Abstract

This review focuses on the pathogenesis, diagnosis, staging, and treatment of pancreatic cancer. Although much is needed to improve the still dismal outlook for patients with this disease, significant progress has been made in its surgical and oncologic management. Furthermore, our deepening understanding of the molecular genetics of pancreatic cancer lends hope for the possibility of earlier detection, which would result in substantial improvements in survival. (CA Cancer J Clin 2000;50:241-268.)

Introduction

Pancreatic carcinoma is the fourth leading cause of cancer mortality in the US, with more than 28,000 people deaths attributed to the disease each year. Considered by many to be one of the deadliest malignancies, pancreatic cancer is associated with a death:incidence ratio of approximately .99. Despite this grim picture, significant advances have been made in recent years, both in our understanding of the pathogenesis of the disease and in its clinical management. This article reviews the epidemiology and risk factors of pancreatic cancer, as well as recent developments in the field of molecular genetics and the influence of growth factors on disease progression. Moreover, it serves to update the current thinking about the management of pancreatic cancer, including diagnosis and staging, surgical resection, adjuvant therapy, and palliation.

Epidemiology and Risk Factors

The incidence of pancreatic cancer increased in the US nearly three-fold from 1920 to 1978. Since that time, rates have remained constant, with approximately nine new cases diagnosed per 100,000 population. By contrast, in nearly all European countries, the incidence of pancreatic cancer has continued to rise.

The risk factors for pancreatic cancer have been extensively studied (Table), with advancing age perhaps the strongest risk factor. Incidence rates for pancreatic cancer increase steadily with age, with over 80% of cases occurring between the ages of 60 and 80. The diagnosis of pancreatic cancer in individuals younger than age 40 is uncommon.

The incidence and mortality rates for both male and female African Americans with pancreatic cancer are higher than for whites. Although gender differences in pancreatic cancer incidence have been equalizing over recent years, the disease still occurs more frequently in men. Incidence and mortality rates have increased in women since 1974 while having stabilized or decreased slightly in white men.

Several studies in US populations...
have reported that pancreatic cancer occurs more frequently among Jews than among Catholics or Protestants. The incidence of pancreatic cancer is also higher among Jews than among non-Jews in Israel. No consistent relationship has been demonstrated between development of the disease and socioeconomic status or immigration from other countries. Finally, although worldwide geographic differences in the incidence of pancreatic cancer are not striking, it is generally true that incidence rates of pancreatic cancer are highest in Western and industrialized countries and lowest in underdeveloped nations.

Genetic alterations are important in the development of pancreatic cancer, and six specific genetic syndromes have been associated with an increased incidence of the disease (Table). These syndromes include hereditary nonpolyposis colon cancer (HNPCC), familial breast cancer associated with the BRCA2 mutation, the Peutz-Jeghers syndrome, ataxia-telangiectasia syndrome, familial atypical multiple mole-melanoma (FAMMM) syndrome, and hereditary pancreatitis.

### Table

**Risk Factors for Pancreatic Cancer**

| Increased Risk                          | Possible Risk               | Unproven Risk                      |
|-----------------------------------------|-----------------------------|------------------------------------|
| **Demographic Factors**                 |                             |                                    |
| Advancing age                           | Geography                   | Socioeconomic status               |
| Black race                              |                             | Migrant status                     |
| Male gender                             |                             |                                    |
| Jewish religion                         |                             |                                    |
| **Host Factors**                         |                             |                                    |
| Hereditary nonpolyposis colorectal cancer| Diabetes                    | Peptic ulcer surgery               |
| Familial breast cancer                   | Chronic pancreatitis        | Cholecystectomy                    |
| Peutz-Jeghers                           | Endocrine tumors            |                                    |
| Ataxia-telangiectasia                    | Cystic fibrosis             |                                    |
| Familial atypical multiple mole-melanoma| Sex hormones                |                                    |
| Hereditary pancreatitis                  | Pernicious anemia           |                                    |
| **Environmental Factors**                | Tobacco                     | Diet                               |
|                                       | Occupation                  | Alcohol                            |
|                                       |                             | Radiation                          |

Adapted from Gold, with permission.
that the relative risk of developing pancreatic cancer declined from 3.2 in the first five years after diagnosis of diabetes, to 2.3 between five to nine years afterward, and to 1.3 after 10 or more years from diagnosis. These relationships suggest that diabetes is more commonly an early symptom of pancreatic cancer rather than a causative influence.

Conflicting data, however, were reported in a meta-analysis by Everhart and Wright of 20 published case-control and cohort studies, which indicated that pancreatic cancer occurred with increasing frequency among people with long-standing diabetes. Furthermore, a study of approximately 50,000 college students showed a six-fold increased risk of pancreatic cancer associated with a prior history of diabetes.

The relationship between chronic pancreatitis and pancreatic cancer has also stimulated considerable interest. A cohort study of more than 2,000 patients with well-defined chronic pancreatitis in six countries revealed a significantly elevated risk of pancreatic cancer. Patients with chronic pancreatitis followed for two or more years had a 16-fold increased risk of pancreatic cancer. Patients with a minimum follow-up period of five years had a 14-fold increase in risk. Similar risks were found in males and females and in both alcoholic and idiopathic forms of pancreatitis. The cumulative 25-year risk of pancreatic cancer in patients with any form of chronic pancreatitis appears to be about 4%. As with diabetes, however, other data have shown that the increased risk is only relevant for cases of pancreatitis that occur fewer than 10 years before the cancer diagnosis, suggesting either a common risk factor for both diseases or that some forms of chronic pancreatitis may represent an indolent manifestation of pancreatic cancer.

Other conditions in which a possible association with pancreatic cancer have been demonstrated in individual studies include thyroid and other benign endocrine tumors, cystic fibrosis, and pernicious anemia. In addition, potential estrogen effects associated with aging and number of pregnancies have raised the possibility of hormonal influences in the development of pancreatic cancer.

Finally, there are equivocal data linking pancreatic cancer to previous peptic ulcer surgery and cholecystectomy. The initial symptoms of pancreatic cancer can mimic those of biliary tract disease, perhaps explaining why investigators in some studies have observed an association between the onset of biliary tract disease, cholecystectomy, and the subsequent development of pancreatic cancer.

Tobacco, Diet, and Environmental Risk Factors

A wealth of solid scientific evidence indicates that cigarette smoking increases the risk of cancer of the pancreas. Data from animal studies suggest that nitrosamines and tobacco smoke are carcinogenic for the pancreas. Hyperplastic changes in pancreatic ductal cells, with atypical nuclear patterns have been observed in smokers at autopsy, with some relationship to the amount of tobacco smoked.

Numerous prospective studies have shown a positive association of smoking with pancreatic cancer, with most noting increasing pancreatic cancer risk with increasing number of cigarettes smoked. Case-control studies, too, have found a significant positive association between smoking and pancreatic cancer, with odds ratios for current smokers ranging from 1.3 to 5.5.

The relationship between nutrition and diet in pancreatic cancer has been addressed in several reviews. While a number of case-control studies have been performed, the results of the various studies often conflict. Nevertheless, some general observations have been made. There appears to be an association between pancreatic cancer and increasing total caloric intake, as well as for inges-
tion of carbohydrate, cholesterol, meat, salt, dehydrated food, fried food, refined sugar, soy beans, and nitrosamines. The risks are unproven for ingestion of fat, beta carotene, and coffee. A protective influence has been reported for dietary fiber, vitamin C, fruits, vegetables, no preservatives, raw foods, pressure cooking, and microwave cooking.

Numerous studies have evaluated potential relationships between occupational exposures and pancreatic cancer. Chemical workers, coal gas workers, metal and aluminum workers, and workers in textile and tanning industries are believed to be at increased risk of pancreatic cancer, although the degree of increased risk and the mechanisms involved remain poorly understood.

Three environmental factors that do not appear to be risk factors for pancreatic cancer, despite conflicting previous reports, include alcohol, coffee, and radiation. The evidence that relates alcoholism to pancreatic cancer is weak and inconsistent, and the current data suggest that past studies linking alcohol to pancreatic cancer may have been confounded by the association with tobacco use. Data from three recent case-control studies in Europe have found no association between alcohol and pancreatic cancer after controlling for gender, age, smoking, and socioeconomic status, and no evidence of a trend relating to total amount of alcohol consumed.4

While several older ecologic studies have shown a positive correlation between age-adjusted death rates for cancer of the pancreas and per capita coffee consumption, these data have been largely disproven.4,11 Similarly, there appear to be no epidemiologic data to support ionizing radiation as a cause of pancreatic cancer.

Pathology

Approximately 75% of pancreatic malignancies arise from the exocrine pancreas and are histologically classified as adenocarcinomas.13 Most pancreatic carcinomas arise from the pancreatic ductal system and are associated with a desmoplastic reaction, pancreatitis, and fibrosis. Approximately 65% of pancreatic ductal cancers arise in the proximal pancreas and are considered part of the larger group of periampullary malignancies that includes cancers of the ampulla, distal bile duct, and duodenum. These tumors usually present at an earlier stage due to the development of obstructive jaundice. Tumors of the pancreatic body and tail account for 15% of ductal carcinomas and are often diagnosed only at a more advanced stage due to their lack of specific symptoms. Finally, 20% of pancreatic duct carcinomas diffusely involve the entire gland.

Cystic neoplasms of the pancreas also arise from the exocrine pancreas and are classified as either benign serous cystadenomas, potentially malignant mucinous cystadenomas, or malignant cystadenocarcinomas. These cystic neoplasms are much less common than ductal adenocarcinoma, tend to occur in women, and are distributed throughout the entire gland.14,15 Endocrine or islet cell tumors of the pancreas comprise the remainder of primary pancreatic malignant neoplasms. These tumors can be either histologically malignant or benign. Many islet cell neoplasms are functional, with excessive hormone production resulting in clinical manifestations. Non-functional islet cell tumors produce no recognizable hormonal manifestations and are either detected due to their space-occupying characteristics or as incidental findings.

Pancreatic lymphomas are exceedingly rare, but recognition is important because they often respond dramatically to chemotherapy.16 Finally, metastatic cancers can involve the pancreas by hematogenous or lymphatic spread.

Microscopically, ductal adenocarcinomas contain infiltrative glands of vari-
ous shapes and sizes surrounded by dense, reactive fibrous tissue. The epithelial cells sometimes form papillae and cribriform structures, and frequently contain mucus. Cellular nuclei can show marked pleomorphism, hyperchromasia, loss of polarity, and prominent nucleoli. Many ductal adenocarcinomas infiltrate into vascular spaces, lymphatic spaces, and perineural spaces. Survival rates of patients with tumors showing perineural invasion are typically lower than those of patients whose tumors do not show such invasion. Additionally, most resected ductal adenocarcinomas have metastasized to peripancreatic lymph nodes.

In addition to lymph node metastasis, by the time of death, pancreatic ductal adenocarcinomas have frequently metastasized to the liver (up to 80% of all cases), peritoneum (60%), lungs and pleura (50% to 70%), and to the adrenal glands (25%). Furthermore, these tumors may grow by direct extension and may thus involve the duodenum, stomach, spleen, transverse mesocolon and colon, and adrenal glands.

Accumulating data suggest that histologically identifiable precursor lesions may progress to infiltrating ductal carcinoma of the pancreas. Histologic examination of pancreatia resected for pancreatic cancer frequently reveals lesions in the pancreatic ducts and ductules adjacent to the cancers. In these abnormal ductal structures, a mucin-producing proliferative epithelium, with varying degrees of cytologic and architectural atypia, replaces the normal cuboidal cells of ducts and ductules.

Several lines of evidence suggest that these ductal lesions are precursors of infiltrating ductal carcinoma. First, there is the association of ductal lesions found concurrently with cancer. Second, three-dimensional mapping techniques have demonstrated a step-wise transformation from mild dysplasia to severe dysplasia in pancreatic duct lesions. Finally, ductal lesions display, to some degree, the genetic changes observed in infiltrating adenocarcinomas, most notably activating point mutations in codon 12 of k-ras, as well as mutations in the p16 and p53 tumor suppressor genes.

In summary, these lines of evidence suggest that, just as colon cancer can progress from a benign adenoma, pancreatic cancer may progress from flat ductal lesions, to papillary ductal lesions without atypia, to papillary ductal lesions with atypia, and finally, to infiltrating adenocarcinoma. Importantly, the existence of such a progression suggests that the ability to detect a curable precursor lesion and early cancers with a molecular test may be possible, perhaps by mutant k-ras shed from the pancreatic intraepithelial neoplasia and detected in stool, duodenal fluid, or pancreatic juice samples.

There are a number of variants of pancreatic adenocarcinoma, including adenosquamous carcinoma, acinar cell carcinoma, and giant cell carcinoma. These variants account for only a small percentage of pancreatic ductal carcinomas. Patients diagnosed with adenosquamous and giant cell carcinomas tend to have poorer prognoses, while acinar cell cancer is associated with a better prognosis than is typical ductal adenocarcinoma.

**Molecular Genetics**

At the genetic level, cancer of the pancreas has been the focus of much recent study, making it one of the better characterized cancers. A large number of resected pancreatic adenocarcinomas have been examined for genetic alterations in cancer-causing genes. In general, these genes can be divided into three broad groups.

First, tumor suppressor genes are genes that normally function as genetic barriers to control cellular proliferation. When these genes are inactivated by genetic events such as mutation, deletion, chromosome rearrangements, or mitotic recombination, their function as growth
suppressors can be lost, resulting in abnormal growth regulation. The second type of cancer-causing gene is an oncogene. Oncogenes are derived from normal cellular genes called proto-oncogenes, and they encode for proteins that, when overexpressed or activated by mutation, possess transforming properties. The third broad class of cancer-causing genes is the DNA mismatch repair genes. When these DNA repair genes, which normally function to insure the fidelity of DNA replication, become dysfunctional, errors in DNA replication are not repaired.

The tumor suppressor genes p53, p16, and DPC4 are inactivated frequently in sporadic carcinoma of the pancreas. p53, the Science molecule of the year in 1993, is a well-characterized tumor suppressor gene that lies on chromosome 17p. p53 function appears to be inactivated in up to 75% of all pancreatic carcinomas. The p53 gene product is a DNA binding protein that acts as both a cell cycle check point and as an inducer of cell death (apoptosis). Inactivation of the p53 gene function in pancreatic cancer therefore leads to the loss of two important controls of cell growth: regulation of cellular proliferation and the induction of cell death.

The p16 gene resides on chromosome 9p, a chromosome that is a frequent site of allelic loss in pancreatic cancer. Accumulating data suggest, in fact, that approximately 80% of all pancreatic cancers have loss of the p16 gene function. The p16 gene encodes a protein that binds cyclin to cyclin D-Cdk4 complexes. When the p16 gene product binds to these complexes, it inhibits the phosphorylation of a number of growth and regulatory proteins, leading to a failure of cellular growth, and relatively unchecked proliferation.

Recently Hahn identified a new tumor suppressor gene, designated DPC4, which appears to be more specific than p53 and p16 for pancreatic cancer. DPC4 resides on chromosome 18q, a chromosome shown by allelotyping to be lost in 90% of pancreatic carcinomas. The DPC4 suppressor gene mutation appears to be a homozygous deletion in 30% of pancreatic cancers, and a point mutation in another 20% of tumors. DPC4 is therefore inactivated in approximately 50% of all pancreatic cancers. DPC4 has a similar amino acid homology to a family of proteins called MAD proteins, which play a role in signal transduction via the transforming growth factor-β family of cell surface receptors.

Activating point mutations in the k-ras oncogene are the most common genetic alteration identified in pancreatic cancer. Point mutations on codons 12, 13, or 61 of the k-ras oncogene impair the intrinsic GTPase activity of its gene product, resulting in a protein that is constitutively active in signal transduction. K-ras mutations have been found in 80% to 100% of pancreatic cancers, most of these being mutations in codon 12. Importantly, these mutations are relatively easy to detect, making k-ras a potential candidate for the development of molecular-based screening tests for pancreatic cancer.

Six human genes responsible for DNA mismatch repair—hMSH2, hMLH1, hPMS1, hPMS2, hMSH6/GTBP, and hMSH3—have been discovered to date. These mismatch repair enzymes function as heterodimers to repair single based pair changes in small insertions/deletions that occur during DNA replication. A recent report by Goggins and colleagues noted that 4% of pancreatic adenocarcinomas were characterized by disorders of DNA repair genes. Of note, these tumors were poorly differentiated and were marked histologically by expanding borders and a prominent syncitial growth pattern. Limited data suggest that this subgroup of tumors may have a more favorable prognosis than that of the typical adenocarcinoma without mutation in DNA repair genes.
FAMILIAL LINK IN PANCREATIC CANCER

For a number of years it was suggested that cancer of the pancreas clusters within families. Case-control studies have now confirmed the anecdotal observations that there is a familial link in pancreatic cancer. The familial association with pancreatic cancer can be divided into two broad groups: Those cases that arise as a result of known syndromes, and those without such an association. To date, six syndromes have been identified as being associated with pancreatic cancer: Hereditary pancreatitis, HN-PCC, familial breast cancer, FAMMM, ataxia telangiectasia, and Peutz-Jeghers syndrome (Table). Although the aggregation of pancreatic cancer may occur by chance, or because the affected members share a nongenetic environmental exposure (such as cigarette smoking or an occupational exposure), a growing body of evidence also suggests that such familial clustering has some genetic basis.

To better study the genetics of pancreatic cancer and its familial aggregation, the National Familial Pancreas Tumor Registry has been established at The Johns Hopkins Medical Institutions. A recent analysis of the database looked for similarities and differences between familial and sporadic cases. In contrast to familial breast cancer and familial colon cancer (which are characterized by younger age of onset in familial cases), no difference in the age at which pancreatic cancer was diagnosed was observed between the familial cases and the sporadic cases, as both groups had a mean age of 65 years at diagnosis.

Growth Factors

Accumulating data suggest there is an emerging role for various polypeptide growth factors and their receptors in the regulation of pancreatic cancer. These growth factors are produced by many cells; act at or near their sites of expression through autocrine and paracrine mechanisms; and may also exert their effects before release from the cell via a so-called "juxtacrine mechanism." Evidence suggests that overexpression of some specific growth factors and their receptors may play a role in the biologic aggressiveness of pancreatic cancer.

The epidermal growth factor (EGF) receptor is a transmembrane protein that binds a family of peptides and includes EGF, transforming growth factor α, heparin-binding EGF-like growth factor, amphiregulin, betaclullin, and epiregulin. All six of these growth factors are potent mitogens for a variety of cell types, and all may influence pancreatic cancer cell growth.

The transforming growth factor β polypeptide family has also been implicated in the regulation of many cellular processes including cellular growth and differentiation, regulation of extracellular matrix, and the expression of cell adhesion molecules. All three mammalian transforming growth factor-β isoforms are overexpressed in human pancreatic cancer, and such overexpression has been associated with significant decreases in patient survival. A current hypothesis developed to explain the role of overexpressed transforming growth factor-β in pancreatic cancer stipulates that overexpression enhances tumor aggressiveness by promoting tumor angiogenesis, altering various components of extracellular matrix, and enhancing adhesiveness that facilitates tumor metastasis.

The fibroblast growth factor family consists of numerous polypeptide growth factors that are mitogenic and angiogenic and have affinity for heparin, with resultant alterations in cell differentiation and tissue repair. It is currently believed that fibroblast growth factors participate in the enhancement of pancreatic cell growth and may contribute to abnormal epithelial-mesenchymal interactions within the growing neoplasm.

Finally, the insulin-like growth factor, IGF-1, is overexpressed in pancreat-
ic cancer cells, and the addition of exogenous IGF-1 enhances the growth of pancreatic cells in culture.\textsuperscript{22} It appears that IGF-1 may act via autocrine and paracrine mechanisms to enhance cancer growth in-vivo.

**Diagnosis and Staging**

The early symptoms of pancreatic carcinoma include anorexia, weight loss, abdominal discomfort, and nausea. Unfortunately, the nonspecific nature of these symptoms often contributes to a delay in diagnosis by both the patient and physician. Specific symptoms usually only develop after invasion or obstruction of a nearby structure. As most pancreatic cancers arise in the head of the pancreas, obstruction of the biliary tree resulting in jaundice is the hallmark presentation. Jaundice is progressive and often associated with significant pruritus.

Pain is a common symptom of pancreatic carcinoma. The most common pain pattern is described by patients as a dull epigastric pain often accompanied by back pain, often worse in the supine position, and relieved by sitting forward. Pain can be caused by invasion of the tumor into the splanchnic plexus and retroperitoneum, as well as by obstruction of the pancreatic duct. Although intractable pain is frequently associated with pancreatic carcinoma, it is seldom an early manifestation, with fewer than one-third of patients presenting with moderate to severe pain.\textsuperscript{25,26} Duodenal obstruction, with nausea and vomiting, is usually a late manifestation of cancer of the head of the pancreas. New onset of diabetes is observed in 15\% to 20\% of patients,\textsuperscript{27} and an occasional patient may present with acute pancreatitis.\textsuperscript{28}

The most common physical finding at initial presentation is jaundice. Hepatomegaly and a palpable gallbladder may be present in some patients. In cases of advanced disease, there may be evidence of cachexia, muscle wasting, or an enlarged, nodular liver consistent with metastatic disease. In patients with advanced cancer, ascites or findings of dropped metastasis in the pelvis encircling the perirectal region (Blumer’s shelf) may be present.

**LABORATORY STUDIES**

Results of laboratory studies in patients with cancer of the head of the pancreas typically are marked by elevated serum total bilirubin, alkaline phosphatase, and $\gamma$-glutamyl transpeptidase, with mild elevations of the hepatic aminotransferases. In patients with localized cancer of the body and tail of the pancreas, laboratory values are frequently normal early in the course. Normochromic anemia and hypoalbuminemia may reflect a chronic nature of the neoplastic process and its nutritional sequelae. It is uncommon for patients with carcinoma of the pancreas to have either hyperamylasemia or hyperlipasemia. In patients with deep jaundice, the coagulation parameters should be checked because prolonged exclusion of bile from the gastrointestinal tract leads to malabsorption of the fat-soluble vitamins and decreased the hepatic production of vitamin K-dependent clotting factors.

A wide variety of serum tumor markers have been proposed for use in the diagnosis and follow-up of pancreatic carcinoma. The most extensively studied
of these is CA19-9, a Lewis blood group-related mucin. The accuracy of CA19-9 is dependent upon the set upper limit of normal with an increased accuracy of up to 90% with a cut-off value of 200 units/ml.\textsuperscript{29} Currently, the use of CA19-9 remains experimental and is not approved by the FDA, largely because CA19-9 has not been proven to be useful as an independent test for pancreatic cancer and because its ability to identify early potential curable tumors remains unproven. In addition to its use for diagnosis, CA19-9 has also been used to assess prognosis and monitor tumor recurrence. In general, higher CA19-9 values prior to surgery indicate a larger primary tumor and an increasing rate of unresectability. Additionally, CA19-9 has been used to monitor combined modality treatments, typically neoadjuvant chemoradiation treatment or postoperative combined modality treatments. In general, increasing levels of CA19-9 reflect progression of disease, while stable or declining levels of CA19-9 are associated with a stable tumor burden, absence of tumor recurrence by imaging studies, and an improved prognosis.\textsuperscript{30} Although a number of other tumor markers have been identified, the overall accuracy rates have not achieved the accuracy of CA19-9.

**Radiologic Studies**

The early diagnosis of pancreatic carcinoma requires a high index of suspicion and appropriate aggressiveness in pursuing the diagnosis. The prompt evaluation of a patient with jaundice, however, offers the opportunity for early diagnosis. Any patient presenting with jaundice should promptly undergo diagnostic imaging with either ultrasound or computed tomography (CT). Both tests can confirm the obstructive nature of the jaundice by demonstrating dilated intra- and extrahepatic bile ducts. CT is generally considered more useful in defining the level of obstruction, demonstrating the presence of a pancreatic mass, and detecting liver metastases or local vascular invasion (Fig. 1). Currently, the use
of intravenous and oral contrast enhanced spiral CT offers the best form of imaging of the pancreas.\(^3\)

In general, magnetic resonance imaging (MRI) scanning offers no dramatic advantage over CT because of low signal-to-noise ratio, motion artifacts, lack of bowel opacification, and low spatial resolution. More recently, however, the introduction of MR-cholangiopancreatography (MRCP) has shown promise as a noninvasive technique with the ability to visualize both the bile duct and the pancreatic duct with images similar to those obtained by endoscopic retrograde cholangiopancreatography (ERCP) (Fig. 2).

Traditionally, the next step in evaluation of the jaundiced patient has been cholangiography, either by the endoscopic or percutaneous approach. The choice of technique depends primarily on local expertise. Using the endoscopic approach, ampullary and duodenal carcinomas can be visualized and biopsied. In addition, a pancreatogram may be obtained, which may be important if the differential diagnosis includes chronic pancreatitis. In most cases of pancreatic carcinoma, the pancreatic ductal system will be obstructed, with no distal filling of the duct (Fig. 3).

The percutaneous approach to cholangiography is usually technically easier with a dilated biliary tree and is useful in defining the proximal biliary system, which will be used in reconstruction (Fig. 4). In recent years with improved sophistication of spiral CT scanning, the routine use of diagnostic cholangiography for suspected pancreatic cancer is unsupported. The diagnostic ERCP is probably best reserved for the evaluation of a patient with presumed pancreatic cancer and obstructive jaundice in whom no mass is evident on CT; the symptomatic but nonjaundiced patient without an obvious pancreatic mass; or the patient with chronic pancreatitis in whom the development of a pancreatic neoplasm is sus-
expected based on clinical determination or the development of jaundice.

In addition to cholangiography for diagnostic purposes, a biliary stent can be placed through the obstructing lesion by either the endoscopic or percutaneous approach to alleviate jaundice. The placement of biliary stents preoperatively in an attempt to improve overall operative risk has been addressed by a number of prospective randomized studies, with mixed results. In a study by Pitt and colleagues, percutaneous biliary decompression preoperatively did not affect morbidity or mortality although it increased total hospital stay. In contrast, by using preoperative endoscopic biliary drainage, Lygidakis and co-workers significantly reduced operative morbidity and mortality. More recently, it has been suggested that the use of routine preoperative biliary stenting may result in increased postoperative surgical complications. It appears likely, therefore, although not indicated routinely, that in selected patients with advanced malnutrition, sepsis, and/or correctable medical conditions, or in whom a time delay prior to surgery is necessary, preoperative biliary drainage can be useful.

Percutaneous fine needle aspiration of pancreatic masses is useful in selected patients. The technique is safe and generally reliable, but is of limited value in patients in whom surgical exploration for attempted resection or palliation is planned. The reason for not using fine needle aspiration cytology or biopsy in potentially resectable lesions is two-fold. First, even after repeated sampling, a negative result cannot exclude malignancy; in fact, it is the smaller and more potentially curable tumors that are most likely to be missed by the needle. The second concern is seeding of the tumor, either along the needle tract or with intraperitoneal spread.

The primary indication for percutaneous biopsy is in unresectable cancer, based on preoperative staging, where nonsurgical palliation is appropriate. The results may then be used to direct palliative chemoradiation therapy. The technique is also useful in patients with cancer of the head of the pancreas in whom neoadjuvant protocols are being considered. Finally, percutaneous biopsy may also be useful if the CT picture suggests pancreatic lymphoma, which is best managed nonoperatively.

**PREOPERATIVE STAGING**

The goal of preoperative staging in pancreatic carcinoma is to determine the feasibility of surgery and the optimal treatment for the individual. In many patients, dynamic CT with oral and intravenous contrast may provide all relevant information by demonstrating liver metastasis or major vascular invasion. The use of dual phase CT scanning with both arterial and venous timed injection is currently the best noninvasive technique for determining the proximity of
the primary neoplasm to major peripancreatic vascular structures such as the celiac axis, superior mesenteric artery, and mesenteric venous structures (superior mesenteric vein, splenic vein, and portal vein) (Fig. 5). Preservation of fat planes around each of these vessels suggests a lack of direct invasion by the primary neoplasm and is consistent with resectability.42 For tumors of the head, neck or uncinate process of the pancreas, occlusion of the superior mesenteric vein or portal vein along with the presence of periportal collateral vessels are signs of unresectability and typically preclude resection for cure. In contrast, for tumors of the body and tail of the pancreas, occlusion of the splenic vein with perigastric collaterals does not always preclude resection, and should not be used as a sign of unresectability.

The extent of further staging procedures depends on the patient’s and the surgeon’s preference. If the surgeon’s philosophy is to pursue a surgical treatment for all patients, either in an attempt to resect or to provide palliation, then additional staging is unnecessary. However, if the findings of staging could preclude an operation and lead to nonsurgical palliation, then these efforts are worthwhile.

Preoperative visceral angiography with arterial injection of the celiac and superior mesenteric arteries with venous phase studies provides the best demonstration of vascular anatomy and major vessel encasement or occlusion. In a review of this technique in patients with periampullary cancers at The Johns Hopkins Medical Institutions, 77% of patients with normal major visceral vessels were resectable.43 Major vessel encasement, however, indicated a low resectability rate (35%). Furthermore, in all patients with major vessel occlusion, the tumor was found at operation to be unresectable. Finally, visceral angiography will also detect possible anatomic variations, such as a replaced right hepatic artery or atherosclerotic stenosis or occlusion of the celiac axis, which may alter operative management.43,44 These considerations notwithstanding, with the advent of sophisticated spiral CT for diagnosis and staging purposes, angiography is no longer considered a routine step in the staging of patients with pancreatic cancer.42

Endoscopic ultrasound (EUS) is a relatively new, minimally invasive technique in which a high frequency transducer is placed in the gastric and duodenal lumen in close proximity to the pancreas to image the gland and adjacent organs. The technique’s primary utility is for the detection of small pancreatic lesions (smaller than 2 cm) as well as lymph node and vascular involvement.45,46 Another technique, EUS-guided fine needle aspiration (FNA), also can be used to acquire tissue samples for cytologic analysis, therefore avoiding the percutaneous approach and the risks of tumor seeding. A large international multicenter experience with EUS-FNA in 124 patients demonstrated results with a sensitivity of 86%, specificity 94%, a positive predictive value of 100%, a nega-
tive predictive value of 86%, and an accuracy of 88%.47 Studies in preoperative patients suggested that endoscopic ultrasound is superior to conventional sonography, CT, MRI, and angiography in assessing resectability.48,49 Unfortunately, experience with this technique, which is operator-dependent, is still limited, precluding its widespread use.

**Sites of Metastatic Spread**

Liver metastasis and peritoneal implants are the most common sites of distant spread of pancreatic carcinoma. Once distant metastases are established, survival is so limited that a conservative therapeutic approach is indicated. Liver metastases larger than 2 cm in diameter can usually be detected by CT, but approximately 30% of these metastases are small and may not be routinely detected.50 Furthermore, peritoneal and omental metastases are usually only 1 to 2 mm in size and frequently can only be detected by direct visualization.

The use of diagnostic laparoscopy to detect such small metastatic implants before the patient is subjected to laparotomy has been extensively studied at the Massachusetts General Hospital.51-53 In the initial report by that group, 40% of patients without demonstrable extrapancreatic involvement on the basis of CT scan were nevertheless found at laparoscopy to have small liver or peritoneal metastases precluding resection.51 Laparoscopic findings, therefore, eliminated the need for laparotomy in these patients with a limited survival.

More recently with improved CT imaging, the rate of positive peritoneal findings approaches 20% to 25% for all patients with pancreatic cancer, with a notable difference in the site of origin of the pancreatic primary.52,53 For example, patients presenting with obstructive jaundice secondary to tumors in the head of the pancreas typically have only 15% to 20% incidence of unexpected intraperitoneal metastasis after routine staging studies. In contrast, 50% of patients with cancer of the body and tail of the pancreas have unexpected peritoneal metastasis.

Based on these data, staging laparoscopy appears to be valuable for patients with cancer of the body and tail. Because the primary tumor does not typically cause biliary gastric outlet obstruction in these patients, palliation of biliary or gastric obstruction is not routinely required. Thus, laparoscopy can spare such patients unnecessary treatment, as there is little role for operative palliation.

The role of preoperative laparoscopic staging is not clear, however, in patients with localized tumor by spiral CT, who present with obstructive jaundice, symptoms of gastric outlet obstruction, and tumor-related abdominal and back pain. Many surgeons believe that such patients are best managed via surgical palliation, which would include biliary-enteric bypass, gastrojejunostomy, and alcohol celiac nerve block. Preoperative staging laparoscopy would serve no purpose in such a setting.

At the time of laparoscopy, irrigation of the peritoneal cavity can be performed and the washings analyzed cytologically for evidence of shed tumor cells. In a review by Warshaw,41 30% of patients with potentially resectable tumors were found to be cytologically positive—only one of these tumors was ultimately resected. Nevertheless, if complete staging, including CT and arteriography, suggests resectability, this percentage falls to less than 10%.54

The information gained from preoperative staging provides the basis for treatment planning. If preoperative staging for tumors in the head of the pancreas using CT, angiography, and laparoscopy is normal, resectability rates may approach 80%.55 Appropriate preoperative staging, therefore, considerably improves resectability rates, previously reported as less than 25%.56 and thus eliminates unnecessary surgical procedures.
Resection of Pancreatic Carcinoma

In 1912, Kaush reported the first successful resection of the duodenum and a portion of the pancreas for an ampullary cancer.\(^5^7\) In 1935, Whipple and associates described a technique for radical excision of a periampullary carcinoma.\(^5^8\) The operation was performed in two stages, with a cholecystogastrostomy performed to decompress the obstructing biliary tree and a gastrojejunostomy performed to relieve gastric outlet obstruction in the first stage.

The second stage was performed several weeks later when the jaundice had resolved and nutritional status was improved. During the second stage, an *en bloc* resection of the second portion of the duodenum and the head of the pancreas was performed without reestablishing pancreatic-enteric continuity. Despite earlier contributions, the report by Whipple and colleagues represents the beginning of the modern-day approach to the treatment of pancreatic carcinoma.

Since Whipple’s original description, pancreaticoduodenal resection has undergone numerous modifications and technical refinements. Unfortunately, during most of its first 50 years, reported morbidity and mortality rates associated with the procedure were unacceptably high and long-term survival rates were disappointing. In fact, during the late 1960s and 1970s, the high operative morbidity and mortality and the poor long-term survival associated with the procedure were unacceptable.\(^5^9-6^1\) During the last decade, however, a number of reports have documented both improved operative results and better long-term survival rates for patients with peri-ampullary tumors following the Whipple procedure.\(^6^2-6^9\) leading to a resurgence in its popularity.

**Operative Technique**

The operative management of pancreatic cancer consists of two phases: First, assessment of tumor resectability and second, if the tumor is resectable, completion of a pancreaticoduodenectomy with reconstruction. The operative technique has been described in detail elsewhere\(^7^0\) and will be discussed here only briefly. The determination of resectability is based both on preoperative assessments and operative findings. In many cases, the former complements the latter.

Specifically, evidence of major vascular encasement on spiral CT or preoperative arteriography certainly warrants special attention to that area. A careful search for tumor outside the limits of a pancreaticoduodenal resection is initiated. The liver and peritoneal surfaces are inspected and palpated, with suspicious lesions biopsied and submitted for frozen section examination. Regional lymph nodes are evaluated for the presence of tumor. Tumor present in the periaortic lymph nodes of the celiac axis indicates that the disease extends beyond the limits of standard resection. However, the presence of tumor-bearing lymph nodes that normally would be incorporated within the resection specimen does not constitute a contraindication to resection, since long-term survival may be possible.\(^6^7\)

Once distant metastases have been excluded, an assessment is made as to whether the primary tumor is resectable. Local factors that preclude pancreaticoduodenal resection include retroperitoneal extension of the tumor to the inferior vena cava or aorta, or direct involvement or encasement of the superior mesenteric artery, superior mesenteric vein, or portal vein. In selected patients, major *en bloc* venous resection with pancreaticoduodenectomy can be performed.\(^7^1-7^3\) The addition of a major venous resection, however, adds to the potential for postoperative morbidity and mortality, and should be performed by only the most experienced pancreatic surgeons in selected patients.

Having excluded regional and dis-
tant metastases and demonstrated no tumor involvement in major vascular structures, the surgeon can proceed with pancreaticoduodenectomy with a high degree of certainty that the tumor is resectable with potential for cure. Most experienced pancreatic surgeons, at this point, will proceed with a pancreaticoduodenectomy without obtaining a tissue diagnosis. The clinical presentation, the results of preoperative CT scanning and cholangiography, and the operative findings of a palpable mass in the head of the pancreas surpass the ability of an intraoperative biopsy to define the diagnosis of malignancy. Although transduodenal needle biopsies can provide a tissue diagnosis in a high percentage of patients, it remains likely that small, potentially curable cancers may be missed by this technique. Therefore, in light of the improved operative morbidity and mortality following pancreaticoduodenectomy, surgical resection without a prior tissue diagnosis is appropriate.

EXTENT OF RESECTION
The classic pancreaticoduodenectomy performed for decades included a distal gastrectomy. In 1978, Traverso and Longmire described the pylorus-preserving modification of the Whipple procedure (Fig. 6). Preserving antral and pyloric function, the pylorus-preserving Whipple procedure reduces the incidence of troublesome postgastrectomy symptoms reported by patients, including marginal ulceration, with a number of studies having documented that gastrointestinal function is better preserved by the pylorus-sparing modification than by the traditional operation.

Concerns exist, however, regarding the use of the pylorus-preserving Whipple procedure for the management of periampullary tumors because of the possibility of compromising the already small surgical margins of resection. This question has been addressed by a number of authors, and there appears to be no difference in survival among those treated with the pylorus-sparing Whipple procedure and those managed by the traditional Whipple resection.

The extension of the Whipple procedure to include a total pancreatectomy with removal of the spleen and more extensive regional lymph nodes has been advocated by some. The overall poor long-term survival following the standard Whipple operation was the impetus for the concept of extending resection to include total pancreatectomy. Advocates
cite eliminating multicentric disease as well as eradicating the spread of the disease to the distal pancreas by direct extension, intraductal seeding, or lymphatic permeation. In addition, the latter is a better cancer operation, including a wider en bloc resection of the pancreas, as well as regional lymph nodes. Another advantage is the elimination of the pancreaticojejunal anastomosis, which is a major cause of morbidity and mortality with the Whipple operation.

Despite these potential benefits, there has been no evidence that a total pancreatectomy offers any survival advantage for patients with carcinoma of the head of the pancreas who undergo the procedure. Furthermore, there has been no reduction in morbidity and mortality in patients managed by a total pancreatectomy. The major disadvantage of the total pancreatectomy is the inevitable total loss of pancreatic endocrine function, often with resultant brittle diabetes. Therefore, total pancreatectomy should be reserved for patients with histologic evidence of tumor at the margin resection or for those with gross multicentric disease.

The concept of an even wider resection, or radical pancreatectomy, has also been proposed. These procedures include total resection of the portal vein with reanastomosis or graft and/or an extensive regional lymph node dissection. Some reports from Japanese centers suggested a potential improvement in long-term survival with extended lymphadenectomy. However, these studies were uncontrolled, and results do not appear significantly better than recent Western reports. A recent multicenter prospective randomized trial did not show a significant survival advantage to the wider resection.

Finally, although major vascular resection in experienced hands is not associated with increased perioperative morbidity and mortality, the procedure does increase operative time, blood loss and, in most series, length of hospital stay.

**SURGICAL RECONSTRUCTION**

There are a number of techniques for restoring gastrointestinal continuity after pancreatecoduodenal resection. In the most common technique, the end of the divided jejunum is placed in a retrocolic position, with creation of a pancreaticojejunostomy, followed by hepaticojejunostomy and a duodeno- or gastrojejunostomy (Fig. 6). The pancreaticojejunostomy is the most problematic anastomosis in the reconstruction, accounting for much of the morbidity and mortality that are conventionally associated with this operation. A number of techniques have been developed to manage the pancreatic remnant, including end-to-end and end-to-side pancreaticojejunostomy, either stented or unstented, or more recently, an end-to-side pancreaticogastrostomy.

**DISTAL PANCREATECTOMY FOR CANCER OF THE BODY AND TAIL**

The surgical management of adenocarcinoma of the body and tail of the pancreas is much more limited than that of the head of the pancreas due to the usual advanced extent of the disease at presentation. Most patients are found to have unresectable tumors because of major vascular involvement of the superior mesenteric/splenic vein junction with the portal vein. If the preoperative spiral CT or arteriogram with venous phase studies are normal and there is no evidence of liver metastases, however, exploration with intent to resect is appropriate.

**POSTOPERATIVE RESULTS**

During the 1960s and 1970s, many centers reported operative mortality rates following pancreatecoduodenectomy in the 20% to 40% range, with postoperative morbidity rates as high as 40% to 60%. During the last decade, a dramatic decline in operative morbidity and mortality following pancreatecoduo-
Denectomy has been reported at a number of centers, with operative mortality rates in the range of 2% to 3%. Some centers have reported large series in excess of 100 patients without one perioperative death. These dramatic improvements might be attributed to: 1) Fewer but more experienced surgeons performing the operation more frequently, taking less time and with less blood loss; 2) improved preoperative and postoperative care; 3) better anesthetic management; and 4) concentration of these patients in high volume centers. Although selection bias may have contributed to these improvements, recent data would also extend the improved operative mortality rates to patients older than 80 years of age. A poor functional status, however, as measured by the Karnofsky index, can be an independent risk factor for increased perioperative morbidity and mortality.

Unfortunately, complication rates following pancreaticoduodenectomy remain high, usually in excess of 25% to 35%. Pancreatic fistula remains the most common, serious complication following pancreaticoduodenectomy, with incidence ranging from 5% to 15%. In the past, the development of pancreatic fistula following pancreaticoduodenectomy was associated with mortality rates of 10% to 40%. Thus, although the incidence of pancreatic fistula following pancreaticoduodenectomy remains stable, the overall mortality associated with it has diminished, thanks to improved management.

Control of the anastomotic leak with careful placement of drains in the area of the pancreatic anastomosis is essential to minimizing morbidity. Important supportive measures include careful maintenance of fluid and electrolyte balance, parenteral nutrition, and meticulous care of the drainage site to avoid skin excoriation and autodigestion by activated pancreatic enzymes. The use of the Somatostatin analog, octreotide, which decreases pancreatic secretion, may also be useful in the management of a postoperative pancreatic fistula. Perioperative use of octreotide may also decrease the incidence of fistula formation following pancreaticoduodenectomy, although the results of prospective trials have been inconsistent.

The most frequent complication following pylorus-preserving pancreatic resection is delayed gastric emptying, with incidence ranging from 20% to 40%. The cause of this complication is unknown, and in most patients mechanical obstruction should be ruled out by either contrast studies or endoscopic evaluation. Management of delayed gastric emptying includes gastric decompression and maintenance of parenteral or enteral nutrition. In most cases, delayed gastric emptying is temporary and resolves spontaneously after a variable period of time, resulting simply in a delay in hospital discharge.

The use of prokinetic agents such as metoclopramide may be useful in the treatment of postoperative delayed gastric emptying. Furthermore, erythromycin, a motilin antagonist and prokinetic agent, has been shown in a recent prospective randomized study to improve gastric emptying as measured by both liquid and solid radionuclide studies. These results did not translate to improved clinical gastric emptying, but it is hoped that with the availability of improved prokinetic agents, the incidence of this complication may be reduced.

**Long-Term Survival**

Survival following pancreaticoduodenectomy for periampullary carcinoma is highly dependent on the tumor’s site of origin. For instance, survival after resection of distal bile duct, ampullary, and duodenal carcinoma has always been significantly greater than that for pancreatic carcinoma, with five-year survival rates ranging from 30% to 50%.

In contrast, five-year survival rates...
for patients with adenocarcinoma in the head of the pancreas managed by pancreaticoduodenectomy historically were only about 5%.[56-61,111,112] However, a number of recent studies have suggested an improved survival for patients following pancreaticoduodenectomy.[63-66,67,69,113]

In 1987, for example, Crist and colleagues reported a five-year survival rate of 18% among 50 patients with adenocarcinoma at the head of the pancreas.[64] Moreover, the five-year survival for 13 patients with negative lymph nodes was 48%. Similar results have been reported by Braasch and associates,[63] Trede,[65] and Geer and Brennan.[113] In 1995, Yeo and associates updated the Hopkins’ series to 201 patients with adenocarcinoma of the head of the pancreas managed by pancreaticoduodenectomy.[67] The actuarial five-year survival for those patients was 21%, with a median survival of 15.5 months (Fig. 7).

A number of variables were evaluated by both univariate and multivariate analysis in an attempt to identify factors predictive of long-term survival. Tumor characteristics found by these investigators to be important predictors of survival by univariate analysis included tumor diameter, lymph node status, and resection margin status. Based on multivariate analysis, tumor biology factors that affected survival included tumor DNA content, tumor size, lymph node status, and resection margin status. Interestingly, the decade in which resection was performed was also a significant predictor of survival. Improved survival was seen in each successive decade from the 1970s to the 1990s (Fig. 8).

Neoadjuvant and Adjuvant Therapy

At present, the general consensus of most surgeons treating pancreatic carcinoma is that any future improvement in the management of this disease will necessarily involve improved adjuvant therapy. The importance of adjuvant radiation therapy is emphasized by the pattern of relapse
after surgical resection, as more than half of resected patients develop local-regional recurrence without evidence of distant metastases.\textsuperscript{114}

In 1985, the Gastrointestinal Tumor Study Group reported encouraging results from a prospective, randomized trial designed to evaluate the efficacy of adjuvant radiation and chemotherapy following curative resection for adenocarcinoma at the head of the pancreas.\textsuperscript{115} Forty-three patients were randomized to receive either adjuvant therapy with radiation and 5-fluorouracil (5-FU) or to no adjuvant therapy. Median survival for the 21 patients who received adjuvant therapy was 20 months and three patients (14\%) survived five years or longer. Among the 22 patients who received no adjuvant therapy, median survival was 11 months, and only one patient (4.5\%) survived five years. These results have been subsequently confirmed and provide strong support for the concept of postoperative combined adjuvant therapy.\textsuperscript{116}

A recent study from The Johns Hopkins Medical Institutions prospectively evaluated 174 patients with resected, pathologically confirmed adenocarcinoma of the head, neck, or uncinate process of the pancreas who were resected between October 1991 and September 1995.\textsuperscript{117} In this group, all resections consisted of standard pancreaticoduodenectomies without extended retroperitoneal lymph node dissection.

Postoperatively, patients were evaluated by a multidisciplinary group that included surgeons, radiation oncologists, medical oncologists, and pathologists, and were offered three options for postoperative treatment: 1) Standard therapy consisting of external beam radiation to the pancreatic bed (4,000-4,500 cGy) given with two three-day courses of 5-FU and followed by a weekly bolus of 5-FU for an additional four months; 2) intensive therapy consisting of external beam radiation to the pancreatic bed (5,040-5,760 cGy) with prophylactic hepatic irradiation (2,340-2,700 cGy) followed by infusional 5-FU plus leucovorin for five of seven days per week for four months; or 3) no therapy. All patients who had satisfactorily recovered from pancreaticoduodenectomy by postoperative day 60 were encouraged to accept either standard therapy or the more intensive regimen.

In the four-year period of this study, 174 patients underwent pancreaticoduodenectomy for pancreatic carcinoma. The median survival for the entire cohort of 174 patients was 19 months, with actuarial one-, two- and three-year survivals of 68\%, 36\%, and 29\%, respectively. No differences in survival were noted on the basis of age, gender, or race. Patients who received either type of adjuvant therapy had a median survival of 19.5 months and a two-year survival of 39\%, which were significantly higher than those of patients who received no therapy (13.5 months, and 30\%; p=0.003) (Fig. 9).

Using a Cox proportional hazards model, a multivariate analysis determined that the use of either of the two adjuvant therapy protocols had a significant impact on survival, with both hazard ratios less than 1.0, indicating improvement in survival with therapy. Standard therapy appeared to be a more powerful predictor of survival than intensive therapy because of both the smaller probability value and the small hazard ratio. Based on these data and the earlier results from the Gastrointestinal Tumor Study Group, standard 5-FU-based chemotherapy with external beam radiation appears to be indicated after pancreaticoduodenectomy for adenocarcinoma of the pancreas.

A number of clinical trials are currently underway utilizing preoperative chemoradiation for the treatment of pancreatic cancer. Preliminary results suggest that neoadjuvant therapy can be completed without increasing the morbidity and mortality of subsequent surgical resection.\textsuperscript{118-120} Researchers at MD Anderson Cancer Center have recently reported on the mul-
timodality treatment of 142 consecutive patients with localized adenocarcinoma of the pancreatic head. A subset of 41 patients treated with preoperative chemoradiation and pancreaticoduodenectomy were compared with 19 patients who received pancreaticoduodenectomy and postoperative adjuvant chemoradiation. No patient who received preoperative chemoradiation experienced a delay in surgery because of chemoradiation toxicity, but 24% of eligible patients did not receive their intended postoperative chemoradiation because of delayed recovery following pancreaticoduodenectomy. Patients who were treated with rapid fractionation were reported to have significantly shorter duration of treatment (median 62.5 days) compared with patients who received postoperative chemoradiation (median 98.5 days).

In early follow-up, no patient who received preoperative chemoradiation experienced a local recurrence, while peritoneal recurrence occurred in only 10% of these patients. In contrast, local or regional recurrence occurred in 21% of patients who received postoperative chemoradiation. Overall survival curves were similar for both cohorts. The use of neoadjuvant therapy remains controversial, with some groups reserving neoadjuvant therapy for patients with evidence of locally unresectable tumors (as defined by imaging studies or laparotomy).

**Palliation of Pancreatic Carcinoma**

Unfortunately, only a minority of patients with carcinoma of the pancreas are suitable for resection and potential cure by the time their diagnoses are made. Thus, optimal palliation of symptoms to maximize remaining quality of life is of primary importance to most patients.

---

**Figure 9**

The actuarial survival curves for patients undergoing pancreaticoduodenectomy, comparing patients receiving adjuvant therapy (n=120) to those declining adjuvant therapy (n=53; p=0.003). From Yeo, with permission.
SURGICAL VERSUS NONOPERATIVE PALLIATION

In recent years, nonoperative palliation has become available as an option to treat obstructive jaundice, the most common symptom of periampullary cancer.

Four prospective, randomized studies have been completed in which surgical biliary bypass was compared with nonoperative biliary stenting for malignant obstructive jaundice. The conclusions of these studies are similar, demonstrating that both techniques are equally effective for relief of jaundice. Nonoperative palliation, however, appears to be associated with lower complication rates, lower procedure-related mortality rates, and shorter initial periods of hospitalization. Unfortunately, there appears to be no advantage with respect to long-term survival.

Advocates of surgical palliation, however, criticize these studies on two counts: First, the 30-day mortality rates in the surgical arms of these studies range from 15% to 24%, which is much higher than reported in many recent surgical series. A recent series of patients undergoing surgical palliation of periampullary carcinoma at The Johns Hopkins Medical Institutions, for example, reported a hospital mortality of 1.9% and an overall postoperative complication rate of 22%, with nearly all complications being non-life-threatening.

The second reason that some experts favor surgical palliation is that nonoperative palliation is frequently associated with late complications of gastric outlet obstruction and recurrent jaundice, resulting in the need for rehospitalization and, potentially, intervention. Although newly designed endoprostheses and self-expanding stents may be associated with fewer late biliary complications, late gastric outlet remains a potential problem.

Surgical palliation offers the only chance for long-term palliation of all three major symptoms of pancreatic carcinoma: Obstructive jaundice, duodenal obstruction, and pain. Biliary bypass can be performed as either a cholecysto- or choledocho- (hepatico-) jejunostomy. Results of a randomized, prospective study, as well as of a collective review, favor the use of the bile duct for better long-term results without increased perioperative morbidity or mortality. In Johns Hopkins’ series, recurrent jaundice developed in only 2% of patients prior to death.

A gastrojejunostomy for the treatment or prevention of gastric outlet obstruction is the only palliative procedure that cannot be performed nonoperatively. According to a review of more than 8,000 patients reported in the English-language literature from 1965 to 1990, the creation of a gastrojejunostomy did not increase the operative mortality rate. Moreover, if a gastrojejunostomy was not performed, 13% of patients had subsequent duodenal obstruction requiring a
gastrojejunostomy before death, and nearly one in five of the remaining patients died with symptoms of duodenal obstruction.

This question, namely whether to perform a prophylactic gastrojejunostomy, was recently addressed by a prospective randomized study at our institution. In this series, patients with periampullary cancer found to be unresectable at laparotomy were randomized to undergo either a retrocolic gastrojejunostomy or no gastrojejunostomy. There was no difference in perioperative morbidity, mortality, or postoperative length of stay. On follow-up, however, 19% of patients not undergoing gastrojejunostomy developed late duodenal obstruction requiring intervention (p<0.01).

The final major advantage of operative palliation is in the management of pain. A prospective randomized study has demonstrated that intraoperative celiac axis injection with 50% alcohol can both successfully relieve pain in patients with pain and prevent the development of pain in patients without pain at the time of exploration. Celiac axis injection was not associated with significant morbidity, mortality, or prolonged hospital of stay. Standard pain assessment completed until death showed a significant reduction in both pain scores and narcotic use. In addition, a surprising benefit revealed by the study was prolonged survival in those patients undergoing chemical splanchnicectomy who had significant preoperative pain (Fig. 11).

**Pain Control**

The management of pain in patients dying of carcinoma of the pancreas is one of the most important aspects of their care. The appropriate use of oral analgesic agents can be successful in most patients. Patients with significant pain should receive their medication on a regular schedule rather than on an “as needed” basis. Long-acting morphine deriva-tive compounds appear to be best suited for such treatment. Percutaneous neurolytic block of the celiac axis, either using fluoroscopic or CT guidance, is also successful for eliminating pain in the vast majority of patients.

The selection of nonoperative versus surgical palliation for periampullary cancer is influenced by a number of factors, including the patient’s symptoms, overall health status, predicted procedure-related morbidity and mortality, and projected survival. It would appear that surgical palliation can be completed with acceptable perioperative morbidity and mortality and postoperative length of stay. Avoiding the late complications of recurrent jaundice, duodenal obstruction, and disabling pain further strengthens the argument in favor of surgical palliation for those patients expected to survive six months or more.

A recent analysis suggests that advanced age, male gender, liver metastases, and large tumor diameters are unfavorable prognostic factors. An aggressive surgical approach also allows occasional resection for potential cure in patients who might otherwise not be considered for resection. Finally, a recent study from our institution suggests that pancreaticoduodenectomy, even with
positive surgical margins, offers a survival advantage over palliative bypass.\textsuperscript{140}

**Radiation and Chemotherapy for Unresectable Pancreatic Carcinoma**

Specific antitumor therapies in patients with advanced pancreatic carcinoma have been studied for years, with limited success. Trials evaluating the use of chemotherapy and radiation therapy both alone and in combination have shown only marginal improvements in survival, often with relatively high toxicity rates and with some negative impact on quality of life.

A new novel chemotherapeutic agent, gemcitabine, a deoxycytidine analogue that inhibits DNA replication and repair, is now available for patients with advanced pancreatic carcinoma. Following a phase I study, gemcitabine was evaluated in a multicenter trial of 44 patients with advanced pancreatic cancer, with results that indicated frequent subjective symptomatic benefit, often in the absence of objective tumor response.\textsuperscript{141} Currently available data suggest that gemcitabine represents an improvement over 5-FU-based chemotherapy in patients with advanced pancreatic cancer, with improved median survival (generally a few weeks to a month or two), and pain control, performance status, and weight gain. Additionally, preliminary data have demonstrated that gemcitabine is also a potent radiation sensitizer of human pancreatic cancer cells in vitro.\textsuperscript{142} This effect is currently being evaluated in various trials of gemcitabine plus radiation therapy worldwide.

Other agents are also being studied for their potential value in the palliation of patients with pancreatic adenocarcinoma, and include paclitaxel, matrix metalloproteinase inhibitors (e.g., marimastat), perillyl alcohol, as well as inhibitors of angiogenesis such as TNP-470.\textsuperscript{119} The results of such studies are eagerly awaited.

**Hormone Therapy**

Hormonal therapies are often used in patients with prostatic, breast, endometrial, and ovarian cancers, and some data suggest that this approach may be of value in pancreatic cancer, as well.\textsuperscript{143}

Some in vivo and in vitro experiments indicate that estrogen promotes pancreatic cancer growth. Additionally, several sex steroid biosynthetic enzymes have been localized to malignant pancreatic tissue. Furthermore, androgen receptors have been found in pancreatic cancers, and testosterone has been found to stimulate pancreatic tumor growth. Nevertheless, the role of both estrogens and androgens in human pancreatic cancer currently remains unclear. Although several phase II and III clinical trials of the antiestrogen tamoxifen for pancreatic cancer have been published, overall results showed a lack of benefit on survival.\textsuperscript{144,145}

Two gastrointestinal hormones, cholecystokinin (CCK) and gastrin, have been extensively studied regarding their influence on the growth of pancreatic adenocarcinoma.\textsuperscript{143} CCK and its analogues are known to induce exocrine pancreatic hypertrophy, and CCK receptors have been found on human pancreatic cancer cells. There are several reports of CCK antagonists inhibiting experimental pancreatic carcinogenesis, yet a clinical trial of the CCK antagonist devazepide in patients with advanced pancreatic cancer failed to demonstrate any impact on tumor progression and caused intolerable toxic reactions.\textsuperscript{146}

The effect of gastrin on the exocrine pancreas remains controversial. Gastrin and its analogues have been shown to stimulate the growth of experimental pancreatic cancer cells and several human pancreatic cancer cell lines. Further studies of both CCK and gastrin alone or in combination with other agents are necessary to further elucidate their possible roles in the therapy of pancreatic cancer.
New Directions: Gene Therapy, Vaccines

The term gene therapy has been used to describe a number of approaches that involve recombinant DNA technology. Currently, an extensive number of anticancer phase I protocols incorporating an array of gene transfer systems are under investigation. Unfortunately, human pancreatic cancer has not been the target of extensive experimentation with gene therapy for the following reasons: The aggressive behavior of the tumor (with typical late presentation), the local aggressiveness of the tumor, and the fact that nearly all patients with pancreatic cancer eventually die as a result of their disease.

Currently, a phase I trial of a cytokine-secreting pancreatic adenocarcinoma vaccine from primary tumors has been undertaken at The Johns Hopkins Medical Institutions. Preliminary results from this phase I trial using a granulocyte/macrophage colony stimulating factor-secreting allogeneic whole cell vaccine in patients with resected pancreatic adenocarcinoma have indicated no treatment-related toxicity, and measurable improvements in cell-mediated immunity. While the impact of this vaccine strategy on survival rates in pancreatic cancer remains unknown, it is possible that such therapy, combined with surgical resection and chemoradiation, may eventually lead to improved outcomes.

Conclusion

Carcinoma of the pancreas remains a disease with a generally dismal prognosis. Potentially curable lesions are typically confined to the head of the pancreas and present early with obstructive jaundice. Aggressive evaluation with appropriate staging should be performed. Surgical management with either resection for cure by a pancreaticoduodenectomy or operative palliation should be performed by surgeons experienced in the management of this disease to minimize morbidity and mortality. Following resection, postoperative adjuvant radiation and chemotherapy should be offered to most patients for improved long-term survival.

References

1. Greenlee RT, Murray T, Bolden S, Wingo PA: Cancer statistics, 2000. CA Cancer J Clin 2000;50:7-33.
2. Niederhuber JE, Brennan MF, Menck HR: The National Cancer Data Base report on pancreatic cancer. Cancer 1995;76:1671-1677.
3. Devesa SS, Blot WJ, Stone BJ, et al: Recent cancer trends in the United States. J Natl Cancer Inst 1995;87:175-182.
4. Gold EB, Goldin SB: Epidemiology of and risk factors for pancreatic cancer. Surg Oncol Clin N Am 1998;7:67-91.
5. Hruban RH, Petersen GM, Ha PK, Kern SE: Genetics of pancreatic cancer. From genes to families. Surg Oncol Clin N Am 1998;7:1-23.
6. La Vecchia C, Negri E, D’Avanzo B, et al: Medical history, diet and pancreatic cancer. Oncology 1990;47:463-466.
7. Everhart J, Wright D: Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA 1995;273:1605-1609.
8. Whittemore AS, Paffenbarger RS Jr, Anderson K, Halpern J: Early precursors of pancreatic cancer in college men. J Chronic Dis 1983;36:251-256.
9. Lowenfels AB, Maisonneuve P, Cavallini G, et al: Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med 1993;328:1433-1437.
10. Karlson BM, Ekbom A, Josephsson S, et al: The risk of pancreatic cancer following pancreatitis: An association due to confounding? Gastroenterology 1997;113:587-592.
11. Gold EB: Epidemiology of and risk factors for pancreatic cancer. Surg Clin North Am 1995;75:819-843.
12. Howe GR, Burch JD: Nutrition and pancreatic cancer. Cancer Causes Control 1996;7:69-82.
13. Cabilla AL, Fitzgerald PF: Tumors of the exocrine pancreas. Atlas of tumor pathology, 2nd series. Fascicle 19. Washington DC: Armed Forces Institute of Pathology 1984.
14. Warshaw AL, Compton CC, Lewandrowski K, et al: Cystic tumors of the pancreas. New clinical, radiologic, and pathologic observations in 67 patients. Ann Surg 1990;212:432-445.
15. Talalmini MA, Pitt HA, Hruban RH, et al: Spectrum of cystic tumors of the pancreas. Am J Surg 1992;163:117-124.
16. Webb TH, Lillemoe KD, Pitt HA, et al: Pancreatic lymphoma. Is surgery mandatory for diagnosis or treatment? Ann Surg 1989;209:25-30.
17. Wilentz RE, Hruban RH. Pathology of cancer of the pancreas. Surg Oncol Clin N Am 1998;7:43-65.
18. DiGiuseppe JA, Yeo CJ, Hruban RH: Molecular biology and the diagnosis and treatment of adenocarcinoma of the pancreas. Adv Anat Pathol 1996;3:139-155.
19. Hahn SA, Schute M, Hoque A, et al: DPC4, a candidate tumor-suppressor gene at human chromosome 18q21.1. Science 1996;271:350-353.
20. Caldas C, Hahn SA, Hruban RH, et al: Detection of K-ras mutations in the stool of patients with pancreatic adenocarcinoma and pancreatic ductal hyperplasia. Cancer Res 1994;54:3568-3573.
21. Goggins M, Offerhaus GJA, Hilgers W, et al: Pancreatic adenocarcinomas with DNA replication errors (RER+) are associated with wild-type K-ras and characteristic histopathology. Poor differentiation, a syncytial growth pattern, and pushing borders suggest RER+. Am J Pathol. 1998;152:1501-1507.
22. Korec M: Role of growth factors in pancreatic cancer. Surg Oncol Clin N Am 1998;7:25-41.
23. Friess H, Yamanaka Y, Buchler M, et al: Enhanced expression of transforming growth factor beta isoforms in pancreatic cancer correlates with decreased survival. Gastroenterology 1993;105:1846-1856.
24. Leung HY, Gullick WJ, Lemoine NR: Expression and functional activity of fibroblast growth factors and their receptors in human pancreatic cancer. Int J Cancer 1994;59:667-675.
25. Hudis C, Kelsen D, Niedzwiecki D, et al: Pain is not a prominent symptom in most patients with early pancreatic cancer. Proc Am Soc Clin Oncol 1991;10:326.
26. Lillemoe KD, Cameron JL, Kaufman HS, et al: Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. Ann Surg 1993;217:447-457.
27. Rosa JA, Van Linda BM, Abourizk NN: New-onset diabetes mellitus as harbinger of pancreatic carcinoma. A case report and literature review. J Clin Gastroenterol 1989;11:211-215.
28. Lin A, Feller ER: Pancreatic carcinoma as cause of unexplained pancreatitis: report of ten cases. Clin Gastroenterol 1989;11:211-215.
29. Ritts RE, Pitt HA: CA19-9 in pancreatic cancer. Surg Oncol Clin N Am 1998;7:93-101.
30. Bluemke DA, Abrams RA, Yeo CJ, et al: Recurrent pancreatic adenocarcinoma: spiral CT evaluation following the Whipple procedure. Radiology 1997;204:303-313.
31. Bluemke DA, Fishman EK: CT and MR evaluation of pancreatic cancer. Surg Oncol Clin N Am 1998;7:103-124.
32. Smith RC, Pooley M, George CR, Faithful GR: Preoperative percutaneous transhepatic internal drainage in obstructive jaundice: A randomized controlled trial examining renal function. Surgery 1985;97:641-648.
33. Pitt HA, Gomes AS, Lois JF, et al: Does preoperative percutaneous biliary drainage reduce operative risk or increase hospital cost? Ann Surg 1985;201:545-553.
34. Lygidakis NJ, van der Heyde MN, Lubbers MJ: Evaluation of preoperative biliary drainage in the surgical management of pancreatic head carcinoma. Acta Chir Scand 1987;153:665-668.
35. Heslin MJ, Brooks AD, Hochwald SN, et al: A preoperative biliary stent is associated with increased complications after pancreatoduodenectomy. Arch Surg 1998;133:149-154.
36. Povoski SP, Karpeh MS, Conlon KL, et al: Positive intraoperative bile culture at the time of pancreaticoduodenectomy are associated with preoperative biliary drainage and subsequent development of postoperative infectious complications and mortality. Gastroenterology 1998;114:A537.
37. Parsons L Jr, Palmer CH: How accurate is fine-needle biopsy in malignant neoplasia of the pancreas? Arch Surg 1989;124:681-683.
38. Al-Kaisi N, Siegler EE: Fine needle aspiration cytology of the pancreas. Acta Cytol 1989;33:145-152.
39. Ferrucci JT, Wittenberg J, Margolies MN, Carey RW: Malignant seeding of the tract after thin-needle aspiration biopsy. Radiology 1979;130:345-346.
40. Weiss SM, Skibber JM, Mohiuddin M, Rosato FE: Rapid intra-abdominal spread of pancreatic cancer. Influence of multiple operative biopsy procedures. Arch Surg 1985;120:415-416.
41. Warshaw AL: Implications of peritoneal cytology for staging of early pancreatic cancer. Am J Surg 1991;161:26-30.
42. Savadver BL, Fishman EK, Savader SJ, Cameron JL: CT arterial portography vs pancreatic arteriography in the assessment of vascular involvement in pancreatic and periampullary tumors. J Comput Assist Tomogr 1994;18:916-920.
43. Dooley WC, Cameron JL, Pitt HA, et al: Is preoperative angiographic usefulness in patients with periampullary tumors? Ann Surg 1990;211:649-655.
44. Biehl TR, Traverso LW, Hauptmann E, Ryan JA Jr: Preoperative visceral angiography alters intraoperative strategy during the Whipple procedure. Am J Surg 1993;165:607-612.
45. Kaufman AR, Sivak MV Jr: Endoscopic ultrasonography in the differential diagnosis of pancreatic disease. Gastrointest Endosc 1989;35:214-219.
46. R'sch T, Lorenz R, Braig C, et al: Endoscopic ultrasonography in pancreatic tumor diagnosis. Gastrointest Endosc 1991;37:347-352.
47. Wiersema MJ, Vilmann P, Giovannini M, et al: Endosonography-guided fine-needle aspiration biopsy: the Scandinavian experience in 2000. Gastrointest Endosc 1991;37:347-352.
48. Rösch T, Braig C, Gain T, et al: Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography. Comparison with conventional sonography, computed tomography, and angiography. Gastroenterology 1992;102:188-199.
49. Muller MF, Meyenberger C, Bertschinger P, et al: Pancreatic tumors: evaluation with endoscopic US, CT and MR imaging. Radiology 1994;190:745-751.
50. Ward EM, Stephens DH, Sheedy FPII: Computed tomographic characteristics of pancreatic carcinoma: An analysis of 100 cases. Radiographics 1983;3:547-565.
51. Warshaw AL, Tepper JE, Shipley WU: Laparoscopy in the staging and planning of therapy for pancreatic cancer. Am J Surg 1986;151:76-80.
52. Fernandez-del Castillo C, Rattner DW, Warshaw AL: Further experience with laparoscopy and peritoneal cytology in the staging for pancreatic cancer. Br J Surg 1995;82:1127-1129.
53. Fernandez-del Castillo CL, Warshaw AL: Pancreatic cancer. Laparoscopic staging and peritoneal cytology. Surg Oncol Clin N Am 1998;7:135-142.
54. Leach SD, Rose JA, Lowy AM, et al: Significance of peritoneal cytology in patients with potentially resectable adenocarcinoma of the pancreatic head. Surgery 1995;118:472-478.
55. Warshaw AL, Gu ZY, Wittenberg J, Waltman AC: Preoperative staging and assessment of resectability of pancreatic cancer. Arch Surg 1990;125:230-233.
56. Connolly MM, Dawson PJ, Michelassi F, et al: Survival in 1001 patients with carcinoma of the pancreas. Ann Surg 1987;206:366-373.
57. Kausch W: Das Carcinom der Papilla Duodeni und seine radikale Entfernung. Beitrage zur Klinische Chirurgie 1912;78:439-486.
58. Whipple AO, Parsons WB, Mullins CR: Treatment of carcinoma of the ampulla of Vater. Ann Surg 1935;102:763-779.
59. Crile G Jr: The advantages of bypass operations over radical pancreatoduodenectomy in the treatment of pancreatic carcinoma. Surg Gynecol Obstet 1978;146:959-962.
60. Plainfosse MC, Bouillot JL, Rivaton J, et al: The computed tomographic characteristics of pancreatic carcinoma: An analysis of 100 cases. Ann Surg 1985;120:283-288.
61. Fuhrman GM, Leach SD, Staley CA, et al: Rationale for an en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic Tumor Study Group. Ann Surg 1996;223:154-162.
62. Roder JD, Stein HJ, Siewert JR: Carcinoma of the periampullary region: who benefits from portal vein resection? Am J Surg 1996;171:170-175.
63. Harrison LE, Brennan MF: Portal vein resection for pancreatic adenocarcinoma. Surg Oncol Clin N Am 1998;7:165-181.
64. Campanale RP 2d, Frey CF, Farias R, et al: Reliability and sensitivity of frozen-section pancreatic biopsy. Arch Surg 1985;120:283-288.
65. Plainfosse MC, Bouillot JL, Rivaton J, et al: The use of operative sonography in carcinoma of the pancreas. World J Surg 1987;11:654-658.
66. Traverso LW, Longmire WP Jr: Preservation of the pylorus in pancreaticoduodenectomy. Surg Gynecol Obstet 1978;146:959-962.
67. Itani KM, Coleman RE, Meyers WC, Akwari OE: Pylorus-preserving pancreatoduodenectomy. A clinical and physiologic appraisal. Ann Surg 1986;204:655-664.
68. Hunt DR, McLean R: Pylorus-preserving pancreatocutaneous diversion: functional results. Br J Surg 1989;76:173-176.
69. Kozuscheck W, Reith HB, Waleczek H, et al: A comparison of long-term results of the standard Whipple procedure and the pylorus preserving pancreateoduodenectomy. J Am Coll Surg 1994;178:443-453.
70. Grace PA, Pitt HA, Longmire WP: Pancreateoduodenectomy with pylorus preservation for adenocarcinoma of the head of the pancreas. Br J Surg 1986;73:647-650.
71. Tsao JJ, Ross RL, Howell JA: Pylorus-preserving pancreatocutaneous diversion: is it an adequate cancer operation? Arch Surg 1994;129:405-412.
72. DeWeese TL, Pisters WT, Judd ES, King JR: Total pancreatectomy: The Whipple operation for periampullary carcinoma. Arch Surg 1990;125:230-233.
73. Price A, Pitt HA, Longmire WP Jr: Pancreateoduodenectomy with pylorus preservation for adenocarcinoma of the head of the pancreas. Br J Surg 1994;135:139-142.
74. Ihse I, Lilja P, Arnesjo B, Bengmark S: Total pancreatectomy for cancer of the head of the pancreas. Ann Surg 1995;221:721-733.
75. Fernandes-del Castillo C, Rattner DW, Warshaw AL: Standards for pancreatic resection in the 1990s. Arch Surg 1995;130:295-300.
76. Yeo CJ, Cameron JL, Sohn TA, et al: Six hundred fifty consecutive pancreatoduodenectomies in the 1990s: Pathology, complications, outcomes. Ann Surg 1997;226:248-260.
77. Fuhrman GM, Leach SD, Staley CA, et al: Rationale for an en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic Tumor Study Group. Ann Surg 1996;223:154-162.
78. Roder JD, Stein HJ, Siewert JR: Carcinoma of the periampullary region: who benefits from portal vein resection? Am J Surg 1996;171:170-175.
79. Harrison LE, Brennan MF: Portal vein resection for pancreatic adenocarcinoma. Surg Oncol Clin N Am 1998;7:165-181.
80. Campanale RP 2d, Frey CF, Farias R, et al: Reliability and sensitivity of frozen-section pancreatic biopsy. Arch Surg 1985;120:283-288.
81. Plainfosse MC, Bouillot JL, Rivaton J, et al: The use of operative sonography in carcinoma of the pancreas. World J Surg 1987;11:654-658.
82. Traverso LW, Longmire WP Jr: Preservation of the pylorus in pancreaticoduodenectomy. Surg Gynecol Obstet 1978;146:959-962.
83. Itani KM, Coleman RE, Meyers WC, Akwari OE: Pylorus-preserving pancreatoduodenectomy. A clinical and physiologic appraisal. Ann Surg 1986;204:655-664.
84. Hunt DR, McLean R: Pylorus-preserving pancreatocutaneous diversion: functional results. Br J Surg 1989;76:173-176.
85. Kozuscheck W, Reith HB, Waleczek H, et al: A comparison of long-term results of the standard Whipple procedure and the pylorus preserving pancreateoduodenectomy. J Am Coll Surg 1994;178:443-453.
86. Grace PA, Pitt HA, Longmire WP: Pancreateoduodenectomy with pylorus preservation for adenocarcinoma of the head of the pancreas. Br J Surg 1986;73:647-650.
87. Tsao JJ, Ross RL, Howell JA: Pylorus-preserving pancreatocutaneous diversion: is it an adequate cancer operation? Arch Surg 1994;129:405-412.
88. DeWeese TL, Pisters WT, Judd ES, King JR: Total pancreatectomy: The Whipple operation for periampullary carcinoma. Arch Surg 1990;125:230-233.
89. Plam MB, ReMine WH: Further evaluation of total pancreatectomy. Arch Surg 1975;110:506-512.
90. Ihse I, Lilja P, Arnesjo B, Bengmark S: Total pancreatectomy for cancer. An appraisal of 65 cases. Ann Surg 1977;186:675-680.
91. Tryka AF, Brooks JR: Histopathology in the
evaluation of total pancreatectomy for ductal carcinoma. Ann Surg 1979;190:373-381.

86. van Heerden JA, ReMine WH, Weiland LH, et al: Total pancreatectomy for ductal adenocarcinoma of the pancreas. Mayo Clinic experience. Am J Surg 1981;142:308-311.

87. Reber HA, Gloor B: Radical pancreatectomy. Surg Oncol Clin N Am 1998;7:157-163.

88. Fortner JG: Regional pancreatectomy for cancer of the pancreas, ampulla, and other related sites. Tumor staging and results. Ann Surg 1984;199:418-425.

89. Ishikawa O, Ohhigashi H, Sasaki Y, et al: Practical usefulness of lymphatic and connective tissue clearance for the carcinoma of the pancreas head. Ann Surg 1988;208:215-220.

90. Manabe T, Ohshio G, Baba N, et al: Radical pancreatectomy for ductal cell carcinoma of the head of the pancreas. Cancer 1989;64:1132-1137.

91. Tashiro S, Uchino R, Hiraoka T, et al: Surgical indication and significance of portal vein resection in biliary and pancreatic cancer. Surgery 1991;109:481-487.

92. Pedrazzoli S, DiCarlo V, Dionigi R, et al: Standard versus extended lymphadenectomy associated with pancreateoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: A multicenter, prospective, randomized study. Lymphadenectomy Study Group. Ann Surg. 1998;228:508-517.

93. Yeo CJ, Cameron JL, Maher MM, et al: A prospective randomized trial of pancreatecogastrectomy versus pancreateicjejunostomy after pancreateicoduodenectomy. Ann Surg 1995;222:580-592.

94. Nordback IH, Hruban RH, Boitnott JK, et al: Carcinoma of the body and tail of the pancreas. Am J Surg 1992;164:26-31.

95. Dalton RR, Sarr MG, van Heerden JA, Colby TV: Carcinoma of the body and tail of the pancreas: is curative resection justified? Surgery 1992;111:489-494.

96. Brennan MF, Mocca RD, Klimstra D: Management of adenocarcinoma of the body and tail of the pancreas. Ann Surg 1996;222:506-512.

97. Monge JJ, Judd ES, Gage RP: Radical pancreatectoduodenectomy: A 22-year experience with complications, mortality rate, and survival rate. Ann Surg 1964;160:711-722.

98. Lansings PB, Blalock JB, Ochsner JL: Pancreateoduodenectomy: A retrospective review 1949-1969. Am Surg 1972;38:79-86.

99. Gilsdorf RB, Spanos P: Factors influencing morbidity and mortality in pancreateico-duodenectomy. Ann Surg 1973;177:332-337.

100. Gordon TA, Burleyson GP, Tielsch JM, Cameron JL: The effects of regionalization on cost and outcome for the general high-risk surgical procedure. Ann Surg 1995;221:43-49.

101. Sosa JA, Bowman HM, Bass EB, et al: Importance of hospital volume in the surgical management of pancreatic cancer. Surg Forum 1997;48:584-586.

102. Liebermann MD, Kilburn H, Lindsey M, Brennan MF: Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. Ann Surg 1995;222:638-645.

103. Sohn TA, Yeo CJ, Cameron JL, et al: Should pancreateicoduodenectomy be performed in octogenarians? J Gastrointest Surg 1998;2:207-216.

104. Bakkevold KE, Kamstead B: Morbidity and mortality after radical and palliative pancreatic cancer surgery. Risk factors influencing the short-term results. Ann Surg 1993;217:356-368.

105. Kwan D, Aulfes AH Jr: Short-term administration of SMS 201-995 in the management of an external pancreatic fistula. Am J Gastroenterol 1989;84:326-328.

106. Büchler M, Friess H, Klämpf I, et al: Role of octreotide in the prevention of postoperative complications following pancreatic resection. Ann J Surg 1992;163:125-131.

107. Pederzoli P, Bassi C, Falconi M, Camboni MG: Efficacy of octreotide in the prevention of complications of elective pancreatic surgery. Italian Study Group. Br J Surg 1994;81:265-269.

108. Montorsi M, Zago M, Mosca F, et al: Efficacy of octreotide in the prevention of pancreatic fistula after elective pancreatic resections: A prospective, controlled, randomized clinical trial. Surgery 1995;117:26-31.

109. Warshaw AL, Torchiana DL: Delayed gastric emptying after pylorus-preserving pancreateicoduodenectomy. Surg Gynecol Obstet 1985;160:1-4.

110. Yeo CJ, Barry MK, Sauter PK, et al: Erythromycin accelerates gastric emptying after pancreateicoduodenectomy. A prospective, randomized placebo-controlled trial. Ann Surg 1993;218:229-238.

111. Jones BA, Langer B, Taylor BR, Girotti M: Periampullary tumors: which ones should be resected? Am J Surg 1985;149:46-52.

112. Warren KW, Christophi C, Armendariz R, Basu S: Current trends in the diagnosis and treatment of carcinoma of the pancreas. Am J Surg 1983;145:313-318.

113. Geer RJ, Brennan MF: Prognostic indicators for survival after resection of pancreatic adenocarcinoma. Am J Surg 1993;165:68-73.

114. Tepper J, Nardi G, Sutt H: Carcinoma of the pancreas: review of MGH experience from 1963-1973. Analysis of surgical failure and implications for radiation therapy. Cancer 1976;37:1519-1524.

115. Kalser MH, Ellenberg SS: Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg 1985;120:899-903.

116. Gastrointestinal Tumor Study Group: Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Cancer 1987;59:2006-2010.

117. Yeo CJ, Abrams RA, Grochow LB, et al: Pancreateicoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. Ann Surg 1997;225:621-636.

118. Coia L, Hoffman J, Scher R, et al: Preoperative chemoradiation for adenocarcinoma
of the pancreas and duodenum. Int J Radiat Oncol Biol Phys 1994;30:161-167.

119. Evans DB, Rich TA, Byrd DR, et al: Preoperative chemoradiation and pancreatoduodenectomy for adenocarcinoma of the pancreas. Arch Surg 1992;127:1335-1339.

120. Miller AR, Robinson EK, Lee JE, et al: Neoadjuvant chemoradiation for adenocarcinoma of the pancreas. Surg Oncol Clin N Am 1998;7:183-197.

121. Spitz FR, Abbruzzese JL, Lee JE, et al: Preoperative and postoperative chemoradiation strategies in patients treated with pancreatoduodenectomy for adenocarcinoma of the pancreas. J Clin Oncol 1997;15:928-937.

122. Singh SM, Longmire WP Jr, Reber HA: Surgical palliation for pancreatic cancer. The UCLA experience. Ann Surg 1990;212:132-139.

123. Sarr MG, Cameron JL: Surgical management of unresectable carcinoma of the pancreas. Surgery 1982;91:123-133.

124. Bornman PC, Harries-Jones EP, Tobias R, et al: Prospective controlled trial of transhepatic biliary endoprosthesis versus bypass surgery for incurable carcinoma of head of pancreas. Lancet 1986;1:69-71.

125. Shepherd HA, Royle G, Ross AP, et al: Endoscopic biliary endoprosthesis in the palliation of malignant obstruction of the distal common bile duct: A randomized trial. Br J Surg 1988;75:1166-1168.

126. Andersen JR, Sorensen SM, Kruse A, et al: Randomised trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. Gut 1989;30:1132-1135.

127. Speer AG, Cotton PB, Russell RC, et al: Randomised trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. Lancet 1987;2:57-62.

128. Potts JR 3d, Broughan TA, Hermann RE: Palliative operations for pancreatic carcinoma. Am J Surg 1990;159:72-78.

129. DeRooij PD, Rogatko A, Brennan MF: Evaluation of palliative surgical procedures in unresectable pancreatic cancer. Br J Surg 1991;78:1053-1058.

130. Lillemoe KD, Sauter PK, Pitt HA, et al: Current status of surgical palliation of periampullary carcinoma. Surg Gynecol Obstet 1993;176:1-10.

131. Sohn TA, Lillemoe KD, Cameron JL, et al: Surgical palliation of unresectable periampillary adenocarcinoma in the 1990s. J Am Coll Surg 1999;188:658-669.

132. Huijbregts K, Carr-Locke DL, Cremer M, et al: Biliary stent occlusion—a problem solved with self-expanding stents? European Wallstent Study Group. Endoscopy 1992;24:391-394.

133. Sarfeh JJ, Rypins EB, Jakowitz JG, Juler GL: A prospective, randomized clinical investigation of cholecystoenterostomy and choledochoenterostomy. Am J Surg 1988;155:411-414.

134. Watanapa P, Williamson RC: Surgical palliation for pancreatic cancer: Developments during the past two decades. Br J Surg 1992;79:8-20.

135. Lillemoe KD, Cameron JL, Hardacre JM, et al: Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial. Ann Surg 1999;230:322-330.

136. Saltzberg D, Foley KM: Management of pain in pancreatic cancer. Surg Clin North Am 1989 Jun;69:629-649.

137. Lebovits A, Lefkowitz M: Pain management of pancreatic carcinoma: A review. Pain 1989;36:1-11.

138. Brown DL, Bulley CK, Quiel EL: Neurolytic celiac plexus block for pancreatic cancer pain. Anesth Analg 1987;66:869-873.

139. van den Bosch RP, van der Schelling GP, Klinkenberg JJ: Guidelines for the application of surgery and endoprosthesis in the palliation of obstructive jaundice in advanced cancer of the pancreas. Ann Surg 1994;219:18-24.

140. Lillemoe KD, Cameron JL, Yeo CJ, et al: Pancreatoduodenectomy: Does it have a role in the palliation of pancreatic cancer? Ann Surg 1996;223:718-728.

141. Casper ES, Green MR, Kelsen DP, et al: Phase II trial of gemcitabine (2',2'-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Invest New Drugs 1994;12:29-34.

142. Lawrence TS, Chang EY, Hahn TM, et al: Radiosensitization of pancreatic cancer cells by 2',2'-difluoro-2'-deoxycytidine. Int J Radiat Oncol Biol Phys 1996;34:867-872.

143. Andersen JR, Sorensen SM, Kruse A, et al: Prospective controlled trial of transhepatic biliary endoprosthesis versus bypass surgery for incurable carcinoma of head of pancreas. Lancet 1986;1:69-71.

144. Wong A, Chan A, Arthur K: Tamoxifen therapy and immunotherapy, in Howard JM, Idezuki Y, Ilse I, Prinz RA (eds): Surgical Diseases of the Pancreas ed 3. Baltimore, Williams and Wilkins, 1998, pp. 613-622.

145. Bakkevold KE, Pettersen A, Arnesjo B, Espehaug B: Tamoxifen therapy in unresectable adenocarcinoma of the pancreas. Cancer Treat Rep 1987;71:749-750.

146. Ji Z, Qian J, Li A, et al: Randomised trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. Gut 1989;30:1132-1135.

147. Speer AG, Cotton PB, Russell RC, et al: Randomised trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. Lancet 1987;2:57-62.

148. Potts JR 3d, Broughan TA, Hermann RE: Palliative operations for pancreatic carcinoma. Am J Surg 1990;159:72-78.

149. DeRooij PD, Rogatko A, Brennan MF: Evaluation of palliative surgical procedures in unresectable pancreatic cancer. Br J Surg 1991;78:1053-1058.

150. Lillemoe KD: Palliative therapy for pancreatic cancer. Philadelphia, JB Lippincott, 1988, pp 717, 718.

149. Yeo CJ, Cameron JL: The pancreas. In Hardy JD (ed): Hardy's Textbook of Surgery, ed. 2. Philadelphia, JB Lippincott, 1988, pp 717, 718.

151. Lillemoe KD: Palliative therapy for pancreatic cancer. Surg Oncol Clin NA 1998;7:199-216.