was significantly improved compared with those receiving no therapy (13.5 months and 30%, $P = .003$). By multivariate analysis, both adjuvant protocols had a significant impact on survival. The more intensive regimen did not appear to improve survival over standard therapy. Additional, well-designed trials of new chemoradiation protocols are needed to evaluate the role of adjuvant therapy further.

**Neoadjuvant Therapy**

Neoadjuvant therapy involves the use of chemoradiation before surgical exploration and attempted resection. Major proponents of neoadjuvant therapy suggest that the advantages include decreased locoregional tumor burden, the sterilization of tumor before surgical manipulation, and earlier administration of systemic therapy. After administration of neoadjuvant therapy, restaging with a chest radiograph and abdominal CT scan is performed. Laparotomy is avoided in patients with disseminated disease evident at restaging. Early reports of neoadjuvant therapy used standard fractionation with concomitant bolus 5-FU. Newer approaches involve rapid fractionation with a smaller total radiation dose and continuous 5-FU infusion. Local tumor control and patient survival are equal with the rapid and standard fractionation techniques. The group from the M.D. Anderson Cancer Center in Houston reported the results of multimodality therapy in 142 patients with pancreatic cancer. Forty-one of these patients received neoadjuvant therapy and pancreaticoduodenectomy. They were compared with 19 patients treated with pancreaticoduodenectomy and adjuvant therapy. No patients receiving neoadjuvant therapy experienced a delay in surgery, whereas 24% of the eligible postsurgical patients did not receive the intended adjuvant therapy secondary to prolonged recovery. In addition, with the rapid fractionation technique used in the neoadjuvant protocol, patients receiving preoperative therapy had a 1-month shorter total duration of treatment. Although the overall survival was similar in the two groups, locoregional or peritoneal recurrence was more common in the adjuvant therapy group (21%) than in the neoadjuvant therapy group (10%).

The controversy between neoadjuvant and adjuvant proponents continues. The two regimens are difficult to compare because up to one third of the patients in neoadjuvant protocols do not undergo tumor resection as a result of disseminated disease at the time of restaging. Our current policy is to attempt resection when possible and to reserve neoadjuvant therapy for patients with locally unresectable tumors.

**Palliative Therapy**

In patients with unresectable disease, many antitumor therapies have been studied with limited success, includ-
ing trials of chemotherapy and radiation both alone and in combination. Gemcitabine, an agent that inhibits DNA replication and repair, has been used in several trials. In phase I and II trials, patients with advanced disease showed subjective symptomatic benefit, without a dramatic objective tumor response after treatment with gemcitabine. Gemcitabine appears to be an improvement over 5-FU-based therapy in advanced disease, with a 1- to 2-month improvement in median survival and with improved pain control, performance status, and weight gain observed with gemcitabine. Gemcitabine is a powerful radiosensitizer and is being evaluated in combined-modality regimes worldwide. Other agents currently being evaluated include paclitaxel (Taxol), matrix metalloproteinase inhibitors (marimastat), perillyl alcohol, and angiogenesis inhibitors.\(^{115,116}\)

**HORMONE THERAPY**

Hormonal therapy is routinely used in some tumors including prostate, breast, endometrial, and ovarian cancers. Some data suggest that hormonal therapy may also be beneficial in pancreatic cancer. In vitro and in vivo evidence indicates that estrogen promotes pancreatic cancer growth. In addition, sex steroid biosynthetic enzymes have been localized to pancreatic cancers. Androgen receptors have been found on pancreatic cancer cells, and testosterone has been shown to stimulate pancreatic cancer cell growth. Based on these data, several clinical experiences with the antiestrogen tamoxifen have been performed, showing no benefit.\(^{117,118}\) In a multicenter Norwegian trial, tamoxifen was noted to improve survival in post-menopausal women.

Two gastrointestinal hormones, cholecystokinin and gastrin, have been studied in pancreatic cancer.\(^{119}\) Investigators demonstrated that cholecystokinin antagonists inhibited pancreatic carcinogenesis, but clinical trials failed to demonstrate an impact on tumor growth and were attended by significant side effects.\(^{119,120}\)

**GENE THERAPY**

The term gene therapy has been used to describe several approaches involving recombinant DNA technology. The technology of gene transfer was first made possible in the 1980s. Although the concept of gene therapy was initially founded on the correction of a single gene defect as in thalassemia and severe combined immune deficiency, it has now been applied to cancer, in which multiple genetic defects occur. Currently, many phase I trials are using an array of gene transfer systems in many cancers. Unfortunately, human pancreatic cancer has not been well studied, owing primarily to its aggressive nature.

A phase I clinical trial of a cytokine-secreting pancreatic cancer vaccine made from primary tumors has been undertaken at the Johns Hopkins Hospital.\(^{121}\) Tumor cell vaccines in murine models have been engineered to secrete cytokines in a paracrine fashion, which can, in turn, elicit an immune response capable of eliminating established tumors.\(^{122,123}\) The impact of vaccine therapy on the survival of patients with pancreatic cancer is currently unknown, but perhaps such therapy, combined with surgical resection and chemoradiation, may be associated with improved long-term outcomes.

**References**


