

splanchnicectomy, percutaneous celiac block, or use of appropriate long-acting opioid analgesics. Splanchnicectomy and blocks avoid the adverse effects associated with opioids.

Exocrine pancreatic insufficiency should be treated with a dose of 10% of the normal postprandial output of lipolytic activity (30,000 IU or 90,000 USP units) with meals by giving one third of the dose after a few bites of the meal, one third during the meal, and one third at the end of the meal.

Chemotherapy or Radiation Therapy

- Adjuvant therapy with a 5-fluorouracil-based chemoradiation regimen should be considered after surgical resection.

Neoadjuvant chemoradiation is an acceptable alternative to postoperative chemoradiation. Before neoadjuvant therapy, contrast helical CT should be performed to carefully stage the tumor. In addition, laparoscopy can be used to further exclude occult visceral and peritoneal metastases.

Patients with unresectable locoregional or metastatic disease should be considered candidates for investiga-

tional trials if they have good performance status (able to carry out normal activities).

In lieu of an investigational study, standard treatment for patients with unresectable locoregional disease is radiation and concomitant 5-fluorouracil or gemcitabine alone.

Gemcitabine is an option for treatment of all patients with poor performance status and/or pain or for management of metastatic disease.

This medical position statement has been endorsed in principle by the American College of Gastroenterology.

References

1. DiMagno EP, Reber HA, Tempero MA. AGA technical review on the epidemiology, diagnosis, and treatment of pancreatic ductal adenocarcinoma. *Gastroenterology* 1999;117:1464-1484.
2. Gloor B, Todd KE, Reber HA. Diagnostic workup of patients with suspected pancreatic carcinoma: the University of California-Los Angeles approach. *Cancer* 1997;79:1780-1786.

Address requests for reprints to: Chair, Clinical Practice and Practice Economics Committee, AGA National Office, c/o Membership Department, 7910 Woodmont Avenue, 7th Floor, Bethesda, Maryland 20814. Fax: (301) 654-5920.

AGA Technical Review on the Epidemiology, Diagnosis, and Treatment of Pancreatic Ductal Adenocarcinoma

This literature review and the recommendations therein were prepared for the American Gastroenterological Association Clinical Practice and Practice Economics Committee. The paper was approved by the Committee in March 1999 and by the AGA Governing Board in May 1999.

The focus of this review is ductal adenocarcinoma of the pancreas, which accounts for 90% of pancreatic cancers. This cancer is deadly and is an increasing public health problem. In the United States, it kills more than 26,000 persons per year, is the fourth and the fifth most common cancer in men and women, respectively,¹ and has the lowest 5-year survival rate of any cancer. The incidence is increasing in women but has stabilized in men. For example, in a community-based study, the age-adjusted incidence per 100,000 person-years in women increased from 4.5 for the years 1940-1949 to 7.9 for the years 1980-1988. The incidence in men rose from 9.2 in 1940-1949 to 12.8 in 1960-1969 but has remained stable since then.²

The national 5-year survival has increased from 1% to 3% in whites and from 3% to 5% in blacks in the past

decade.¹ The dismal survival of patients with pancreatic cancer is caused by the late diagnosis and low resection rates. According to the 1995 National Cancer Data Base Report on Pancreatic Cancer,³ of the 17,490 patients with pancreatic cancer surveyed from 937 hospital cancer registries in the years 1985, 1986, and 1991 (32% of pancreas cancer patients in the United States), 52% had stage IV disease at diagnosis, and the overall curative resection rate (pancreatectomy) was only 14%. Overall, survival was longer in patients who underwent tumor resection than in those who did not (1-year survival, 48% vs. 23%; 2-year, 24% vs. 9%; 3-year, 17% vs. 6%), and 2-year survival was better for stage I (20%) than for stage IV disease (6%).

The specific objectives of this review are to discuss the epidemiology, diagnosis, and medical (chemotherapy and radiation therapy) and surgical treatment of pancreatic

adenocarcinoma. Although "early" diagnosis of pancreatic cancer is uncommon, we focus on this aspect of pancreatic cancer in the epidemiology, diagnosis, and prognosis sections.

Literature Review Methods

We included only studies published after 1980. A literature search was initiated using MEDLINE and the medical subject terms *pancreatic cancer* with the cross-references *epidemiology, diagnosis, chemotherapy, radiotherapy, and surgery*. Secondary searches were also performed for each major category.

For epidemiology, secondary searches were undertaken using *pancreatic cancer*. To ascertain the national incidence of pancreatic cancer in the United States, we used cancer statistics from the National Cancer Institute.¹ To determine rates in a typical community in middle America, we referred to a population-based study.² Only cohort or case-control studies were used to obtain information regarding risk for pancreatic cancer in certain populations (chronic pancreatitis, hereditary pancreatitis, diabetes mellitus) and for information regarding environmental risks (smoking, diet, and occupation).

To find relevant articles about the diagnosis of pancreatic cancer, secondary searches were conducted for each of the tests we discuss (computerized tomography [CT], ultrasonography [US], endoscopic ultrasonography [EUS], tumor markers, etc). With rare exceptions, we considered only peer-reviewed articles of prospective studies.

All but five of the articles chosen for the surgical section were published in 1990 or later. The discussion of the nonsurgical management of pancreatic adenocarcinoma focuses primarily on randomized trials in chemotherapy or radiotherapy that meet the criteria of a randomized trial design with treatment arms balanced for important characteristics such as performance status and extent of disease. As a rule, we included only studies conducted by cooperative groups involving multiple institutions or by an institution with a large patient population.

Epidemiology

Populations at Risk for Developing Pancreatic Cancer

Early diagnosis of cancer has been thwarted because populations at risk for developing pancreatic cancer have not been identified until recently. Although there is some debate about the risk of pancreatic cancer in patients with chronic pancreatitis, the strongest evidence for this association is in hereditary pancreatitis. In this disease, the estimated cumulative risk of pancreatic

cancer to age 70 is 40%, but the estimated cumulative risk for developing pancreatic cancer in patients with a paternal pattern of inheritance is approximately 75%.⁴ In this hereditary pancreatitis cohort, there were 8 pancreatic adenocarcinomas (age at onset, 38–71 years) compared with 0.15 expected pancreatic cancer cases. Because two gene mutations for hereditary pancreatitis have been identified,^{5,6} it is now possible to screen families to determine who is at risk for pancreatic cancer and to plan a rational screening program. In a multinational study, patients with chronic pancreatitis developed pancreatic cancer at a cumulative risk of 2% per decade independent of country of residence or type of pancreatitis⁷; the relative risk (ratio of observed to expected cases) was 16. This relative risk in patients compares with 4 in a U.S. Veterans Administration hospital population⁸ and nearly 8 in Sweden.⁹ However, the overall contribution of populations with chronic pancreatitis to pancreatic cancer populations is small, and continued investigation is needed to find larger risk groups.

Intraductal papillary mucinous tumor (IPMT), a disease heretofore commonly confused with chronic pancreatitis,¹⁰ is becoming more frequently recognized since its original description by Ohashi and Takagi¹¹ in 1982. This disease is characterized by dilation of the main pancreatic duct or branch ducts associated with mucin overproduction. There may be peripheral lesions consisting of ectatic branch ducts connected to the main duct or cysts that do not connect with the main duct.¹⁰ Either of these can mimic so-called mucinous cystic neoplasm (MCN). Because the incidence of invasive cancer at surgery is 25%–50%,^{10,12} it is important to distinguish the lesion from chronic pancreatitis. This is usually done on the basis of typical changes evident on CT and endoscopic retrograde cholangiopancreatography (ERCP). The ERCP examination may reveal mucus exuding from the papilla or characteristic intraductal filling defects.¹³ The lesion, even if it does not contain invasive cancer, is premalignant, and benign lesions contain several genetic mutations associated with pancreatic cancer.^{12,14} Therefore, surgical excision is the treatment of choice.

Onset of diabetes mellitus may herald the appearance of pancreatic cancer, particularly if the diabetes occurs during or beyond the sixth decade.¹⁵ Diabetes mellitus is present in 60%¹⁶ to 81%¹⁷ of patients with pancreatic cancer, and the majority of patients receive the diagnosis within 2 years of recognition of pancreatic cancer. In a recent study,¹⁶ 72% of patients with pancreatic cancer had diabetes (all non-insulin dependent); 56% had diabetes diagnosed concomitantly with the tumor; and 16% received the diagnosis of diabetes 2 years before the

diagnosis of the cancer. The risk of pancreatic cancer in patients with new-onset diabetes mellitus is unknown. However, in a recent meta-analysis of 20 case-control and cohort studies, the risk of developing pancreatic cancer in patients with diabetes of more than 1 year's duration was 2.1 (95% confidence interval [CI], 1.6–2.8).¹⁸ Sixty-six percent of patients with pancreatic cancer and diabetes have no family history of diabetes.¹⁵ Thus, a subgroup of patients with new-onset diabetes mellitus who are >50 years old and have no family history of diabetes may have an increased risk for pancreatic cancer.

There is increasing evidence that some pancreatic cancer is inherited. In several population-based studies, 7%–8% of patients with pancreatic cancer have a family history of pancreatic cancer (first-degree relative), an approximate 13-fold increase compared with 0.6% of control.^{19,20} Other disorders also are associated with increased incidence of pancreatic cancer. In familial adenomatous polyposis (FAP) syndrome, there is 4.46 relative risk (95% CI, 1.2–11.4) for development of pancreatic cancer in polyposis patients and in family members at risk, but the absolute risk is low—21/100,000 person-years.²¹ Pancreatic cancer risk is increased in familial atypical multiple mole melanoma (FAMMM) syndrome (hereditary dysplastic nevus syndrome)²² but only in some kindreds.²³ In this disorder, a gene on chromosome 9p, *p16INK4*, has been implicated in the pathogenesis of the melanoma. However, the relative risk of pancreatic cancer was increased 13-fold only in kindreds with impaired function of the p16INK4 protein (p16M alleles). In kindreds with FAMMM without impaired function of p16INK4 protein (p16W alleles), there was no increased risk for pancreatic cancer.

Ideally, all patients at risk for pancreatic cancer should be investigated and followed up closely for development of pancreatic cancer. However, it is unknown when screening should begin and whether any of our current methods can detect early pancreatic cancer. Therefore, specific recommendations cannot be given. It seems prudent to initiate screening 10 years before the age at which pancreatic cancer has been first diagnosed in familial pancreatic cancer and in the various syndromes and at age 35 in hereditary pancreatitis. Spiral CT and EUS have the best sensitivity for detection of pancreatic cancer and are the imaging tests that should be considered for screening. However, differentiation between inflammatory and neoplastic masses with imaging tests is problematic. Current tumor markers, including *K-ras* in pancreatic secretions, are too insensitive and nonspecific (see below).

Environmental Factors That Predispose to Development of Pancreatic Cancer

Many environmental factors that are associated with increased risk for pancreatic cancer may be related to exposure to aromatic amines. The most consistent risk factor is cigarette smoking, and approximately 30 aromatic amines are present in cigarette smoke,²⁴ including 2-naphthylamine and 4-aminobiphenyl, which are carcinogens for human bladder cancer. Similarly, the association between meat and fish consumption and the risk of pancreatic cancer, reported by many investigators,^{25–27} may be associated with the carcinogenic and mutagenic heterocyclic aromatic amines present in cooked meat and fish (formed during cooking as pyrolysis products of amino acids and proteins).^{28–30} There are some experimental data to support this epidemiological evidence; ingestion of dietary fish oil enhances pancreatic carcinogenesis in azaserine-treated rats³¹ and probably in *N*-nitrosobis(2-oxopropyl) amine (BOP)-treated hamsters.³² Occupations with a greater risk of pancreatic cancer, such as chemistry, petrochemical work, hairdressing, and rubber work,^{33,34} may be associated with increased exposure to aromatic amines. Conversely, ingestion of fruits and vegetables may confer protection against development of pancreatic cancer. Some components of plants (dithiolthiones and limonene) may induce glutathione transferase and increase levels of glutathione, which may inhibit mutagenic activation of heterocyclic amines.^{35,36} Together, these data suggest an association between exposure to aromatic amines and pancreatic cancer.

Diagnosis

Symptoms and Signs

The suspicion of pancreatic cancer arises because of symptoms of pain, jaundice, anorexia, early satiety, or weight loss. Some symptoms may predict tumor location³⁷ and prognosis.³⁸ Painless jaundice is the most common presentation in patients with a potentially resectable and curable lesion (52% of patients with a resectable lesion). However, pain is the most frequent symptom (80% of all patients) and is present in 80% and 85% of patients with locally unresectable and advanced cancer, respectively. The combination of pain and jaundice is present in 50% of patients with a locally unresectable lesion.³⁷ In another study of patients who underwent curative resection,³⁸ preoperative steatorrhea was associated with prolonged survival, and back pain was associated with shortened survival.

Tumor markers

The serum concentration of many tumor markers may be increased in pancreatic cancer, but they all lack sensitivity and tumor specificity.³⁹ In a review of tumor markers,⁴⁰ CA 19-9 was found to have the greatest sensitivity (70%) and specificity (87%)⁴¹ for diagnosis of pancreatic cancer with a cutoff value of 70 U/mL. In other studies, with a lower cutoff of 37 U/mL, sensitivity was somewhat higher (86%) and specificity was identical (87%).⁴² However, biliary tract obstruction with cholangitis caused by a lesion other than cancer causes high levels of CA 19-9. For example, in one study CA 19-9 values ranged from 190 to 32,000 in 7 patients with acute cholangitis secondary to bile duct obstruction caused by a gallstone⁴³ but were normal in patients with asymptomatic cholelithiasis, common duct obstruction without cholangitis, or acute cholecystitis.

Concentrations of islet amyloid polypeptide (IAPP), the main pancreatic amyloid found in the pancreas of 90% of patients with non-insulin-dependent diabetes mellitus,⁴⁴ may be increased in patients with pancreatic cancer compared with normal subjects, patients with other cancers, and patients with either insulin-dependent or non-insulin-dependent diabetes mellitus.¹⁶ Because 60%–80%^{16,17} of patients with pancreatic cancer develop glucose intolerance within 2 years before the diagnosis of pancreatic cancer, plasma concentrations of IAPP have the potential for detecting early pancreatic cancer in approximately this proportion of patients. In addition, because IAPP produces glucose intolerance⁴⁵ and reduces food intake⁴⁶ in experimental animals, it may contribute to insulin-resistant diabetes and weight loss, early signs of pancreatic cancer.

Genetic markers may detect pancreatic cancer, but it is unknown whether they are of value for detection of early pancreatic cancer. The most common gene abnormality (90%) described in pancreatic cancer is a codon 12 *K-ras* mutation.^{47–49} Mutations of the *p53* tumor cell suppressor gene are found in 50%–70% of pancreatic cancers,^{50,51} and approximately 50% have reduced expression of the *DCC* gene.^{51,52} A number of other gene deletions are less frequent in pancreatic cancer, including homozygous deletion or mutations of tumor suppressor genes *16/MTS1*^{53,54} and *p15/MTS2* but not *p27*.^{55,56}

K-ras mutations also have been detected in metastases and in pancreatic cancer cells obtained by transcutaneous needle aspiration for cytological examination. It also has been detected in pancreatic juice obtained at ERCP in 55%–77% of patients,^{57–60} in duodenal juice of 9 of 16 patients obtained after secretin stimulation,⁶¹ and in

stools from 6 of 11 patients.⁶² The *K-ras* mutations have been found in the peripheral blood only in the patients with metastatic pancreatic cancer and then only infrequently (2 of 6 patients with metastatic pancreatic cancer).⁵⁸

K-ras in pancreatic secretions may be an early marker for pancreatic cancer, but whether *K-ras* mutations found in duodenal or pancreatic juice⁶⁰ or stools⁶³ of patients with chronic pancreatitis herald pancreatic cancer is not clear. *K-ras* mutations can be found in the stools of patients with IPMT⁶³; in one report,⁶⁴ *K-ras* mutation was found in pancreatic juice obtained at ERCP in 1 patient, although results of conventional tests were nondiagnostic. At a later date, pancreatic cancer was found at surgery. Recently, *K-ras* mutations were found in the duodenal juice of 20 of 54 patients with chronic pancreatitis⁶⁵; 17 of the mutations were GAT or GTT, commonly found in pancreatic cancer, but no patients developed pancreatic cancer during a mean follow-up of 78 months. However, *K-ras* mutations not found in pancreatic cancer (TGT or AGT) were present in 24% of hyperplastic foci of specimens from patients with chronic pancreatitis.⁶⁶ More recently, *K-ras* mutations were found only in microdissected specimens of pancreatic ducts of patients with chronic pancreatitis with duct hyperplasia.⁶⁷ Collectively these data may indicate that patients with hyperplastic foci are at increased risk of developing pancreatic cancer, can be identified by *K-ras* mutations in pancreatic secretions, and perhaps should be followed up more intensely.

Imaging Tests for Diagnosis

At present, the common tests used for imaging of pancreatic cancer are CT, abdominal US, and ERCP. However, results of these tests may not be abnormal until the tumor is large and not resectable. Of these, spiral CT is the primary imaging study for evaluation of patients with symptoms that suggest the presence of the disease. CT is an appropriate initial imaging test because it detects tumors in the pancreas and can be used to stage for resectability and to detect liver metastases. The sensitivity of conventional CT for the diagnosis of tumors of <3 cm is 53%,⁶⁸ but the sensitivity of dual-phase spiral CT for resectable tumors is higher—85%,⁶⁹ 90%,⁷⁰ and 95%.⁷¹ However, the sensitivity of dual-phase spiral CT is related to the size of the tumor; the sensitivity for tumors of 0–15 mm is 67%, compared with 100% for tumors of >15 mm.⁷⁰

Magnetic resonance imaging (MRI) is gaining popularity as an imaging tool for diagnosis. Although MRI is no more accurate than CT for the diagnosis of pancreatic

cancer, it may demonstrate a definite mass in patients who have indeterminate head enlargement on CT. Semelka et al.⁷² report that in 10 of 16 patients with indeterminate head enlargement on spiral CT, a tumor was seen with MRI.

At present, EUS may be the most accurate imaging test for diagnosing⁷³ pancreatic cancer. In studies by Rösch et al.,⁷³⁻⁷⁵ sensitivity and specificity of EUS (99% and 100%) were greater than those of transabdominal US (67% and 40%) or conventional CT (77% and 53%). Small tumors <3 cm in diameter were detected in 32 patients. Even smaller tumors can be detected by EUS. For example, EUS is the best test to detect small intrapancreatic islet cell tumors that cannot be detected by other imaging tests,⁷⁶ and pancreatic cancers of 15 mm or less can be detected by EUS.⁷⁰

With a gold standard of results at surgery, in a direct comparison between conventional CT and EUS, the sensitivities of EUS and CT were 99% and 77%, respectively, for the diagnosis of pancreatic cancer.⁷⁷ Furthermore, in studies comparing conventional CT and EUS for the diagnosis of pancreatic cancer,^{68,73-76} EUS was more accurate than CT for the diagnosis of small, resectable tumors in the peripancreatic area. Thus, compared with conventional or single-phase spiral CT, EUS may provide a more precise diagnosis, avoid delays, and eliminate use of more invasive diagnostic imaging procedures (endoscopic retrograde pancreatography and/or angiography). However, in a very recent study comparing dual-phase spiral CT with EUS, the sensitivity of the dual-phase spiral CT was 92% and 100% for EUS; the overall accuracy was 93% for both imaging tests.⁷⁰ Thus, "a thin-section dual-phase helical (spiral) CT acquisition during optimal pancreatic, arterial and portal venous enhancement, followed by a second acquisition during the hepatic phase, significantly improves the accuracy of helical (spiral) CT for the detection. . .of pancreatic neoplasms."⁷⁰ Furthermore, "dual-phase helical (spiral) CT and endoscopic sonography do not differ significantly for diagnosis. . .of pancreatic tumors."⁷⁰

EUS also may be used to obtain a tissue diagnosis at the time of the examination, particularly in patients with inconclusive CT results. Recently, Chang et al.⁷⁸ reported the safety, accuracy, and clinical utility of EUS-guided fine-needle aspiration. In 44 patients, CT identified only 25% of 47 focal pancreatic lesions seen by EUS. Adequate specimens were obtained by EUS-guided aspiration in 94% of pancreatic lesions with sensitivity, specificity, and diagnostic accuracy of 92%, 100%, and 95%, respectively. EUS-guided fine-needle aspiration (FNA) excluded the need for further diagnostic tests in 57% of patients and influenced clinical decisions in 68%. In a

multicenter prospective evaluation of 124 patients with pancreatic masses (out of a total of 457 patients), the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for EUS-FNA were 86%, 94%, 100%, 86%, and 88%.⁷⁹ Complications, all nonfatal, occurred in 0.5% of patients.⁷⁹ Thus, EUS-guided FNA is a safe and effective method to accurately diagnose and stage pancreatic cancer and possibly reduce cost by eliminating the need for additional tests or surgery. However, in our opinion, EUS-guided FNA is rarely helpful in guiding the clinical decision to recommend surgery in patients with a suspected cancer that appears resectable. Thus, we recommend EUS FNA only in patients who have unresectable lesions.

Tests to Stage the Tumor

The best imaging test for staging of pancreatic tumors is unknown. EUS may be the most accurate for staging of the local extent (T) and nodal (N) status of pancreatic cancer.⁷⁴ In a direct comparison, visualization of vessel invasion by EUS was superior to conventional CT (95% vs. 73%).⁷⁷ However, there are reports of correctly interpreting resectability by contrast enhanced CT in 72%⁸⁰ and 88%⁶⁹ of patients and in 95% of patients by dual-phase spiral CT,⁷¹ values similar to EUS. Prediction of unresectability is nearly 100% correct by dual-phase spiral CT.⁷⁹ In a recent study of a direct comparison between EUS and dual-phase spiral CT to assess resectability, the overall accuracy of both tests was 90%.⁷⁰

MRI may be as accurate as spiral CT to assess resectability. Trede et al.⁸¹ reported that the overall accuracy of detection of vascular involvement was 89% for ultrafast magnetic imaging, 83% for percutaneous US, 80% for spiral CT, and 69% for angiography. However, the results of this study are difficult to evaluate because the investigators did not provide a statistical analysis and included patients with ampullary tumors.

In 10%–15% of patients, small hepatic or peritoneal metastases are found that were not seen on preoperative imaging studies. For this reason, laparoscopy has been recommended for viewing of the liver and peritoneal surfaces and for biopsy of any suspicious areas⁸²⁻⁸⁴ before laparotomy. If a metastatic tumor is found, laparotomy is not done unless gastric and biliary bypasses are required for palliation. In some cases, these procedures may be done laparoscopically.^{85,86} The major drawbacks of laparoscopy are the additional time required for the procedure and the inability to determine the presence of vascular invasion. The latter requires more extensive dissection and is aided by the tactile senses available only during laparotomy. The advantage of finding unresectable dis-

ease by laparoscopy is that laparotomy and its attendant morbidity and expense are not needed. If patients require laparotomy for palliative biliary and/or gastric bypass, laparoscopy is contraindicated.

With the current data, we recommend using dual-phase spiral CT to diagnose and stage pancreatic tumors. EUS can be used to stage tumors, but it is especially useful in patients suspected of having a small resectable tumor that was not seen on CT. Hence, dual-phase spiral CT seems to be the best test to both diagnose and stage pancreatic tumors, and EUS should be reserved to search for small resectable tumors suspected clinically but not seen by CT. Laparoscopy is used in some centers for staging because small hepatic and/or peritoneal metastases can be seen that are not visualized by less invasive tests. Although laparoscopy should not be done in all patients, it is indicated if there is a high likelihood of unresectability that has not been confirmed by imaging tests.⁸⁷ Examples include pancreatic cancer and CT evidence of liver or other metastases that have not been proved with FNA; pancreatic body or tail cancers, all of which have a very low chance being resectable; and pancreatic cancer and ascites, which is probably caused by unrecognized peritoneal metastases.

Treatment

Preoperative Management

All patients undergoing pancreatic surgery require preoperative optimization of cardiac, pulmonary, and renal function, which is usually done in the outpatient setting. Although patients often have lost weight, the nutritional status of most is satisfactory enough for them to undergo surgery safely. However, if the serum albumin concentration is <3 g/dL or surgery is delayed for more than several weeks, supplemental enteral nutrition is indicated. Pancreatic enzyme replacement also should be given with enteral nutrition if the tumor is in the head of the gland and obstructs the pancreatic duct (see later).

Obstructive jaundice can cause defects in hepatic, renal, and immune function. However, results of several studies show that routine preoperative stenting of the bile duct to relieve jaundice does not decrease postoperative morbidity and mortality.⁸⁸⁻⁹⁰ Trials do not support preoperative stenting of the bile duct. It is our opinion, however, that jaundiced patients who are candidates for resection in whom surgery is delayed for more than several weeks should have endoscopic placement of a 10F or larger plastic biliary stent to relieve the jaundice and to minimize the chance of cholangitis. Expandable metal stents are preferable to treat biliary obstruction if patients

have unresectable tumors, but they should not be used if patients are candidates for resection. Metal stents incite a severe inflammatory reaction and are eventually incorporated into the bile duct wall. This can complicate or even prohibit the resection.

Advanced age and large tumor size are not contraindications for consideration of resection.⁹¹⁻⁹³ Each patient must be evaluated for the associated risks of coexistent cardiovascular, pulmonary, and renal disease. Many patients who undergo Whipple resection are octogenarians; some patients under age 65 may present unacceptable surgical risks. Although small pancreatic tumors (<2 cm in diameter) are more likely to be resectable than larger ones, no patient should be denied the opportunity for cure because the tumor is "too large." Indeed, in several major U.S. centers, most of the Whipple resections for cancers in the head of the gland are done for tumors between 3 and 5 cm in diameter.⁹³

Operative Management

Determination of resectability at the time of surgery. Although most patients who undergo resection for pancreatic cancer die of the disease, curative resection is performed if cure appears possible. Thus, resection is not done in the presence of liver or peritoneal metastases or if there are metastases to lymph nodes that are not normally removed as part of the Whipple operation.⁹⁴⁻⁹⁷ The operation is begun by carefully examining the peritoneal cavity and its contents, and obtaining biopsy specimens of any areas suspicious for metastasis. Frozen-section diagnoses are usually available within 20 minutes, and a preliminary decision can be made about resectability. In the absence of distant metastases, resectability depends on whether the tumor has invaded any major vascular structures. Assessment of vascular involvement requires mobilization of the tumor from surrounding structures, which is done next. Involvement of the superior mesenteric, celiac, or hepatic arteries and usually invasion of the mesenteric vein precludes resection. Resection proceeds only if the vessels appear to be free of tumor.

Experienced pancreatic surgeons often will proceed with pancreaticoduodenectomy without a preoperative or operative biopsy of the primary tumor to confirm the diagnosis of malignancy because biopsy results will not alter the decision to resect the tumor. Indeed, if the history and clinical picture, preoperative test results, and surgical findings are all consistent with the diagnosis, then the chances that cancer is present are more than 90%.^{98,99} If cancer is not the cause of symptoms, chronic pancreatitis is the most likely diagnosis and pancreaticoduodenectomy is also appropriate. In part, this approach

has evolved because it may be difficult to establish the diagnosis of pancreatic cancer intraoperatively and to distinguish the tumor, which is often surrounded by a zone of chronic pancreatitis. This is especially true when the cancer is small and most likely to be cured by resection.

Resection. The first successful resection for a periampullary cancer was performed as a two-stage operation by the German surgeon Kausch in 1909. In 1935, Whipple performed a similar procedure for an ampullary carcinoma; he perfected the procedure into a one-stage resection by 1942. This operation, a pancreaticoduodenectomy, or Whipple resection, is similar to that performed today. It consists of a 40%–50% gastrectomy (antrectomy), cholecystectomy, and removal of the distal common bile duct, head of the pancreas, duodenum, proximal jejunum, and regional lymph nodes. Reconstruction requires pancreaticojejunostomy, hepaticojejunostomy, and gastrojejunostomy. The surgical mortality for this procedure is now $\leq 2\%$ ^{100,101} if it is performed by an experienced pancreatic surgeon.

Modifications of the pancreaticoduodenectomy.

Pylorus-preserving Whipple resection. Because the standard Whipple resection is associated with weight loss and nutritional disturbances, many surgeons have performed this modification, which preserves the stomach, the pylorus, and the first 3–4 cm of the duodenum. This procedure maintains gastric reservoir function, and postoperative gastric emptying is closer to normal. The operation was first described in 1944 but did not become popular until the 1970s, when it was performed for patients with chronic pancreatitis; later it also became an accepted procedure for pancreatic cancer. Although it is a less extensive operation, it does not appear to decrease survival compared with the standard Whipple.

It was assumed that retention of the pylorus and the entire stomach would improve postoperative nutrition compared with the Whipple operation. However, in several studies, similar weight loss and nutritional deficiencies accompanied the operations.^{102–104} Others claim that weight gain is more rapid and the nutritional state is better after the pylorus-preserving operation. However, to date such studies have suffered from a variety of methodological problems. For example, they are almost all retrospective in nature, and the patients were not randomly assigned to the pylorus-preserving and standard Whipple groups. This raises obvious concerns about whether the groups are truly comparable. In one recent study, although all patients in the Whipple group had pancreatic ductal adenocarcinoma, almost half of those who underwent the pylorus-preserving operation had a variety of other periampullary cancers known to be

associated with a better prognosis (e.g., cancers of the bile duct, papilla, duodenum, carcinoid, islet cell tumor). In this study, the patients who underwent the Whipple operation had a two-thirds gastrectomy, which would have been expected to produce significant nutritional problems in some. Most surgeons only remove 40%–50% of the stomach.^{105,106} Nevertheless, even in the absence of absolute proof of the superiority of the pylorus-preserving operation, many surgeons perform the two procedures interchangeably, reserving the standard Whipple for patients with larger, more extensive tumors.

Radical (extended) Whipple resection. Some Japanese surgeons have advocated the use of a more radical pancreatic resection to improve cure rates.^{107–110} The standard Whipple procedure is modified by removal of more peripancreatic soft tissue and lymph nodes, often with resection of segments of the superior mesenteric and portal veins as well. Some surgeons have reported improved survival,¹¹⁰ but no properly designed prospective trials have compared this procedure with the standard resection. Most surgeons in the United States are skeptical that the radical procedure cures more patients, and it is rarely performed in this country.

Prognosis: Results of Surgery

Surgical mortality rates for the Whipple resection are now $\leq 2\%$ in major centers around the world.^{100,101} The best outcomes (surgical mortality rates and long-term survival figures) at a lower cost are achieved at institutions with the most experience (>20 Whipple resections a year).^{111,112} This appears to be related to surgical expertise and the increased ability of practitioners in other disciplines (e.g., nursing, radiology, gastrointestinal endoscopy) to treat these patients.

Surgical resection is the only chance for cure, but the median survival after resection is only 18–20 months, the overall 5-year survival is 10%, and up to 50% of those who survive 5 years may die of recurrent cancer.¹¹³ Other reported 5-year survival rates for patients undergoing pancreaticoduodenectomy include 25%,¹⁰⁰ 19%,¹⁰¹ and 6.8%.¹¹⁴ Variation of tumor characteristics and behavior (e.g., tumor size, nodal status) and completeness of resection probably contribute to differences in survival.

Patients with smaller tumors tend to have a better prognosis than those with larger tumors.¹¹⁵ In one surgical series of 174 consecutive patients who underwent curative resection,¹¹⁴ 42 patients with pancreatic tumors of <2 cm had a 5-year survival rate of 20% compared with 1% of patients who had tumors of >3 cm. Patients with stage I, II, or III tumors had 5-year survival rates of 14%, 0%, and 1%, respectively.¹¹⁴ An even higher 5-year survival rate of 41% has been reported by Japanese

surgeons in patients with small (<2 cm) tumors.¹¹⁶ If lymph nodes are negative for tumors, median survival may be 4.5 years, compared with 11 months for node-positive patients.¹¹⁷⁻¹²⁰ Unfortunately, even small tumors metastasize to lymph nodes in 75%-80% of patients treated by resection. Poorly differentiated tumors have a worse prognosis than well-differentiated ones (10% vs. 50% 5-year survival).¹²¹ An additional important prognostic factor is whether the tumor is present at the margins of the Whipple resection specimen.¹²² For this reason, the pancreatic and bile duct margins are routinely evaluated during surgery. If tumor is present, more tissue is resected if possible until negative margins are obtained.

Some of these variables are confounding (e.g., small tumors of the head are more likely to be confined to the pancreas and not have node metastases than large tumors). There is some controversy regarding the relative importance of these variables to survival after resection,¹²³ but in a multivariate analysis¹²² it was found that tumor size <3 cm, negative nodal status, and negative resection margins were the strong predictors of long-term survival. Overall, these data support the hypothesis that surgical extirpation of "early pancreatic cancer," defined as tumor of <2 cm, confined to the pancreas (that is without local extension or metastases), will improve survival.

Palliation

Surgical and medical palliation of pancreatic adenocarcinoma is important because 88% of patients present with unresectable disease due to local extension or metastatic disease.¹²⁴ When resection of the primary tumor is not possible, the surgeon must decide whether to perform any palliative procedures to relieve biliary or duodenal obstruction. If surgery is not performed, medical palliation is needed to relieve jaundice, pain, weight loss, pancreatic insufficiency, fatigue, and depression.

A bypass to relieve biliary obstruction is the most common palliative surgery because most patients with cancer in the head of the pancreas are jaundiced. Either an anastomosis between the gallbladder and jejunum (cholecystojejunostomy) or common bile duct and jejunum (choledochojejunostomy) is effective.¹²⁵⁻¹²⁷ Jaundice is relieved and the bilirubin concentration returns to normal in 90% of patients; in 10%, the bilirubin concentration may not return to normal because of impaired hepatic function, probably caused by long-standing obstruction or extensive hepatic metastases.¹²⁵ The gallbladder should be used for decompression only if the cystic duct enters the common bile duct distant from the tumor. If the cystic duct is near the tumor, it may become obstructed as the cancer grows, preventing function of

the cholecystojejunostomy and causing recurrent jaundice. If a biliary stent is present, it should be removed and a cholecystojejunostomy performed if it is technically possible. This will eliminate the need for stent changes during the patient's life. If a cholecystojejunostomy cannot be performed, a choledochojejunostomy should be done only if the common duct is >1 cm in diameter. Anastomosis of smaller ducts is technically possible, but it may be simpler to avoid the surgical bypass altogether because most surgeons use a stent to keep such a small anastomosis patent. Instead, an endoscopically placed stent, which also provides effective palliation, should be left in place or inserted later.

Patients who require relief of bile duct obstruction and are not candidates for possible curative resection should undergo endoscopic stent placement. In a randomized trial of percutaneous vs. endoscopic stenting in 75 patients with malignant bile duct obstruction, patients treated with an endoscopic stent had a higher success rate for relief of jaundice (81% vs. 61%) and a significantly lower 30-day mortality rate (15% vs. 33%).¹²⁸ The preferred endoscopic prosthesis for palliation is an expandable metal stent. In a randomized trial of endoscopic stents for inoperable malignant strictures of the common bile duct in which 65 of 101 patients had pancreatic cancer,¹²⁹ patients with plastic stents who had stent exchanges performed every 3 months and patients who had metal stents had a longer complication-free interval than patients who had stent exchanges only when stents malfunctioned. Patients who receive stents need ongoing surveillance and management by a multidisciplinary team for postprocedure complications such as stent-associated cholangitis.

Patients rarely have obstruction of the duodenum by tumor at the initial exploration, but 15%-20% develop it before they die.¹²⁵ Because it is difficult to predict who will eventually have obstruction, many surgeons perform prophylactic gastrojejunostomy with a biliary bypass. This is not associated with increased morbidity or mortality rates.¹²⁵ Occasionally, patients vomit preoperatively and are mistakenly assumed to have duodenal obstruction. Gastrojejunostomy does not relieve the vomiting because it is probably caused by abnormal gastric motility, perhaps secondary to tumor infiltration of the nerve plexuses. Slowed gastric emptying occurs in 60% of patients with pancreatic cancer who have no evidence of gastroduodenal invasion or obstruction.¹³⁰ One third of these patients have nausea and vomiting, and some have nonspecific abdominal complaints; in others, delayed gastric emptying may be subclinical. Although prokinetic agents may help,¹³⁰ vomiting is often refractory to all treatment.

There have been recent reports of safe and successful alleviation of gastric outlet and duodenal malignant obstructions by endoscopically placed expandable metallic prostheses.^{131,132} In these reports, 16 of 20 patients were able to eat solid or pureed food after the procedure. Treatment failure was associated with nonrecognition of multiple sites of obstruction and deployment of stents either too proximally or too distally. These new palliative procedures require further evaluation before they can be recommended routinely.

Pain is a significant problem in pancreatic cancer. Fortunately, chemical intraoperative splanchnicectomy or celiac block or percutaneous celiac block and use of appropriate long-acting opioid analgesics can provide adequate pain control. In a prospective randomized trial of intraoperative 50% alcohol splanchnicectomy vs. placebo in 127 patients, splanchnicectomy significantly reduced or prevented pain and prolonged survival in patients with preexisting pain.¹³³ Increasingly, data are being accumulated to suggest that celiac plexus block may be superior to pharmacological therapy. For example, in a prospective, randomized double-blind trial of neurolytic celiac plexus block compared with pharmacological therapy,¹³⁴ patients receiving the block had immediate significant reduction in pain relief compared with those treated with drug therapy. Patients with the celiac block had significantly fewer complications (constipation, nausea, vomiting). Similar results were recorded in a comparison between celiac plexus block and nonsteroidal anti-inflammatory drug-morphine oral analgesics.¹³⁵ Other surgical or neurolytic procedures such as thoracoscopic splanchnicectomy and EUS alcohol injection of the celiac ganglion have been developed but have not been subjected to control trials.

In pancreatic cancer, depression is prevalent, may be debilitating, and is associated with presence of pain and impairment of function and quality of life. Among patients referred to a tertiary center for surgery ($n = 83$) or chemotherapy ($n = 47$), 38% had significant depression (Beck depression score, >15), and there was a significant association between increasing pain and depression.¹³⁶ Patients with moderate or severe pain had significantly impaired functional activity and poorer quality of life scores. Recognition and treatment of depression can improve patients' sense of well-being and activity level.¹³⁷

Patients with exocrine pancreatic insufficiency who have weight loss and/or stools characteristic of malabsorption should be treated with pancreatic enzymes. Only two studies have compared the results of pancreatic enzyme-replacement therapy with those of no treatment¹³⁸ or placebo¹³⁹ in patients with pancreatic cancer, and only in

12 and 21 patients, respectively. Only patients with head cancers have malabsorption (9 of 12 patients), and in these patients malabsorption significantly contributes to weight loss.¹³⁸ This association correlates with the finding that only patients with obstruction of the pancreatic duct in the head had pancreatic enzyme output reduced below 10% of normal, the level necessary to produce malabsorption.¹⁴⁰

In only one of the studies¹³⁸ was the dose of lipolytic activity appropriate, 10% of the normal postprandial output of lipolytic activity (30,000 IU) as 8 tablets with meals (2 after a few bites, 4 during a meal, and 2 at the end), which increased the coefficient of fat absorption 20% and abolished protein malabsorption in most patients. In the recent study,¹³⁹ microencapsulated enteric-coated microspheres were administered with meals over 8 weeks in an insufficient dose of $\sim 17,500$ IU (50,000 USP units, see below). Predictably, this dose did not increase fat absorption, but body weight increased 0.7 kg compared with 2.2-kg loss in the placebo group. The increase in body weight without correction of steatorrhea probably was caused by correction of protein absorption.

Similarly, in patients with chronic pancreatitis, capsules of microencapsulated enteric-coated microspheres are not universally effective because the pH-dependent enteric coating, to eliminate acid denaturation of lipase, prevents release of enzymes in the proximal gut.¹⁴¹ If these preparations are used, the number of capsules should contain a total of 30,000 IU of lipolytic activity, the minimum amount needed to correct steatorrhea. For example, the most potent commonly used enteric preparation contains ~ 8800 IU, and thus at least 3–4 capsules are theoretically needed to correct steatorrhea.

There is confusion regarding doses of pancreatic enzyme replacement because amounts of lipase in commercial preparations are measured as USP units, whereas IU were used in studies of pancreatic enzyme secretion to determine the amounts of enzymes required to abolish malabsorption. Approximately 1 IU equals 2–3 USP units. Thus, a common error is to underestimate the dose of pancreatic enzymes required to abolish steatorrhea by 2–3-fold.

Chemotherapy and Radiation

For this discussion, the term *locoregional* indicates malignancy involving the pancreas and regional lymph nodes and *metastatic* indicates distant nodal, organ, peritoneal, or pleural involvement.

Discussion of chemotherapy and radiation for pancreatic cancer requires definition of efficacy. Traditional endpoints for efficacy of cancer therapy in any disease include the objective response rate, disease-free survival,

overall survival, and quality of life. For solid tumors, objective response is generally accepted as a 50% or greater reduction in the sum of the products of all bidimensionally measurable lesions. The criterion of bidimensional measurement was originally developed by the World Health Organization and used for nodules on chest radiographs or palpable lesions such as enlarged lymph nodes, skin metastases, and abdominal masses. It is now commonly applied to lesions seen with three-dimensional imaging techniques such as CT or MRI. Application of this criterion to pancreatic cancer is difficult. A histological hallmark of pancreatic adenocarcinoma is an associated desmoplastic reaction which, in a given tumor mass, can vastly overestimate the malignant cell mass. Furthermore, associated pathological changes in the pancreas such as varying degrees of acute or chronic pancreatitis or cyst formation can cause architectural changes in the pancreas that may be difficult to distinguish radiographically from the border of the malignancy. Furthermore, the location of the pancreas adjacent to unopacified or poorly opacified small bowel complicates radiographic interpretation of changes in size of the pancreas.¹⁴² For these reasons, it is becoming widely accepted that accurate disease measurements in pancreatic cancer are difficult to achieve.^{143,144} Thus, there is growing interest in identification of alternate endpoints to gauge effective therapy. If concentrations of CA 19-9, a tumor-associated antigen that is highly expressed in pancreatic adenocarcinoma, return to normal after surgical resection, survival is increased.¹⁴⁵ Similarly, in patients undergoing chemotherapy, a decrease in CA 19-9 levels correlates with increased survival.¹⁴⁶ However, CA 19-9 concentration is not yet an accepted test to screen for antitumor efficacy.

Global quality of life or symptom assessment also is not used routinely to measure efficacy in clinical trials of patients with pancreatic adenocarcinoma. However, these measures may show that chemotherapy provides important palliation that is underestimated by the objective response rate. For example, Glimelius et al.¹⁴⁷ applied a standard and validated quality of life instrument developed by the European Organization for Research and Treatment of Cancer (EORTC) to pancreatic cancer patients receiving either best supportive care or chemotherapy with 5-fluorouracil (5-FU) and leucovorin with or without etoposide. Thirty-six percent of the patients receiving chemotherapy had improved quality of life compared with 10% of those receiving the best supportive care. With a symptom assessment tool developed for phase II and phase III randomized trials of gemcitabine (2',2'-difluoro-2'-deoxycytidine)¹⁴⁸ for patients with pancreatic cancer, Rothenberg et al.¹⁴⁹ found that 20% of the

patients had fewer tumor-associated symptoms (considered a clinical benefit response by the authors). Similarly, Burris et al.¹⁵⁰ reported a clinically beneficial response in 24% of patients treated with gemcitabine compared with 5% of those treated with 5-FU. In the latter trial, the objective response rates of the two arms of the study were similar (5% vs. 0%). These findings emphasize that the objective response cannot be measured adequately in pancreatic adenocarcinoma using standard criteria and reinforces the need for alternate efficacy endpoints.

The most powerful measure of efficacy in cancer therapy is survival. However, demonstration of greater survival requires a randomized trial design with treatment arms balanced for important characteristics such as performance status and extent of disease. As a rule, these studies can be conducted only by cooperative groups involving multiple institutions or institutions with large patient populations. The rest of this discussion focuses on randomized trials of chemotherapy (as the primary form of management and as a radiosensitization adjunct to radiotherapy) or radiotherapy (commonly applied radiotherapy techniques, external beam radiotherapy, including intraoperative radiotherapy [IORT], and brachytherapy) that meet these criteria.

Chemotherapy. Several recent reviews detail the efficacy data for single-agent and combination chemotherapy.¹⁵¹⁻¹⁵³ As previously noted, acceptance or rejection of many chemotherapy regimens, including single agents, has been based on objective response rates. However, the median survival with these single agents is rarely more than 5 months, leading to the conclusion that there are no highly effective single agents. Only two chemotherapy drugs have been associated with a reproducible survival of more than 5 months, 5-FU and gemcitabine. 5-FU has primarily been studied using bolus administration rather than short-term continuous infusion (generally over 5 days) or protracted infusion (uninterrupted delivery to toxicity). These last schedules have been suggested to demonstrate higher antitumor activity in patients with other gastrointestinal cancers, particularly colorectal cancer.¹⁵⁴ Protracted infusion of 5-FU has been studied in combination with interferon alfa administration in pancreatic cancer, producing a median survival of 5.5 months, which does not appear to be superior to that achieved with 5-FU alone.¹⁵⁵ Biochemical modulation of 5-FU with leucovorin, interferon alfa, or *N*-(phosphonacetyl)-L-aspartate (PALA) has also been studied but without compelling survival data to suggest that these regimens are superior to therapy with bolus 5-FU.¹⁵⁶ The experience with gemcitabine has provided modest optimism that it may be possible to break the chemoresistant barrier commonly associated with pancreatic adenocarci-

Table 1. Randomized Trials of Single and Combined Chemotherapies for Pancreatic Cancer

Agents, dose, and schedule	No. of patients	Percent response	Median survival (mo [range])	Percent surviving 1 year	Study
Adriamycin 60 mg/m ² every 3 wk vs. Methotrexate 40 mg/m ² every wk vs. Actinomycin D 0.4 mg/m ² × 5 days every 4 wk	25 25 28	8% 4% 3%	3 (0.25–14.5) 2 (0.25–25+) 2.5 (0.25–15+)	NS NS NS	Schein et al. 1978 ¹⁸³
5-FU 500 mg days 1–5 + cyclophosphamide 300 mg days 1 and 5 + vincristine 1 mg days 2 and 5 + methotrexate 20 mg days 1 and 4 followed by 5-FU 10 mg/kg days 1–5 + mitomycin 100 fg/kg days 1–5 every 6 wk (Mallinson regimen) vs. No therapy	21 19	NS NS	11 ^a 2.25	35% 5%	Mallinson et al. 1980 ¹⁶⁵
5-FU 350 mg/m ² days 1–5 and 400 mg/m ² days 36–40 + methyl CCNU 150 mg/m ² day 1 every 10 wk vs. 5-FU 350 mg/m ² days 1–5 and 400 mg/m ² days 36–40 + methyl CCNU 150 mg/m ² day 1 + streptozocin 400 mg/m ² days 1–5 every 10 wk vs. Melphalan 6 mg/m ² days 1–5 every 6 wk vs. VP-16 (initial or crossover) 125 mg/m ² every other day ×3, every 4 wk	41 43 43 28	10% 7% 2% 0%	3.5 3 2 2.25	NS NS NS NS	Horton et al. 1981 ¹⁸⁴
5-FU 9 mg/kg days 1–5 + CCNU 70 mg/m ² day 1 every 6 wk vs. Best supportive care	65 87	0% 0%	3 3.9	NS NS	Frey et al. 1981 ¹⁸⁵
5-FU 500 mg PO days 2–5 + CCNU 40 mg/m ² PO days 2 and 3 + vincristine 1 mg/m ² day 1 every 6 wk vs. No therapy	25 22	NS NS	5 (1–17) 4 (1–20)	NS NS	Andren-Sandberg, et al. 1983 ¹⁸⁶
5-FU 1000 mg/m ² days 1–4 and 29–32 + mitomycin C 15–20 mg/m ² day 1 every 56 days vs. 5-FU 1000 mg/m ² days 1–4 and 29–32 + mitomycin C 10–15 mg/m ² day 1 + streptozocin 400 mg/m ² days 1–4 and 29–32 every 56 days	73 72	8% 34% ^a	4.25 4.75	9% 19% ^a	Bukowski et al. (SWOG) 1983 ¹⁸⁷
5-FU 500 mg/m ² days 1–5 every 4 wk vs. 5-FU 400 mg/m ² days 1–4 + Adriamycin 40 mg/m ² day 1 every 4–5 wk vs. 5-FU 600 mg/m ² days 1, 8, 29, and 36 + Adriamycin 30 mg/m ² days 1 and 29 + mitomycin C 10 mg/m ² day 1 every 8 wk	50 44 50	NS NS NS	5.1 (1–24) 4.7 (1–31) 4.7 (1–28)	12% 18% 12%	Cullinan et al. (NCCTG) 1985 ¹⁶³
Maytansine 0.6 mg/m ² days 1–3 every 3 wk ×3 then every 4 wk vs. Chlorozotocin 120 mg/m ² every 6 wk vs. Chlorozotocin 175 mg/m ² every 6 wk	48 27 30	0% 0% 10%	2.3 2.65 2.0	NS NS NS	GITSG 1985 ¹⁸⁸
5-FU 600 mg/m ² days 1, 8, 29, and 36 + Adriamycin 30 mg/m ² days 1 and 29 + mitomycin C 10 mg/m ² day 1 every 8 wk vs. 5-FU 600 mg/m ² days 1, 8, 29, and 36 + streptozocin 1 g/m ² days 1, 8, 29, and 36 + mitomycin C 10 mg/m ² day 1 every 8 wk	90 94	14% 4%	6.5 4.5	NS NS	Oster et al. (CALGB) 1986 ¹⁶¹
5-FU 600 mg/m ² days 1, 8, 29, and 36 + Adriamycin 30 mg/m ² days 1 and 29 + mitomycin C 10 mg/m ² day 1 every 8 wk vs. 5-FU 600 mg/m ² days 1, 8, 29, and 36 + streptozocin 1 g/m ² days 1, 8, 29, and 36 + mitomycin C 10 mg/m ² day 1 every 8 wk vs. 5-FU 300–350 mg/m ² days 1–5 every 5 wk + streptozocin 350 mg/m ² days 1–5 every 5 wk + mitomycin C 10 mg/m ² day 1 every 10 wk	29 28 27	13% 15% 14%	2.9 4.4 3.3	5% 12% 12%	GITSG 1986 ¹⁶²
Bakers's Antifol (TZT) 250 mg/m ² days 1–3 every 3 wk vs. Diaziquone (AZO) 20 mg/m ² every week ×4 of 6 vs. Epirubicin 75 mg/m ² every 3 wk	31 21 34	0% 0% 5%	2.9 2 2.5	19% 5% 12%	GTSG 1987 ¹⁸⁹

(Continued on following page)

Table 1 (Cont'd). Randomized Trials of Single and Combined Chemotherapies for Pancreatic Cancer

Agents, dose, and schedule	No. of patients	Percent response	Median survival (mo [range])	Percent surviving 1 year	Study
Tamoxifen 20 mg daily	37	NS	5.25	20%	Keating et al. 1989 ¹⁹⁰
vs. Cyproterone acetate 100 mg ×3 daily	32	NS	4.25	12%	
vs. No therapy	39	NS	3.0	10%	
5-FU 500 mg/m ² days 1–5 every 5 wk	64	7%	4.5	6%	Cullinan et al. NCCTG 1990 ¹⁶⁶
vs. 5-FU 300 mg/m ² days 1–5 + Adriamycin 40 mg/m ² day 1 + cisplatin 60 mg/m ² day 1 every 5 wk	59	15%	3.5	8%	
Induction: 5-FU 270 mg/m ² days 1–5 + methotrexate 11 mg/m ² days 1 and 4 + vincristine 0.7 mg/m ² days 2 and 5 + cyclophosphamide 160 mg/m ² days 1 and 5; maintenance: 5-FU 350 mg/m ² days 1–5 + mitomycin C 3.5 mg/m ² days 1–5 every 6 wk (Mallinson regimen)	61	21%	4.5	8%	
Cisplatin 100 mg/m ² day 1 + ARA-C 2 mg/m ² days 1 and 2 + caffeine 400 mg/m ² days 1 and 2 every 28 days ×3 then every 42 days	40	5%	5 (.4–17)	NS	Kelsen, et al. 1991 ¹⁹¹
vs. 5-FU 600 mg/m ² days 1, 8, 29, and 36 + mitomycin C 10 mg/m ² day 1 + streptozocin 1 g/m ² days 1, 8, 29, and 36 every 8 wk	42	10%	10 (.3–24.6) ^a	NS	
Somatostatin 250 fg subq every 8 h	43	0%	3.8	10%	Huguier et al. 1992 ¹⁹²
vs. LH-RH 3.75 mg IM every 4 wk	39	0%	5.5	25%	
vs. Somatostatin 250 fg subq every 8 h + LH-RH 3.75 mg IM every 4 wk	38	0%	6.0	30%	
vs. No therapy	43	0%	4.3	15%	
MGBG 60 mg/m ² every wk	32	6%	7.6	NS	Bukowski et al. (SWOG) 1993 ¹⁹³
vs. DHAD 6–12 mg/m ² every 3 wk	29	0%	2.7	NS	
vs. AZQ 30–40 mg/m ² every 3 wk	21	0%	2	NS	
5-FU 400–600 mg/m ² days 1, 8, 29, and 36 + doxorubicin 20–20 mg/m ² days 1 and 29 + mitomycin C 5–10 mg/m ² day 1 + streptozocin 400 mg/m ² days 1, 8, 29, and 36	71	11%	4.8	NS	
DHAD 4 mg/m ² days 1–3 every 3 wk	23	0%	2.25	0	Ashbury et al. (ECOG) 1994 ¹⁹⁴
vs. Aclacinomycin A 85–100 mg/m ² every 3 wk	16	0%	2.75	0	
vs. Spirogermanium 200 mg/m ² twice a week	20	0%	2.75	0	
vs. VP-16 140 mg/m ² days 1, 3, and 5 every 4 wk	21	0%	3	0	
5-FU 600 mg/m ² days 1, 8, 29, and 36 + Adriamycin 30 mg/m ² days 1 and 29 + mitomycin C 10 mg/m ² days 1 and 29 every 8 wk	23	NS	8.25 (2.25–20) ^a	25%	Palmer et al. 1994 ¹⁶⁴
vs. No therapy	20	NS	3.75 (0.25–15.5)	2%	
5-FU 500 mg/m ² + leucovorin 60 mg/m ² ± etoposide 120 mg/m ² ; days 1–3 every 3 wk (with etoposide) or days 1 and 2 every other week (without etoposide)	29	3%	6 ^a	25% ^a	Glimelius et al. 1996 ¹⁴⁷
vs. Best supportive care	24	0	2.5	15%	
Gemcitabine 1000 mg/m ² weekly ×7 of 8 wk then weekly ×3 of 4 wk	63	5.4%	5.65	18% ^a	Burriss et al. 1997 ¹⁵⁰
vs. 5-FU 600 mg/m ² every wk	63	0%	4.41	2%	

^aStatistically significant difference.

NS, not stated; CCNU, chloroethylcyclohexyl nitrosourea; LH-RH, luteinizing hormone-releasing hormone; TZT, triazinate; AZQ, azinidinybenzoquinone; MGBG, mitoguanzone; DHAD, dihydroxyanthracenedione.

noma. As noted above, Burriss et al.¹⁵⁰ found in a phase III randomized trial that gemcitabine (1000 mg/m² weekly for up to 7 weeks followed by a week of rest and then weekly for 3 weeks every 4 weeks thereafter) had a

disappointingly low objective response rate. However, there was a small, statistically significant improvement in overall survival compared with administration of 600 mg/m² of 5-FU weekly (5.7 vs. 4.4 months). Further-

more, 1-year survival with gemcitabine treatment was 18%, compared with 2% for 5-FU.

Several combination regimens have been promoted as promising in the treatment of pancreatic cancer. These include 5-FU, Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH), and mitomycin (FAM) with or without streptozocin,^{157,158} and a modification of this regimen with 5-FU, mitomycin C, and streptozocin (SMF),¹⁵⁹ and cisplatin, cytosine arabinoside, and caffeine.¹⁶⁰ Table 1 details the single-agent and combination-agent randomized chemotherapy trials, including drug dosages and schedules in patients with pancreatic cancer. From the low objective response rates and the narrow ranges in median survival, there is not a superior combination regimen. Although patients treated with SMF have a significantly prolonged median survival compared with those treated with cisplatin, cytosine arabinoside, and caffeine,¹⁶⁰ other trials failed to demonstrate an advantage of SMF over FAM.^{161,162} More importantly, in a North Central Cancer Treatment Group (NCCTG) trial,¹⁶³ combination therapy with FAM or 5-FU and Adriamycin was not superior to 5-FU monotherapy. Thus, the only systemic treatment that may have an advantage over 5-FU is monotherapy with gemcitabine.¹⁵⁰ To date, no other randomized trials have compared 5-FU or gemcitabine with another single agent.

Three studies suggest that combination chemotherapy may result in longer survival than best supportive care. Palmer et al.¹⁶⁴ reported that FAM prolonged median survival (33 vs. 15 weeks). Similarly, Glimelius et al.¹⁴⁷ reported longer survival with 5-FU and leucovorin with or without etoposide. Finally, Mallinson et al.¹⁶⁵ reported superior survival with a complicated five-drug regimen using 5-FU, mitomycin C, methotrexate, vincristine, and cyclophosphamide. A subsequent NCCTG trial did not demonstrate an advantage of this regimen over monotherapy with 5-FU.¹⁶⁶ Thus, although there may be some survival advantage with chemotherapy treatment in pancreatic cancer, a review of all available data suggests that combination therapy is not superior to monotherapy, and any improvement in median survival is small.

Radiation therapy. Radiation therapy as part of the nonsurgical management of pancreatic cancer has been evaluated with external beam and IORT, interstitial brachytherapy, and, more recently, radioimmunotherapy.¹⁶⁷ The role of radiotherapy was initially defined in pivotal studies performed by the Gastrointestinal Tumor Study Group (GITSG). Radiotherapy in these studies was used as adjuvant therapy (treatment after potentially curative resection) and as treatment for unresectable locoregional disease (Table 2).

The GITSG has published the only randomized trial of adjuvant therapy in pancreatic cancer. The EORTC has recently completed a trial, and results will be forthcoming. In the GITSG trial, patients were randomized after resection to observation or radiation therapy combined with 5-FU.¹⁶⁸ A total dose of 4000 cGy was given in a split course. 5-FU was given as bolus of 500 mg/m² daily for 3 days at the beginning of each 2-week radiation cycle. After completion of radiation therapy, 5-FU was administered weekly for 2 years. The treated group had a 2-year actuarial survival of 43%, compared with 18% in the control group. These results were upheld in a follow-up single-arm trial in which patients were randomized to the treatment.¹⁶⁸

Contemporary approaches to adjuvant therapy have focused on preoperative therapy with the hope of increasing the rate of resection and improving overall survival. Hoffman et al.¹⁶⁹ and Jessup et al.¹⁷⁰ suggested that preoperative chemoradiation therapy can convert selected cases of unresectable disease to a resectable status or can increase the overall resection rate. Most neoadjuvant chemoradiation studies include staging laparoscopy before treatment and re-evaluation of extent of disease after treatment before surgery. Evans et al.¹⁷¹ have shown that approximately 18% of patients progress with metastases during neoadjuvant therapy, eliminating their candidacy for resection. A randomized trial has not been conducted to assess this approach, but Spitz et al.¹⁷² analyzed results of 142 patients treated with either preoperative or postoperative chemoradiation and showed no difference in survival between patient groups. However, they concluded that preoperative rapid-fractionation chemoradiation could be delivered over a shorter duration and that up to one fourth of eligible patients did not receive postoperative therapy because of prolonged recovery after pancreaticoduodenectomy. Thus, preoperative adjuvant strategies may have a practical advantage.

The role of chemotherapy combined with radiation treatment for unresectable locoregional pancreatic cancer was initially defined by a GITSG trial.¹⁷³ In this randomized trial design, the combination of 5-FU and split-course radiation (total dose, 4000 cGy) was compared with either a radiation dose alone or 6000 cGy combined with 5-FU. The regimen of 5-FU and 4000 cGy increased median survival nearly 2-fold compared with radiation alone (23 vs. 42 weeks). This group also demonstrated that chemotherapy with SMF was inferior to therapy with SMF plus radiation (1-year survival, 19% vs. 41%).¹⁷⁴ Attempts to optimize this therapy have

Table 2. Randomized Trials With Radiation Therapy for Adjuvant and/or Primary Management of Locoregional Pancreatic Cancer

Agents, dose, and schedule	No. of patients	Median survival (mo)	Percent surviving 1 yr	Study
Adjuvant therapy				
No adjuvant therapy	22	11	49%	Kaiser et al. 1985 ¹⁹⁵
vs.				
200 rad/day 5 days/wk over 2 wk followed by 2-wk rest for total of 4000 rad + 5-FU 500 mg/m ² days 1–3 of each 2000-rad course followed by 5-FU 500 mg/m ² weekly	21	20 ^a	63%	
Locoregional therapy				
200 rad/day 5 days/wk over 2 wk followed by 2-wk rest for total of 6000 rad	25	5.7	15%	Moertel et al. (GITSG) 1981 ¹⁷³
vs.				
200 rad/day 5 days/wk over 2 wk followed by 2-wk rest for total of 4000 rad + 5-FU 500 mg/m ² days 1–3 of each 2000-rad course followed by 5-FU 500 mg/m ² weekly	83	9.12 ^a	35%	
vs.				
200 rad/day 5 days/wk over 2 wk followed by 2-wk rest for total of 6000 rad + 5-FU 500 mg/m ² days 1–3 of each 2000-rad course followed by 5-FU 500 mg/m ² weekly	86	12.35 ^a	50%	
5-FU 600 mg/m ² days 1, 8, 29, and 36 + streptozocin 1 g/m ² days 1, 8, 29, and 36 + mitomycin C 10 mg/m ² day 1 every 8 wk	21	4	19%	GITSG 1988 ¹⁷⁴
vs.				
180 rad × 5 days every week for 6 wk for a total of 5400 rad + 5-FU 350 mg/m ² days 1–3 and last 3 days of radiotherapy, followed on day 64 by 5-FU 600 mg/m ² days 1, 8, 29, and 36 + streptozocin 1 g/m ² days 1, 8, 29, and 36 + mitomycin C 5 mg/m ² day 1 then 10 mg/m ² subsequent cycles every 8 wk	22	10.5	41% ^a	

^aStatistically significant difference.

included the use of protracted-infusion 5-FU as well as other radiation-sensitizing drugs. Ishii et al.¹⁷⁵ have evaluated protracted-infusion 5-FU with external beam radiation using a dose of 5040 cGy in 28 fractions over 5.5 weeks. The median survival of 10 months and the 1-year overall survival of 42 are not superior to those in other reports. Other radiation sensitizers under study include bromodeoxuridine,¹⁷⁶ paclitaxel,^{177,178} cisplatin,¹⁷⁷ and more recently gemcitabine.¹⁷⁹ The value of these approaches awaits further efficacy and eventually comparative efficacy studies.

The role of IORT has been best defined in a retrospective review of 159 patients¹⁸⁰ who received either external beam radiation 4000–6000 cGy or 4500–5500 cGy in combination with an intraoperative electron boost. There was no significant difference in median or long-term survival between treatments, but local control was 82% in the patients treated with IORT compared with 48% in patients treated with external beam radiation alone.

Another form of local control is interstitial brachytherapy with radionuclides such as iodine 125 or palladium 103. However, enthusiasm for brachytherapy has

waned because it has increased toxicity without documented improvement in survival.^{181,182}

Conclusions and Clinical Practice Recommendations

Epidemiology

Pancreatic cancer is deadly; overall 5-year survival is <5%. However, 5-year survival rates of >20% may accompany resection of “early tumors,” defined as tumors that measure ≤2 cm and are confined to the pancreas. Identification of patients with early cancer in populations at risk for developing pancreatic cancer should increase 5-year survival. At present, patients with idiopathic and alcoholic chronic pancreatitis and new-onset diabetes mellitus (<2 years, no family history, age >50 years) have a low but increased risk of having or developing pancreatic cancer. Patients with hereditary pancreatitis who are older than 45 years and have a paternal inheritance (paternal imprinting), cystic diseases of the pancreas, IPMT, or pancreatic masses have a high risk of developing pancreatic cancer. Ideally, these patients should be carefully evaluated for pancreatic cancer.

Diagnosis

No screening strategy has been shown to detect early pancreatic cancer in patients with an increased risk of developing pancreatic cancer, and none can be recommended. At present the most sensitive imaging test is EUS, but its sensitivity for detection of early pancreatic cancer is unknown. Similarly, the sensitivity of current serum or genetic markers to detect early tumors is unknown, but the sensitivity of CA 19-9 in small stage 1 tumors is low. The best that can be offered to these patients is spiral CT, followed by EUS if the CT results are nondiagnostic and measurement of serum CA 19-9. However, there is no guarantee that this strategy will detect "early lesions."

The following recommendations for diagnosis are based on the assumption that all tests are available in all communities and are performed with a high degree of expertise. However, availability and expertise varies among localities. Thus, the practitioner should select the technique(s) appropriate to the community based on understanding of the important principles.

All patients with suspected pancreatic or periampullary neoplasm should undergo a high-quality abdominal CT scan early, ideally a dual-phase helical CT. If pancreatic cancer is present, an experienced radiologist usually can make a definitive statement concerning whether the cancer is unresectable (95%–100% confidence) or resectable (85%–90% confidence), and a decision can be made to proceed to treatment (see below). Additional diagnostic tests (e.g., ERCP), except for FNA to establish the diagnosis in inoperable cases, are not required, and other tests for disease staging in operable cases (e.g., EUS) usually are unnecessary.

If CT is not performed using an ideal technique and the radiologist is unable to make a definite diagnosis or stage the disease, helical CT is recommended. EUS is recommended if the diagnosis remains uncertain after an optimal CT and the clinician suspects a periampullary neoplasm on the basis of a family history of pancreatic cancer, inexplicable symptoms, or elevated CA 19-9 concentration because small lesions not seen by CT may be seen by EUS.

If a patient has undergone EUS or ERCP as the first test, usually because of jaundice, helical CT is still required if the patient is a candidate for resection because CT is the best test to assess the relationship of the tumor to adjacent structures and to detect liver metastases. With the availability of CT, magnetic resonance cholangiopancreatography, and EUS, use of ERCP to diagnose pancreatic cancer has decreased greatly. However, ERCP still has a therapeutic role.

Treatment Recommendations

Surgery. At major centers in which there is a multidisciplinary approach to the management of pancreatic cancer, patients with resectable tumors undergo exploration. Sometimes, even if there is a low chance of resection, resection is performed if the patient desires to exclude even the smallest possibility for cure. In these centers, often the bias is toward interpretation of imaging test results as indicating "resectable" tumors because of an aggressive, safe surgical approach.

Patients who have undergone surgical resection appear to benefit from adjuvant therapy using chemoradiation with a 5-FU-based regimen. The use of neoadjuvant chemoradiation does not appear to have an adverse impact on the overall treatment of patients with resectable pancreatic cancer. Patients selected for this approach should be carefully staged with contrast spiral CT scanning. In addition, laparoscopy can be used to further exclude occult visceral and peritoneal metastases. However, at present there is no evidence that neoadjuvant therapy improves survival more than adjuvant therapy.

Chemotherapy and radiation. All patients with unresectable locoregional or metastatic pancreatic cancer should be considered for inclusion into investigational trials. The outcome of treatment for patients with an extremely poor performance status (unable to carry out normal activities even with effort) is dismal; in these cases, emphasis should be placed on palliative measures rather than on aggressive attempts at treatment with either chemoradiation or combination chemotherapy. However, the option of gemcitabine therapy should be considered even in patients with a poor performance status and pain because of its potential for palliative benefit.

In lieu of entry into an investigational study, standard treatment of patients with unresectable locoregional disease may include radiation and concomitant 5-FU therapy. Another option for both patients with unresectable locoregional and those with metastatic disease is monotherapy with gemcitabine.

Future Research

Improving survival of pancreatic cancer patients depends on identification of patients who are at risk for developing pancreatic cancer, detection of disease at an early curable stage, and elucidation of the basic mechanisms of differentiation and transformation involved in pancreatic carcinogenesis that will lead to development of effective treatment to prevent or counteract these abnormalities. The best lead for early identification of pancreatic cancer is exploration of genetic and other markers in

populations at risk and continuation of the quest for imaging modalities that can identify tiny tumors and distinguish between inflammatory and neoplastic masses.

At present, treatment research is developing along several lines of investigation. These include development of surrogate endpoints for objective response and survival to screen new treatments, determination of whether more extended surgical resection increases survival, definition of the role of neoadjuvant (preoperative) therapy and radiation-sensitizing drugs (especially compared with 5-FU) for chemoradiation of locally unresectable pancreatic cancer, and exploration of new drugs that have unique biologic targets. This last category includes inhibitors of farnesyl transferase and metalloproteinase, radioimmunoconjugates, tumor vaccines, ligands for delivery of cytotoxic agents, and the initial exploration of gene therapy.

EUGENE P. DiMAGNO, M.D.

*Mayo Clinic
Rochester, Minnesota*

HOWARD A. REBER, M.D.

*UCLA School of Medicine
Los Angeles, California*

MARGARET A. TEMPERO, M.D.

*University of Nebraska Medical Center
Omaha, Nebraska*

References

- Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics 1996. *CA Cancer J Clin* 1996;46:5-27.
- Riela A, Zinsmeister AR, Melton LJ III, Weiland LH, DiMagno EP. Increasing incidence of pancreatic cancer among women in Olmsted County, Minnesota, 1940 through 1988. *Mayo Clin Proc* 1992;67:839-645.
- Niederhuber JE, Brennan MF, Menck HR. The National Cancer Data Base report on pancreatic cancer. *Cancer* 1995;76:1671-1677.
- Lowenfels AB, Maisonneuve P, DiMagno EP, Elitsur Y, Gates LK Jr, Perrault J, Whitcomb DC, International Hereditary Pancreatitis Study Group. Hereditary pancreatitis and the risk of pancreatic cancer. *J Natl Cancer Inst* 1997;89:442-446.
- Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, Martin SP, Gates JK Jr, Amann ST, Toskes PP, Liddle R, McGrath K, Uomo G, Post JC, Ehrlich GD. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nat Genet* 1996;14:141-145.
- Gorry MC, Ghabbaizedeh D, Furey W, Gates LK Jr, Preston RA, Aston CE, Zhang Y, Ulrich C, Ehrlich GD, Whitcomb DC. Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. *Gastroenterology* 1997;113:1063-1068.
- Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, DiMagno EP, Andren-Sandberg A, Domellof L, International Pancreatitis Study Group. Pancreatitis and the risk of pancreatic cancer. *N Engl J Med* 1993;328:1433-1437.
- Bansal P, Sonnenberg A. Pancreatitis is a risk factor for pancreatic cancer. *Gastroenterology* 1995;109:247-251.
- Karlson BM, Ekblom A, Josefsson S, McLaughlin JK, Fraumeni JF Jr, Nyren O. The risk of pancreatic cancer following pancreatitis: an association due to confounding? *Gastroenterology* 1997;113:587-592.
- Loftus EV Jr, Olivares-Pakzad BA, Batts KP, Adkins MC, Stephens DH, DiMagno EP, Kelly DG, Miller LJ, Pearson RK, Clain JE, Petersen BT, Farnell MB, Sarr MG, Thompson GB, van Heerden JA, Nagorney DM, Donohue JH. Intraductal papillary-mucinous tumors of the pancreas—clinicopathologic features, outcome, and nomenclature. *Gastroenterology* 1996;110:1909-1918.
- Ohashi K, Takagi K. ERCP and imaging diagnosis of pancreatic cancer [in Japanese; English abstract]. *Gastrointest Endosc* 1997;77:1493-1495.
- Rivera JA, Fernandez-del Castillo C, Pins M, Compton CC, Lewandrowski KB, Rattner DW, Warshaw AL. Pancreatic mucinous ductal ectasia and intraductal papillary neoplasms. A single malignant clinicopathologic entity. *Ann Surg* 1997;225:637-644.
- McDowell RK, Gazelle GS, Murphy BL, Boland GW, Mayo-Smith WW, Warshaw AL, Mueller PR. Mucinous ductal ectasia of the pancreas. *J Comput Assist Tomogr* 1997;21:383-388.
- Sessa F, Solcia E, Capella C, Bonato M, Scarpa A, Zamboni G, Pellegata NS, Ranzani GN, Rickaert F, Kloppel G. Intraductal papillary-mucinous tumours represent a distinct group of pancreatic neoplasms: an investigation of tumour cell differentiation and K-ras, p53 and c-erbB-2 abnormalities in 26 patients. *Virchows Arch* 1994;425:357-367.
- Gullo L, Pezzilli R, Morselli-Labate AM, Italian Pancreatic Cancer Study Group. Diabetes and the risk of pancreatic cancer. *N Engl J Med* 1994;331:81-84.
- Permert J, Larsson J, Westermark GT, Herrington MK, Christmansson L, Pour PM, Westermark P, Adrian TE. Islet amyloid polypeptide in patients with pancreatic cancer and diabetes. *N Engl J Med* 1994;330:313-318.
- Schwartz SS, Zeidler A, Moossa AR, Kuku SF, Rubenstein AH. A prospective study of glucose intolerance, insulin, C-peptide, and glucagon in patients with pancreatic carcinoma. *Am J Dig Dis* 1978;23:1107-1114.
- Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. *JAMA* 1995;273:1605-1609.
- Ghadirian P, Boyle P, Simard A, Baillargeon J, Maisonneuve P, Perret C. Reported family aggregation of pancreatic cancer within a population-based case-control study in the Francophone community in Montreal, Canada. *Int J Pancreatol* 1991;10:183-196.
- Lynch HT, Fitzsimmons ML, Smyrk TC, Lanspa SJ, Watson P, McClellan J, Lynch JF. Familial pancreatic cancer: clinicopathologic study of 18 nuclear families. *Am J Gastroenterol* 1990;85:54-60.
- Giardiello FM, Offerhaus GJ, Lee DH, Krush AJ, Tersmette AC, Booker SV, Kelley NC, Hamilton SR. Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis. *Gut* 1993;34:1394-1396.
- Lynch HT, Fusaro RM. Pancreatic cancer and the familial atypical multiple mole melanoma. *Pancreas* 1991;6:127-131.
- Goldstein AM, Fraser MC, Struewing JP, Hussussian CJ, Ranade K, Zametkin DP, Fontaine LS, Organic SM, Dracopoli NC, Clark WH Jr, Tucker MA. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. *N Engl J Med* 1995;333:970-974.
- Patrianakos C, Hoffman D. Chemical studies on tobacco smoke LXIV. On the analysis of aromatic amines in cigarette smoke. *J Anal Toxicol* 1979;3:150-159.

25. Mack TM, Yu MC, Hanisch R, Henderson BE. Pancreas cancer and smoking, beverage consumption and past medical history. *J Natl Cancer Inst* 1986;76:49-60.
26. Falk RT, Pickle LW, Fontham ET, Correa P, Fraumeni JF. Life-style risk factors for pancreatic cancer in Louisiana: a case-control study. *Am J Epidemiol* 1988;128:324-336.
27. Mills PK, Beeson L, Abbey DE, Fraser GE, Phillips RL. Dietary habits and past medical history as related to fatal pancreas cancer risk among Adventists. *Cancer* 1988;61:2578-2585.
28. Norell SE, Ahlbom A, Erwald R, Jacobson G, Lindberg-Navier I, Olin R, Tornberg B, Wiechel KL: Diet and pancreatic cancer: a case-control study. *Am J Epidemiol* 1986;124:894-902.
29. Sugimura T. Carcinogenicity of mutagenic heterocyclic amines formed during the cooking process. *Mutat Res* 1985;150:33-41.
30. Sugimura T, Sato S. Mutagens-carcinogens in foods. *Cancer Res* 1983;43:2415s-2421s.
31. Appel MJ, Woutersen RA. Dietary fish oil (MaxEPA) enhances pancreatic carcinogenesis in azaserine-treated rats. *Br J Cancer* 1996;73:36-43.
32. Appel MJ, Woutersen RA. Effects of dietary fish oil (maxEPA) on *N*-nitrosobis(2-oxopropyl)amine (BOP)-induced pancreatic carcinogenesis in hamsters. *Cancer Lett* 1995;94:179-189.
33. Mack TM. Pancreas. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer epidemiology and prevention*. Philadelphia: Saunders, 1982:638-667.
34. Falk RT, Pickle LW, Fontham ET, Correa P, Morse A, Chen V, Fraumeni JF Jr. Occupation and pancreatic cancer risk in Louisiana. *Am J Intern Med* 1990;18:565-576.
35. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. I. Epidemiology. *Cancer Causes Control* 1991;2:325-237.
36. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. II. Mechanisms. *Cancer Causes Control* 1991;2:427-442.
37. Kalsner MH, Barkin J, MacIntyre JM. Pancreatic cancer. Assessment of prognosis by clinical presentation. *Cancer* 1985;56:397-402.
38. Mannell A, van Heerden JA, Weiland LH, Ilstrup DM. Factors influencing survival after resection for ductal adenocarcinoma of the pancreas. *Ann Surg* 1986;203:403-407.
39. Metzgar RS, Asch HL. Antigens of human pancreatic adenocarcinomas: their role in diagnosis and therapy. *Pancreas* 1988;3:352-371.
40. Posner MR, Mayer RJ. The use of serologic tumor markers in gastrointestinal malignancies. *Hematol Oncol Clin North Am* 1994;8:533-552.
41. Pleskow DK, Berger HJ, Gyves J, Allen E, McLean A, Podolsky DK. Evaluation of a serologic marker, CA 19-9, in the diagnosis of pancreatic cancer. *Ann Intern Med* 1989;110:704-709.
42. Safi F, Schlosser W, Falkenreck S, Beger HG. CA 19-9 serum course and prognosis of pancreatic cancer. *Int J Pancreatol* 1996;20:155-161.
43. Albert MB, Steinberg WM, Henry JP. Elevated serum levels of tumor marker CA19-9 in acute cholangitis. *Dig Dis Sci* 1988;33:1223-1225.
44. Westermarck P, Wilander E, Westermarck GT, Johnson KH. Islet amyloid polypeptide-like immunoreactivity in the islet B cells of type 2 (non-insulin-dependent) diabetic and non-diabetic individuals. *Diabetologia* 1987;32:887-892.
45. Sowa R, Sanke T, Hirayama J, Tabata H, Furuta H, Nishimura S, Nanjo K. Islet amyloid polypeptide amide causes insulin resistance in vivo in dogs. *Diabetologia* 1990;33:118-120.
46. Chance WT, Balasubramaniam A, Zhang FS, Wimalawansa SJ, Fischer JE. Anorexia following the intrahypothalamic administration of amylin. *Brain Res* 1991;539:352-354.
47. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M. Most carcinomas of the exocrine pancreas contain mutant c-Kras genes. *Cell* 1988;53:549-559.
48. Hruban RH, van Mansfeld AOM, Offerhaus GJA, van Weering DHJ, Allison DC, Goodman SN, Kensler TW, Bose KK, Cameron JL, Bos JL. K-ras oncogene activation in adenocarcinomas of the human pancreas: a study of 82 carcinomas using a combination of mutant-rich PCR analysis and allele oligonucleotide hybridization. *Am J Pathol* 1993;143:545-554.
49. Lemoine NR, Jain S, Hughes C, Staddon SL, Mailliet B, Kloppel G. K-ras oncogene activation in preinvasive pancreatic cancer. *Gastroenterology* 1992;102:230-236.
50. Pellagata S, Sessa F, Renault B, Bonato M, Leone BE, Solcia E, Ranzani RN. K-ras and p53 gene mutations in pancreatic cancer: ductal and nonductal tumors progress through different genetic lesions. *Cancer Res* 1994;54:1156-1160.
51. Redston MS, Caldas C, Seymour AB, Hruban RH, da Costa L, Yeo CH, Kern SE. p53 mutations in pancreatic carcinoma and evidence of common involvement in homopolymer tracts in DNA microdeletions. *Cancer Res* 1994;54:3025-3033.
52. Hohne MW, Halatsch ME, Dahl GF, Winel RJ. Frequent loss of expression of the potential tumor-suppressor gene DCC in ductal pancreatic adenocarcinoma. *Cancer Res* 1992;52:2616-2619.
53. Simon B, Weinel R, Hohne Mw, Watz J, Schmidt J, Kortner G, Arnold R. Frequent alterations of the tumor suppressor genes p53 and DCC in Human pancreatic carcinoma. *Gastroenterology* 1994;106:1645-1651.
54. Caldas C, Hahn SA, da Costa LT, Redston MS, Shutte M, Seymour AB, Weinstein CL, Hruban RH, Yeo CJ, Kern SE. Frequent somatic mutations and homozygous deletions of the MTS1 gene in pancreatic adenocarcinoma. *Nat Genet* 1994;8:27-32.
55. Liu Q, Yan YX, McClure M, Nakagawa H, Fufimera F, Rustgi AK. MTS-1 (CDKN2) tumor suppressor gene deletions are a frequent event in esophagus squamous cancer and pancreatic adenocarcinoma cell lines. *Oncogene* 1995;10:619-622.
56. Ponce-Castaneda MV, Lee MH, Latres E, Polyak K, Lacombe L, Montgomery K, Mathew S, Krauter K, Sheinfeld J, Massague J, Cordon-Cardo C. p27Kipl: chromosomal mapping to 12p12-12p13.1 and absence of mutations in human tumors. *Cancer Res* 1995;55:1211-1214.
57. Naumann M, Savitskaia N, Ilert C, Schramm A, Kalthoff H, Schmiegel W. Frequent codelation of p16/MTS1 and p15/MTS2 and genetic alterations in p16/MTS1 in pancreatic tumors. *Gastroenterology* 1996;110:1215-1224.
58. Watanabe H, Sawabu N, Ohta H, Saatomura Y, Yamakawa O, Motoo Y, Okai T, Takahashi H, Wakabayashi T. Identification of K-ras oncogene mutations in pure pancreatic juice of patients with ductal pancreatic cancers. *Jpn J Cancer Res* 1993;84:961-965.
59. Tada M, Omata M, Kawai S, Saisho H, Ohto M, Saikki RK Sninsky JJ. Detection of ras gene in pancreatic juice and peripheral blood of patients with pancreatic adenocarcinoma. *Cancer Res* 1993;53:2472-2474.
60. Kondo H, Sugano K, Fukayama N, Kyogoku A, Nose H, Shimada K, Ojkura H, Ohtsu A, Yoshida S, Shimosato Y. Detection of point mutations in the K-ras oncogene at codon 12 in pure pancreatic juice for diagnosis of pancreatic carcinoma. *Cancer* 1994;73:1589-1594.
61. Betehelemy P, Bouisson M, Escourrou J, Vaysse N, Rumeau JL Pradayrol L. Identification of K-ras mutations in pancreatic juice in the early diagnosis of pancreatic cancer. *Ann Intern Med* 1995;123:188-191.
62. Iguchi H, Sugano K, Fukayama N, Ohkura H, Sadamoto K, Ohkoshi K, Seo Y, Tomoda H, Funakoshi A, Wakasugi H. Analysis of the K-ras codon mutations in duodenal juice: possible application of a secretin test as a diagnostic tool for pancreatic cancers. *Gastroenterology* 1996;110:221-226.

63. Caldas C, Hanh SA, Hruban RH, Redston MS, Yeo CJ, Kern SE. Detection of K-ras mutation in stool of patients with pancreatic adenocarcinoma and pancreatic ductal hyperplasia. *Cancer Res* 1994;54:3568-3573.
64. Microsatellite instability and K-ras mutations associated with pancreatic adenocarcinoma and pancreatitis. *Cancer Res* 1995;55:4264-4267.
65. Furuya N, Kawa S, Akamatsu T, Furihata K. Long-term follow-up of patients with chronic pancreatitis and K-ras gene mutation detected in pancreatic juice. *Gastroenterology* 1997;113:595-598.
66. Tada M, Ohashi M, Shiratori Y, Okudaira T, Komatsu Y, Dawabe T, Yoshida H, Machinami R, Kishi K, Omata M. Analysis of K-ras gene mutation in hyperplastic duct cells of the pancreas without pancreatic disease. *Gastroenterology* 1996;110:227-231.
67. Rivera JA, Fernandez-del Castillo C, Rall CJN, Graeme-Cook F, Shu P, Lakey N, Tepper R, Rattner DW, Warshaw AL, Rustgi AK. Analysis of K-ras oncogene mutations in chronic pancreatitis with ductal hyperplasia. *Surgery* 1997;121:42-49.
68. Muller MF, Meyenberger C, Bertschinger P, Schaer R, Marincek B. Pancreatic tumors: evaluation with endoscopic US, CT and MR imaging. *Radiology* 1994;190:745-751.
69. Bluemke DA, Cameron JL, Hruban RH, et al. Potentially resectable pancreatic adenocarcinoma: spiral CT assessment with surgical and pathologic correlation. *Radiology* 1995;197:381-385.
70. Legman P, Vignaus O, Dousser B, Baraza A-P, Palazzo L, Dumontier I, Coste J, Louvel A, Rouseau G, Couturier D, Bonnin A. Pancreatic tumors: comparison of dual-phase helical CT and endoscopic sonography. *Am J Radiol* 1998;170:1315-1322.
71. Lu DS, Reber HA, Krasny RM, Kadell BM, Sayre J. Local staging of pancreatic cancer: criteria for unresectability of major vessels as revealed by pancreatic-phase, thin-section helical CT. *Am J Radiol* 1997;168:1439-1443.
72. Semelka RC, Kelekis NL, Molina PL, Sharp TJ, Calvo B. Pancreatic masses with inconclusive findings on spiral CT: is there a role for MRI? *J Magn Reson Imaging* 1996;6:585-588.
73. Rösch T, Lorenz R, Braig C, Feurbach S, Siewert JR, Schudziarra V, Classen M. Endoscopic ultrasound in pancreatic tumor diagnosis. *Gastrointest Endosc* 1991;37:347-342.
74. Rösch T, Braig C, Gain T, Feurbach S, Siewert JR, Schudziarra V, Classen M. Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography. Comparison with conventional sonography, computed tomography and angiography. *Gastroenterology* 1992;102:188-189.
75. Rösch T, Lorenz R, Braig C, Dancygier H, Classen M. Endoscopic ultrasound in small pancreatic tumors. *Z Gastroenterol* 1991;29:110-115.
76. Rösch T, Lightdale CJ, Botet JF, Boyce GA, Sivak MV Jr, Yasuda K, Heyder N, Palazzo L, Dancygier H, Schudziarra V, Classen M. Localization of pancreatic endocrine tumors by endoscopic ultrasonography. *N Engl J Med* 1992;326:1721-1726.
77. Rösch T, Lorenz R, Braig C, Classen M. Endoscopic ultrasonography in diagnosis and staging of pancreatic and biliary tumors. *Endoscopy* 1992;24:304-308.
78. Chang KJ, Nguyen P, Erickson RA, Durbin TE, Katz KD. The clinical utility of endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of pancreatic carcinoma. *Gastrointest Endosc* 1997;45:387-393.
79. Wiersma MJ, Vilmann P, Giovanni M, Chang KJ, Wiersma LM. Endoscopy-guided fine needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology* 1997;112:1087-1095.
80. Freeny PC, Traverso LW, Ryan JA. Diagnosis and staging of pancreatic adenocarcinoma with dynamic computed tomography. *Am J Surg* 1993;165:600-606.
81. Trede M, Rumstadt B, Wendl K, Gaa J, Tesdal K, Lehmann K-J, Meier-Willerson H-J, Pescatore P, Schmolli J. Ultrafast magnetic resonance imaging improves the staging of pancreatic tumors. *Ann Surg* 1997;226:393-407.
82. Warshaw AL, Gu Z, Wittenberg J, Waltman AC. Preoperative staging and assessment of resectability of pancreatic cancer. *Arch Surg* 1990;125:230-233.
83. Conlon KC, Dougherty E, Klimstra DS, Coit DG, Turnbull ADM, Brennan MF. The value of minimal access surgery in the staging of patients with potentially resectable peripancreatic malignancy. *Ann Surg* 1996;223:134-140.
84. Conlon KC, Minnard EA. The value of laparoscopic staging in upper gastrointestinal malignancy. *Oncologist* (in press).
85. Shimi S, Banting S, Cuschieri A. Laparoscopy in the management of pancreatic cancer: endoscopic cholecystojejunostomy for advanced disease. *Br J Surg* 1992;79:317-319.
86. Rhodes M, Nathanson L, Fielding G. Laparoscopic biliary and gastric bypass: a useful adjunct in the treatment of carcinoma of the pancreas. *Gut* 1995;36:778-780.
87. Gloor B, Todd KE, Reber HA. Diagnostic workup of patients with suspected pancreatic carcinoma: the University of California-Los Angeles approach. *Cancer* 1997;79:1780-1786.
88. Pitt HA, Gomes AS, Lois JF, Mann LL, Deutsch LS, Longmire WP Jr. Does preoperative percutaneous biliary drainage reduce operative risk or increase hospital cost? *Ann Surg* 1985;201:545-553.
89. Heslin MJ, Brooks AD, Hochwald SN, Harrison LE, Blumgart LH, Brennan MF. A preoperative biliary stent is associated with increased complications after pancreatoduodenectomy. *Arch Surg* 1998;133:149-154.
90. Povoski SP, Karpeh MS, Conlon KC, Blumgart LH, Brennan MF. Effect of preoperative biliary drainage on postoperative outcome following pancreatoduodenectomy. *Ann Surg* 1999 (in press).
91. Spencer MP, Sarr MG, Nagorney DM. Radical pancreatectomy for pancreatic cancer in the elderly. Is it safe and justified? *Ann Surg* 1990;212:140-143.
92. Todd KE, Lane J, Reber HA. Questions most commonly asked regarding pancreatic cancer. *Prob Gen Surg* 1997;141:27-32.
93. Reber HA. Small pancreatic tumors: is size and indication of curability? *J Hepatobiliary Pancreat Surg* 1995;2:384-386.
94. Reber H. The classic Whipple operation for pancreatic cancer. *Dig Surg* 1994;11:387-389.
95. Pitt HA. Curative treatment for pancreatic neoplasms. *Standard resection. Surg Clin North Am* 1995;75:891-904.
96. Yeo CJ, Cameron JL, Lillemoe KD, Sitzmann JV, Hruban RH, Goodman SN, Dooley WC, Coleman J, Pitt HA. Pancreatoduodenectomy for cancer of the head of the pancreas. 201 patients. *Ann Surg* 1995;221:721-733.
97. Reber HA, Ashley SW, McFadden D. Curative treatment for pancreatic neoplasms. *Surg Clin North Am* 1995;75:905-912.
98. Trede M, Carter DC. Preoperative assessment and indications for operation in chronic pancreatitis. In: Trede M, Carter DC, eds. *Surgery of the pancreas*. Edinburgh: Churchill Livingstone, 1993:283-298.
99. Trede M, Schwall G, Saeger HD. Survival after pancreatoduodenectomy: 118 consecutive resections without an operative mortality. *Ann Surg* 1990;211:447-458.
100. Trede M, Schwall G, Saeger HD. Survival after pancreatoduodenectomy. *Ann Surg* 1990;211:447-458.
101. Cameron JL, Pitt HA, Yeo CJ, Lillemoe KD, Kaufman HS, Coleman J. One hundred and forty-five consecutive pancreatoduodenectomies without mortality. *Ann Surg* 1993;217:430-438.
102. Patti MG, Pelligrini CA, Way LW. Gastric emptying and small bowel transit of solid food after pylorus-preserving pancreaticoduodenectomy. *Arch Surg* 1987;122:528-532.
103. Fink AS, DeSouza LR, Mayer EA, Hawkins R, Longmire WP Jr.

- Long-term evaluation of pylorus preservation during pancreaticoduodenectomy. *World J Surg* 1988;12:663-670.
104. Roder JD, Stein HJ, Huttli W, Siewert JR. Pylorus-preserving versus standard pancreaticoduodenectomy: an analysis of 110 pancreatic and periampullary carcinomas. *Br J Surg* 1992;79:152-155.
 105. Kozuschek W., Reith HB. Lessons learned from experience with pancreatoduodenectomy for pancreatic cancer: German experience from Bochum. In: Traverso LW, ed. *Problems in general surgery—pancreatic cancer*. Philadelphia: Lippincott-Raven, 1997:67-74.
 106. Kozuschek W, Reith HB, Waleczek H, Haarman W, Edelmann M, Sonntag D. A comparison of the standard Whipple procedure and the pylorus preserving pancreatoduodenectomy. *J Am Coll Surg* 1994;178:443-458
 107. Ishikawa O, Ohhigashi H, Sasaki Y, Kabuto T, Fukuda I, Furukawa H, Imaoka S, Iwanaga T. Practical usefulness of lymphatic and connective tissue clearance for the carcinoma of the pancreas head. *Ann Surg* 1988;208:215-220.
 108. Takahashi S, Ogata Y, Miyazaki H, Maeda D, Murai S, Yamataka K, Tsuzuki T. Aggressive surgery for pancreatic duct cell cancer: feasibility, validity, limitations. *World J Surg* 1995;19:653-660.
 109. Reber HA, Gloor B. Radical pancreatectomy. *Surg Oncol Clin North Am* 1998;7:157-164.
 110. Hanyu F, Suzuki M, Imaizumi T. Whipple operation for pancreatic carcinoma: Japanese experience. In: Beger HG, Buchler MW, Malfertheiner P, eds. *Standard in pancreatic surgery*. Heidelberg, Germany: Springer-Verlag, 1993:646-653.
 111. Gordon TA, Burleyson GP, Tielschi JM, Cameron JL. The effects of regionalization on cost and outcome for one general high-risk surgical procedure. *Ann Surg* 1995;221:43-49.
 112. Glasgow RE, Mulvihill SJ. Hospital volume influences outcome in patients undergoing pancreatic resection for cancer. *West J Med* 1996;165:294-300.
 113. Livingston EH, Welton ML, Reber HA. The United States' experience with surgery for pancreatic cancer. *Int J Pancreatol* 1991;9:153-157.
 114. Nitecki SS, Sarr MG, Colby TV, van Heerden JA. Long-term survival after resection for ductal adenocarcinoma of the pancreas: is it really improving? *Ann Surg* 1994;221:59-66.
 115. Tsuchiya R, Noda T, Harada N, Miyamoto T, Tomioka T, Yamamoto K, Yamaguchi T, Izawa K, Tsunoda T, Yoshino R, Eto T. Collective review of small carcinomas of the pancreas. *Ann Surg* 1986;203:77-81.
 116. Onoyama H, Kamigaki T, Yamamoto M, Saitoh Y. Treatment and present status of pancreatic cancer. *Jpn J Cancer Chemother* 1992;19:2304-2310.
 117. Cameron JL, Crist DW, Stizmann JV, Hruban RH, Boitnott JK, Seidler AJ, Coleman J. Factors influencing survival after pancreaticoduodenectomy for pancreatic cancer. *Am J Surg* 1991;161:120-125.
 118. Mannell A, van Heerden JA, Weiland LH, Ilstrup DM. Factors influencing survival after resection of ductal adenocarcinoma of the pancreas. *Ann Surg* 1986;203:403-407.
 119. Bottger TC, Storkel S, Wellek S, Stockle M, Junginger T. Factors influencing survival after resection of pancreatic cancer: a DNA analysis and histomorphologic study. *Cancer* 1994;73:63-73.
 120. Allison DC, Bose KK, Hruban RH, Piantadosi S, Dooley WC, Boitnott JK, Cameron JL. Pancreatic cancer cell DNA content correlates with long-term survival after pancreaticoduodenectomy. *Ann Surg* 1991;214:648-656.
 121. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. *Am J Surg* 1993;165:68-73.
 122. Yeo CJ, Cameron JL, Lillemoe KD, Sitzmann JV, Hruban RH, Goodman SN, Dooley WC, Coleman J, Pitt HA. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. *Ann Surg* 1995;221:721-731.
 123. Kobari M, Sunamura M, Ohashi O, Saitoh Y, Yusa T, Matsuno S. Usefulness of Japanese staging in the prognosis of patients treated operatively for adenocarcinoma of the head of the pancreas. *J Am Coll Surg* 1996;182:24-32.
 124. Warshaw AL, Fernández-del C. Pancreatic carcinoma. *N Engl J Med* 1992;326:455-465.
 125. Singh SM, Longmire WP Jr, Reber HA. Surgical palliation for pancreatic cancer. The UCLA experience. *Ann Surg* 1990;212:132-139.
 126. Watanapa P, Williamson RCN. Surgical palliation for pancreatic cancer: developments during the past two decades. *Br J Surg* 1992;79:8-20.
 127. DeRooij PD, Rogatko A, Brennan MF. Evaluation of palliative surgical procedures in unresectable pancreatic cancer. *Br J Surg* 1991;78:1053-1058.
 128. Speer AG, Cotton PB, Russell RC, Mason RR, Hatfield AR, Leung JW, MacRae KD, Houghton J, Lennon CA. Randomized trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. *Lancet* 1987;2:57-62.
 129. Prat F, Chapat O, Ducto B, Ponchon T, Pelletier G, Fritsch J, Choury AD, Buffet C. A randomized trial of endoscopic drainage methods for inoperable malignant strictures of the common bile duct. *Gastrointest Endosc* 1998;47:1-7.
 130. Barkin JS, Goldberg RI, Sfakianakis GN, Levi J. Pancreatic carcinoma is associated with delayed gastric emptying. *Dig Dis Sci* 1986;31:265-267.
 131. Soetikno RM, Lichtenstein DR, Vandervoort J, Wong RCK, Roston AD, Slivka A, Montes H, Carr-Locke DL. Palliation of malignant gastric outlet obstruction using an endoscopically placed Wallstent. *Gastrointest Endosc* 1998;47:267-270.
 132. Nevitt AW, Vida F, Kozarek RA, Traverso LW, Raltz SL. Expandable metallic prostheses for malignant obstructions of gastric outlet and proximal small bowel. *Gastrointest Endosc* 1998;47:271-276.
 133. Lillimoe KD, Cameron JL, Kaufman HS, Yeo CJ, Pitt HA, Sauter PK. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A Prospective randomized trial. *Ann Surg* 1993;217:447-455.
 134. Polati E, Finco G, Gottin L, Bassi C, Pederzoli P, Ischia S. Prospective randomized double-blind trial of neurolytic coeliac plexus block in patients with pancreatic cancer. *Br J Surg* 1998;85:199-201.
 135. Kawamata M, Ishitani K, Ishikawa K, Sasaki H, Ota K, Omote K, Namiki A. Comparison between coeliac plexus block and morphine treatment on quality of life in patients with pancreatic cancer pain. *Pain* 1996;64:597-602.
 136. Kelsen DP, Portenoy RK, Thaler HT, Niedzwiecki D, Passik SD, Tao Y, Banks W, Brennan MF, Foley KM. Pain and depression in patients with newly diagnosed pancreas cancer. *J Clin Oncol* 1995;13:748-755.
 137. Passik SD, Breithart WS. Depression in patients with pancreatic carcinoma: diagnostic and treatment issues. *Cancer* 1996;78:615-626.
 138. Perez MM, Newcomer AD, Moertel CG, Go VLW, DiMagno EP. Assessment of weight loss, food intake, fat metabolism, malabsorption, and treatment of pancreatic insufficiency in pancreatic cancer. *Cancer* 1983;52:346-352.
 139. Bruno MJ, Haverkort EB, Tijssen GP, Tytgat GN, van Leeuwen DJ. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. *Gut* 1998;42:92-96.
 140. DiMagno EP, Malagelada J-R, Go VLW. The relationships between pancreatic ductal obstruction and pancreatic secretion in man. *Mayo Clin Proc* 1979;54:157-162.

141. Guarner L, Rodriguez R, Guarner F, Malagelada J-R. Fate of oral enzymes in pancreatic insufficiency. *Gut* 1993;34:708-712.
142. Freeny PC. Radiologic diagnosis and staging of pancreatic ductal adenocarcinoma. *Radiol Clin North Am* 1989;27:121-128.
143. Rothenberg ML, Abbruzzese JL, Moore M, Portenoy RK, Robertson JM, Wanebo HJ. A rationale for expanding the endpoints for clinical trials in advanced pancreatic carcinoma. *Cancer* 1996;78:627-632.
144. Ahlgren JD. Chemotherapy for pancreatic carcinoma. *Cancer* 1996;78:654-663.
145. Glenn J, Steinberg WM, Kurtzman SH, Steinberg SM, Sindelar WF. Evaluation of the utility of a radioimmunoassay for serum CA19-9 levels in patients before and after treatment of carcinoma of the pancreas. *J Clin Oncol* 1988;6:462-468.
146. Ishii H, Okada S, Sato T, Wakasugi H, Saisho H, Furesu J, Ishikawa O, Matsuno S, Yokoyama S. CA19-9 in evaluating the response to chemotherapy in advanced pancreatic cancer. *Hepatogastroenterology* 1997;44:279-283.
147. Glimelius B, Hoffman K, Sjöden PO, Jacobsson G, Sellström H, Enander LK, Linné T, Svensson C. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol* 1996;7:593-600.
148. Rothenberg ML. New developments in chemotherapy for patients with advanced pancreatic cancer. *Oncol Hunt* 1996;10:18-22.
149. Rothenberg ML, Moore MJ, Cripps MC, Andersen JS, Portenoy RK, Burris HA, Green MR, Tarassoff PG, Brown TD, Casper ES, Storniolo AM, Von Hoff DD. A phase II trial of gemcitabine in patients with 5-FU refractory pancreas cancer. *Ann Oncol* 1996;7:347-353.
150. Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreatic cancer: a randomized trial. *J Clin Oncol* 1997;15:2403-2413.
151. Kelsen D. The use of chemotherapy in the treatment of advanced gastric and pancreas cancer. *Semin Oncol* 1994;4:172-174.
152. Fennelly D, Kelsen DP. The role of chemotherapy in the treatment of adenocarcinoma of the pancreas. *Hepatogastroenterology* 1996;43:356-362.
153. Riess H, Htun P, Loffel J, Huhn D. Chemotherapy for patients with adenocarcinoma of the pancreas: recent results. *Cancer Res* 1996;142:415-424.
154. Lokich JJ, Ahlgren JD, Gullo JJ, Philips JA, Fryer JG. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma. A mid-Atlantic Oncology Program Study. *J Clin Oncol* 1989;7:425-432.
155. Scheithauer W, Pfeffel F, Kornek G, Marczell A, Wiltshcke C, and Funovics J. A phase II trial of 5-fluorouracil, leucovorin, and recombinant alpha-2b-interferon in advanced adenocarcinoma of the pancreas. *Cancer* 1992;70:1864-1866.
156. Tempero MA. Chemotherapy of pancreatic cancer. In: Reber H, ed. *Advances in pancreatic cancer*. Totowa, NJ: Humana, 1998: 265-280.
157. Bukowski RM, Schacter LP, Groppe CW, Hewlett JS, Weick JK, Livingston RB. Phase II trial of 5-fluorouracil, adriamycin, mitomycin-C and streptozotocin (FAM-S) in pancreatic carcinoma. *Cancer* 1982;50:197-200.
158. Smith FP, Hoth DF, Levin BF, Karlin DA, MacDonald JS, Woolley PV, Schein PS. 5-Fluorouracil, adriamycin and mitomycin C (FAM) chemotherapy for advanced adenocarcinoma of the pancreas. *Cancer* 1980;46:2014-2018.
159. Wiggans RG, Woolley PV, MacDonald JS, Smythe T, Ueno W, Schein PS. Phase II trial of streptozotocin, mitomycin C and 5-fluorouracil (SMF) in the treatment of advanced pancreatic cancer. *Cancer* 1978;41:387-391.
160. Dougherty J, Kelsen D, Kemeny N, Magill G, Bottet J, Niedzwiecki D. Advanced pancreatic cancer: a phase I-II trial of cisplatin, high dose cytarabine and caffeine. *J Natl Cancer Inst* 1989;81:1735-1738.
161. Oster MW, Gray R, Panasci L, Perry MC. Chemotherapy for advanced pancreatic cancer: a comparison of 5-fluorouracil, adriamycin, and mitomycin (FAM) with 5-fluorouracil, streptozotocin, and mitomycin (FSM). *Cancer* 1986;57:29-33.
162. Gastrointestinal Tumor Study Group. Phase II studies of drug combinations in advanced pancreatic carcinoma: fluorouracil plus doxorubicin plus mitomycin C and two regimens of streptozotocin plus mitomycin C plus fluorouracil. *J Clin Oncol* 1986;4:1794-1798.
163. Cullinan SA, Moertel CG, Fleming TR, Rubin JR, Krook JE, Everson LK, Windschitl HE, Twito DI, Marschke RF, Foley JF, Pfeifle DM, Barlow JF. A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. *JAMA* 1985;253:2061-2067.
164. Palmer KR, Kerr M, Knowles G, Cull A, Carter DC, Leonard CF. Chemotherapy prolongs survival in inoperable pancreatic carcinoma. *Br J Surg* 1994;81:882-885.
165. Mallinson CN, Rake MO, Cocking JB, Fox CA, Cwynarski MT, Diffey BL, Jackson GA, Hanley J, Wass VJ. Chemotherapy in pancreatic cancer: results from a controlled, prospective, randomized, multicentre trial. *Br Med J* 1980;281:1589-1591.
166. Cullinan S, Moertel CG, Wieand HS, Schutt AJ, Krook JE, Foley JF, Norris BD, Kardinal CG, Tschetter LK, Barlow JF. A phase II trial on the therapy of advanced pancreatic carcinoma: evaluations of the Mallinson regimen and combined 5-fluorouracil, doxorubicin, and cisplatin. *Cancer* 1990;65:2207-2212.
167. Tempero M, Lechner P, Dalrymple G, Harrison K, Augustine S, Schlom J, Anderson J, Wisecarver J, Colcher D. High-dose therapy with iodine-131-labeled monoclonal antibody CC49 in patients with gastrointestinal cancers: a phase I trial. *J Clin Oncol* 1997;4:1518-1528.
168. Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. *Cancer* 1987;58:2006-2010.
169. Hoffman JP, Weese JL, Solin LJ, Agarwal P, Scher R, Paul AR, Litwin S, Watts P, Eisenberg BL. A single institutional experience with preoperative chemoradiotherapy for stage I-III pancreatic adenocarcinoma. *Am Surg* 1993;59:772-781.
170. Jessup JM, Steele G, Mayer RJ, Posner M, Busse P, Cady B, Stone M, Jenkins R, Osteen R. Neoadjuvant therapy for unresectable pancreatic adenocarcinoma. *Arch Surg* 1993;128:559-564.
171. Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg* 1992;127:1335-1339.
172. Spitz FR, Abbruzzese JL, Lee JE, Pisters PW, Lowy AM, Fenoglio CJ, Cleary KR, Janjan NA, Goswitz MS, Rich TA, Evans DB. Preoperative and postoperative chemoradiation strategies in patients with pancreaticoduodenectomy for adenocarcinoma of the pancreas. *J Clin Oncol* 1997;15:928-937.
173. Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, Schutt AJ, Weiland LH, Childs DS, Holbrook MA, Lavin PT, Livstone E, Spiro H, Knowlton A, Kalser M, Barkin J, Lessner H, Mann-Kaplan R, Ramming K, Douglas HO, Thomas P, Nave H, Bateman J, Lokich J, Brooks J, Chaffey J, Corson JM, Zamcheck N, Novak JW. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (600 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluoro-

- uracil), and high dose radiation + 5-fluorouracil. *Cancer* 1981;48:1705-1710.
174. Gastrointestinal Tumor Study Group. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. *J Natl Cancer Inst* 1988;80:751-755.
 175. Ishii H, Okada S, Tokuyue K, Nose H, Okusaka T, Yoshimori M, Nagahama H, Sumi M, Kagami Y, Ikeda H. Protracted 5-fluorouracil infusion with concurrent radiotherapy as a treatment for locally advanced pancreatic carcinoma. *Cancer* 1997;79:1516-1520.
 176. Robertson JM, Ensminger WD, Walker S, Lawrence TS. A phase I trial of intravenous bromodeoxyuridine and radiation therapy for pancreatic cancer. *Int J Radiat Oncol Biol Phys* 1997;37:331-335.
 177. Boz G, De Paoli A, Roncadin M, Franchin G, Galligioni E, Arcicasa M, Bortolus R, Gobitti C, Minatel E, Innocente R, Trovo MG. Radiation therapy combined with chemotherapy for inoperable pancreatic carcinoma. *Tumori* 1991;77:61-64.
 178. Safran H, King TP, Choy H, Hesketh PJ, Wolfe B, Altenhein E, Sikov W, Rosmarin A, Akerley W, Radie-Keane K, Cicchetti G, Lopez F, Bland K, Wanebo HJ. Paclitaxel and concurrent radiation for locally advanced pancreatic and gastric cancer: a phase I study. *J Clin Oncol* 1997;15:901-907.
 179. Lawrence TS, Chang EY, Hahn TM, Hertel LW, Shewach DS. Radiosensitization of pancreatic cancer cells by 2',2'-difluoro-2'-deoxycytidine. *Int J Radiat Oncol Biol Physiol* 1996;34:867-872.
 180. Roldan GE, Gunderson LL, Nagorney DM, Martin JK, Ilstrup DM, Holbrook MA, Kvols LK, McIlrath DC. External beam versus intraoperative and external beam irradiation for locally advanced pancreatic cancer. *Cancer* 1988;61:1110-1116.
 181. Dobelbower RR, Montemaggi P. Brachytherapy for pancreatic cancer: a review. *Hepatogastroenterology* 1996;43:333-337.
 182. Raben A, Mychalczak B, Brennan MF, Minsky B, Anderson L, Casper ES, Harrison LB. Feasibility study of the treatment of primary unresectable carcinoma of the pancreas with 103Pd brachytherapy. *Int J Radiat Oncol Biol Physiol* 1996;35:351-356.
 183. Schein PS, Lavin PT, Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reteimeier RJ, Rubin J, Schutt AJ, Weiland LH, Kalsner M, Barkin J, Lessner H, Mann-Kaplan R, Redhammer D, Silverman M, Troner M, Douglass HO, Milliron S, Lokich J, Brooks J, Chaffe J, Like A, Zamchck N, Ramming K, Bateman J, Spiro H, Livstone E, Knowlton A. Randomized phase II clinical trial of adriamycin, methotrexate, and actinomycin-D in advanced measurable pancreatic carcinoma: a Gastrointestinal Tumor Study Group report. *Cancer* 1978;42:19-22.
 184. Horton J, Gelber RD, Engstrom P, Falkson G, Moertel C, Brodovsky H, Douglass H. Trials of a single-agent and combination chemotherapy for advanced cancer of the pancreas. *Cancer Treat Rep* 1981;65:65-68.
 185. Frey C, Twomey P, Keehn R, Elliott D, Higgins G. Randomized study of 5-FU and CCNU in pancreatic cancer. *Cancer* 1981;47:27-31.
 186. Andren-Sandberg A, Holmberg JT, Ihse I. Treatment of unresectable pancreatic carcinoma with 5-fluorouracil, vincristine and CCNU. *Scand J Gastroenterol* 1983;18:609-612.
 187. Bukowski RM, Balcerzak SP, O'Bryan RM, Bonnet JD, Chen TT. Randomized trial of 5-fluorouracil and mitomycin C with or without streptozotocin for advanced pancreatic cancer. *Cancer* 1983;52:1577-1582.
 188. Gastrointestinal Tumor Study Group. Phase II trials of maytansine, low-dose chlorozotocin, and high-dose chlorozotocin as single agents against advanced measurable adenocarcinoma of the pancreas. *Cancer Treat Rep* 1985;69:417-420.
 189. Gastrointestinal Tumor Study Group. Phase II trials of single agents Baker's antifol, diaziquone, and epirubicin in advanced pancreatic cancer. *Cancer Treat Rep* 1987;71:865-867.
 190. Keating JJ, Johnson PJ, Cochrane AMG, Gazzard BG, Krasner N, Smith PM, Trewby PN, Wheeler P, Wilkinson SP, Williams R. A prospective randomized trial of tamoxifen and cyproterone acetate in pancreatic carcinoma. *Br J Cancer* 1989;60:789-792.
 191. Kelsen D, Hudis C, Niedzwiecki D, Dougherty J, Casper E, Botet J, Vinciguerra V, Rosenbluth R. A phase III comparison trial of streptozotocin, mitomycin, and 5-fluorouracil with cisplatin, cytosine arabinoside, and caffeine in patients with advanced pancreatic carcinoma. *Cancer* 1991;68:965-969.
 192. Huguier M, Samama G, Testart J, Mauban S, Fingerhut A, Nassar J, Houry S, Jaeck D, De Mestier P, Favre JO, Michot F, Vidrequin A, Mantion G, Veyrieres M, Fournier G, Lointier P, Gignoux M. Treatment of adenocarcinoma of the pancreas with somatostatin and gonadoliberin (leuteinizing hormone-releasing hormone). *Am J Surg* 1992;164:348-353.
 193. Bukowski RM, Fleming TR, MacDonald JS, Oishi N, Taylor SA, Baker LH. Evaluation of combination chemotherapy and phase II agents in pancreatic adenocarcinoma. A Southwest Oncology Group study. *Cancer* 1993;71:322-325.
 194. Ashbury RF, Cnaan A, Johnson L, Harris J, Zaentz SD, Haller DG. An Eastern Cooperative Oncology Group phase II study of single agent DHAD, VP-16, aclacinomycin, or spirogermanium in metastatic pancreatic cancer. *Am J Clin Oncol* 1994;17:166-169.
 195. Kalsner MH, Ellenberg SS. Pancreatic cancer: adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg* 1985;120:899-903.

Address requests for reprints to: Chair, Clinical Practice and Practice Economics Committee, AGA National Office, c/o Membership Department, 7910 Woodmont Avenue, 7th Floor, Bethesda, Maryland 20814. Fax: (301) 654-5920.

© 1999 by the American Gastroenterological Association
0016-5085/99/\$10.00