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SECTION 3

Cancer of the Pancreas

EPIDEMIOLOGY AND RISK FACTORS

EPIDEMIOLOGY

Pancreatic cancer (PC) is the fifth leading cause of cancer death in the United States, with 28,000 to 30,300 newly diagnosed cases (ductal adenocarcinoma being the most common form) per year.¹ Approximately an equal number of deaths occur annually from PC.¹ The incidence rate for PC is approximately nine new cases per 100,000 people, with the peak incidence in the seventh and eighth decades of life and an average age of 60 to 65 years at diagnosis.¹ The incidence rate is slightly higher in men than in women (relative risk, 1.35) and 30% to 40% higher in African American men.

Survival in patients with untreated PC is poor. For all stages combined, the 1-year survival rate is 19% and the 5-year survival rate is 4%.¹ The majority (80%) of PCs are metastatic at the time of diagnosis. Surgical resection (when margin negative, node negative) offers the best possibility for cure, with 5-year survival approaching 40% when performed at specialized major medical institutions.^{2,3}

In the United States, incidence rates of PC increased three-fold between 1920 and 1978, an increase that has also been observed in other developed countries.^{3,4} Rates for men and for women have modestly declined since 1978 and appear to have stabilized at the current rates. A portion of the increased incidence may have been attributable to more accurate disease diagnosis and less disease misclassification. Additionally, improved surveillance may account for a small portion of the increased incidence.

A positive relationship exists between certain environmental exposures and cases of PC, including personal cigarette smoking, environmental tobacco smoke (ETS), and chemical exposures.^{3,4} Cigarette smoking in the United States and in other countries increased greatly in the first half of the twentieth century. In fact, 40% of adult Americans were smokers in 1965. Increased cigarette smoking likely accounts for a large portion of the increased incidence of PC. By 1990, the prevalence of smoking among Americans had decreased to 25%, with modest declines again noted in 1999.³ Because of the long latency period before diagnosis, it remains to be seen if this will translate into lower PC incidence rates in the future.

ETIOLOGIC (RISK) FACTORS

Tobacco Smoke Exposure

Tobacco smoke exposure plays a significant role in the development of PC. It has been estimated that tobacco smoking contributes to the development of 20% to 30% of PCs.⁴ The strongest associations between cigarette smoking and PC have been observed when the pack-years smoked were within the previous 10 years.³ Smoking cessation can reduce this risk. Indeed, Mulder et al.⁵ have estimated that moderate reduction in smoking in Europe could save almost 68,000 lives that would otherwise be lost to PC by the year 2020.

Environmental Tobacco Smoke

ETS contains the same toxins, irritants, and carcinogens, such as carbon monoxide, nicotine, cyanide, ammonia, benzene, nitrosamines, vinyl chloride, arsenic, and hydrocarbons, as do cigarettes. Thirty-seven percent of American adult nonsmokers report that they either live with a smoker or are exposed to ETS at work.⁶ A Department of Health and Human Services' Centers for Disease Control and Prevention study estimated that nearly 9 out of 10 nonsmoking Americans are exposed to ETS, as measured by the level of cotinine in their blood.⁶

Demographic and Host Risk Factors

A number of demographic risk factors have been associated with the development of PC worldwide and are summarized in Table 29.3-1. Included are older age (most PCs occur between the ages of 60 and 80), African American race, low socioeconomic status, and Ashkenazi Jewish heritage (related to germline mutations).⁴

Diabetes Mellitus

Host etiologic factors associated with an increased risk of PC include a history of diabetes mellitus (DM), chronic cirrhosis, pancreatitis, a high-fat/cholesterol diet, and prior cholecystectomy.^{3,4} The association between DM, pancreatitis, and the

TABLE 29.3-1. Factors Associated with Increased Risk of Pancreatic Cancer

Advancing age
African American males
Low socioeconomic status
Native female Hawaiians
Ashkenazi Jewish heritage
Cigarette smoking
Six genetic syndromes (see Table 29.3-2)
Diabetes mellitus
Chronic pancreatitis
Cirrhosis
Obesity
Increased height
Low level of physical activity
High-fat and cholesterol diet
Occupational exposure to carcinogens (PCBs, DDT, NNK, benzidine)
DDT, dichlorodiphenyl trichloroethane; PCBs, polychlorinated biphenyls.

development of PC is complex because PC, by destroying the pancreatic parenchyma, can itself cause DM and pancreatitis.

Metaanalysis of 20 epidemiologic studies on the association between DM and PC confirms that the pooled relative risk of PC in persons with DM for 5 years is double (relative risk, 2.0; confidence interval, 1.3 to 2.2) the risk of persons without DM.³ The analysis further suggested that impaired glucose tolerance, insulin resistance, and hyperinsulinemia are involved in the etiology of PC.

Obesity and Physical Activity

High body mass index (a measure of obesity), increased height, and a low level of physical activity all increased the risk of PC, as demonstrated in a cohort study of 160,000 health professionals.⁷ Moderate physical activity resulted in decreased PC rates, and merely walking or hiking 1.5 hours or more per week was associated with a 50% reduction in PC. Likewise, body mass index had no effect if the participant was a moderate exerciser. For cigarette smoking, the strongest associations with PC were observed when the pack-years smoked were within the previous 15 years. These findings clearly suggest that weight loss and exercise may reduce the risk of developing PC independent of smoking cessation.

Occupational Factors

A metaanalysis of 20 population studies of occupational exposures and PC from journal publications during the period 1969 to 1998 was performed.⁸ Exposure to chlorinated hydrocarbon solvents, nickel and nickel compounds, chromium compounds, polycyclic aromatic hydrocarbons, organochlorine insecticides, silica dust, and aliphatic solvents conveyed elevated risk ratios. Overall, the occupational etiologic fraction for PC was estimated at 12%, but it increased to 29% when the chlorinated hydrocarbon solvents were considered in a subpopulation.

Elevated serum levels of organochloride compounds (dichlorodiphenyltrichlorethane, dichlorodiphenyldichloroethylene, and polychlorinated biphenyls), are also associated with the development of PC.⁹ Approximately 90% of PC patients have an acquired K-ras oncogene mutation. In a case-control study, PC patients with K-ras mutations had significantly higher levels of dichlorodiphenyltrichlorethane, dichlorodiphenyldichloroethylene, and three polychlorinated biphenyl compounds compared to PC patients without the K-ras mutation and to those in the control group. These compounds are postulated to enhance the actions of K-ras rather than cause the mutation, suggesting a gene-environment interaction or effect modification. It may also be that these compounds interact with premalignant ductal precursor lesions and accelerate their malignant progression.

Other Possible Factors

Factors that have been repeatedly studied, with no consistent association with the development of PC, include moderate alcohol intake, nonhereditary and acute pancreatitis, and coffee drinking.

GENETIC PREDISPOSITIONS

PC is characterized by inherited and acquired genetic mutations.¹⁰ Genetic predisposition plays a small but significant role in PC risk. Activation of the oncogene K-ras plus inactivation of

tumor suppressor genes (p53, DPC4, p16, and BRCA2) are associated with the development of PC. Nearly 90% of all cases of PC have p16 mutations, 75% have p53 mutations, and 55% have DPC4 mutations. Fewer than 4% of PC cases appear to involve dysfunction of the various DNA mismatch repair genes [microsatellite instability (MIN)].

It is estimated that 10% to 20% of PCs are hereditary or have a familial link. Multiple lines of evidence support this. Cohort studies have shown an increased risk of developing PC among individuals who report a family history of PC. Tersmette et al.¹¹ have shown that this risk increases with the number of affected members in the family. Risk was estimated by comparing new observed cases of PC to expected cases based on the United States population-based Surveillance, Epidemiology, and End Results program data. An 18-fold increased risk of PC was found in familial PC kindreds compared to sporadic groups. When three or more family members were affected with PC, there was a 57-fold increased risk. When stratified according to age, the risk of PC was largely confined to relatives older than 60 years of age.

Segregation analyses suggest that aggregation of PC in families has a genetic rather than an environmental basis.¹² Nongenetic transmission models were rejected ($P < .0001$) in the segregation analysis of 287 families, ascertained through an index case diagnosed with PC. The most parsimonious model included autosomal dominant inheritance of a rare allele (still to be identified), estimated to be carried by approximately 0.5% of the population.¹²

INHERITED SYNDROMES

Although accounting for less than 20% of the familial aggregation of PC, several genetic syndromes (caused by germline mutations) associated with an increased risk of PC have been identified.^{3,10} These are summarized in Table 29.3-2 and include

1. Familial breast cancer with germline mutations in the *BRCA2* gene. Carriers of germline *BRCA2* mutations have a 3.5- to 10.0-fold increased risk of developing PC, and 17% (1 in 6) of patients with PC and a strong family history of PC (at least 3 family members with PC) have been shown to have germline *BRCA2* mutations. This makes *BRCA2* mutation the most common germline mutation in patients with hereditary PC.
2. Familial atypical multiple mole melanoma syndrome with germline mutations in the *p16* gene. Carriers of *p16* germline mutations have a 12- to 20-fold increased risk of developing PC, as well as an increased risk of melanoma.

TABLE 29.3-2. Genetic Syndromes and Gene Alterations Associated with Familial Pancreatic Cancer

Syndrome	Gene Alteration (Chromosomal Locus)
Hereditary pancreatitis	<i>PRSS1</i> (7q35)
Hereditary nonpolyposis colorectal cancer (Lynch II variant)	<i>hMSH2</i> , <i>hMLH1</i> , others
Hereditary breast and ovarian cancer	<i>BRCA2</i> (13q12q13)
Familial atypical multiple mole melanoma (FAMMM) syndrome	<i>p16</i> (9p21)
Peutz-Jeghers syndrome	<i>STK11/LKB1</i> (19p13)
Ataxia-telangiectasia	<i>ATM</i> (11q22-23)

TABLE 29.3-3. Solid Exocrine Neoplasms of the Pancreas

Neoplasm	Age (Y)	Direction of Differentiation	Most Common Genetic Alterations	Overall 5-Y Survival Rates (%)
Ductal adenocarcinoma	Most, 60–80	Infiltrating glands with an intense desmoplastic reaction	Activating mutations in <i>K-ras</i> , inactivation of <i>DPC4</i> , <i>p16</i> , <i>p53</i>	4
Acinar cell carcinoma	Mean, 58	Pancreatic exocrine enzymes, including trypsin, chymotrypsin, and lipase	One-fourth have <i>APC/β-catenin</i> mutations	6
Pancreatoblastoma	Mean age, 2.5 in children, 40 in adults	Multiple, including acinar; distinctive squamoid nests	LOH on 11p	55

APC, advanced pancreatic cancer; LOH, loss of heterozygosity.

3. The Peutz-Jeghers syndrome (PJS), characterized by mucocutaneous melanocytic macules and hamartomatous polyps of the gastrointestinal (GI) tract. Patients with the PJS have a greater than 100-fold increased risk of developing PC.
4. The hereditary nonpolyposis colorectal cancer syndrome, characterized by germline mutations in one of the DNA mismatch repair genes (*hMSH1*, *hMSH2*, etc.).
5. Hereditary pancreatitis with germline mutations in the *PRSS1* (cationic trypsinogen) gene. Patients develop severe pancreatitis at a young age (often children and adolescents) and have a 50-fold excess risk of developing PC.
6. Ataxia-telangiectasia, a rare autosomal recessive inherited disorder, characterized by cerebellar ataxia, oculocutaneous telangiectasias, and cellular and humoral immune deficiencies. The gene, ATM, is also associated with an increased risk of leukemia, lymphoma, and cancers of the breast, ovaries, biliary tract, stomach, and, occasionally, the pancreas.

A seventh syndrome, that of PC, pancreatic insufficiency, and DM, has been described in a family (called *Family X*), and the phenotype has been linked to chromosome 4q32-34.³

DATA FROM THE NATIONAL FAMILIAL PANCREAS TUMOR REGISTRY

The above genetic syndromes do not explain the vast majority of cases in which there is a familial aggregation of PC. The National Familial Pancreas Tumor Registry has therefore been established at Johns Hopkins, with the hope of identifying the causes for the aggregation of PC in families. To date, more than 1200 families have enrolled in this registry. Early analyses of the kindreds enrolled in the National Familial Pancreas Tumor Registry have shown that the risk of cancer is 18-fold greater in first-degree relatives of familial PC cases (at least 2 first-degree relatives with PC in the family) than it is in first-degree relatives of sporadic PC cases (families in which there has been only 1 member with PC).¹¹ In addition, the increased risk of PC in familial PC kindreds extends to second-degree relatives, as a significantly increased rate of PC was identified in second-degree relatives of familial cases compared with sporadic pancreatic cases (3.7% vs. 0.6%; $P < 0.0001$).

PATHOLOGY

Although we tend to think of "PC" as a single entity, in fact, an array of biologically and clinically distinct neoplasms can arise

in the pancreas. Neoplasms of the pancreas can be broadly grouped into those with predominantly exocrine differentiation and those with endocrine differentiation. Exocrine neoplasms of the pancreas can be further subdivided into cystic and solid tumors. The vast majority of malignancies of the pancreas are solid infiltrating ductal adenocarcinomas, and the term *PC* is therefore often used synonymously with infiltrating ductal adenocarcinoma.

SOLID NEOPLASMS OF THE EXOCRINE PANCREAS

The most common solid neoplasms of the exocrine pancreas are the infiltrating ductal adenocarcinoma and variants of ductal adenocarcinoma, acinar cell carcinoma, and pancreatoblastoma (Table 29.3-3). *Infiltrating ductal adenocarcinomas* are malignant epithelial neoplasms that show glandular or ductal differentiation.¹³ Most arise in patients between the ages of 60 and 80 years, and men outnumber women (male-female ratio, 1.35:1.0). The majority of ductal adenocarcinomas arise in the head of the gland, but they can also arise in the body or in the tail or even diffusely involve multiple parts of the pancreas. Grossly, infiltrating ductal adenocarcinomas form firm, poorly defined white-yellow masses. These carcinomas often extend beyond the grossly identifiable tumor, and invasion into large vessels and adjacent organs is common.

Three features characterize infiltrating ductal adenocarcinomas at the light microscopic level.¹³ First, by definition, the neoplastic cells show evidence of glandular/ductal differentiation. The second feature that characterizes ductal adenocarcinomas is that they induce an intense nonneoplastic desmoplastic stromal reaction. This desmoplastic stroma contains myofibroblasts, lymphocytes, extracellular collagen, and trapped nonneoplastic pancreatic tissue, including trapped islets of Langerhans. An infiltrative growth pattern is the third feature that characterizes infiltrating ductal adenocarcinoma. This infiltrative growth is manifested in the haphazard arrangement of the neoplastic glands; in extension of the carcinoma beyond the pancreas into adjacent structures, including large vessels, the duodenum, the stomach, the adrenals, and the peritoneum; and by perineural and lymphovascular invasion (Fig. 29.3-1). Growth along nerves is one route by which infiltrating ductal adenocarcinomas extend out of the gland and into the retroperitoneum, and lymphovascular invasion is associated with lymph node and more distant metastases.

A growing body of evidence suggests that histologically well-defined noninvasive epithelial proliferations begin in the

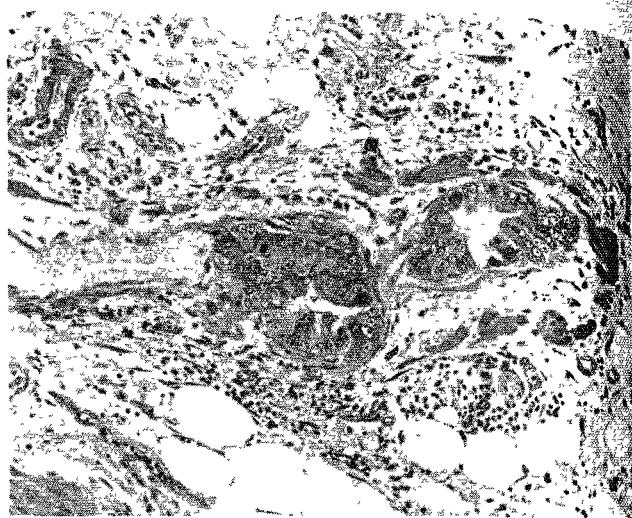


FIGURE 29.3-1. Infiltrating ductal adenocarcinoma of the pancreas. Perineural (A) and vascular (B) invasion are common.

smaller pancreatic ducts (Fig. 29.3-2A) and progress to invasive ductal adenocarcinoma. These lesions, called *pancreatic intraepithelial neoplasia* (PanIN), often accompany infiltrating ductal adenocarcinomas, and PanINs harbor many of the same molec-

ular genetic alterations as are found in infiltrating ductal adenocarcinomas.¹⁴ PanINs are important to recognize because they can mimic an infiltrating carcinoma microscopically and because they are reasonable targets for chemoprevention and

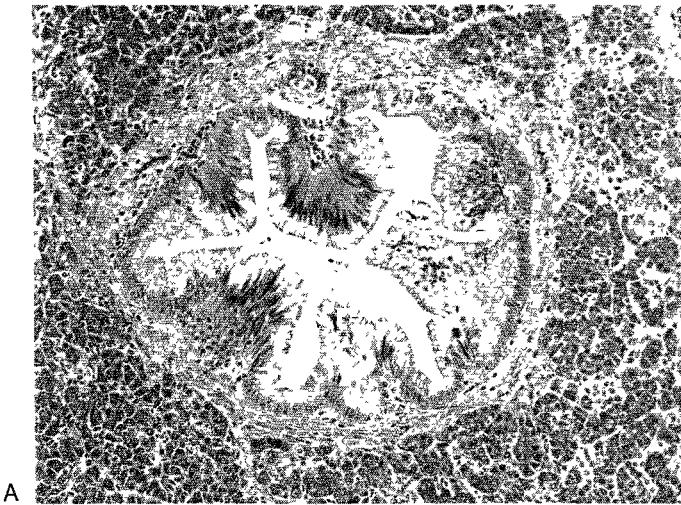
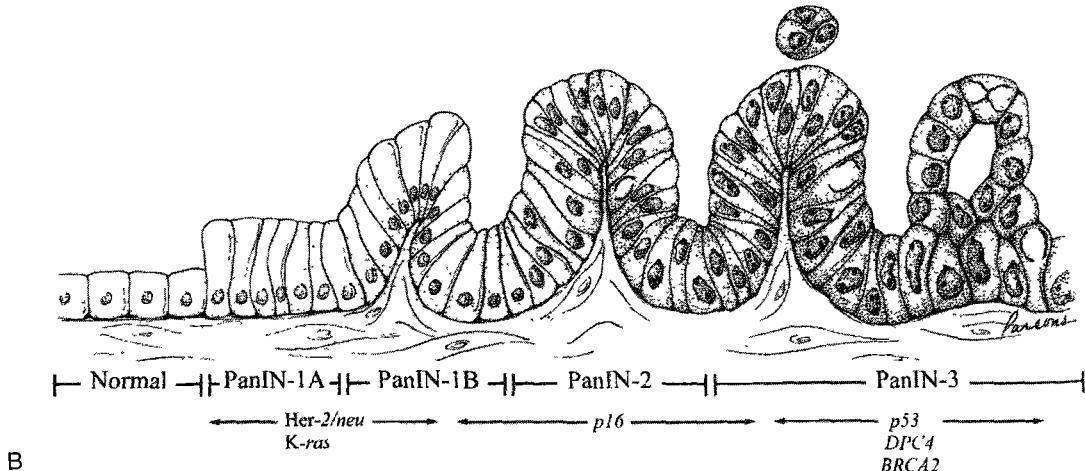


FIGURE 29.3-2. A: Pancreatic intraepithelial neoplasia (PanIN). These lesions in the small pancreatic ducts can progress to an infiltrating ductal adenocarcinoma. B: Histologic-genetic progression model of infiltrating pancreatic ductal adenocarcinoma from PanIN (From Wilentz RE, Iacobuzio-Donahue CA, Argani P, et al. Loss of expression of Dpc4 in pancreatic intraepithelial neoplasia: evidence that DPC4 inactivation occurs late in neoplastic progression. *Cancer Res* 2000;60:2002, with permission.)



screening for early pancreatic neoplasia. Figure 29.3-2B depicts the postulated progression model from PanIN to invasive ductal adenocarcinoma.

Immunohistochemically, most infiltrating ductal adenocarcinomas express cytokeratins 7 and 19, carcinoembryonic antigen, epithelial membrane antigen, CA 19-9, and the mucins (MUC1, MUC3, MUC4, and MUC5).¹³ Fifty-five percent of ductal adenocarcinomas show a complete loss of DPC4 protein expression.

Infiltrating ductal adenocarcinomas are fully malignant neoplasms. The overall 5-year survival rate is less than 4%, but 5-year survival approaches 20% for all patients who undergo surgical resection.

Several variants of infiltrating adenocarcinoma exist. These include *signet-ring cell*, *medullary*, *adenosquamous*, *colloid ductal* (mucinous noncystic), and *anaplastic carcinomas*, as well as the *undifferentiated carcinoma with osteoclast-like giant cells*.¹³ Of importance, signet-ring cell carcinomas have to be distinguished from metastases from a gastric or breast primary, and medullary carcinomas of the pancreas are associated with specific genetic alterations (inactivation of one of the DNA mismatch repair genes).

Acinar cell carcinomas are malignant epithelial neoplasms that show evidence of exocrine enzyme production.^{15,16} Most acinar cell carcinomas arise in adults (mean age, 58 years), although cases have been reported in children. The male-female ratio is 3.6:1.0. Most patients present nonspecifically with signs and symptoms related to a large pancreatic mass, but 15% present with the syndrome of metastatic fat necrosis (subcutaneous fat necrosis, peripheral eosinophilia, and polyarthralgias) caused by the release of lipase into the circulation. Grossly acinar cell carcinomas are usually softer than most ductal adenocarcinomas, and by light microscopy they grow in sheets and at least focally form acinar structures. Acini are composed of pyramidal cells with basal nuclei and granular cytoplasm, oriented around small lumina. Immunohistochemical labeling is often needed to establish a diagnosis. In most cases the neoplastic cells label with antibodies to trypsin, chymotrypsin, and/or lipase. At the ultrastructural level the presence of zymogen granules can be used to confirm acinar differentiation. Acinar cell carcinomas are fully malignant neoplasms.

Pancreatoblastomas are malignant epithelial neoplasms that show several directions of differentiation.^{13,17,18} At a minimum,

acinar differentiation and distinctive squamoid nests are present. In addition, many pancreatoblastomas show endocrine, ductal, and even mesenchymal differentiation. Most pancreatoblastomas arise in children, but up to a third may arise in adults. At the genetic level, pancreatoblastomas frequently show loss of heterozygosity (LOH) on the short arm of chromosome 11 near the WT-2 locus, a finding that links them with other embryonal neoplasms such as hepatoblastomas.¹⁸ Pancreatoblastomas are malignant neoplasms. A third of the patients have metastases at diagnosis. The outcome for children is slightly better than for adults.

CYSTIC NEOPLASMS OF THE EXOCRINE PANCREAS

The most common cystic neoplasms of the pancreas include mucinous cystic neoplasms, intraductal papillary mucinous neoplasms (IPMNs), serous cystic neoplasms, and solid and pseudopapillary neoplasms (Table 29.3-4). A review of the diagnostic features of cystic neoplasms of the pancreas can be found on the Web (<http://pathology2.jhu.edu/pancreascyst/index.cfm>).

Mucinous cystic neoplasms are much more common in women (90%) than in men.¹⁹ These distinctive neoplasms arise in the tail of the gland more frequently than in the head of the gland. Grossly, mucinous cystic neoplasms are composed of large cysts that contain thick tenacious mucus.^{13,19} The cysts are separated by thick septae and do not communicate with the larger pancreatic ducts. These cysts are lined by a columnar mucin-producing epithelium, and the stroma surrounding the cysts has a histologic appearance similar to ovarian stroma. The epithelium can show varying degrees of cytologic and architectural atypia, and one-third of mucinous cystic neoplasms are associated with an invasive carcinoma, usually an invasive ductal adenocarcinoma. Based on the degree of cytologic and architectural atypia and the presence or absence of an invasive carcinoma, mucinous cystic neoplasms have been categorized into mucinous cystadenoma (no atypia, no invasion), borderline mucinous cystic neoplasm (moderate atypia, no invasion), mucinous cystic neoplasm with *in situ* carcinoma (marked atypia, no invasion), and mucinous cystadenocarcinoma (an associated invasive carcinoma).¹³ The critical prognosticator for patients with a mucinous cystic neoplasm is the presence or absence of an invasive

TABLE 29.3-4. Cystic Neoplasms of the Exocrine Pancreas

Neoplasm	Gender	Involvement of Larger Ducts	Cyst Contents	Cyst Lining	Stroma	Immunolabeling
Mucinous cystic neoplasm	90% female	No	Mucoid	Columnar mucinous epithelium	Distinctive ovarian type	Cytokeratin, MUC2, CEA, stroma labels for inhibin and progesterone receptors
Intraductal papillary mucinous neoplasm	60% male	Yes	Mucoid	Columnar mucinous epithelium	Collagenous	Cytokeratin, MUC2, CEA
Serous cystic neoplasm	70% female	No	Clear, watery	Low cuboidal glycogen-rich	Collagenous	Cytokeratin
Solid pseudopapillary neoplasm	90% female	No	Hemorrhagic necrotic	Discohesive uniform cells	Collagenous	CD10, nuclear β -catenin

CEA, carcinoembryonic antigen; MUC, mucin.

carcinoma. Patients with completely resected mucinous neoplasms without an associated invasive carcinoma are cured.¹⁹ By contrast, the 5-year survival rate for patients with a completely resected invasive mucinous cystadenocarcinoma is approximately 50%.

IPMNs also produce mucin, but in contrast to mucinous cystic neoplasms, IPMNs involve the larger pancreatic ducts and lack a distinctive stroma.^{13,20} Because these neoplasms involve the larger pancreatic ducts, mucin can often be seen on endoscopy oozing from a patent ampulla of Vater. Grossly, IPMNs reveal villous projections into a dilated pancreatic duct that contains thick mucin. By light microscopy IPMNs are composed of papillae lined by tall columnar mucin-producing epithelium. One-third of IPMNs have an associated invasive carcinoma, and this invasive carcinoma often shows abundant extracellular mucin production (colloid carcinoma). The 5-year survival rate for patients with resected invasive carcinomas arising in association with IPMNs is approximately 40%.

Serous cystic neoplasms are almost always benign.^{13,21} The average age is 65 years, and the male-female ratio is 3:7. Serous cystic neoplasms have a characteristic gross appearance. They are well demarcated and on cross section are composed of multiple (at times innumerable) small cysts, often with a central stellate scar. By light microscopy the cysts are lined by low cuboidal cells with uniform centrally placed nuclei and clear cytoplasm. Special stains will demonstrate

that the cytoplasmic clearing is caused by abundant amounts of glycogen.

Solid pseudopapillary neoplasms are distinctive neoplasms of uncertain histogenesis that almost always arise in young women (90% female; average age, 26 years).^{13,22} They are well demarcated and grossly are composed of solid areas admixed with cystic areas with hemorrhage and necrosis. By light microscopy the solid areas are composed of sheets of relatively uniform cells and delicate blood vessels. The nuclei are uniform, and the cells appear somewhat dis cohesive. In some areas the neoplastic cells appear to "drop out," forming pseudopapillae around small blood vessels. Immunohistochemically, the neoplastic cells label for CD 10 and α_1 -antitrypsin and show an abnormal nuclear labeling for β -catenin. The abnormal nuclear labeling for β -catenin is a manifestation of genetic mutations in the β -catenin gene. Surgical resection is the treatment of choice for these neoplasms, and, if completely resected, most patients are cured of their disease.

MOLECULAR GENETICS

Four categories of mutated genes play a role in the pancreatic tumorigenesis: oncogenes, tumor suppressor genes, genome-maintenance genes, and tissue-maintenance genes (summarized in Table 29.3-5). Some of these mutations are germline;

TABLE 29.3-5. Genetic Profile of Pancreatic Carcinoma^a

Gene	Gene Locations	Frequency in Cancers (%)	Timing during Tumorigenesis ^b	Mutation Origin
ONCOGENES				
KRAS2	12p	95	Early-mid	Som.
BRAF	7q	4	—	Som
AKT2	19q	10-20	—	Som.
MYB	6q	10	—	Som.
EBY genome		<1	—	
TUMOR SUPPRESSORS/GENOME-MAINTENANCE GENES				
P16/RB1	9p/13q	>90	Mid-late	Som.>germ
TP53	17p	50-75	Late	Som.
MADH4	18q	55	Late	Som
BRCA2	13q	7	Late	Germ >som
FANCC/FANCG	9q/9p	3	—	Germ, or som
MKK4	17p	4	—	Som
LKB1/STK11	19p	4	—	Som >germ
ACVR1B	12q	2	—	Som.
TGFBR1	9q	1	—	Som. ^c
MSI ⁻ /TGFBR2	3p	1	—	Som. ^c
MSI ⁺ /TGFBR2	3p	4	—	Som.>germ ^d
ACVR2	2q	4	—	Som.>germ ^d
BAX	19q	4	—	Som.>germ ^d
MLH1	3p	4	—	Som.>germ ^d
FBXW7/cyclin E deregulation	4q	6	—	Som. ^e
TISSUE-MAINTENANCE GENES				
PRSS1	7q	<1	Prior	Germ

Germ., (prevalence of) germline mutation; som., (prevalence of) somatic mutation or methylation.

^aReferences are given in the text.

^bStage of appearance of the genetic changes during the intraductal precursor phase of the neoplasm, where known. For BRCA2, most mutations are inherited, but the loss of the second allele is reported only in a single advanced pancreatic intraepithelial neoplasm.

^cSingle examples of homozygous deletion of the TGFBR1 gene and TGFBR2 gene have been identified in MSI⁻ pancreatic cancer.

^dIn MSI⁺ tumors, the mismatch repair defect is usually somatic in origin; the TGFBR2, ACVR2, and BAX alterations are somatic.

^eA single example of homozygous mutation of the FBXW7 gene is reported in a series having a 6% prevalence of cyclin E overexpression. Cyclin E amplification is reported to date only in cell lines.

that is, they are transmitted within a family. Others that are mutated during life, termed *somatic mutations*, contribute to tumorigenesis within a tissue but are not passed to offspring. Telomere abnormalities and signs of chromosome instability are the most common alterations. Four genes are mutated in most cases (the *KRAS2*, *p16*, *p53*, and *MADH4* genes). Other genetic abnormalities are seen at a much lower frequency: *BRCA2*, *FANCC*, *FANCG*, *FBXW7*, *BAX*, *RB1*, the transforming growth factor- β (TGF- β) receptors *TGFB1* and *TGFB2*, the activin receptors *ACBR1B* and *ACVR2*, *MKK4*, *STK11*, *p300*, sites of gene amplification, various deletion patterns, the mitochondrial genome, the DNA mismatch-repair genes, cationic trypsinogen, and the Epstein-Barr virus genome, among others.

The analysis of these genes has had direct clinical impact. For example, many cases occur on an inherited basis, and these patients and their families may benefit from genetic counseling. A routine distinction must be made between conventional ductal adenocarcinoma and a histologically and genetically distinct variant having a medullary growth pattern.²³ The analysis of the genetic alterations in preinvasive pancreatic neoplasia has indicated that most carcinomas arise by a process of progressive intraductal tumorigenesis (see Fig. 29.3-2B).

COMMON GENETIC CHANGES

Telomere shortening is the earliest and most prevalent genetic change identified in the precursor lesions.²⁴ Telomere erosion is thought to predispose to chromosome fusion (translocations) and their missegregation during mitosis. Later during tumorigenesis, telomerase is reactivated,²⁵ moderating the telomere erosive process while permitting continued chromosomal instability.

The *KRAS2* gene mediates signals from growth factor receptors and other signaling inputs. The mutations convert the normal K-ras protein (a protooncogene) to an oncogene, causing the protein to become overactive in transmitting the growth factor-initiated signals. The gene is mutated in more than 90% of conventional pancreatic ductal carcinomas.²⁶ The first genetic change in the ducts is probably not (or not always) a *KRAS2* mutation, for the prevalence of this mutation rises in the more advanced lesions (see Table 29.3-5).²⁷

The Smad pathway mediates signals initiated on the binding of the extracellular proteins TGF and activin to their receptors. These signals are transmitted to the nucleus by the SMAD family of related genes that includes *MADH4* (*SMAD4*, *DPC4*). SMAD protein complexes bind specific recognition sites on DNA and cause the transcription of certain genes. Mutations in the *DPC4* gene are found in 55% of pancreatic carcinomas, and these include homozygous deletions and intragenic mutations combined with LOH.²⁸

The *p16*/Rb1 pathway is a key control of the cell division cycle. The retinoblastoma protein (Rb1) is a transcriptional regulator and regulates the entry of cells into S phase. A complex of cyclin D and a cyclin-dependent kinase (Cdk4 and Cdk6) phosphorylates and thereby regulates Rb1. The *p16* protein is a Cdk inhibitor that binds Cdk4 and Cdk6. Virtually all pancreatic carcinomas suffer a loss of *p16* function, through homozygous deletions, mutation/LOH, or promoter methylation associated with a lack of gene expression.²⁹ In addition, inherited mutations of the *p16* gene cause familial melanoma/PC, the familial atypical multiple mole melanoma.³⁰

The *p53* protein binds to specific sites of DNA and activates the transcription of certain genes. The *p53* gene has point mutations that inhibit its ability to bind DNA in 50% to 75% of PCs.

Most human carcinomas have chromosomal instability, which produces changes in chromosomal copy numbers or aneuploidy. Most PCs have complex karyotypes, including deletions of whole chromosomes and subchromosomal regions. Chromosomal instability is the process that causes most of the tumor deletions (LOH). Some tumors, however, do not have significant gross or numeric chromosomal changes and have a different form of genetic instability; they have defects in DNA mismatch repair, producing high mutation rates at sites of simple repetitive sequences termed *microsatellites*.³¹ MIN occurs in a small percentage of PCs.^{23,32} The pattern of genetic damage in these tumors differs considerably from that in tumors with chromosomal instability.

LOW-FREQUENCY GENETIC CHANGES

The causative genes of Fanconi's anemia play a role in human tumorigenesis. The *BRCA2* gene represents Fanconi complementation group D1 and is thought to aid DNA strand repair. Because of this function, it is perhaps best to categorize *BRCA2* as a genome-maintenance gene rather than a standard tumor suppressor. Of "sporadic" PCs, 7% to 10% (more in instances of familial aggregation) harbor an inactivating intragenic inherited mutation of one copy of the *BRCA2* gene, accompanied by LOH.³³ The *FANCC* and *FANCG* genes have somatic or germline mutations in some PC patients, again with loss of the wild-type allele in the cancer.³⁴ The known hypersensitivity of Fanconi's cells to interstrand DNA-cross-linking agents, such as cisplatin and mitomycin C (MMC), has suggested that PCs with Fanconi's pathway genetic defects would be especially susceptible to treatment with such agents.

The mitochondrial genome may be mutated in a majority of PCs. These mutations most likely represent genetic drift and perhaps do not directly contribute to the process of tumorigenesis.³⁵ Such mutations, however, could potentially serve as a diagnostic target because of the large number of copies of the mitochondrial genome in human carcinoma cells.

The *MKK4* gene participates in a stress-related protein kinase pathway. It is stimulated by various influences, including chemotherapy, and its downstream effects, including apoptosis and cellular differentiation. The *MKK4* gene has homozygous deletions or mutation/LOH in approximately 4% of PC cases.³⁶

Germline mutations of the *STK11* (*LKB1*) gene, a serine-threonine kinase, are responsible for the PJS. PJS was anecdotally associated with PC decades ago. A follow-up study examined lifetime risk, finding PC to develop in nearly a third of PJS patients. Sporadic PCs, independent of PJS, also lose the *STK11* gene by homozygous deletion or by somatic mutation/LOH in approximately 4% of cases.³⁷

Gene amplification occurs occasionally in PC. Amplified regions include the *AKT2* gene within an amplicon on chromosome 19q and the *MYB* gene on 6q, involving approximately 10% to 20% of cases studied.³⁸ Approximately 6% of PCs over-express the oncogene, *CCNE1* (cyclin E). Two mechanisms have been demonstrated: cyclin E gene amplification and the genetic inactivation of the *FBXW7* (AGO) gene, which normally serves to degrade cyclin E during the normal phases of the cell division cycle.³⁹

The patterns of chromosomal deletion in PC are complex. In one study, an average of 40% of all chromosomal arms in each cancer had a deletion. For most lost regions, no particular tumor suppressor genes are known to be targeted by the deletions. Conversely, in some regions known to harbor tumor suppressor genes, the known mutated genes do not justify the high observed prevalence rates of LOH. Individual homozygous deletions are found at some additional genetic locations, again without a definitive target gene for these events.

Defects in DNA mismatch repair (MIN) are seen in some PCs.^{23,39} These cancers typically have a medullary histologic phenotype and mutations of the type II TGF- β (*TGFB2*) and activin (*ACVR2*) receptor genes. They can also have mutations of the proapoptotic *BAX* gene and of the growth factor pathway mediator *BRAF* gene (analogous, presumably, to mutations of the *KRAS2* gene). The MIN tumors do not have the propensity for large chromosomal alterations and gross aneuploidy.⁴⁰ In a study of four cases of PCs having MIN, all lacked expression of the Mlh1 protein.²³ Not all medullary phenotype cancers have MIN. Yet, medullary pancreatic carcinomas as a whole have a number of clinical and genetic differences compared to those with conventional histologic appearance; the tumors have pushing rather than infiltrative borders, the *KRAS2* gene often is wild-type, and the patient frequently has a family history of malignancy.^{23,39}

Inherited mutations of the cationic trypsinogen (*PRSS1*) gene permit the premature activation of the proenzyme within the pancreas, causing a familial recurrent form of acute pancreatitis. Some affected kindreds have a cumulative risk of PC that approaches 40% by the time the affected individuals reach 60 years of age.⁴¹ This cancer diathesis falls in a unique category of cancer susceptibility in that the predisposition emanates from genetic alterations of a gene tissue-maintenance gene, one that is neither an oncogene, tumor suppressor gene, nor a genome-maintenance gene.

GENE EXPRESSION PROFILING AND BEYOND

Studies using global gene expression methodologies have provided a unique opportunity to better understand this lethal tumor and to have a potential impact on patient care. These methods include serial analysis of gene expression, complementary DNA microarrays, oligonucleotide arrays, and proteomics.

Gene and protein expression profiling using each of these technologies has advanced our understanding of pancreatic ductal adenocarcinoma in three important ways. First, in excess of 200 genes have been identified that are highly expressed in pancreatic duct adenocarcinomas but not in normal pancreatic ductal epithelium. Each of these highly expressed genes offer new opportunities for development of diagnostic tests or therapeutic targets. Second, many genes relating to the clinicopathologic features of infiltrating ductal adenocarcinomas have been identified, providing new insights into the biology of this PC. Third, gene expression studies have revealed novel features related to the process of tissue invasion by PCs. In this regard, new possibilities for drug delivery focused on tumor-stromal interactions have been identified. Each of these advances is discussed in more detail below.

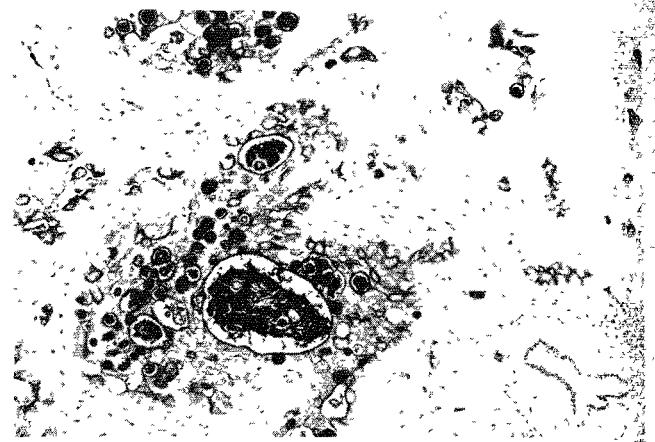


FIGURE 29.3-3. Immunohistochemical staining of mesothelin protein in infiltrating pancreatic ductal adenocarcinoma. Intense protein labeling is seen within the neoplastic epithelium in a membranous distribution. Luminal secretions also strongly label for mesothelin protein. In contrast, normal ductal epithelium is negative (inset). (See Color Fig. 29.3-3 in the CD-ROM.)

NOVEL MARKERS OF PANCREATIC DUCTAL ADENOCARCINOMA

Perhaps the most urgent need in the battle against PC is the identification of specific tumor markers for the interpretation of difficult biopsies and for early diagnosis (Fig. 29.3-3). Overexpressed genes now recognized as potentially important in PC are depicted in Table 29.3-6.⁴²⁻⁴⁷ These potential tumor markers represent a variety of protein functions, including cell adhesion, cell motility, cytoskeletal assembly, proteolysis, or matrix remodeling. Some have now been validated as specific markers of pancreatic carcinoma, whereas others are in the process of being confirmed.

NEW INSIGHTS INTO THE BIOLOGY OF PANCREATIC DUCTAL ADENOCARCINOMA

Gene expression profiling has also provided novel insight into the complex biology of PC.^{48,49} Recent evidence provided through global gene expression profiling has revealed that certain cellular processes play a more prominent role in PCs than were previously recognized. For example, genes whose protein products are involved in cell membrane junctions and cell/matrix interactions have consistently been identified as upregulated in PCs by several investigators. This observation could correspond to altered cellular attachments and cell surface architecture, resulting in aberrant cell-cell interactions that are a reproducible characteristic of cancer cells. Several ion-homeostasis-dependent proteins, especially those specific for the calcium ion (Ca^{2+}), such as S100A4, S100A10, or Trop-2, have been identified as overexpressed in PC. The consistent expression of these genes in PCs may indicate key homeostatic mechanisms necessary for cancer cell survival, and interference with their expression may promote cancer cell death. Finally, several genes whose protein products may contribute to chemoradioresistance in PCs have also been identified, such as ataxiatelangiectasia group D-associated protein (ATDC), topoisomerase II alpha, and transglutaminase II. ATDC protein has been shown to be induced by ionizing radiation and to

TABLE 29.3-6. Examples of Novel Markers of Pancreatic Ductal Adenocarcinoma Identified by Gene Expression Profiling

Name	Normal Cellular Function	Expression in Pancreatic Cancer	Potential Use
Claudin 4	Component of epithelial tight junctions	Overexpressed in neoplastic epithelium; membranous distribution	Radiomaging, immunotherapy
Fascin	Cytoskeletal protein, cellular motility	Overexpressed in neoplastic epithelium, cytoplasmic distribution	Diagnostic marker
HIP/PAP	?	Normal acinar cells; released during acute/chronic pancreatitis	Screening marker
Hsp47	Collagen-specific chaperone	Desmoplastic stromal cells	Diagnostic marker/radiomaging
Mesothelin	GP1-anchored protein, ?adhesion	Overexpressed in neoplastic epithelium, membranous distribution	Diagnostic marker immunotherapy screening
Muc4	Apomucin, epithelial protection	Overexpressed in neoplastic epithelium, membranous distribution	Diagnostic marker/immunotherapy
PSCA	GP1-anchor protein, ?adhesion	Overexpressed in neoplastic epithelium; membranous distribution	Diagnostic marker immunotherapy screening
S100A4	S100 calcium-binding protein	Overexpressed in neoplastic epithelium; cytoplasmic distribution	Diagnostic marker

HIP/PAP, hepatocarcinoma-intestine-pancreas/pancreatitis-associated protein I.

suppress the radiosensitivity of ataxia-telangiectasia fibroblast cell lines, whereas expressed genes such as topoisomerase II alpha or transglutaminase II may relate to the chemotherapeutic resistance often observed for PCs. Thus, global gene expression technologies can provide important insights into pancreatic carcinomas, many of which may affect how future therapies are designed and administered.

NEW INSIGHTS INTO THE INVASIVE PROCESS IN PANCREATIC DUCTAL ADENOCARCINOMA

Gene expression profiling of PC has also provided new insights into the process of tumor invasion. Specifically, gene expression studies of PC tissues have been used to identify expression patterns associated with the exuberant desmoplastic response.⁵⁰ These genes were found to be expressed in surgically resected PC tissues, but not in normal pancreas tissue or in cultured PC cell lines, thus reflecting the cellular components of the host stromal response seen in the presence of infiltrating carcinoma. Investigations into the cellular localization of these genes using *in situ* hybridization have identified a specific “architecture” for their expression in invasive pancreatic carcinomas. Gene expression within invasive PCs can be segregated into distinct and reproducible compartments: the neoplastic epithelium, angioendothelium, juxtatumoral stroma (those stromal cells immediately adjacent to the invasive neoplastic epithelium), or the panstromal compartment (all stromal tissue within the host response), indicating that a highly organized and structured process of tumor invasion exists in the pancreas. The finding of genes expressed by the neoplastic epithelium in invasive carcinomas, but not in cancer cell lines derived from invasive carcinomas, also highlights the importance of gene expression related to a neoplastic cell’s interactions with its environment.

deadly disease, there is great interest in improving the early detection of PC. The optimal approach for early detection of PC is still under study. Ideally, one would like to identify lesions that have a high chance of cure after surgical resection, such as a high-grade benign PanIN 3 lesion, a benign IPMN, or less than 1 cm pancreatic ductal adenocarcinoma using a noninvasive imaging test or a biomarker.⁵¹

Currently, imaging modalities for screening and early detection include computed tomography (CT) scan, magnetic resonance imaging (MRI)/magnetic resonance (MR) cholangiopancreatography, and endoscopic ultrasonography (EUS). With the development of multidetector techniques, CT angiography, and three-dimensional reconstruction, CT imaging continues to improve.⁵² For early detection, EUS may be the imaging modality of choice because it detects smaller pancreatic lesions than those detected with thin-section dual-phase spiral CT.⁵³ The accuracy of diagnosis of PC in patients with pancreatic masses who are suspected of having cancer is close to 100% for EUS and approaches 92% for dual-phase CT. Furthermore, EUS can readily discriminate between solid and cystic lesions (unlike CT) and, when combined with fine-needle aspiration (FNA), provides a cytologic diagnosis of minute lesions as small as 2 to 5 mm that are not visualized by CT, ultrasound, or MRI. FNA performed during an EUS procedure can help to establish a diagnosis of malignancy, although the diagnostic yield from cytology in this setting is variable. Endoscopic retrograde cholangiopancreatography (ERCP) is less likely to detect small tumors, and it is a relatively more invasive test for screening due to the risk of developing pancreatitis (5% to 10%).

Serum CA 19-9, the only widely used tumor marker, is valuable for following the therapeutic response of patients with PC who have an elevated serum CA 19-9 level.⁵⁴ CA 19-9 is of limited value as a screening marker, however, as approximately 10% to 15% of individuals do not secrete CA 19-9 because of their Lewis antigen status. In addition, CA 19-9 levels may be within the normal range while the cancer is still at a small and asymptomatic stage, and CA 19-9 can be elevated in benign biliary or pancreatic conditions. Similar problems with diagnostic accuracy have been observed for other investigational markers. Attempts have been made to combine markers to improve the diagnostic performance of CA 19-9 by combining it with other markers.

SCREENING AND EARLY DETECTION

APPROACHES TO CLINICAL SCREENING

Most pancreatic ductal adenocarcinomas (approximately 85%) are diagnosed at a late, incurable stage. Because complete resection of small cancers may improve the outcome of this

One current approach to screen high-risk individuals uses EUS of the pancreas, multidetector CT with three-dimensional reconstruction, and serum CA 19-9 measurements as the initial screening tests. ERCP, EUS-FNA, and other investigations can be performed if abnormalities are found on EUS or CT, or both. In an ongoing clinical trial at Johns Hopkins using this approach in patients with PJS and at-risk relatives from familial PC kindreds, six pancreatic masses were found by EUS (four also detected by CT) in 37 individuals screened. One invasive PC, one IPMN, two cystic neoplasms, and two nonneoplastic masses (chronic pancreatitis) were detected, corresponding to a diagnostic yield of 10.5% for pancreatic neoplasms.⁵⁵ The one patient with an invasive adenocarcinoma was resected and is still alive and disease free 5 years after surgery. Overall, these data suggest that it may be worthwhile to screen for pancreatic neoplasia in high-risk populations. However, there is not yet enough information to determine the clinical use and cost effectiveness of such a screening approach, the risks involved, and the appropriate screening intervals and optimal type of surgery (partial vs. total pancreatectomy). Brentnall et al.⁵⁶ at the University of Washington in Seattle reported their experience with screening three high-risk families with unique phenotypic features (including DM and chronic pancreatitis). Of 14 patients from three families surveyed primarily by EUS, 7 were found to have EUS and ERCP abnormalities suggestive of unique pancreatic duct lesions (saccular or grape-like deformities) and chronic pancreatitis. Pathologic analysis of total pancreatectomy resection specimens revealed diffuse, often high-grade pancreatic duct lesions (PanIN). However, total pancreatectomy is associated with a significant morbidity and obligate insulin-dependent diabetes and at present probably should only be considered for patients with a very high lifetime risk of PC, such as those with hereditary pancreatitis and a confirmed PRSS1 mutation.

DEVELOPING BIOMARKERS FOR EARLY DETECTION

Better markers of PC are needed for early diagnosis of symptomatic individuals whose initial workup fails to yield a diagnosis and as a screening test to permit the early detection of PC in asymptomatic individuals at high risk of developing the disease. Although a serum test would have wide application, the inability to find an accurate diagnostic serum test for PC and the need to identify small pancreatic lesions have led to interest in using pancreatic juice as a specimen for searching for novel markers of PC. The potential high concentration of DNA and proteins makes pancreatic juice a potentially optimal specimen to use when screening high-risk patients for PC, analogous to sputum for lung cancer or nipple aspirates for breast cancer. Pancreatic juice can be collected during routine upper GI endoscopy after secretin stimulation without the need for ERCP. Often when PC is suspected, imaging tests fail to identify a pancreatic mass. Molecular markers could facilitate early diagnosis by aiding in the interpretation of inconclusive cytology specimens obtained by sampling the pancreatic duct or from fine-needle aspirates obtained during EUS.

Biomarkers can be divided into three biochemical targets. DNA, RNA, and proteins. DNA-based techniques aim to detect cancer-specific DNA alterations. The diagnostic potential of DNA- and RNA-based markers has improved with the use of quantitative polymerase chain reaction. Markers that have prom-

ise are the detection of DNA methylation changes and mitochondrial mutations that arise during PC development. DNA methylation abnormalities may be particularly suitable for use in early detection strategies. Numerous aberrant methylation events occur during carcinogenesis (e.g., methylation of *hMLH1* and *p16*), and they can be detected in secondary sources using the very sensitive methylation-specific polymerase chain reaction technique. Pancreatic carcinomas harbor aberrant methylation of a number of cancer-related genes (*SPARC*, *ppENK*, *p16*, *TSLC1*, and others).⁵⁷ Efforts to use DNA methylation as a diagnostic tool in the pancreas are complicated by tissue-specific differences in normal methylation patterns. Many genes that are aberrantly methylated in PCs, whereas not normally methylated in the pancreas, are often methylated in normal duodenum. Therefore, quantification of DNA methylation changes in pancreatic juice obtained directly from the pancreatic duct may be needed if these markers are to be diagnostically useful in the differential diagnosis of pancreatic lesions in the clinical setting. Mitochondrial mutations are commonly found in cancers of multiple types and may be amenable to assay in the clinical setting. Mutations occur throughout the mitochondrial genome in pancreatic and other cancers, and thus sophisticated assays are needed to reliably identify such mutations.

As with detection of PC DNA, detection of PC messenger RNA is more appropriate for the analysis of pancreatic juice or fine-needle aspirates. The main RNA-based marker investigated to date has been hTERT. Approximately 90% of cancers express the telomerase hTERT subunit, and approximately 90% of patients with PC have detectable telomerase activity in their pancreatic juice.⁵⁸ The detection of telomerase enzymatic activity or the

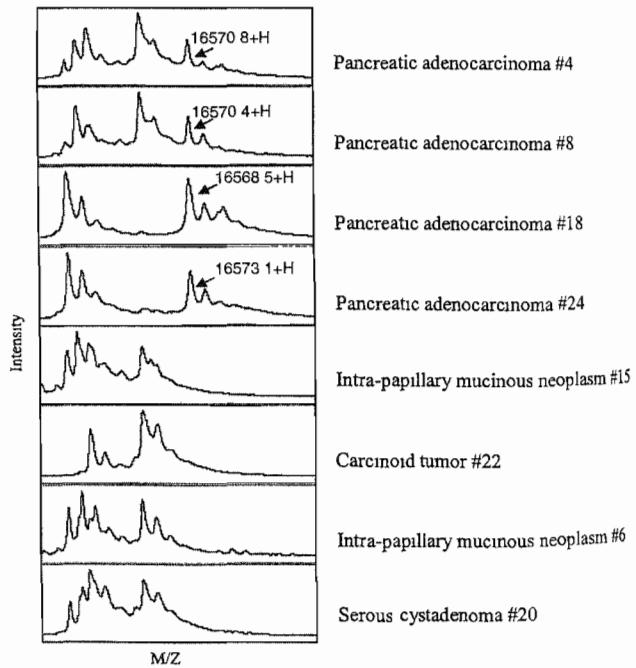


FIGURE 29.3-4. Representative spectrum examples of SELDI (surface-enhanced laser desorption ionization mass spectrometry) analysis of pancreatic juice samples bound to IMAC-3 copper protein chip array. A peak at approximately 16,570 d (arrow) was present in the four pancreatic juice samples from patients with pancreatic adenocarcinoma (PC4, PC8, PC18, PC24) but absent in four patients with other pancreatic diseases (bottom 4 spectra). (From ref. 4, with permission.)

hTERT subunit may be helpful in differentiating PC from benign pancreatic disease. Because telomerase is expressed in inflammatory cells, however, it may not be sufficiently specific for use as a cancer screening marker. Many genes have been identified as overexpressed at the RNA level in PCs compared to normal pancreas.⁴⁸ Gene-chip profiling or other RNA-based methodologies may be promising approaches for the early detection of PC.

Protein-based markers ultimately may have the most application for PC diagnostics. The ultimate goal of such a marker would be a "prostate-specific antigen test" for PC. One approach toward the identification of protein markers involves the large-scale analysis of proteins in biologic fluids or cells, termed *proteomics*. One such proteomics technique is SELDI (surface-enhanced laser desorption ionization mass spectrometry), which analyzes protein profiles of samples applied to protein chips.⁵⁹ SELDI profiling of pancreatic juice led to the identification of markedly elevated hepatocarcinoma-intestine-pancreas/pancreatitis-associated protein I (HIP/PAP) levels in pancreas juice samples from patients with PC compared to patients with other pancreatic diseases (Fig. 29.3-4). Serum profiling using SELDI and other mass spectrometry approaches is being explored as a diagnostic tool in a variety of cancers.

CLINICOPATHOLOGIC STAGING

Staging of pancreatic exocrine cancers depends on the size and extent of the primary tumor, as well as the status of regional

lymph node involvement and metastasis to distant sites.⁶⁰ The newest version of the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*, published in 2002, updated and revised the PC staging system (Table 29.3-7). Because only a minority of patients with PC undergo surgical resection, this system applies to clinical and to pathologic staging.

ANATOMY

The pancreas is a coarsely lobulated yellowish gland that lies somewhat obliquely in the retroperitoneum, extending from the duodenal C loop and running cephalad to the splenic hilum (Fig. 29.3-5). The gland is divided into somewhat arbitrary sections: the head (with a small, posterior uncinate process), neck, body, and tail. Tumors of the pancreatic head arise to the right of the superior mesenteric vein–portal vein confluence and include tumors of uncinate origin. Tumors of the pancreatic body arise between the superior mesenteric vein–portal vein confluence and the left lateral aspect of the aorta. Tumors of the pancreatic tail are located lateral to the aorta, extending out to the splenic hilum.

STAGING

Unfortunately, only a minority of patients with PC are able to undergo surgical resection of the pancreas and adjacent structures, and therefore a single TNM (tumor, node, metastasis) classification system is best applied to the clinical and the pathologic staging. The newest edition of the AJCC *Cancer Staging Manual* has

TABLE 29.3-7. American Joint Committee on Cancer Cancer Staging: Exocrine Pancreas

PRIMARY TUMOR (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma <i>in situ</i> (also PanIN 3)		
T1	Tumor limited to pancreas, 2 cm or less in greatest dimension		
T2	Tumor limited to pancreas, more than 2 cm in greatest dimension		
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery		
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)		
REGIONAL LYMPH NODES (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
DISTANT METASTASIS (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
STAGE GROUPING			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

PanIN, pancreatic intraepithelial neoplasia.
(From ref. 60, with permission.)

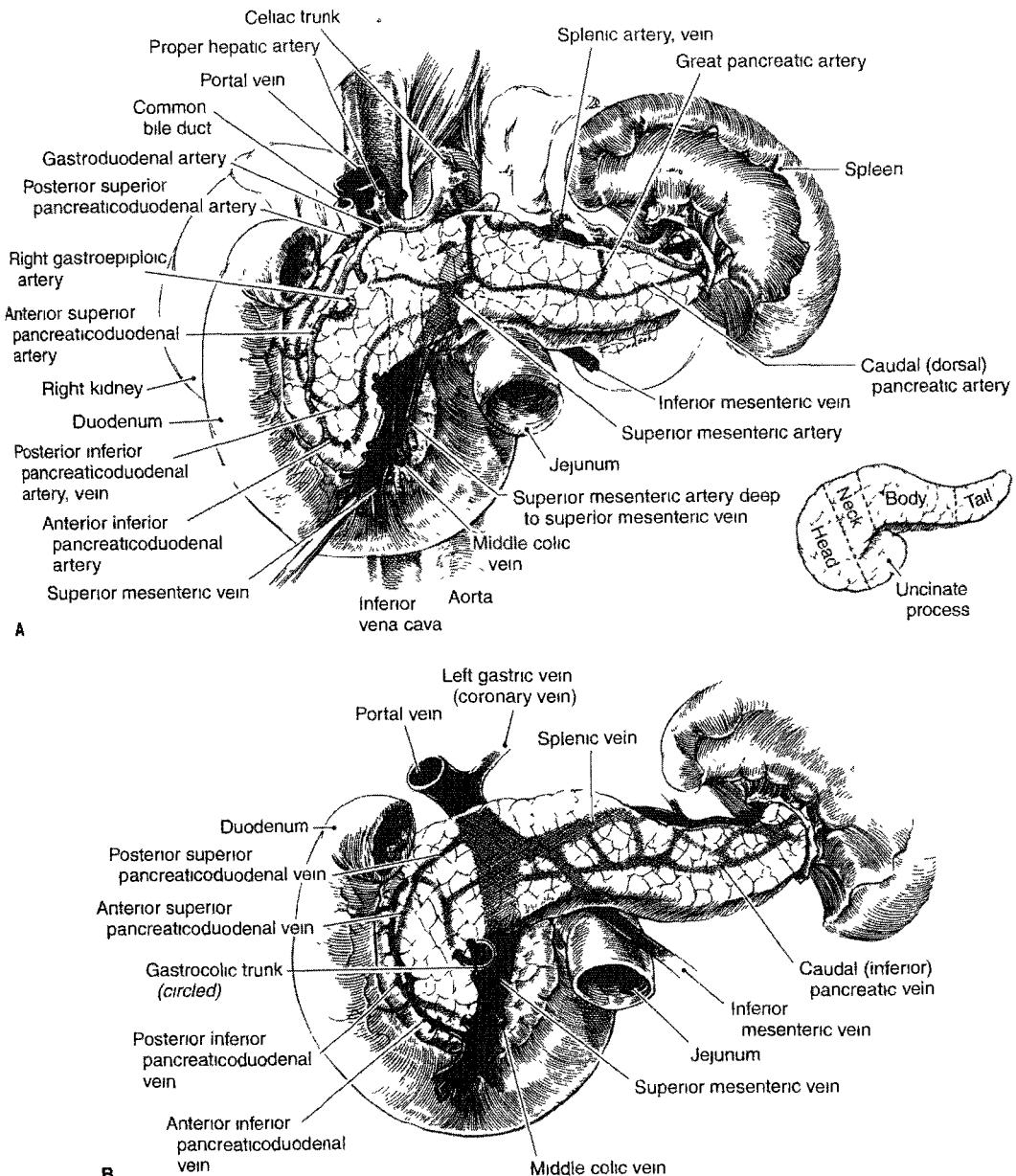


FIGURE 29.3-5. **A:** Gross anatomy and vascular anatomy of the pancreas. The pancreas is divided into five major regions: the head, neck, uncinate process, body, and tail (inset). The arterial blood supply to the pancreas consists of the gastroduodenal artery and a branch of the celiac trunk, which divides into the posterior and anterior superior pancreaticoduodenal arteries. These two vessels form an arcade and communicate with the anterior and posterior inferior pancreaticoduodenal arteries, which are branches of the proximal superior mesenteric artery. The body and tail of the pancreas are supplied by branches from the splenic artery. **B:** The venous drainage of the pancreas parallels the arterial supply, with an anterior and posterior venous arcade around the head of the pancreas, draining into the superior mesenteric vein below and the portal vein above. The body and tail of the pancreas drain to the inferior pancreatic vein and to the branches of the splenic vein. (From Bastidas JA, Niederhuber JE. Pancreas. In: Abeloff MD, et al, eds. *Clinical oncology*. New York: Churchill Livingstone, 1995:1374, with permission.)

made two changes, altering the key classification to a more clinically relevant system (see Table 29.3-7). First, because pancreatic tumors are judged unresectable when they encase or encircle large arterial structures such as branches of the celiac axis or superior mesenteric artery, T1, T2, and T3 lesions all fulfill criteria for local resectability, whereas T4 lesions that involve the branches of the celiac axis or the superior mesenteric artery are considered

unresectable. The second major change involves stage grouping III. In the current edition, stage III is used to classify patients with unresectable, locally advanced PC, with major visceral arterial involvement. Stage III no longer is used to denote the presence of lymph node metastasis.

Although the extent of resection is not part of the TNM staging system, the extent of resection is quite important for pancre-

atic adenocarcinoma. Patients with complete resection, including grossly and microscopically negative margins of resection, are considered to have R0 disease. Patients with grossly negative but positive microscopic margins of resection are considered to have R1 disease. Patients with grossly and microscopically positive margins of resection are considered to have R2 disease.

CLINICAL PRESENTATION AND EVALUATION

CLINICAL PRESENTATION

The majority of patients with PC present clinically with the development of jaundice. This occurs as a result of a right-sided neoplasm obstructing the intrapancreatic portion of the common bile duct. Seen with the jaundice are accompanying signs and symptoms, such as abdominal pain, dark urine, light stools, weight loss, pruritus, weakness, and anorexia.³

In a minority of patients, PC presents without jaundice. In patients with left-sided tumors, a gnawing epigastric or back pain may be present. New-onset DM may be the first clinical feature in approximately 10% of all patients. Occasionally, acute pancreatitis may be the first manifestation of a PC, related to partial obstruction of the pancreatic duct, which causes pancreatic inflammation. It is important to consider the diagnosis of a pancreatic tumor in elderly patients presenting with pancreatitis, particularly when there is no obvious cause for the pancreatitis such as gallstones or alcohol abuse.³

Additional symptoms found in a small percentage of patients may include nausea or vomiting, or both, related to mechanical gastroduodenal obstruction. Mechanical obstruction of the proximal duodenum can be related to right-sided neoplasms, or an obstruction at the ligament of Treitz can be seen with cancers of the midbody of the pancreas.

The most common physical finding at initial presentation is jaundice. Often, patients with deep jaundice may exhibit cutaneous signs of scratching, related to pruritus. Hepatomegaly, temporal wasting, and a palpable gallbladder may also be present. In patients with disseminated advanced PC, findings may include palpable hepatic metastases, left supraclavicular adenopathy (Virchow's node), periumbilical lymphadenopathy (Sister Mary Joseph's nodes), or the unusual finding of drop metastases in the pelvis encircling the perirectal region (Blumer's shelf).³

Laboratory studies in patients with cancer of the right side of the pancreas often reveal elevated serum bilirubin, alkaline phosphatase, and γ -glutamyl transpeptidase, with mild elevations of the hepatic aminotransferases. A normochromic anemia and mild hypoalbuminemia may reflect the chronic nature of the neoplastic process and its nutritional sequelae. Hepatitis serologies are often assessed, and they are typically negative. Although uncommon, patients with ductal adenocarcinoma of the pancreas may have hyperamylasemia or hyperlipasemia, findings more commonly seen in patients with IPMN. A prolongation of the prothrombin time may be seen in deeply jaundiced patients due to malabsorption of fat-soluble vitamins.³

DIAGNOSTIC IMAGING

At the current time, diagnostic and staging imaging for PC best uses multidetector CT acquisition with three-dimensional

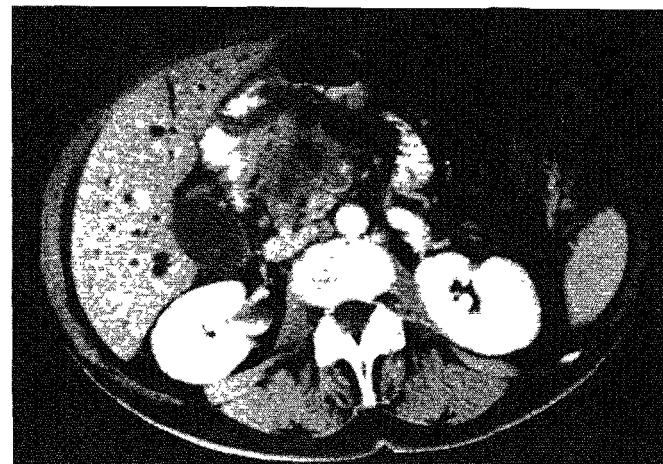


FIGURE 29.3-6. Late arterial phase of a spiral computed tomographic scan, using contrast as the oral agent. The kidneys and aorta are contrast enhanced, as is the inferior vena cava. Dilated bile ducts are seen in the liver, and the gallbladder is distended. A large (5 cm) hypodense mass is seen in the head of the pancreas, and the superior mesenteric vein (SMV) is not seen. Additional caudal images confirmed occlusion of the SMV, with numerous mesenteric venous collaterals. This tumor was deemed unresectable based on the advanced local disease. (From ref 4, with permission.)

reconstruction.⁶¹ This technology was introduced in the late 1990s and has supplanted spiral or helical CT as the preferred noninvasive imaging modality for the diagnosis and staging of PC. Multidetector CT incorporates dual-phase imaging in the arterial and the venous phases of enhancement. Water is used as the oral contrast agent of choice. Nonionic contrast medium is administered via a peripheral intravenous catheter at a rate of 3 mL/sec, and slices through the pancreas are obtained every 1.25 mm, with all images being acquired during one 20-second breath hold. For visualizing the study on film, 3- to 5-mm slices are printed. However, the 1.25-mm acquired slices are reviewed at a three-dimensional work station using a standard software platform, allowing for three-dimensional viewing of the data sets to improve detection, staging, and surgical planning. Using this technology, adenocarcinoma of the pancreas typically appears as a low-density (hypodense) mass within the pancreas, generally best seen on the venous phase of enhancement (Figs. 29.3-6 to 29.3-8). Right-sided pancreatic tumors typically obstruct the common bile duct or the pancreatic duct, or both, resulting in intrahepatic and extrahepatic bile ductal dilatation and pancreatic ductal dilatation in the body and tail of the gland. Left-sided pancreatic tumors may obstruct the pancreatic duct toward the splenic side of the gland and may obstruct the splenic vein, creating splenic vein thrombosis and the sequelae of perigastric varices. Tumor involvement of the major peripancreatic vascular structures can be seen as circumferential hypodense tissues surrounding the branches of the celiac axis, the superior mesenteric artery or vein, or the splenic artery or vein. CT scanning also has the ability to detect hepatic metastases or peripancreatic lymph node enlargement, although a pathologic diagnosis cannot be obtained from imaging alone.

Advances in MRI, including high-resolution imaging, fast imaging, volume acquisitions, functional imaging, and MR cholangiopancreatography, have led to an improved ability of MRI to



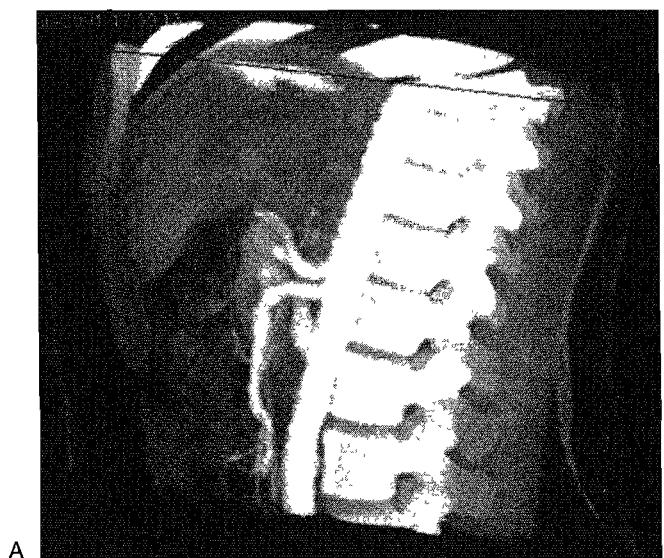
FIGURE 29.3-7. Arterial phase of a multidetector computed tomography scan, using water as the oral agent. The kidneys and aorta are contrast enhanced. A 3-cm hypodense tumor mass is seen in the pancreatic uncinate process, anterior to the aorta and inferior vena cava. The tumor abuts the right lateral aspect of the superior mesenteric vein. The superior mesenteric artery is contrast enhanced, patent, and not approached by tumor. This tumor was resected via pancreaticoduodenectomy, with negative resection margins. (From ref. 4, with permission.)

diagnose and stage PC.^{62,63} Arterial and venous patency can be evaluated using appropriate phase studies. Because the majority of PCs have significant desmoplasia with sparse vascularity, most tumors appear with low signal intensity on T1-weighted fat-suppressed images and diminished enhancement on dynamic contrast-enhanced images (Fig. 29.3-9). Although some controversy exists, current, modern multidetector CT acquisition and MRI appear comparable for tumor detection and staging. No advantage appears to be gained by obtaining CT as well as MR studies in patients with suspected, apparently resectable, PC.

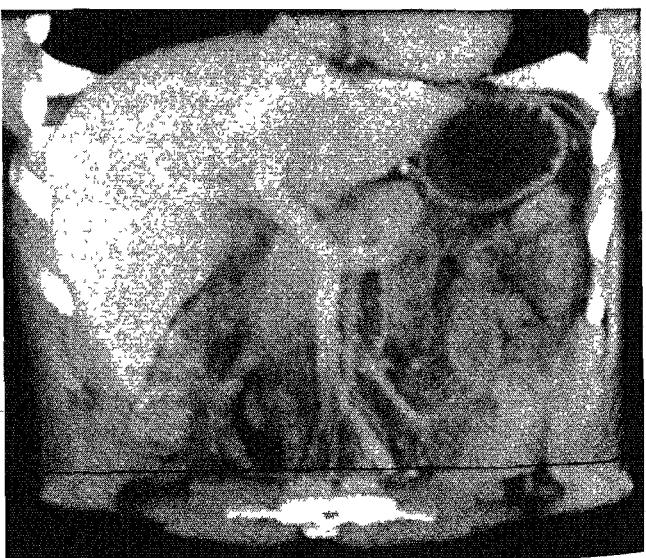
ERCP has lost favor as a routine imaging test for patients being evaluated for PC. Although ERCP does allow direct imaging of the pancreatic duct, and its sensitivity for the diagnosis of PC remains high, the use of endoscopic pancreatography for diagnosis is rarely necessary. Of course, the finding of a long irregular stricture in an otherwise normal pancreatic duct, without a past history of pancreatitis, is highly suspicious for PC (Fig. 29.3-10). However, with the current technologic advances in CT scanning and MRI, the routine practice of diagnostic ERCP is unsupported.

EUS has gained popularity and is now increasingly available for pancreatic imaging.⁶⁴ Numerous studies have evaluated EUS in distinguishing benign from malignant pancreatic masses (Fig. 29.3-11). In general, EUS performed by a well-trained observer has generally been shown to be more sensitive and specific than either CT or MR in the assessment of pancreatic masses. However, EUS is time intensive and invasive. EUS can be combined with FNA to acquire cellular material for cytologic analysis. EUS-FNA appears to be most efficacious in acquiring a tissue diagnosis of PC when such a diagnosis is required before surgical treatment. Of note, unless protocol-based neoadjuvant chemotherapy or chemoradiation therapy is planned, in most patients with a resectable tumor seen by imaging, such a tissue diagnosis is not necessary. Thus, although EUS-FNA is able to yield a tissue diagnosis of PC in many patients, it must be stressed that patients with resectable lesions suspicious for PC do not require such a tissue diagnosis before surgical resection.

Although CT or MRI remains the mainstay of imaging of patients with suspected PC, the newer technique of positron emission tomography (PET) provides additional imaging opportunities. PET uses the increased metabolism of glucose by PC cells as the basis of imaging. PET scanning for PC uses fluorine 18 (a positron-emitting tracer) as a glucose-like substrate *in vivo*.⁶⁵ Fluorine 18 is labeled to fluorodeoxyglucose (FDG), which is rapidly taken up by tumor cells and imaged. FDG-PET has been reported to be highly sensitive and specific



A



B

FIGURE 29.3-8. Multidetector computed tomographic images from a patient with a small cancer in the head of the pancreas. **A:** Sagittal three-dimensional (3D) reconstruction, showing normal aorta, celiac axis, and superior mesenteric artery. **B:** Coronal 3D reconstruction showing normal liver, gastric fundus, and portal vein, as well as intact superior mesenteric artery and vein. (From ref. 4, with permission.)

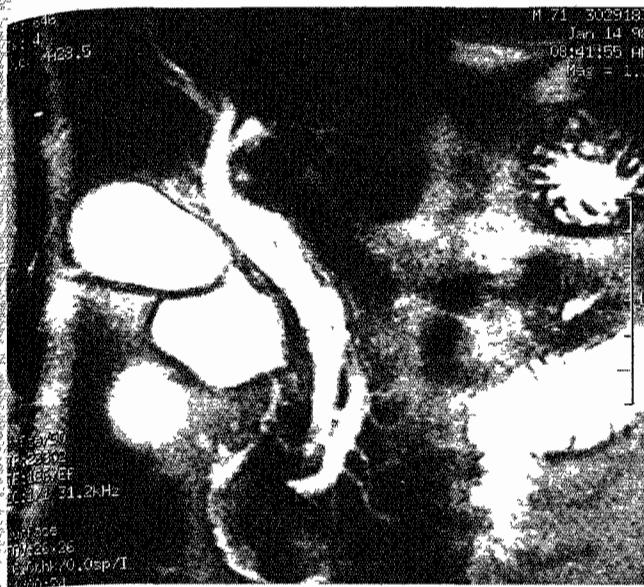


FIGURE 23.3-9. Single-shot, spin-echo magnetic resonance cholangiopancreatogram in a patient with obstructive jaundice. The common bile duct and the pancreatic duct are both dilated, and a hypointense area of tumor is apparent in the periampullary region. (From Yeo CJ, Cameron JL. Pancreatic cancer. *Curr Probl Surg* 1999;36:57, with permission.)

for PC in recent small series. Importantly, FDG localizes not only at tumor sites but at sites of inflammation and infection. Future information about FDG-PET will clarify its role in predicting prognosis and tumor dissemination and in distinguishing between benign and malignant tumors.



FIGURE 29.3-10. Endoscopic retrograde cholangiopancreatography in a patient with obstructive jaundice, revealing a classic "double-duct" sign. No evidence of tumor is seen at the genua (knee) of the common bile duct and pancreatic duct. (From Yeo CJ, Cameron JL. Pancreatic cancer. *Curr Probl Surg* 1999;36:57, with permission.)

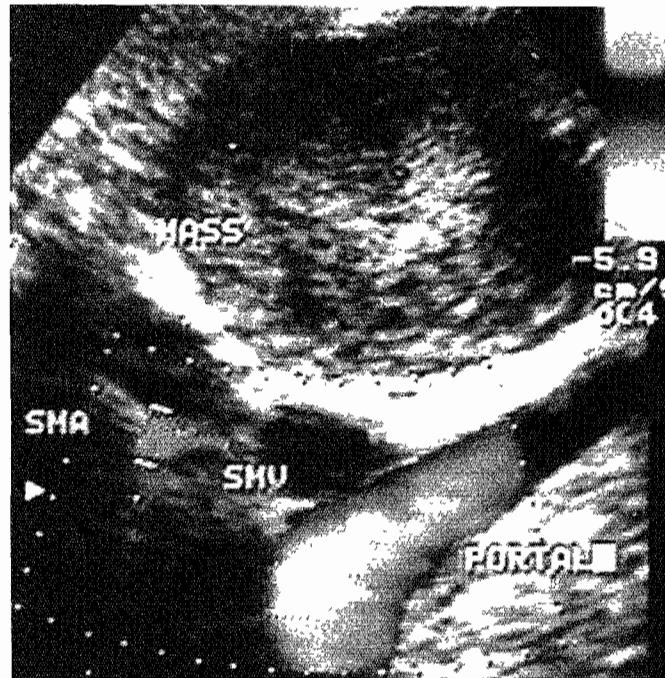


FIGURE 29.3-11. Endoscopic ultrasonography image using linear array echoendoscope, revealing a mass in the head of the pancreas with no vascular invasion of the superior mesenteric artery (SMA), superior mesenteric vein (SMV), or portal vein (portal). (From Yeo CJ, Cameron JL. Pancreatic cancer. *Curr Probl Surg* 1999;36:57, with permission.)

HISTOPATHOLOGIC DIAGNOSIS

It has been the authors' practice at the Johns Hopkins Medical Institutions not to perform routine pancreatic biopsy either preoperatively or intraoperatively in patients who present with obstructive jaundice from a mass in the head of the pancreas. The authors believe that such a biopsy is not indicated in the setting of a good-risk patient who is an operative candidate harboring a clinically resectable pancreatic mass. This is because a positive biopsy result would lead to the recommendation for exploration and resection, and a negative biopsy would also lead to the recommendation for exploration and resection, because we could not be certain there was not an underlying neoplastic lesion requiring resection. As noted in Neoadjuvant Strategies, there is a role for pancreatic biopsy (or biopsy of distant metastases in liver or subcutaneous lymph nodes) in poor-risk patients in whom a major pancreatic resection is not possible or indicated, as they may be candidates for palliative chemoradiation therapy or chemotherapy alone. Additionally, some form of tissue diagnosis to document adenocarcinoma is mandatory in patients who are to undergo preoperative neoadjuvant protocols. Furthermore, biopsy may be considered in patients whose clinical presentation and imaging studies are not suggestive of pancreatic carcinoma but rather of more uncommon entities such as pancreatic lymphoma. In this situation, the diagnosis of lymphoma would preclude surgical exploration and allow treatment via multiple-drug chemotherapy.

In situations in which a pancreatic biopsy is necessary, options include either a percutaneous or an endoscopic approach. Although percutaneous biopsy is generally safe, serious complications, such as hemorrhage, pancreatitis, fistula,

abscess, and death, have been reported. Additionally, there have been reports of tumor seeding along the subcutaneous tract of the needle and concerns regarding tumor dissemination by the act of capsular disruption of the neoplasm. In general, it is the authors' practice, when a pancreatic biopsy is needed, to proceed with the apparently safer technique of EUS combined with FNA.³

LAPAROSCOPY

The role of diagnostic/staging laparoscopy in patients with PC remains controversial. The rationale for the use of laparoscopy comes from data indicating that between 20% and 40% of patients staged with modalities such as CT, MR, or EUS will be determined to have unanticipated peritoneal or liver metastases at laparotomy. Of note, part of the rationale for using laparoscopy involves a presumed but unproven equivalence of nonoperative palliation with operative palliation in patients with PC. Proponents of laparoscopy believe it can identify a substantial number of patients with advanced disease who will not benefit from laparotomy and recommend it be applied to all patients.

Routine laparoscopy only makes sense if the percentage of patients discovered to have disseminated or unresectable disease remains high (20% to 40%) in the era of modern multidetector CT or MRI. In addition, it is important that patients who undergo laparoscopy to be spared laparotomy can be optimally palliated nonoperatively. Diagnostic/staging laparoscopy can unquestionably be performed with minimal morbidity and mortality on an outpatient basis. Any suspicious lesions are biopsied under direct vision with frozen-section analysis. Of note, there are varying degrees of expertise in the application of laparoscopy, with some highly experienced groups performing a more extensive laparoscopic evaluation.^{3,66,67}

At the current time the authors' practice uses staging laparoscopy on a selected basis in patients with suspected adenocarcinoma of the body and tail of the pancreas. In such cases, up to 50% of patients can be expected to have peritoneal metastases not seen by modern imaging studies. In contrast, patients presenting with obstructive jaundice secondary to tumors in the head of the pancreas typically have less than a 20% incidence of unexpected intraperitoneal metastases after modern staging studies. Patients with left-sided tumors do not typically have either biliary or gastric outlet obstruction, and therefore they do not require routine palliation of biliary or gastric obstruction. Thus, in the group of patients with left-sided tumors, laparoscopy can spare the patient an unnecessary laparotomy, because there is little role for operative palliation. However, in patients with right-sided tumors who present with obstructive jaundice, vague symptoms of gastric outlet obstruction, and tumor-related abdominal and back pain, the opportunity to proceed, even if unresectable, to biliary-enteric bypass, gastrojejunostomy, and alcohol celiac nerve block for optimal operative palliation makes it unnecessary to proceed to preoperative laparoscopy.³

A report by Barreiro et al.⁶⁸ underscores this practice of selective laparoscopy based on primary tumor site. In this retrospective review of 188 patients with pancreatic or periampullary cancer, all patients underwent high-quality CT and laparotomy over a 3-year period. The overall resectability rate for all right-sided cancers was 67%, compared to only 18% for left-sided tumors. After patients undergoing operative pallia-

tion were excluded, a nontherapeutic laparotomy could have been avoided by the use of diagnostic laparoscopy in only 2% of patients with right-sided tumors. In contrast, for patients with left-sided tumors, 53% of patients would have benefited from laparoscopy, and 35% of all patients with left-sided tumors could have avoided an unnecessary laparotomy.

TREATMENT OF POTENTIALLY RESECTABLE DISEASE

RESECTIONAL APPROACHES

Resectional approaches to pancreatic adenocarcinoma are divided into two types of procedures. First, procedures that are performed to resect right-sided tumors typically involve some form of pancreaticoduodenectomy. Second, procedures to resect left-sided tumors involve distal or caudal pancreatectomy.

Pancreaticoduodenectomy for Tumors of the Head, Neck, or Uncinate Process

The first successful resection of the duodenum and portion of the pancreas for an ampullary tumor was reported in 1912 by Kausch, a German surgeon from Berlin. More than 20 years later, Allen O. Whipple and his associates in New York City reported three cases of pancreaticoduodenal resection, again for ampullary cancer. Although the early reports describe pancreaticoduodenal resections that spared the pylorus and retained the entire stomach, in the 1950s and 1960s, pancreaticoduodenectomy was most commonly performed in combination with a distal gastrectomy (Fig. 29.3-12A). In the 1970s, the concept of pylorus preservation during pancreaticoduodenectomy was repopularized (Fig. 29.3-12B). Pylorus preservation is favored because it preserves the entire gastric reservoir, maintains the pyloric sphincter mechanism, somewhat shortens the operative time, appears to be associated with no considerable adverse sequelae, and is not associated with a long-term decrement in quality of life. Although some have cautioned that pylorus preservation may compromise cancer therapy, this has not been supported by a significant number of data.^{3,69,70} In 80% to 90% of the authors' patients, the pylorus can be successfully preserved. The two most common causes for sacrificing the pylorus and performing a distal gastrectomy include (1) intraoperative findings of tumor involvement of the first portion of the duodenum, pylorus, or distal stomach or (2) ischemia of the duodenal cuff after resection, related to devascularization.

OPERATIVE TECHNIQUE. In those patients who are being explored for potential pancreaticoduodenectomy, the initial portion of the operative procedure is designed to assess for resectability.³ Tumor involvement is searched for within the liver, on the parietal and visceral peritoneal surfaces, at the level of the celiac axis lymph nodes, and throughout the abdomen. By elevating the duodenum and head of the pancreas off of the retroperitoneum (Kocher maneuver), retroperitoneal involvement can be assessed and the superior mesenteric vein and its branches and the palpable superior mesenteric artery pulse can be identified. The porta hepatis is also carefully assessed by mobilizing the gallbladder out of the gallbladder fossa and following the cystic duct down to its junction with the

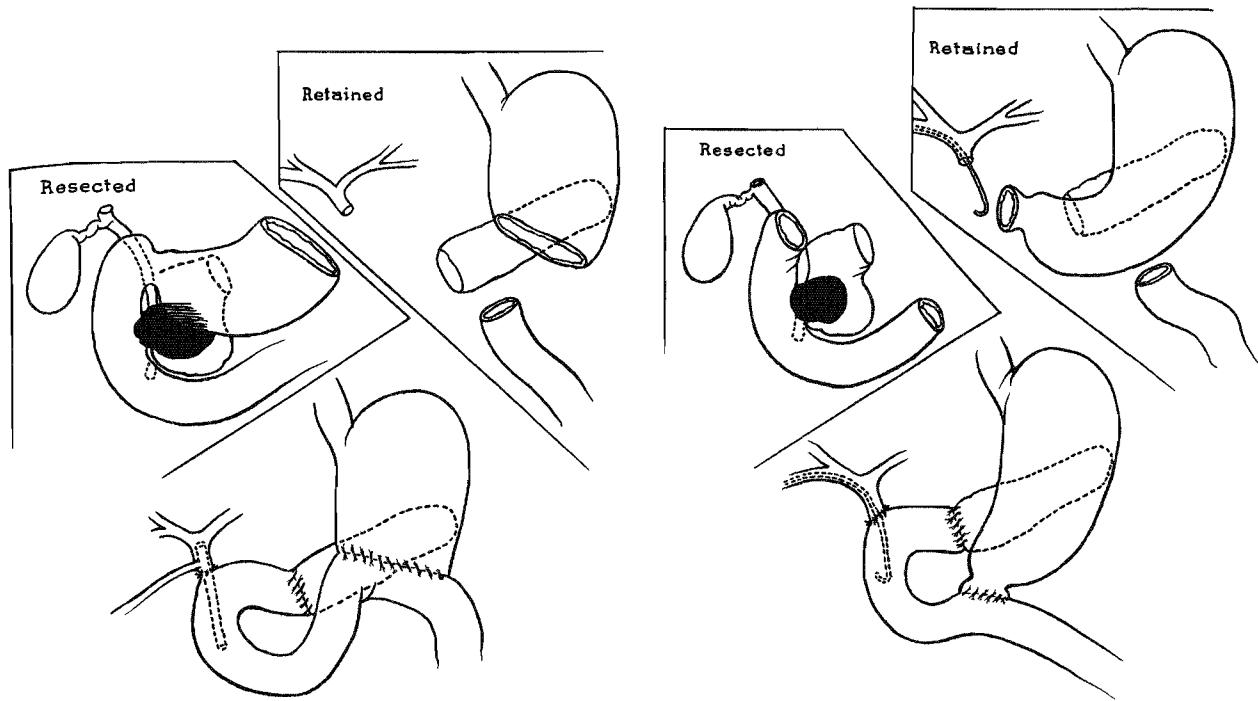


FIGURE 29.3-12. **A:** Classic pancreaticoduodenectomy, to include distal gastrectomy. *Top left:* The structures resected include the distal stomach; entire duodenum and proximal jejunum; head, neck, and uncinate process of the pancreas with tumor (black); gallbladder; and distal extrahepatic biliary tree. *Top right:* The structures retained include the proximal stomach, body and tail of the pancreas, proximal biliary tree, and jejunum distal to the ligament of Treitz. *Bottom:* Reconstruction is shown as a proximal end-to-end pancreaticojejunostomy, hepaticojejunostomy decompressed via a T tube, and a distal gastrojejunostomy. **B:** Pylorus-preserving pancreaticoduodenectomy. *Top left:* The structures resected include the duodenum (except for the initial 1 to 2 cm beyond the pylorus and proximal jejunum); head, neck, and uncinate process of the pancreas, with tumor (black); gallbladder; and distal extrahepatic biliary tree. *Top right:* The structures retained include the entire stomach, pylorus and proximal 1 to 2 cm of duodenum, body and tail of the pancreas, proximal biliary tree, and jejunum distal to the ligament of Treitz. *Bottom:* The reconstruction is shown as a proximal end-to-end pancreaticojejunostomy, hepaticojejunostomy decompressed via a percutaneous transhepatic catheter, and a distal duodenojejunostomy. (From Yeo CJ, Cameron JL. The pancreas. In: Hardy JD, ed. *Hardy's textbook of surgery*, 2nd ed. Philadelphia: JB Lippincott Co, 1988:717, with permission.)

common hepatic duct. In those cases that prove resectable, the intraoperative assessment will determine that the tumor is localized only to the area of the head, neck, or uncinate process of the pancreas, with no tumor involvement outside of the resection zone.

Several maneuvers can speed the performance of a pancreaticoduodenectomy and improve the safety of the operation. Early division of the extrahepatic biliary tree allows caudal retraction of the distal common bile duct, opening the plane to visualize the anterior portion of the portal vein in an inferior direction. The division of the proximal GI tract is typically performed approximately 2 cm distal to the pylorus, and distally the jejunum 10 to 20 cm beyond the ligament of Treitz is divided. The superior mesenteric vein is identified in the plane between the transverse mesocolon and the uncinate process, running anterior to the third portion of the duodenum, frequently surrounded by adipose tissue and receiving tributaries from the uncinate process and the transverse mesocolon. The proximal jejunum and distal duodenum can be delivered dorsal to the superior mesenteric vessels from the patient's left to the right side, allowing easier dissection of the uncinate process off the right lateral aspect of the superior mesenteric vein.

Further steps in pancreaticoduodenal resection involve the division of the pancreatic neck overlying the superior mesenteric vein–portal vein confluence and the final cautious dissection of the head and uncinate process from the right lateral aspects of the superior mesenteric vein, portal vein, and superior mesenteric artery.

Multiple options exist for the reconstruction of the pancreas, bile duct, and GI tract.³ Most commonly the reconstructive technique involves an anastomosis of the pancreas first, followed by the bile duct and the duodenum or stomach (see Fig. 29.3-12). The pancreatic-enteric anastomosis is typically performed as a pancreaticojejunostomy, in either an end-to-end or end-to-side fashion. Controversy continues regarding the importance of duct to mucosal sutures, the use of pancreatic ductal stenting, and the optimal configuration of the pancreaticojejunostomy. An alternative for pancreatic-enteric reconstruction involves the use of a pancreaticogastrostomy.⁷¹ The biliary-enteric anastomosis is typically performed in end-to-side fashion, approximately 10 cm downstream on the jejunal limb from the pancreaticojejunostomy. The third anastomosis is the duodenojejunostomy, performed 10 to 15 cm downstream from the biliary-enteric anastomosis. A more

TABLE 29.3-8. Complications after Pancreaticoduodenectomy

Common	Uncommon
Delayed gastric emptying	Fistula
Pancreatic fistula	Biliary
Intraabdominal abscess	Duodenal
Hemorrhage	Gastric
Wound infection	Organ failure
Metabolic	Cardiac
Diabetes	Hepatic
Pancreatic exocrine insufficiency	Pulmonary
	Renal
	Pancreatitis
	Marginal ulceration

(From ref. 75, with permission.)

complete description of the details of pancreaticoduodenal resection is available from numerous sources.^{72,73}

COMPLICATIONS. The operative mortality after pancreaticoduodenectomy is currently less than 2% to 3% in major surgical

centers with significant experience. The leading causes of postoperative in-hospital mortality include cardiovascular events, sepsis, and hemorrhage. In contrast to the low mortality, the incidence of postoperative complications can approach 40% to 50%.⁷⁴⁻⁷⁶ The leading causes of morbidity include disruption or failure of healing of the pancreatic anastomosis (pancreatic fistula), early delayed gastric emptying, intraabdominal abscess, hemorrhage, and others (Table 29.3-8). Many of these complications have minimal impact on length of postoperative hospital stay. Some complications prolong hospitalization and may require interventional radiologic techniques⁷⁶ or reoperation.

CONTROVERSIES Several controversies are ongoing pertaining to the technique and performance of pancreaticoduodenectomy.⁷⁷ These include (1) extent of pancreatic resection: partial pancreatectomy versus total pancreatectomy, (2) classic pancreaticoduodenectomy versus pylorus-preserving pancreaticoduodenectomy, and (3) extent of peripancreatic and nodal resection: standard pancreaticoduodenectomy versus extended (or radical) pancreaticoduodenectomy.

The controversy regarding the use of total pancreatectomy as a treatment for patients with right-sided PC has diminished in recent years. Current practice avoids total pancreatectomy and

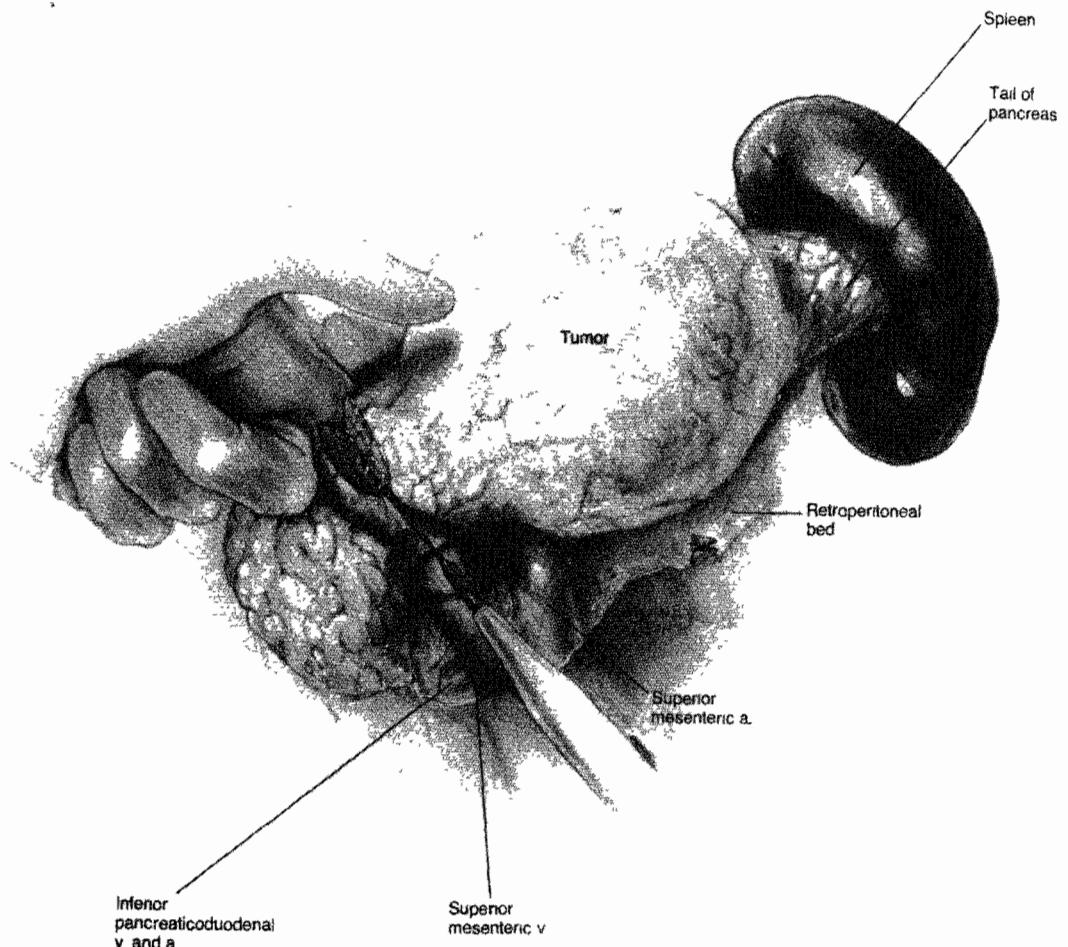


FIGURE 29.3-13. Illustration near the completion of a distal pancreatectomy and splenectomy for a large tumor in the body of the pancreas. The spleen and tail of the pancreas have been mobilized out of the retroperitoneum. The pancreatic parenchyma is being divided using the electrocautery. (From Cameron JL. *Atlas of surgery*. Vol 1. Toronto: BC Decker, 1990:435, Image H, with permission.)

favors the performance of a partial resection. By avoiding total pancreatectomy, one avoids the obligate requirements for exogenous pancreatic enzyme supplements, avoids the inevitable development of insulin-dependent DM, reduces the potential for increased intraoperative blood loss, and avoids splenectomy and the loss of splenic function. Total pancreatectomy is currently reserved for cases in which the pancreatic adenocarcinoma extends from the right side of the gland to the left or in rare cases in which the pancreatic remnant is too soft, friable, or inflamed to allow a safe pancreatic-enteric anastomosis.

Because pylorus-preserving pancreaticoduodenectomy does not appear to be associated with a consistent increased rate of adverse sequelae and has equivalent survival and quality of life as compared to classic resection, most groups are now favoring pylorus-preserving resections in patients with pancreatic adenocarcinoma. Additional reasons to support pylorus preservation include maintenance of pyloric sphincter function, maintenance of the entire gastric reservoir, and more normal physiology as regards gastric acid secretion and hormone release.

Several retrospective reports and a few prospective trials have suggested that extended (radical) pancreaticoduodenectomy may improve survival in patients with pancreatic adenocarcinoma.^{78,79} However, a prospective randomized trial at Johns Hopkins failed to reveal a survival advantage for one type of extended resection.⁸⁰ In this trial, 294 patients with periampullary adenocarcinoma were analyzed, having been allocated to standard pylorus-preserving pancreaticoduodenectomy or radical pancreaticoduodenectomy (which included distal gastrectomy and retroperitoneal lymphadenectomy). Although the mortality between the two groups was similar (2% to 4%), significantly more complications occurred in the radical group (29% standard vs. 43% radical; $P < 0.01$). Patients with pancreatic adenocarcinoma ($n = 163$) had no differences in either median, 1-year, 3-year, or 5-year actuarial survival when comparing between the standard and radical groups (median survival, 20 to 21 months; 2-year survival, 75%; 3-year survival, 37%; 5-year survival, 17%). From this, the largest prospective, randomized clinical trial of standard versus radical resection, no survival benefit appears to be derived from the addition of distal gastrectomy and retroperitoneal lymphadenectomy over a pylorus-preserving pancreaticoduodenectomy.

Distal Pancreatectomy for Tumors of the Body and Tail

A minority of patients with pancreatic adenocarcinoma have tumors arising in the left side of the pancreas. Such tumors do not obstruct the intrapancreatic portion of the bile duct, do not present with early jaundice, and typically grow to a larger size before diagnosis. Left-sided tumors are associated with a much higher incidence of metastatic disease, and the likelihood that curative resection will be possible is therefore lower for such left-sided tumors. However, if the tumor is discovered when it is localized, not encasing in the celiac axis or the superior mesenteric or portal venous systems, resection remains a surgical option. Importantly, involvement of either the splenic artery or the splenic vein, or both, does not alone render the patient unresectable, as the entirety of these vessels can be resected *en bloc* with the tumor. In addition to routine imaging studies including either multidetector three-dimensional CT or modern MR, there appears to be an important role for staging laparoscopy in patients with left-sided tumors.³

At exploration the entire abdomen is evaluated for metastatic disease. The lesser omentum is opened to allow assessment of the celiac axis and periaortic region. Similarly, the greater omentum is divided through the gastrocolic ligament, allowing the entirety of the pancreatic body and tail to be assessed. Furthermore, the ligament of Treitz is carefully evaluated because tumors in the body of the pancreas may invade the fourth portion of the duodenum at this site.

Localized tumors without extensive vascular or retroperitoneal involvement are appropriate for surgical resection. Splenic preservation is typically not indicated when the resection is being performed for pancreatic adenocarcinoma. Therefore, the spleen is mobilized out of the retroperitoneum, often with early ligation of the splenic artery. The short gastric vessels along the gastric greater curvature require division, as do the vessels within the splenocolic ligament. Mobilization of the spleen from the retroperitoneum facilitates dissection of the tail of the pancreas and elevation of the tumor toward the midline (Fig. 29.3-13).

The resectability rates for adenocarcinoma of the left side of the pancreas in the era before routine staging laparoscopy were approximately 10%. The use of staging laparoscopy, in addition to modern CT and MR, has improved the resectability rates. A comparison between the results for right-sided pancreatic resection (pancreaticoduodenectomy) and left-sided pancreatic resection (distal pancreatectomy) is shown in Table 29.3-9. In general, at the time of resection, left-sided tumors are larger, have a lesser degree of lymph node involvement, and are associated with a somewhat poorer outcome.^{3,80,81}

PALLIATIVE SURGERY

Palliative surgery for pancreatic adenocarcinoma is appropriate in patients discovered to have unresectable disease at the time of planned resection or in good-risk patients whose tumor-related symptoms are poorly alleviated by nonoperative means. Pallia-

TABLE 29.3-9. Right-Sided versus Left-Sided Pancreatic Resection: Johns Hopkins Experience (1984-1999)

	Right-Sided (Pancreati- coduodenectomy; $n = 564$)	Left-Sided (Distal Pancreatectomy; $n = 52$)	P Value
Tumor diameter	3.1 cm	4.7 cm	< 0.01
Positive resection margins	30%	20%	NS
Positive lymph node status (N1)	73%	59%	.03
Postoperative mortality	2.3%	1.9%	NS
Overall complica- tions	31%	25%	NS
Median length of postoperative hospital stay	11 d	7 d	NS
Survival			
1 y	64%	50%	NS
5 y	17%	15%	NS
Median	18 mo	12 mo	NS

NS, not significant.

(From ref. 2, with permission.)

tive surgery is most appropriate for patients with right-sided tumors and is designed to relieve biliary obstruction, avoid or treat duodenal obstruction, palliate tumor-associated pain, and improve quality of life.³

The surgical procedures for palliation of obstructive jaundice all include some form of an internal biliary bypass. The three most common techniques used include hepato- or choledochojejunostomy, choledochoduodenostomy, or cholecystojejunostomy. The preferred technique is hepato- or choledochojejunostomy, with the gallbladder being removed before mobilization of the biliary tree. Although choledochoduodenostomy provides effective relief of obstructive jaundice in a number of benign conditions, it has generally been avoided in patients with PC due to concerns regarding the proximity of the biliary-enteric anastomosis to the tumor, with the possibility of recurrent jaundice. Although cholecystojejunostomy has been advocated by some surgeons (because it can be performed quickly and can be done laparoscopically) and does not require dissection of the extrahepatic biliary tree, data do not support its use because of recurrent jaundice. A number of retrospective reviews have compared the short- and long-term results after hepatico(choledocho)jejunostomy and cholecystojejunostomy for palliation of obstructive jaundice. In a classic review,⁸² although operative mortality and long-term sur-

vival were similar, the incidence of recurrent jaundice was zero after hepatico(choledocho)jejunostomy, compared to 8% in patients undergoing cholecystojejunostomy. Furthermore, a metaanalysis⁸³ found that cholecystojejunostomy carried only an 89% success rate for alleviating jaundice, compared to a 97% success rate with hepatico(choledocho)jejunostomy.³

At the time of diagnosis of right-sided PC, up to one-third of patients have some symptoms of nausea, early satiety, and/or vomiting. Over the years, information has accrued regarding the natural history of duodenal obstruction associated with PC. In a review of more than 8000 surgically managed patients, 13% who did not undergo gastrojejunostomy at their initial operation required gastrojejunostomy before their death, and an additional 20% of patients died with symptoms of duodenal obstruction.⁸² In addition, an analysis of more than 1600 cases found that 17% of patients who underwent biliary bypass alone developed duodenal obstruction at a mean of 8.6 months after operation and required subsequent gastric bypass.⁸³ To date, only one prospective randomized trial has evaluated the role of prophylactic gastrojejunostomy in patients found at laparotomy to have unresectable right-sided PC.⁸⁴ In this study, 87 patients without evidence of preoperative duodenal obstruction or intraoperative tumor encroachment around the duodenal C loop were randomized to

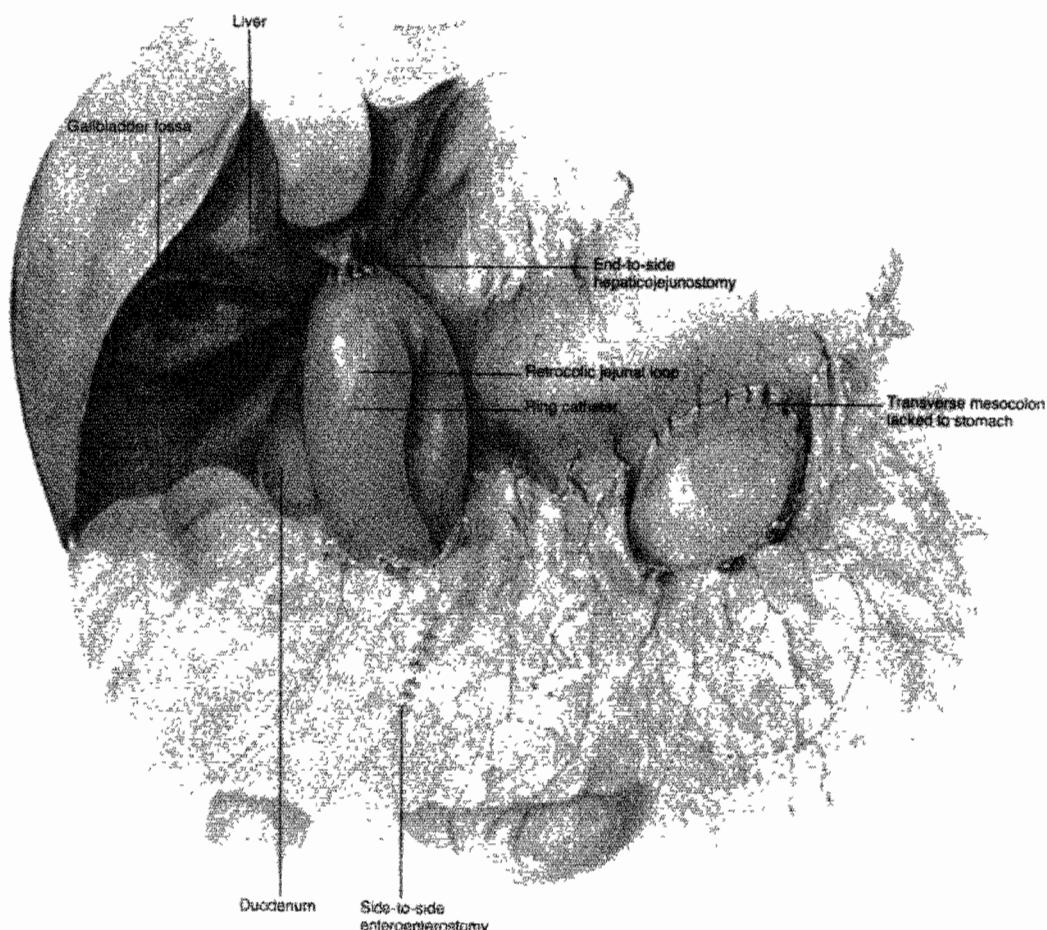


FIGURE 29.3-14. Anatomy after one method of a completed double-bypass procedure. *Right:* Retrocolic gastrojejunostomy, performed to the dependent portion of the gastric greater curvature. *Left:* End-to-side hepaticojejunostomy to a retrocolic jejunal loop, with a downstream side-to-side enteroenterostomy. The gallbladder has been removed. (From Cameron JL. *Atlas of surgery*. Vol 1. Toronto, BC Decker, 1990:427, Image V, with permission.)

receive either a prophylactic retrocolic gastrojejunostomy or no such procedure. Although the postoperative mortality, morbidity, postoperative length of hospital stay, and mean survival were similar, 8 of 43 patients (19%) without gastrojejunostomy developed late gastric outlet obstruction requiring intervention, whereas no patient in the prophylactic gastrojejunostomy group required repeat intervention ($P < .01$). Based on these data and the results of previous retrospective analyses, the authors typically performed retrocolic gastrojejunostomy in patients found at laparotomy to have unresectable right-sided pancreatic adenocarcinoma.³ The gastrojejunostomy is usually performed as an isoperistaltic loop procedure, using the jejunum 20 to 30 cm beyond the ligament of Treitz, and placing the horizontal gastrotomy posterior, in the most dependent portion of the gastric greater curvature (Fig. 29.3-14). Using this technique the incidence of gastric-emptying problems appears to be low, and hospital discharge is not delayed.⁸⁴ Importantly, vagotomy is not performed for the palliation of PC, as it may further contribute to delayed gastric emptying. Instead, proton pump inhibitors are given to reduce gastric acid secretion, designed to prevent marginal ulceration.³

The abdominal and back pain associated with an unresected pancreatic adenocarcinoma can be unremitting, narcotic requiring, and a major debilitating symptom for the patient. At the time of palliative surgery, this symptom can be addressed by intraoperative chemical (alcohol) block. Only one prospective, randomized placebo-controlled trial of intraoperative alcohol block has been reported. In this study from Johns Hopkins, the alcohol block (chemical splanchnicectomy) was performed by injection of either 20 mL 50% alcohol or a saline placebo of either side of the aorta at the level of the celiac axis.⁸⁵ Data analyses indicated that mean pain scores (as recorded on a visual analog scale) were significantly lower in the patients who received the alcohol block, as compared to the patients who were given the saline placebo. These data support the routine performance of intraoperative alcohol block in patients undergoing operative palliation for unresectable pancreatic adenocarcinoma.

The most recently published Johns Hopkins experience with surgical palliation of unresectable pancreatic adenocarcinoma is summarized in Table 29.3-10. Over a 6-year period, 256 patients underwent such operative palliation.⁸⁶ In this group, 68% of the patients were unresectable due to liver or peritoneal metastases, and 32% were unresectable due to local vascular invasion. The most common operative procedures were alcohol block (75%), biliary plus gastric bypass (51%), and gastric bypass alone (19%). Some patients had prior operative procedures for biliary bypass, whereas some individuals had prior nonoperative biliary decompression (via endoprosthesis or percutaneous drain) that was left intact. The postoperative in-hospital mortality was 3.1%, the complication rate was 22%, and the length of postoperative hospital stay was 10 days. The median survival was 6.5 months, with 1- and 2-year survivals of 25% and 9%, respectively.

POSTOPERATIVE ADJUVANT THERAPY

Despite insights into the overall understanding of PC at the molecular level, improved imaging techniques to identify disease at an earlier stage, and improved surgical techniques, the 5-year survival is still approximately 15% to 20% for resectable disease and 3% for all stages combined.^{3,80} The role of adjuvant

TABLE 29.3-10. Johns Hopkins Experience with Surgical Palliation (n = 256 patients)

Age	64 y
Gender	57% male
Presenting symptoms	
Abdominal pain	64%
Jaundice	57%
Procedures	
Chemical splanchnicectomy	75%
Biliary and gastric bypass	51%
Gastric bypass	19%
Operative time	3.9 h
Transfusions (mean)	0
Operative mortality	3.1%
Overall morbidity	22%
Postoperative length of stay	10 d
Median survival	6.5 mo
1-y survival	25%
2-y survival	9%

(From Sohn TA, Lillemoe KD, Cameron JL, et al. Surgical palliation of unresectable periampullary adenocarcinoma in the 1990s. *J Am Coll Surg* 1999;188:658, with permission.)

therapy for patients with resected disease is underscored by the pattern of disease relapse after surgical resection. Several retrospective analyses have demonstrated that, in addition to the development of distant metastases, local-regional recurrence occurs in greater than 50% of patients who have undergone potentially curative resection. The combined use of chemotherapy with regionally directed radiation has long been proposed as a method to control local-regional disease as well as to treat microscopic metastatic disease.

The current standard of 5-fluorouracil (5-FU)-based combined modality chemoradiotherapy is based on *in vitro* data, animal studies, and a series of human studies, the most notable being those from the Gastrointestinal Tumor Study Group (GITSG). This study, using split-course irradiation in modest doses with concurrent bolus (5-FU) followed by maintenance 5-FU, demonstrated a survival advantage for the therapy in comparison to surgery alone.⁸⁷ Although criticized for slow and limited accrual, the GITSG study was the first to document that adjuvant therapy after surgical resection for pancreatic surgery prolonged survival. Additional studies by the GITSG demonstrated the benefit of combined chemoradiotherapy versus chemotherapy alone or radiation therapy alone for patients with resectable disease.⁸⁸

A number of groups have further developed this approach (Table 29.3-11).⁸⁹⁻¹⁰⁰ The Johns Hopkins Hospital published results of a single-institution prospective but nonrandomized trial that was designed to evaluate survival benefit in patients with PC after surgical resection.⁸⁸ This report, involving 174 patients, demonstrated that patients receiving GITSG-style chemoradiotherapy with maintenance 5-FU truncated at 6 months (rather than 2 years), or a more intensive regimen (involving higher doses of irradiation as well as hepatic irradiation administered without interruption and with continuous-infusion 5-FU chemotherapy augmented with leucovorin), did better than patients receiving no postsurgical therapy. The median survival for the more standard regimen was 21 months, with 1- and 2-year survivals at 80% and 44%. For the intensive regi-

TABLE 29.3-11. Adjuvant Studies in Pancreatic Cancer

Adjuvant Study	No. of Patients	EBRT Dose (Gy)	Chemotherapy	Median Survival (Mo)	1-Y Survival (%)	2-Y Survival (%)	5-Y Survival (%)
GITSG, 1985 ⁸⁷	22 surgery alone	None	None	11	49	15	NR
	21 to chemorad	40 split course	5-FU bolus	20 ($P = .01$)	63	42	NR
GITSG, 1987 ⁸⁸	30	40 split course	5-FU bolus	18	67	46	NR
Whittington et al., 1991 ²⁴¹	33 surgery alone	None	None	15	70 (est)	30 (est)	8 (3 y)
	10 rad alone	45–63	None	15	72 (est)	40 (est)	5 (3 y)
	28 chemorad	45–63	5-FU bolus and MMC	16	75 (est)	55 (est)	34 (3 y)
Foo et al., 1993 ²⁴²	29	35.1–60.0	5-FU bolus	22.8	NR	48	12
Spitz et al., 1997 ⁹⁷	19	50.4	5-FU CI	22	70 (est)	42 (est)	40 (est)
Yeo et al., 1997 ⁸⁹	53 surgery alone	None	None	13.5	54	30	NR
	99 "standard"	40–45 split course	5-FU bolus	21 ($P = .002$)	80	44	NR
	21 "intensive"	50.4–57.6 split course With liver 23.4–27.0	5-FU CI + leucovorin	17.5 ($P = .252$)	70	22	NR
Demeure et al., 1998 ²⁴³	30 surgery alone	None	None	16.9	90 (est)	20 (est)	0
(Stage I 29 patients)	31 chemorad	50.4–54.0	5-FU bolus or CI	24.2 ($P < .05$)	100 (est)	50 (est)	50 (est)
Pendurthi and Hoffman, 1998 ²³⁴	23	50.4	5-FU bolus or CI	25			
Abrams et al., 1999 ⁹⁰	23	50.4–57.6, with liver 23.4–27.0	5-FU CI	15.9	62 (est)	25 (est)	NR
EORTC, 1999 ²⁴⁴	54 surgery alone	None	None	12.6	40 (est)	23	10
	60 chemorad	40	5-FU bolus	17.1 ($P = .099$)	65 (est)	37	20
Paulino et al., 1999 ⁹⁸	30 chemorad	30.6–64.8	5-FU bolus or CI	26 ($P = .004$)	84	52	NR
	8 rad alone	30.6–64.8	None	5.5	0	0	0
Mehta et al., 2000 ⁹²	52	54	5-FU CI	32	80	62	39
Nukui et al., 2000 ⁹³	16	45–54	5-FU bolus or CI	18.5	92 (est)	84	Not reached
	17	45–54	5-FU CI with cisplatin and IFN- α	Not reached	80 (est)	50 (est)	25 (est)
Chakravarthy et al., 2000 ⁹⁹	29	50 split course	5-FU CI with MMC and DPM	16	84	60	NR
Sohn et al., 2000 ⁸⁰	119 surgery alone	None	None	11	48	22 (est)	9
(Retrospective study)	333 adjuvant tx	40–50	5-FU/ \pm MMC, DPM	19 ($P < .0001$)	71	38 (est)	20
	200 surgery alone	None	None	16.1	NA	NA	NR
ESPAc1, 2001 ²⁴⁵	103 chemorad	40 split course	None	15.5	NA	NA	NR
	166 chemo alone	None	5-FU bolus	19.7	60 (est)	39 (est)	16 (est)
	72 chemorad with additional chemo	40 split course	5-FU bolus	NA	NA	NA	NR
	53	45–50	5-FU CI with cisplatin and IFN- α	46	88	53	49
Van Laethem et al., 2003 ²⁴⁶	22	40 split course	Gemcitabine	15	50 (est)	15 (est)	NR

chemorad, chemoradiotherapy; CI, continuous infusion, DPM, dipyridamole; EBRT, external-beam radiation therapy; EORTC, European Organization for Research and Treatment of Cancer; est, estimated; 5-FU, 5-fluorouracil; GITSG, Gastrointestinal Tumor Study Group; IFN, interferon; MMC, mitomycin C; NA, not available; NR, not reported; rad, radiotherapy; tx, therapy

men, the median survival was 17.5 months, with 1- and 2-year survivals at 70% and 22%. For the control arm, the median survival was 13.5 months, with survival at 1 and 2 years at 54% and 30%. This approach has been further refined by Sohn et al.⁸⁰

and Abrams et al.⁹⁰ The critical prognostic factors appear to be the status of resection margins, lymph node involvement (especially having more than 3 lymph nodes involved), tumor size greater than 3 cm, and the presence of a poorly differentiated

component within the tumor. Using these factors, patients can be segregated into high-risk and low-risk groups, with median survival after standard adjuvant therapy being 30.5 months for low-risk patients and 14 months for high-risk patients.

In an effort to enhance the activity of chemotherapy in PC, other agents have been examined in combination with 5-FU. MMC is an antitumor antibiotic with activity in several GI cancers including PC. The University of California at Los Angeles group has published their experience using MMC (10 mg/m² IV every 6 weeks) and 5-FU (200 mg/m²/d administered via continuous infusion), in combination with leucovorin (30 mg/m² weekly) and dipyridamole (75 mg PO daily), in 38 patients with locally advanced pancreatic carcinoma.⁹¹ Of these, there were 14 partial responders with one complete response. The median survival for all patients was 15.5 months, which is an improvement over historic data for local-regional advanced disease. This regimen has subsequently been applied to resected PC in combination with radiotherapy. The Johns Hopkins group has presented data on 39 patients with PC after surgical resection, treated with combined radiotherapy (50 Gy in 25 fractions with a planned 2-week break after 25 Gy) and chemotherapy consisting of 5-FU, 400 mg/m² days 1 to 3; MMC, 10 mg/m² day 1; leucovorin, 20 mg/m² days 1 to 3; and dipyridamole, 75 mg PO q.i.d. days 0 to 4 administered on weeks 1 and 4. One month after combined chemoradiotherapy, patients received four additional cycles (4 months) of the same chemotherapy alone. At 12.6 months median follow-up, median survival was 16 months.⁹⁰

The Virginia Mason Medical Center published their experience with 33 patients with resected pancreatic adenocarcinoma who received combined radiotherapy (external beam at a dose of 45 to 54 Gy in standard fractions days 1 to 35) and chemotherapy (5-FU, 200 mg/m²/d as continuous infusion; weekly cisplatin, 30 mg/m² IV bolus; and interferon- α , 3 million units subcutaneously every other day) during radiation or GITSG-type chemotherapy with radiation therapy.⁹³ After combined modality chemoradiotherapy, chemotherapy alone was administered (5-FU, 200 mg/m²/d as continuous infusion) in two 6-week courses during weeks 9 to 14 and 17 to 22. Of note, 13 of 17 patients randomized to the interferon-based chemoradiotherapy had positive lymph nodes compared to only 7 of 16 patients randomized to the GITSG-based chemoradiotherapy. Significant grade III/IV GI toxicities occurred, including vomiting, mucositis, diarrhea, and GI bleeding in the interferon-based chemotherapy group, requiring hospitalization in 35% of patients. However, the majority of patients were still able to receive more than 80% of the planned therapy. The median overall survival and 2-year actuarial survival rates were 18.5 months and 54% for patients receiving the GITSG-based chemoradiotherapy. In contrast, the median survival and 2-year survivals were greater than 24 months and 84% for the interferon-based chemoradiotherapy. The Virginia Mason group has presented a follow-up study of 53 patients with resected pancreas cancer treated with similar interferon-based chemoradiotherapy. Toxicities including anorexia, dehydration, diarrhea, mucositis, nausea, and vomiting necessitated hospitalization in 23 of 53 patients. However, the clinical efficacy remains very encouraging, with a median survival of 46 months and a 2-year survival of 53%.⁹⁴ The American College of Surgeons Oncology Group is coordinating a multiinstitutional phase II study of this interferon-based chemoradiation regimen in patients with pancreatic adenocarcinoma who have undergone resection.

In July 2002, the Radiation Therapy Oncology Group closed R97-04. This phase III study of 518 PC patients randomized patients between two arms: (1) 5-FU continuous infusion (250 mg/m²/d for 3 weeks), followed by 5-FU continuous infusion (250 mg/m²/d) during radiation therapy (50.4 Gy in 1.8-Gy fractions), followed by two cycles 5-FU continuous infusion; and (2) gemcitabine, 1000 mg/m² weekly \times 3, followed by 5-FU continuous infusion during radiation therapy, followed by three cycles gemcitabine alone. The experimental question being asked was whether gemcitabine before and after 5-FU-based chemoradiotherapy would be more efficacious than continuous-infusion 5-FU before and after the same 5-FU-based chemoradiotherapy. In 1997, when this study was designed, there was inadequate knowledge regarding how to safely administer gemcitabine concurrently with irradiation to allow for concurrent gemcitabine and radiotherapy. This study was the first North American cooperative group trial since the GITSG trial. Although the survival results for this trial will not be known until late 2004, a number of important observations have already been made. These include the fact that neither arm was associated with unacceptable acute toxicity during the trial; that accrual was quite rapid (12 to 14 patients per month), reflecting the support of the Eastern Cooperative Oncology Group (ECOG) and the Southwest Oncology Group; and the willingness of patients and their physicians to participate in adjuvant trials for PC.³

Despite a growing body of literature supporting the benefit of adjuvant combined modality therapy after potentially definitive resection in patients with high risk for recurrence, adjuvant chemoradiation has not been universally accepted as standard of care. One of the criticisms has been that none of these studies included an observation-only arm. Two studies have questioned the benefits of adjuvant chemoradiation.

A European Organization for Research and Treatment of Cancer (EORTC) trial randomized 218 patients with pancreatic and nonpancreatic periampullary adenocarcinoma 2 to 8 weeks after potentially curative resection to either observation alone or to combined radiotherapy (40 Gy using a three- or four-field technique in 2-Gy fractions with a 2-week break at midtreatment) and chemotherapy (5-FU administered as a continuous infusion, 25 mg/kg/d during the first week of each 2-week radiation therapy module only).⁹⁵ No postradiation chemotherapy was administered. Median progression-free survival was 16 months in the observation arm versus 17.4 months in the treatment arm ($P = .643$). Median survival was 19 months in the observation group versus 24.5 months in the treatment group but was not statistically significant ($P = .737$). For the subgroup of patients with pancreatic adenocarcinoma ($n = 114$), the median survival was 12.6 months in the observation group versus 17.1 months in the treatment arm but was not statistically significant ($P = .099$). Of note, 21 of 104 patients randomized to the treatment arm were not treated. In addition, although the original dose of 5-FU was already modest, 35 patients in the treatment arm received only 3 days of 5-FU during the second module of radiotherapy, secondary to grade I/II toxicities. Therefore, this study could be reinterpreted as an underpowered, possibly positive study.

The European Study Group for Pancreatic Cancer randomized 541 patients with pancreatic adenocarcinoma in a four-arm trial, based on a two-by-two factorial design: (1) observation, (2) concomitant chemoradiotherapy alone (20 Gy in 10 frac-

tions over 2 weeks with 500 mg/m² 5-FU IV bolus during the first 3 days of radiation therapy; the module is repeated after a planned 2-week break) followed by no additional chemotherapy, (3) chemotherapy alone (leukovorin, 20 mg/m² bolus, followed by 5-FU, 425 mg/m² administered for 5 consecutive days repeated every 28 days for 6 cycles), and (4) chemoradiotherapy followed by chemotherapy.⁹⁶ No significant difference was found in survival between patients assigned to chemoradiotherapy (median survival, 15.5 months) versus observation (median survival, 16.1 months; $P = .24$). The survival data were similar in the subset ($n = 285$ patients) randomized through the two-by-two design. In contrast, there was a survival advantage for those patients treated with chemotherapy alone (median survival, 19.7 months) versus the observation arm (median survival, 14 months; $P = .0005$). For the same subset randomized through the original two-by-two design, survival demonstrated a trend toward improved survival for chemotherapy alone (median survival, 17.4 months) versus observation alone (15.9 months) but was not statistically significant ($P = .19$). Multivariate analysis for known prognostic factors, including margin status, lymph node involvement, tumor grade, and size, did not alter the effect for chemoradiotherapy treatment. The study authors concluded that there was no survival benefit for adjuvant chemoradiotherapy and that a potential benefit existed for adjuvant chemotherapy alone after surgical resection.

Although this European Study Group for Pancreatic Cancer trial was a randomized study consisting of more than 500 patients, its conclusions should be carefully measured.⁹ To encourage maximal patient recruitment, the study was modified in that 68 patients were assigned separately and randomized to either chemoradiotherapy or observation. In addition, 188 patients were subsequently assigned separately and randomized to either chemotherapy alone or observation. In a sense, three randomizations were possible for inclusion into the same study. Also, patients in the additional two randomizations could have potentially received "background chemotherapy or chemotherapy" that was not specifically defined. The background treatment was not known in 82 eligible patients. Of note, these patients were still assigned into an arm of the study despite lack of definitive knowledge of prior therapy. Finally, 25 of the eligible 541 patients refused to accept their randomization, and an additional 25 patients withdrew secondary to treatment toxicities.

NEOADJUVANT STRATEGIES

Neoadjuvant therapy is a potentially attractive alternative to current postoperative adjuvant chemoradiation for several reasons:

1. Radiation is more effective on well-oxygenated cells that have not been devascularized by surgery.
2. Contamination and subsequent seeding of the peritoneum with tumor cells secondary to surgery could theoretically be reduced.
3. Patients with metastatic disease on restaging after neoadjuvant therapy would not need to undergo definitive resection and might benefit from palliative intervention.
4. The risk of delaying adjuvant therapy would be eliminated because it would be delivered in the neoadjuvant setting.

A number of groups have further developed this approach (Table 29.3-12).^{91,97,101-107}

The M. D. Anderson Cancer Center (MDACC) published their experience of 132 patients with localized resectable pancreatic adenocarcinoma treated preoperatively with radiation therapy (45.0 to 50.4 Gy in standard 1.8-Gy fractions or consisting of 30 Gy rapid fractionation in 3 Gy/fraction) combined with chemotherapy (5-FU continuous infusion, 300 mg/m²/d, or gemcitabine, 400 mg/m²/wk, or paclitaxel, 60 mg/m²/wk) followed by surgical resection.¹⁰¹ No surgical delays occurred in the neoadjuvant group, but delays were noted in 6 of 25 patients who underwent surgical resection first. At a median follow-up of 19 months, no significant differences in survival were noted between treatment groups, with overall median survivals of 21 months.

The Fox Chase Cancer Center published their experience of 53 patients with localized resectable PC who were treated preoperatively with radiation therapy (50.4 Gy in 180-cGy fractions) and chemotherapy (MMC, 10 mg/m² day 2, with 5-FU, 1000 mg/m²/d continuous infusion days 2 to 5 and 29 to 32).¹⁰² Forty-one patients subsequently underwent exploratory laparotomy at the conclusion of preoperative chemoradiation. From this group of patients, 17 were not resectable (including 11 patients with hepatic or peritoneal metastases and 6 patients with local extension that precluded resection). Twenty-four patients eventually underwent potentially curative resection. Significant treatment-related hematologic and nonhematologic toxicities were identified, including one patient with treatment-related toxicities that precluded reexploration. Median survival for the entire group was 9.7 months and 15.7 months for the group that underwent surgical resection.

The Fox Chase group has since published a follow-up study of 30 patients with localized resectable PC of whom 26 received preoperative radiation therapy (50.4 Gy) with 5-FU continuous infusion.¹⁰³ Fourteen patients who received preoperative therapy subsequently underwent resection. Median survival was 34 months for the resected group, compared to 8 months in the group that could not be resected.

The MDACC have also used neoadjuvant paclitaxel, 60 mg/m² over 3 hours weekly with 30 Gy radiation therapy rapid fractionation.¹⁰⁴ Of note, if patients could undergo surgical resection, they could also have received intraoperative radiation therapy. Grade III hematologic and nonhematologic toxicities were identified in 16 patients. No delays in surgery were attributable to preoperative therapy. Twenty of 25 patients who underwent exploratory laparotomy underwent surgical resection; there were no histologic complete responders. With a median follow-up of 45 months, 3-year survival for these patients after potentially curative resection was 28%, with an overall median survival of 19 months.

Although the distinction between resectable and locally advanced unresectable disease has been clarified by the AJCC sixth edition staging (locally advanced unresectable = T4, stage III), the distinction between potentially resectable versus unresectable disease can be challenging and can have important implications from a therapeutic and from a reporting perspective. Currently, ECOG is planning to open a prospective randomized trial, allocating patients to intensified gemcitabine-based or gemcitabine/5-FU/platinum-based chemoradiotherapy in a neoadjuvant setting. This trial makes an important distinction between clearly unresectable disease and potentially resectable disease, especially around the issues of partial versus complete encasement of the superior mesenteric artery and

TABLE 29.3-12. Neoadjuvant Studies in Patients with Resectable Pancreatic Cancer

Study	Evaluable Patients	% Resected	EBRT (Gy)	Chemotherapy	Median Survival (All Patients in Mo)	Median Survival (Resected Patients in Mo)	1-Y Survival (%)	2-Y Survival (%)	5-Y Survival (%)
Evans et al., 1992 ²³²	28	17 (61%)	50.4 + IORT	5-FU CI	NA	NA	NA	NA	NA
Hoffman et al., 1995 ²³³	34	11 (32%)	50.4	5-FU bolus and MMC	NA	45	70 (est)	60 (est)	40 (est)
Staley et al., 1996 ¹⁰⁵	39	39 (100%)	30 or 50.4 and IORT	5-FU CI	19	19	75 (est)	35 (est)	NA
Spitz et al., 1997 ⁹⁷	91	52 (57%)	30 or 50.4	5-FU CI	20.2	19.2	76 (est)	38 (est)	28 (est)
Pendurthi and Hoffman, 1998 ²³⁴	70	25 (36%)	50.4	5-FU bolus and MMC	NA	20	75 (est)	40 (est)	8 (est)
Hoffman et al., 1998 ¹⁰²	53	24 (45%)	50.4	5-FU bolus and MMC	9.7	15.7	72	27	8
Pisters et al., 1998 ²³⁵	35	20 (74%)	30 + IORT	5-FU CI	7	25	84	56 (est)	NA
Todd et al., 1998 ⁹¹	38	4 (10%)	None	5-FU CI/MMC/DPM	15.5	41	100	75	NA
White et al., 2001 ¹⁰⁶	53 resectable	28 (53%)	45	5-FU CI and MMC/CDDP	Not reached	Not reached	100	52 (est)	38 (est)
	58 advanced	11 (19%)	45	5-FU CI and MMC/CDDP	Not reached	Not reached	65 (est)	16 (est)	0
Breslin et al., 2001 ¹⁰¹	132	132 (100%)	30.0–50.4 and/or IORT	5-FU CI or Gem or paclitaxel (Taxol)	21	21	78 (est)	50 (est)	23
Moutardier et al., 2002 ¹⁰⁷	19	15 (79%)	30 or 45	5-FU bolus and CDDP	20	30	NA	52	NA
Amoletti et al., 2002 ¹⁰⁹	26	14 (54%)	50.4	5-FU and/or MMC or Gem	NA	34	75 (est)	68	45
Pisters et al., 2002 ¹⁰⁴	35	20 (57%)	30 and IORT	Paclitaxel	12	19	75 (est)	35 (est)	10 (est)
Magnin et al., 2003 ²³⁶	32	19 (59%)	30 or 45	5-FU CI + CDDP	16	30	82 (est)	59	NA

CDDP, cisplatin; CI, continuous infusion; DPM, dipyridamole; EBRT, external-beam radiation therapy; IFN, interferon; IORT, intraop radiation therapy; 5-FU, 5-fluorouracil; Gem, gemcitabine, MMC, mitomycin-C, NA, not available.

the length of superior mesenteric vein involved by tumor at initial presentation.

To date, the current data demonstrate that, although neoadjuvant chemoradiotherapy can be administered safely, there is no clear survival advantage to this strategy compared to postoperative therapy. In the realm of marginally resectable patients, it remains to be seen whether there is a meaningful cohort of patients for whom this approach may represent an important therapeutic advantage based on “down-staging” and subsequent improved surgical outcomes.

TREATMENT OF LOCALLY ADVANCED DISEASE

Locally advanced PC is most commonly defined as patients with AJCC sixth edition T4 lesions, in which the primary tumor involves branches of the celiac axis or the superior mesenteric artery. Such involvement connotes an unresectable primary tumor and represents stage III disease. Such patients may require nonoperative palliation of disease-related processes such

as obstructive jaundice, gastroduodenal obstruction, or abdominal pain. In some settings operative palliation can additionally be used. Focused anticancer treatment for such locally advanced pancreatic adenocarcinoma can involve chemoradiation approaches, chemotherapy alone, or locally directed therapy.

NONOPERATIVE PALLIATION

The nonoperative palliative management of patients with PC can be applied to those with unresectable locally advanced disease, less frequently to patients with distant metastases, or to patients with acute or chronic debilitating diseases that make anesthesia and surgery prohibitive.³ The one exception to these indications favoring nonoperative management are those patients with symptomatic upper GI obstruction (from tumors that obstruct at the duodenal C loop or at the ligament of Treitz) in whom nonoperative palliation is not reliable and gastrojejunostomy may be the best method of palliation. In patients who are to be managed nonoperatively, a tissue diagnosis can be obtained via biopsy of distant metastases or of local tumor. Jaundice is present in the majority of the patients with

pancreatic adenocarcinoma. If untreated, obstructive jaundice can result in progressive liver dysfunction, hepatic failure, and early death.³ Furthermore, the pruritus associated with obstructive jaundice can be quite debilitating and rarely responds to medications. Fortunately, biliary decompression can now be achieved either by endoscopic or by percutaneous transhepatic techniques in nearly all patients who are not candidates for surgical intervention.

The technique of endoscopic biliary stent insertion for palliation of malignant obstructive jaundice is associated with a technical success rate exceeding 90% in the hands of skilled endoscopists performing such endoscopic stenting on a regular basis. Once biliary cannulation has been accomplished, a guidewire is typically manipulated above the malignant stricture, and a No. 7 to 10 French plastic endoprosthesis is secured in position, being pushed over the guidewire. After stent placement, serial liver function tests are obtained to confirm a decline in the serum bilirubin. Early complications after endoprosthesis placement include cholangitis, pancreatitis, bleeding, and bile duct or duodenal perforation. Late complications include stent occlusion, cholecystitis, and stent migration. Metallic expandable endoprostheses have been developed by a number of manufacturers and have been modified to allow endoscopic placement. Once fully deployed, these metallic endoprostheses become embedded in the wall of the bile duct and should be considered permanent, although they can be removed at surgery. Such metallic endoprostheses greatly reduce the problem of stent migration; however, tumor ingrowth remains a problem, causing late stent occlusion.³

Percutaneous transhepatic biliary drainage is now used only if endoscopic biliary endoprosthesis placement cannot be performed. For this technique, diagnostic cholangiography first defines the site of bile duct obstruction and serves as a road map for the advancement of a percutaneous transhepatic biliary catheter through the biliary obstruction, with the catheter being advanced into the duodenum. In most cases biliary drainage with an internal-external catheter serves as the initial management, with subsequent management involving either maintenance of such an internal-external catheter or percutaneous placement of a totally indwelling endoprosthesis. Complications of percutaneous transhepatic catheter drainage include stent occlusion, hemobilia related to the transhepatic route, bile peritonitis, bile pleural effusion, cholangitis, pancreatitis, and acute cholecystitis. The available data support the use of the endoscopic method as the primary approach for nonoperative palliation of jaundice in patients with locally advanced PC.³

The pain associated with locally advanced PC can be an incapacitating symptom of the disease. Unfortunately, for many patients, such pain is poorly controlled, and it can remain a significant problem up until their demise.³ In general, this pain is not relieved by endoscopic or percutaneous biliary decompression. Analgesic therapy is guided by the Three-Step Analgesic Ladder of the World Health Organization.¹⁰⁸ Tumor-associated pain is best treated with long-acting oral analgesics in appropriate doses, with dose escalations as appropriate. In patients who cannot take oral medications, topical analgesics worn as continuous-release patches can be highly effective. Poorly controlled pain is often the result of inadequate analgesic dosing and may require the expertise of pain management specialists. Several nonoperative treatment

modalities, such as percutaneous or endoscopic celiac nerve block or external-beam radiation therapy (EBRT) directed at the primary tumor and celiac plexus, can be considered for management of pain intractable to appropriate oral or topical pain medications. In the authors' experience most patients can be well managed without resorting to such invasive therapies.

OPERATIVE PALLIATION

At times, patients undergo exploration for a presumed resectable pancreatic adenocarcinoma, only to find that they are in fact unresectable due to unanticipated locally advanced disease. At the time of laparotomy, these patients are candidates to undergo palliative procedures such as biliary-enteric bypass, gastrojejunostomy, and chemical (alcohol) nerve block, as discussed previously in Treatment of Potentially Resectable Disease: Palliative Surgery.

CHEMORADIATION APPROACHES

Although EBRT alone can improve symptoms associated with locally advanced disease, the high local failure rate and synergy observed when EBRT is combined with chemotherapy have led to trials using both modalities. Chemoradiation approaches have shown improved survival compared to either modality alone, but the improvements are modest and local control remains a significant challenge. No randomized comparisons have been made of radiation or chemotherapy, or both, versus supportive care (aside from subset analyses in trials for metastatic disease).

Several prospective randomized trials have shown a benefit with chemoradiation compared to either radiation or chemotherapy alone in the management of locally advanced disease (Table 29.3-13). The first trial was published in 1969 and included patients with different types of GI cancers, 64 of whom had locally unresectable PC randomized to either 5-FU or placebo, combined with 35 to 40 Gy radiation.¹⁰⁹ Median survival in the combined modality arm was significantly higher than in the radiation therapy-only arm (10.4 vs. 6.3 months). The GITSG randomized 194 locally advanced PC patients to receive split-course EBRT, either alone (60 Gy) or combined (either 40 or 60 Gy) with 5-FU, 500 mg/m² on the first 3 days of each 20 Gy radiation.¹¹⁰ The EBRT-alone arm was discontinued after an interim analysis showed improved median time to progression and overall survival in the combined modality arms. No significant differences were seen between the high- and low-dose EBRT in the chemoradiation arms, although there were trends favoring the higher-dose arm in time to progression and survival. A second GITSG study compared SMF (streptozotocin, mitomycin, and 5-FU) chemotherapy alone versus SMF combined with EBRT (54 Gy) and showed a significant improvement in median survival (9.7 vs. 7.4 months) for the chemoradiation arm.¹¹¹ In contradistinction to the GITSG studies, a randomized ECOG study of 91 patients comparing 5-FU, 600 mg/m² weekly with or without EBRT (40 Gy, which has been criticized as an insufficient dose), did not find a significant benefit to combined modality therapy over chemotherapy alone.¹¹¹ Thus, three randomized studies have demonstrated a modest survival benefit for combined modality therapy over chemotherapy or EBRT alone, and one ECOG study with a possibly suboptimal dose of EBRT (40 Gy) did not show a benefit over 5-FU alone.

TABLE 29.3-13. Selected Randomized Trials in Locally Advanced Pancreatic Cancer

Reference	Radiation (Gy)	Chemotherapy	No. of Patients	Median Survival (Mo)	1-Y Survival (%)
CHEMORADIATION VS. RADIATION ALONE					
Moertel et al., 1969 ¹⁰⁹	35-40	5-FU	32	10.4 ^a	25 ^{a,b}
	35-40	Placebo	32	6.3	6 ^b
GITSG, 1981 ²³⁷	60	5-FU	111	11.4	44 ^a
	40	5-FU	117	8.4	39 ^a
	60	—	25	5.3	14
CHEMORADIATION VS. CHEMOTHERAPY ALONE					
ECOG, 1985 ²³⁸	40	5-FU	47	8.3	28 ^b
	—	5-FU	44	8.2	31 ^b
GITSG, 1988 ²³⁹	54	5-FU and SMF	22	9.7 ^a	41 ^a
	—	SMF	21	7.4	19
CHEMORADIATION WITH DIFFERENT CHEMOTHERAPY REGIMENS					
SWOG, 1980 ²⁴⁰	60	mCCNU and 5-FU	33	8.8	40 ^b
	60	mCCNU and 5-FU and testolactone	29	6.9	27 ^b
GITSG, 1985 ⁸⁷	60	5-FU	73	8.5	33 ^b
	40	Doxorubicin	70	7.6	26 ^b
Earle et al., 1994 ¹¹⁵	50-60	5-FU	44	7.8	34 ^b
	50-60	Hycanthone	43	7.8	26 ^b

ECOG, Eastern Cooperative Oncology Group; 5-FU, 5-fluorouracil; GITSG, Gastrointestinal Study Group; Gy, Gray; mCCNU, methyl lomustine; SMF, streptozotocin, mitomycin, 5-FU; SWOG, Southwest Oncology Group.

^a $P < .05$.

^bCalculated from survival curve.

[Adapted from Earle CC, Agboola O, Maroun J, et al. The treatment of locally advanced pancreatic cancer: a practice guideline. *Can J Gastroenterol* 2003;17(3):161.]

Several trials have examined the use of different chemotherapy agents with radiation therapy in the locally advanced setting. The first was a Southwest Oncology Group study published in 1980 randomizing 69 patients to mCCNU (methyl lomustine) and 5-FU with or without testolactone, combined with 60 Gy radiation.¹¹³ No significant difference was found in overall survival, and myelosuppression (87%) and GI toxicity (23%) were common. A GITSG study randomized 143 patients to EBRT with either weekly 5-FU or doxorubicin.¹¹⁴ Median survival was similar in both arms (approximately 8 months), but the doxorubicin arm had more frequent severe toxicity. Finally, a randomized phase II study of 87 patients compared the radiation sensitizer hycanthone to 5-FU, both given with 60 Gy of split-course radiation, and found no difference in survival.¹¹⁵ Thus, three trials failed to demonstrate a survival advantage of different chemotherapy regimens given with radiation therapy compared to 5-FU, which tended to have less toxicity.

CHEMORADIATION USING GEMCITABINE

Considerable interest has been shown in combining EBRT with gemcitabine due to its clinical benefit in the metastatic setting and potent radiosensitizing properties. Studies combining radiotherapy with gemcitabine have proceeded cautiously because of this synergy. Early trials were designed to determine the maximal tolerated dose of gemcitabine when delivered weekly and integrated with radiation therapy consisting of 50.4 Gy in standard 1.8-Gy fractions.¹¹⁶ A margin of 3 cm around the gross target volume was required for the initial field of 39.6 Gy. The margin was subsequently reduced to 2 cm for the final

10.8-Gy boost. The starting dose of gemcitabine was 300 mg/m². Hematologic and GI toxicities were identified as dose limiting at 700 mg/m². Blackstock et al.,¹¹⁷ in a phase I study, examined gemcitabine (starting at 20 mg/m²) twice weekly in combination with radiation therapy (total dose 50.4 Gy in 1.8-Gy fractions) in 19 patients with locally advanced pancreatic adenocarcinoma. Thrombocytopenia, neutropenia, and nausea/vomiting were dose-limiting toxicities. Of the 15 patients assessable for response, three partial responses were identified. A dosage of 40 mg/m² twice weekly in combination with radiotherapy to a total dose of 50.4 Gy was subsequently examined by the Cancer and Leukemia Group B (CALGB) in a phase II study of 38 patients with locally advanced PC.¹¹⁸ After chemoradiotherapy, patients without disease progression received gemcitabine alone, 1000 mg/m² weekly \times 3 every 4 weeks for five additional cycles. Grade III/IV hematologic toxicity was significant and identified in 60% of patients. In addition, grade III/IV GI toxicity was identified in 42% of patients. With a median follow-up of 10 months, median survival was 7.9 months.

The MDACC has since published a corollary phase I study of 18 patients with locally advanced disease using rapid fractionation external-beam radiation.¹¹⁹ Patients received dose-escalation gemcitabine from 350 mg/m² to 500 mg/m² weekly \times 7 with concurrent rapid fractionation 3000-cGy EBRT during the first 2 weeks of therapy. Hematologic and nonhematologic toxicities were significant in all three patient cohorts; there were eight responses (four minor and four partial). One of two patients who were subsequently explored had a resection. The recommended phase II testing dose of gemcitabine was 350 mg/m².

These dose-finding studies suggest that the maximal tolerated dose of gemcitabine when combined with radiation therapy is dependent on the radiation therapy field size. Planned confirmatory studies will follow up on these observations.

The University of Michigan has described an alternative approach using standard doses of gemcitabine at 1000 mg/m^2 weekly $\times 3$ every 4 weeks and administering radiation therapy as dose escalation, beginning at 24 Gy (1.6-Gy fractions in 15 fractions) in 34 patients with locally advanced disease.¹²⁰ The majority of patients received chemotherapy after combined modality treatment, at the discretion of the treating physician. Three-fourths of the patients received at least 85% of the planned gemcitabine. Two of six assessable patients experienced dose-limiting toxicity at the final planned radiation dose of 42 Gy in 2.8-Gy fractions. Late GI toxicities developed in an additional two patients at this dose level. Six patients were documented to have a partial response, with a complete radiographic response in two patients. In addition, four patients with documented stable disease at time of study entry experienced objective responses (2 partial and 2 complete responses). Resection was performed in one of three surgically explored patients. With median follow-up of 22 months, median survival for the entire group was 11.6 months. The recommended phase II radiation dose was 36 Gy in 2.4-Gy fractions.

Other chemotherapy agents have been added to gemcitabine combined with radiation therapy. ECOG published a phase I study of seven patients with locally advanced disease using 5-FU/gemcitabine combined with radiation therapy to a maximum dose of 59.4 Gy in 1.8-Gy fractions.¹²¹ 5-FU (200 mg/ m^2/d as continuous infusion throughout radiation therapy) was administered with weekly gemcitabine dose escalation beginning at 100 mg/ m^2 . Because of dose-limiting toxicities seen in two of the first three patients, the study was amended to lower the initial dose of gemcitabine to 50 mg/ m^2 . However, dose-limiting toxicities were subsequently seen in three of four patients at the 50-mg/ m^2 dose. Three of the five dose-limiting toxicities occurred at radiation doses less than 36 Gy. The study was subsequently closed.

Gemcitabine has also been combined with cisplatin and radiation in published phase I trials, following up on promising preclinical synergistic data. A study based at the Mayo Clinic gave twice-weekly gemcitabine and cisplatin for 3 weeks during radiation (50.4 Gy in 28 fractions).¹²² Dose-limiting toxicities consisted of grade 4 nausea and vomiting, and the recommended phase II dose was gemcitabine, 300 mg/ m^2 , and cisplatin, 10 mg/ m^2 . Another trial used strictly time-scheduled gemcitabine (days 2, 5, 26, and 33 because a weekly regimen was too toxic) and cisplatin (days 1 to 5 and 29 to 33) combined with radiation, with a recommended phase II dose of 20 mg/ m^2 for cisplatin and 300 mg/ m^2 for gemcitabine.¹²³ The response to chemoradiation allowed 10 of 30 initially unresectable patients to undergo surgery, with an R0 resection in nine cases and a complete response in two cases.

Given the current published data, would 5-FU or gemcitabine be better suited to be used concurrently with radiation therapy for either resected or locally advanced disease? The MDACC retrospectively examined their database of 114 patients with locally advanced disease treated with combination radiation therapy (rapid fractionation 30 Gy in 10 fractions) with either 5-FU continuous infusion, 200 to 300 mg/ m^2 (61 patients), or gemcitabine, 250 to 500 mg/ m^2 weekly $\times 7$ (53

patients).¹²⁴ A significantly higher incidence of severe acute toxicity (defined as toxicity requiring a hospital stay of more than 5 days, mucosal ulceration with bleeding, more than 3 dose deletions of gemcitabine, or discontinuation of 5-FU, or toxicity resulting in surgical intervention or death) developed in patients receiving gemcitabine compared with those receiving 5-FU (23% vs. 2%, $P < .0001$). Five of 53 patients treated with gemcitabine/radiation therapy subsequently underwent surgical resection compared to 1 of 61 patients treated with 5-FU/radiation therapy. However, with short median follow-up, median survival was similar (11 months vs. 9 months, $P = .19$).

CHEMOTHERAPEUTIC APPROACHES ALONE, WITHOUT RADIATION

Because the benefit of chemoradiation is relatively modest, and the aforementioned randomized ECOG study showed no benefit to radiation added to 5-FU alone,¹¹² some oncologists recommend chemotherapy alone for locally advanced disease. Gemcitabine is the most commonly used agent, extrapolating from the metastatic disease setting. This is based on the randomized trial by Burris et al.,¹²⁵ in which 26% of the study subjects had locally advanced disease. Gemcitabine ameliorated symptoms and modestly improved survival compared to 5-FU, but the results for patients with locally advanced disease were not reported separately. An ECOG phase III trial (E4201) comparing gemcitabine (600 mg/ m^2 weekly)/radiation (50.4 Gy in 28 fractions) followed by weekly gemcitabine (1000 mg/ m^2 weekly, 3 of 4 weeks) versus gemcitabine opened in April 2003 and is examining this issue.

LOCALLY DIRECTED THERAPY

Brachytherapy and intraoperative radiotherapy (IORT) have been used in the setting of locally advanced disease. Both modalities are aimed at improving local-regional tumor control. Given the propensity of this disease to disseminate into the liver, adjacent peritoneum, and systemically, what can be achieved overall for patients by the addition of either of these modalities to external-beam irradiation and chemotherapy is not completely clear.

Mohiuddin et al.¹²⁶ reported on 81 patients with localized unresectable carcinoma of the pancreas managed using intraoperative iodine 125 (^{125}I) implants, external-beam irradiation, and perioperative systemic chemotherapy. The radioactive iodine implant was designed to deliver a minimum peripheral dose up to 1200 cGy over 1 year. Patients were also treated with 50 to 55 Gy external-beam irradiation and systemic chemotherapy consisting of 5-FU, mitomycin, and occasionally CCNU. Implants were performed at laparotomy. The mortality was 5%, and a 34% acute morbidity rate occurred, with cholangitis, upper GI bleeding, and gastric outlet obstruction being the most common. In addition, there was a 32% late morbidity rate, with GI bleeding, cholangitis, and radiation enteritis being the most common late developments. Local control was obtained in 39 of 53 (74%) evaluable patients. Of 14 patients undergoing reexploration more than 6 months after implantation, 86% showed extensive fibrosis and had negative biopsies from the region of the tumor. In eight patients undergoing autopsy, five (63%) were without evidence of local or regional tumor. Nevertheless, 52 of these 81 patients (64%) failed, with intraabdominal disease, primarily hepatic and peritoneal. With a minimum follow-

up of 2 years at the time of publication, the median survival for the total group was 12 months, the 2-year survival was 21%, and the 5-year survival was 7%. Despite satisfactory local control in several patients, many centers would not be willing to accept this level of therapeutic intensity in a group of patients for whom the management paradigm is not curative.

Nori et al.¹²⁷ have reported on a series of 15 patients undergoing similar management but using palladium 103 instead of ¹²⁵I. The implant was designed to provide a matched peripheral dose of 1100 cGy. Patients also received external-beam irradiation of 4500 cGy over 4.5 weeks and chemotherapy with 5-FU and MMC. Median survival was 10 months. The authors concluded that palladium 103 is an alternative to ¹²⁵I for interstitial brachytherapy for unresectable patients and that symptom relief appeared to occur somewhat faster. The study did not show any improvement in the median survival as compared to ¹²⁵I. Finally, a note of caution was raised by Raben et al.¹²⁸ on the use of palladium brachytherapy for locally unresectable carcinoma of the pancreas. In their series of 11 patients, they found an unacceptably high complication rate, including gastric outlet obstruction, duodenal perforation, and sepsis. They did not find an improvement in median survival over other modalities and did not recommend this approach for further study.

The use of IORT using single-fraction electron-beam treatment has also been extensively studied. In experienced hands, IORT can be given with acceptable morbidity. However, there are occasional reports of unacceptably high complication rates. Generally, intraoperative radiation therapy has been given in combination with EBRT in the range of 45.0 to 50.4 Gy with 5-FU alone or 5-FU-based combination chemotherapy. The Radiation Therapy Oncology Group reported on 51 patients with unresected nonmetastatic PC treated with IORT and EBRT/5-FU, and found a major postoperative complication rate of 12%.¹²⁹ Two patients had major morbidity leading to death. Zerbi et al.¹³⁰ have suggested that the use of intraoperative radiation therapy as an adjuvant to resection decreases the risk of local recurrence. As reviewed by Willett and Warshaw,¹³¹ the dose of intraoperative radiation therapy is generally in the range of 10 to 20 Gy, with some investigators prescribing to the 90% line and others prescribing to the 100% line.

In addition to local radiation delivery, a variety of other techniques and agents are under development for the treatment of locally advanced PC. One example is intratumoral injection via endoscopic ultrasound of ONYX-015, an engineered adenovirus that selectively replicates in tumor cells. A phase I/II trial of this agent combined with gemcitabine in 21 patients showed that the technique was feasible, and two partial responses were seen.¹³² Another novel biologic agent in development is TNFerade, a replication-deficient adenovector carrying a transgene encoding for human tumor necrosis factor- α regulated by a radiation-inducible promoter.¹³³ Weekly intratumoral injections have been given in combination with chemoradiation (50.4 Gy along with continuous-infusion 5-FU, 200 mg/m² daily). In a phase I trial, 2 of 17 patients converted from unresectable to resectable, and 1 of these had a pathologic complete response.

TREATMENT RECOMMENDATIONS FOR LOCALLY ADVANCED DISEASE

The optimal treatment for locally advanced PC remains controversial. No randomized trials have compared either chemoradi-

ation strategies versus best supportive care or chemotherapy alone (aside from the GITSG trial in which 5-FU and radiation were added to SMF chemotherapy), and the survival benefit from combined modality therapy for locally advanced disease has been modest in various trials. Nonetheless, most practitioners in the United States use radiation therapy (typically, 54 Gy in 1.8-Gy fractions) with simultaneous chemotherapy, the standard being 5-FU. Although several chemotherapy regimens have been compared to 5-FU in randomized trials, none have proven more efficacious, and they are typically more toxic. Various ways of giving 5-FU have been used in these trials, but most practitioners choose either continuous-infusion 200 mg/m²/d during radiation therapy or a 500-mg/m² bolus given on the first 3 days and last 3 days of radiation. Studies are under way that will examine the role of gemcitabine (alone and combined with radiation) for locally advanced disease. In addition, given the limited success of current treatments, several novel approaches are being actively explored, with the aim of allowing patients who present with unresectable disease to undergo curative surgery.

TREATMENT OF METASTATIC AND RECURRENT DISEASE

The standard treatment of patients with advanced metastatic or recurrent pancreatic adenocarcinoma and adequate performance status, or both, is systemic chemotherapy. The natural history of PC with a high intrinsic tendency to early spread to lymph nodes and other organs, as well as the relative inefficacy of existing treatments for localized or locally advanced disease, implies that the vast majority of patients will eventually be considered candidates for systemic treatments.

Several general considerations can be made regarding the role of chemotherapy in patients with PC. First, PC is intrinsically highly resistant to the majority of existing anticancer agents. The outcome of patients treated with currently available drugs is poor, and treatment should be considered palliative. Second, patients with advanced PC are frequently symptomatic and debilitated, with a poor performance status and symptoms such as pain, nausea and vomiting, fatigue, anorexia, weakness, and weight loss that compromise the ability to administer full and rigorous chemotherapy treatments. Third, patients with PC often have elevated bilirubin and alkaline phosphatase as well as alterations in other liver function parameters, which further limit the administration of drugs that are cleared by the liver. Finally, the assessment of objective response to chemotherapy is difficult, because PC patients frequently lack bidimensional measurable disease. This last factor has resulted in a large variation in response rate in phase II studies published in the literature and complicates the evaluation of new drugs in this disease. More recently, the less biased parameters of time to tumor progression, progression-free survival or overall survival, and quality-of-life end points are frequently used for this purpose.

HISTORICAL PERSPECTIVE

The role of chemotherapy in PC has been evaluated in clinical studies that compare the quality of life and survival of patients with PC who received chemotherapy against patients who were treated with supportive care alone. Glimelius et al.¹³⁴ random-

ized 90 patients with advanced pancreatic or biliary tract cancer to chemotherapy with either 5-FU/leucovorin and etoposide or 5-FU/leucovorin alone versus best supportive care. Patients treated with chemotherapy had better improvement in quality of life as determined by the EORTC Quality of Life Questionnaire-C30 scale (36% improvement in the chemotherapy group vs. 10% in the best supportive group, $P = .01$) and survival (median survival, 6.0 vs. 2.5 months; $P < .01$). A second small randomized trial that compared treatment with 5-FU/adriamycin and MMC with supportive care reported a median survival of 8.5 months in patients treated with chemotherapy and 3.75 months in patients who received best supportive care alone ($P = .002$).¹³⁵ Furthermore, in a Japanese study patients with advanced pancreatic and biliary tract cancer were randomized to either treatment with FAM (5-FU, adriamycin, and MMC) or supportive care. Patients treated with FAM had longer time to tumor progression but not overall survival.¹³⁶ Altogether these studies indicate that systemic chemotherapy has a palliative role in patients with advanced PC.

5-FU had been considered the most active chemotherapeutic agent in the treatment of patients with advanced PC for many years. Response rates ranged from 0 to 20% in phase II studies in which responses were assessed using modern CT, whereas responses were as high as 28% in studies in which rigorous assessment of tumor response was not applied. Median survival of patients treated with 5-FU ranged from 4 to 5 months in most of these studies. No clear evidence has been shown that the varied administration schedules (bolus vs. infusion regimens) and dose-regimens of 5-FU result in a better outcome. In addition, modulation of 5-FU with other agents, such as leucovorin, methotrexate, interferon- α , or N-(phosphonacetyl)-L-aspartate (PALA) did not result in increased response rate in phase II studies. Because of its single-agent activity, 5-FU was also an important component of multichemotherapy regimens. A number of combination chemotherapy regimens were developed and tested from the 1970s to 1990s, such as combinations of 5-FU with adriamycin and MMC (FAM); cyclophosphamide, methotrexate, vincristine, and MMC (Mallison regimen); epirubicin, cisplatin, carboplatin, caffeine, and high-dose cytarabine (CAG); and streptozotocin. The detailed summary of these studies, which have historic interest, is beyond the scope of this chapter and can be found in previous editions of this textbook.¹³⁷ In general, these combination phase II studies showed higher response rates than 5-FU single-agent regimens, with responses as high as 37% to 43% observed in phase II studies with the FAM and SMF regimens. These promising results, however, were not confirmed in randomized phase III studies, in which the survival of patients treated with 5-FU alone was not statistically different from that of patients treated with more aggressive and toxic chemotherapy regimens. In summary, past studies indicated that single-agent 5-FU was the most active agent in PC and that alternate schedules and doses, modulation strategies, and multichemotherapy treatments were not superior to 5-FU alone.

SINGLE-AGENT CHEMOTHERAPY

During the last decade, a large number of chemotherapeutic agents have been tested in phase II and phase III studies in patients with advanced PC. Table 29.3-14 summarizes the most

salient features of selected phase II studies with these drugs, and a discussion of the most relevant agents is provided in the following paragraphs.

GEMCITABINE

Gemcitabine (2',2'-difluorodeoxycytidine, dFdC, Gemzar; Eli Lilly, Indianapolis, IN) is a nucleoside analog that showed anti-tumor activity in various preclinical models of cancer, including PC.^{138,139} On the basis of its favorable toxicity profile in phase I studies, gemcitabine was evaluated in phase II studies in patients with PC. Table 29.3-15 summarizes single-agent gemcitabine phase II and III studies, comparing gemcitabine with other chemotherapy agents in PC. Studies comparing gemcitabine with novel drugs are discussed in Combination Chemotherapy Regimen, later in this chapter. In a multicenter phase II study in which gemcitabine was given at a dose of 800 mg/m² as a 30-minute intravenous injection weekly for 3 consecutive weeks followed by 1 week of rest, 5 of 44 patients (11%) had an objective response.¹⁶¹ In a similar study that enrolled 34 patients, 2 (6.3%) had an objective response, and the median survival was 6.3 months.¹⁶² An important observation in these initial studies was that despite a very modest objective response rate, patients improved in other clinically relevant parameters, such as weight loss, pain, requirements of analgesia, and performance status. This finding prompted the evaluation of the drug in two subsequent studies incorporating a new clinical end point called *clinical benefit response* (CBR). CBR was defined as a composite measurement in two primary parameters, Karnofsky performance status and pain, and a secondary parameter, weight gain. Patients needed to be stable in pain and analgesic consumption before study entry. They were classified as having a positive response if they had an improvement that lasted more than 4 weeks in any of the parameters, without simultaneous deterioration in any other parameter. The first study evaluated the activity of gemcitabine in 74 patients with 5-FU-refractory PC.¹⁶³ Sixty-three patients completed a prestudy pain stabilization phase and were treated with 1000 mg/m² gemcitabine administered weekly for 7 consecutive weeks followed by 1-week rest and then weekly for 3 consecutive weeks every 4 weeks. Seventeen of 63 patients (27%) attained a CBR. The median duration of CBR was 14 weeks, and the median survival for patients treated with gemcitabine was 3.85 months.

A second randomized phase III clinical trial compared the CBR, time to progression, and survival of patients with advanced metastatic adenocarcinoma of the pancreas who had not received prior systemic therapy.¹⁶⁴ One hundred twenty-six patients with advanced symptomatic PC completed a lead-in period to characterize and stabilize pain and then were randomized to receive either gemcitabine at the same dose and schedule described above (63 patients) or to 5-FU, 600 mg/m² once a week (63 patients). More than 70% of the patients had stage IV disease and a Karnofsky performance status of 50% to 70%. A positive CBR was experienced by 23.8% of gemcitabine-treated patients compared with 4.8% of 5-FU-treated patients ($P = .0022$). The median survival durations were 5.65 and 4.41 months for gemcitabine-treated and 5-FU-treated patients, respectively ($P = .0025$). The survival rate at 12 months was 18% for gemcitabine patients and 2% for 5-FU patients. The response rate was 5.4% for gemcitabine and 0% for 5-FU, supporting the notion that the response rate is a poor marker of clinical benefit.

TABLE 29.3-14. Selected Single-Agent Chemotherapy Studies in Patients with Advanced Pancreatic Cancer

Class	Agent	No. of Patients	Patient Characteristics	RR	Median Survival (Mo)	1-Y Survival	Reference
Antimicrotubule	Docetaxel	43	First line	15	7	NR	Rougier et al., 2000 ¹⁴⁰
	Docetaxel	33	First line	6	9	36.4	Androulakis et al., 1999 ¹⁴¹
	Docetaxel	21	First line	4.7	5.9	NR	Lenzi et al., 2002 ¹⁴²
	Docetaxel	21	First line	0	3.9	NR	Okeda et al., 1999 ¹⁴³
	Paclitaxel	18	Second line	5.5	NR	NR	Oettle et al., 2000 ¹⁴⁴
Platinum	DHA-paclitaxel	42	First line	3.3	7.6	NR	Jacobs et al., 2003 ¹⁴⁵
	Oxaliplatin	18	NR	0	2.6	NR	Rougier et al., 2000 ¹⁴⁶
Topoisomerase I inhibitors	Irinotecan	34	First line	9	5.2	NR	Wagener et al., 1995 ¹⁴⁷
	Rubitecan	19	First and second line	28.6	5.25	16.7	Konstadoulakis et al., 2001 ¹⁴⁸
	Exatecan	39	First and second line	5	5.5	27	D'Adamo et al., 2001 ¹⁴⁹
Fluoropyrimidines	Capecitabine	42	First line	7.3	6	NR	Cartwright et al., 2002 ¹⁵⁰
	UFT	14	NR	0	3.75	NR	Mani et al., 1998 ¹⁵¹
	S-1	31	First line	22.6	15.3	NR	Hayashi et al., 2003 ¹⁵²
	5-FU-entiluracil	116	First and second line	8 (first line), 2 (second line)	3.6 (first line), 3.4 (second line)	16 (first line), 10 (second line)	Rothenberg et al., 2002 ¹⁵³
Antifolate	Pemetrexed	42	First line	5.7	6.5	28	Miller et al., 2000 ¹⁵⁴
	Raltitrexed	42	NR	5	NR	NR	Pazdur et al., 1996 ¹⁵⁵
	Raltitrexed ^a	19	Second line	0	4.3	—	Ulrich-Pur et al., 2003 ¹⁵⁶
	ZD9331 ^b	30	First line	3	5	NR	Smith and Gallagher, 2003 ¹⁵⁷
Nucleoside analog	Troxacitabine	55	First line	0	NR	NR	Lapointe et al., 2002 ¹⁵⁸
Antiandrogen	Flutamide	14	Second line	0	4.7	—	Sharma et al., 1997 ¹⁵⁹
	Flutamide ^c	24	First line	NR	8	NR	Greenway, 1998 ¹⁶⁰

DHA, decosahexanoic acid; NR, not reported; RR, response rates; UFT, uracil/fluorouracil.

^aRandomized versus raltitrexed + irinotecan.

^bRandomized comparison to gemcitabine.

^cRandomized comparison to placebo. Statistically significant better survival for flutamide group versus placebo group (4 months, $P = .01$).

in patients with PC. Because of the CBR advantage observed in these studies, gemcitabine was made available through an investigational new drug program before regulatory approval. This program enrolled 3023 patients, 80% of whom had stage IV disease. A retrospective analysis of these patients indicated that 18.4% had improvement in symptoms. The response rate in 982 evaluable patients was 12%, and median progression-free survival and overall survival were 2.7 and 4.8 months in 2012 and 2380 evaluable patients, respectively.^{165,166} Based on these studies, gemcitabine was approved for the treatment of patients with advanced PC in the United States and many other countries and is currently considered the standard agent for the treatment of this disease, as well as the accepted control with which to compare new drugs and interventions.

Other studies have explored alternative schedules for administering gemcitabine. Based on the mechanism of action of the drug, it was postulated that a prolonged administration schedule would result in a more sustained intracellular accumulation of the active metabolite dFdCTP.¹⁶⁷ Phase I studies of gemcitabine using a fixed-dose-rate administration in patients with solid tumors showed that the maximum tolerated dose was 1500 mg/m² administered as 10 mg/m²/min.¹⁶⁸ This promising approach was subsequently tested in a randomized phase II study in patients with chemotherapy-naïve PC.¹⁶⁹ Ninety patients were randomized to receive gemcitabine at a dose of 2200 mg/m² as a 30-minute infusion or 1500 mg/m² at a fixed dose rate of 10 mg/m²/min. The drug was given weekly for 3 consecutive weeks every 4 weeks in both arms of the study.

TABLE 29.3-15. Studies of Single-Agent Gemcitabine in Pancreatic Cancer

Authors	Phase	Dose/Schedule	No. of Patients	Patient Characteristics	RR (%)	CBR (%)	Median Survival (Mo)	I-Y Survival (%)
Casper et al., 1994 ¹⁶¹	II	Gemcitabine, 800 mg/m ² days 1, 8, 15 q4wk	44	First line	11	NR	5.6	23
Carmichael et al., 1996 ¹⁶²	II	Gemcitabine, 800 mg/m ² days 1, 8, 15 q4wk	34	First line, 58% stage IV	6	NR	3.3	NR
Rothenberg et al., 1996 ¹⁶³	II	Gemcitabine, 1000 mg/m ² weekly × 7, 1 wk rest; days 1, 8, 15 q4wk	63	5-FU refractory	10.5	27	3.8	4
Burris et al., 1997 ¹⁶⁴	III	Gemcitabine, 1000 mg/m ² weekly × 7; 1 wk rest, days 1, 8, 15 q4wk	63	First line, >70% stage IV	5.4	23.8 (P = .0022)	5.6 (P = .0025)	18
Storniolo et al., 1999 ¹⁶⁵	TIND	5-FU, 600 mg/m ² weekly Gemcitabine, 1000 mg/m ² weekly × 7; 1 wk rest, days 1, 8, 15 q4wk	63 3023	First and second line	0 12.1	4.8 17.2	4.4 5.7	2 15

CBR, clinical benefit response; 5-FU, 5-fluorouracil; NR, not reported; RR, response rate; TIND, treatment investigational new drug

Patients treated with the fixed-dose-rate regimen experienced more toxicities, with 49% and 37% occurrence of neutropenia and thrombocytopenia versus 28% and 10%, respectively, in patients treated in the conventional schedule. Patients on the fixed-dose-rate had a higher response rate (11.6% vs. 4.1%), median survival (8 vs. 5 months), and 1-year survival (23.8% vs. 7.3%) than patients treated on the conventional schedule. Consistent with prior observations, the fixed-dose-rate infusion resulted in higher intracellular levels of dFdCTP in peripheral blood mononuclear cells. This strategy is now being tested in randomized phase III studies.

COMBINATION CHEMOTHERAPY REGIMENS

The superiority of single-agent gemcitabine versus 5-FU in patients with advanced PC led to the acceptance of this drug as the standard of care for these patients and introduced an agent with which to combine other existing and new drugs. Since the approval of gemcitabine, a large number of phase I/II and, more recently, phase III clinical trials have tested the safety and tolerability of gemcitabine in combination with other drugs and compared the efficacy of the combination regimens with single-agent gemcitabine. In general, the rationale to develop these regimens has been based on clinical and pharmacologic criteria, with the goal to combine drugs with demonstrated single-agent activity, not overlapping toxicity, and different mechanisms of action. Most of the studies have used the conventional 30-minute infusion regimen of gemcitabine, whereas more recent studies have also incorporated the fixed-dose-rate infusion regimens. The next section describes the main features of some of these regimens.

Gemcitabine-Fluoropyrimidine Combinations

The combination of gemcitabine and 5-FU has been extensively studied in multiple clinical trials, the most relevant of which are summarized in Table 29.3-16. The fluoropyrimidine studied has varied substantially and has included single-agent 5-FU (given as bolus, 24- and 48-hour infusion, and

protracted continuous infusion), modulated 5-FU, and oral fluoropyrimidines such as capecitabine and uracil/fluorouracil. The combination of gemcitabine and 5-fluoropyrimidines has been, in general, very well tolerated and has permitted the administration of both agents at full dose in most clinical trials. In noncomparative studies, the combination regimens have been associated with a modest increase in response rate, median survival, and 1-year survival, although a substantial variability is seen among trials. Of interest, the majority of studies that assessed CBR have reported a high rate of symptom improvements in these trials, with responses in the 40% to 50% range.

Three studies have compared the toxicity and efficacy of gemcitabine combined with fluoropyrimidines versus gemcitabine alone. Di Constanzo et al.¹⁸¹ compared a combination of gemcitabine plus continuous-infusion 5-FU with gemcitabine alone in 92 patients with advanced PC in a randomized phase II design. Patients treated with the combined treatment arm experienced more frequent thrombocytopenia and mucositis. No differences in outcome were observed in this trial, which reported 8% and 11% response rates in the single and combined arm, respectively, and an identical 6-month median survival. A similar randomized phase II study compared the combination of gemcitabine plus the oral fluoropyrimidine capecitabine with gemcitabine alone,¹⁸⁸ with no differences in any outcome parameter being observed. Berlin et al.¹⁸² reported a randomized phase III study conducted by the ECOG, in which patients with locally advanced or advanced PC were treated with either gemcitabine alone or the combination of gemcitabine plus weekly bolus 5-FU. Patients treated with the combination arm had a significantly longer progression-free survival (3.4 months) than patients treated with single-agent gemcitabine (2.2 months). No differences were observed with regard to response rate and overall survival. In summary, although the combination of gemcitabine with a fluoropyrimidine is well tolerated, there is no evidence of meaningful improvement in any relevant parameter of outcome, and therefore the combination can not be recommended for routine use.

TABLE 29.3-16. Gemcitabine-Fluoropyrimidine Combinations in Advanced Pancreatic Cancer

Author	Gemcitabine Dose/Schedule	Fluoropyrimidine Dose/Schedule	Phase	No. of Patients	Response Rate (%)	CBR (%)	Median Survival (Mo)	I-Y Survival (%)
Cascinu et al., 1999 ¹⁷⁰	1000 mg/m ² d 1, 8, 15 q4wk	5-FU, 600 mg/m ² bolus d 1, 8, 15 q4wk	II	54	37	51	7	22
Hidalgo et al., 1999 ¹⁷¹	900 mg/m ² d 1, 8, 15 q4wk	5-FU, 200 mg/m ² /d continuous infusion	I/II	26	19	45	10.3	39.5
Berlin et al., 2000 ¹⁷²	1000 mg/m ² d 1, 8, 15 q4wk	5-FU, 600 mg/m ² bolus d 1, 8, 15 q4wk	II	36	14	NR	4.4	8.6
Cascinu et al., 2000 ¹⁷³	1500 mg/m ² at 10 mg/m ² /min d 1, 8 q3wk	5-FU, 600 mg/m ² bolus d 1, 8 q3wk	II	34	17	17	5.7	
Oettle et al., 2000 ¹⁷⁴	1000 mg/m ² d 1, 8, 15 q4wk	Leucovorin, 200 mg/m ² 2-h infusion, and 5-FU, 750 mg/m ² 24-h infusion d 1, 8, 15 q5wk	II	38	5	NR	9.3	32
Matano et al., 2000 ¹⁷⁵	1000 mg/m ² d 1, 8, 15 q4wk	5-FU, 500 mg/m ² continuous infusion d 1-5	II	11	9	64	NR	NR
Feliu et al., 2000 ¹⁷⁶	1000 mg/m ² d 1, 8, 15 q4wk	6S-stereoisomer of leucovorin (6SLV), 250 mg/m ² 2-h infusion on d 1; oral 6SLV, 7.5 mg/12 h on d 2-14, and oral UFT, 390 mg/m ² /d (in 2 doses) on d 1-14	II	42	16	47	7	21
Kurtz et al., 2000 ¹⁷⁷	1000 mg/m ² d 1, 8, 15 q4wk	5-FU, 200 mg/m ² /d continuous infusion d 1, 8, 15 q4wk	II	29	10	39	4	NR
Rauch et al., 2001 ¹⁷⁸	1000 mg/m ² d 1, 8, 15 q4wk	5-FU, 200 mg/m ² /d continuous infusion	II	25	20	65	7	NR
Louvet et al., 2001 ¹⁷⁹	1000-1500 mg/m ² on d 3 q2wk	Leucovorin, 400 mg/m ² over 2 h, followed by 5-FU, 400 mg/m ² bolus and 2-3 g/m ² infused over 46 h q2wk	II	62	26	49	9	32
Marantz et al., 2001 ¹⁸⁰	1000 mg/m ² d 1, 8, 15 q4wk	Leucovorin, 20 mg/m ² ; 5-FU, 600 mg/m ² bolus d 1, 8, 15 q4wk	II	29	21	NR	8.4	36
DiConstanzo et al., 2001 ¹⁸¹	Arm A: 1000 mg/m ² weekly x 7; 1 wk rest; d 1, 8, 15 q4wk	Arm A: None	II	48	8	NR	6	NR
	Arm B: 1000 mg/m ² weekly x 7; 1 wk rest, d 1, 8, 15 q4wk	Arm B: 5-FU, 200 mg/m ² /d continuous infusion 6 wk on 2 wk off		44	11	NR	6	NR
Berlin et al., 2002 ¹⁸²	Arm A: 1000 mg/m ² d 1, 8, 15 q4wk	Arm A: None	III	163	5.6	NR	5.4	NR
	Arm B: 1000 mg/m ² d 1, 8, 15 q4wk	Arm B: 5-FU, 600 mg/m ² bolus d 1, 8, 15 q4wk		164	6.9		6.7 (P=.9)	
Feliu et al., 2002 ¹⁸³	1200 mg/m ² at 10 mg/m ² /min d 1, 8, 15 q4wk	Oral UFT, 400 mg/m ² /d (in 2-3 doses/d) for 3 consecutive wk q4wk	II	43	33	64	11	32
Barone et al., 2003 ¹⁸⁴	1000-1200 mg/m ² d 1, 8, 15 q4wk	5-FU, 2000-2250 mg/m ² 24-h infusion d 1, 8, 15 q4wk	I/II	21	9.5	50	11	33
Murad et al., 2003 ¹⁸⁵	1000 mg/m ² d 1, 8, 15 q4wk	5-FU, 500 mg/m ² bolus days 1, 8, 15 q4wk	II	26	29	41	9	30
Correale et al., 2003 ¹⁸⁶	1000 mg/m ² d 1, 8 q3wk	Leucovorin, 100 mg/m ² , by 5-FU, 400 mg/m ² bolus d 1-3 q2wk	II	42	31	NR	13.1	NR
Hess et al., 2003 ¹⁸⁷	1000 mg/m ² 2 wk on 1 wk off	Capecitabine, 500-800 mg/m ² b1d, continuously for 2 wk q3wk	I/II	36	15	NR	6.3	33
Scheithauer et al., 2003 ¹⁸⁸	Arm A: 2200 mg/m ² every other wk	Arm A: None	II	42	14	33	8.2	37
	Arm B: 2200 mg/m ² every other wk	Arm B: Capecitabine, 1250 mg/m ² b1d 1 wk on 1 wk off		41	17	48.4	9.5	31.8

CBR, clinical benefit response; 5-FU, 5-fluorouracil; NR, not reported; UFT, uracil/fluorafur

Gemcitabine-Cisplatin Combinations

Studies testing the combination of gemcitabine with cisplatin are summarized in Table 29.3-17. The rationale for this combination is based on preclinical studies demonstrating synergistic activity between the two drugs, likely due to a decreased ability of the cell to repair DNA damage induced by cisplatin in the presence of gemcitabine. In addition, cisplatin has modest single-agent activity in PC, with a 21% objective response rate and a 5-month median survival in phase II studies.¹⁹⁵ Furthermore, the toxicity profile of cisplatin (with nausea and vomiting and nephro-, neuro-, and ototoxicity) does not overlap with the preferential hematologic toxic effects of gemcitabine. The combination studies have used a weekly administration schedule of the two drugs and have demonstrated a reasonable tolerability profile. As occurred in the combination studies with fluoropyrimidines, the response rates and median survivals of patients treated with gemcitabine in combination with cisplatin have been higher than those reported with gemcitabine alone and have ranged from response rates of 9% to 31%, with median survival figures ranging from 5.0 to 9.6 months. In a randomized phase II study conducted by Colucci et al.,¹⁹² the combination of gemcitabine and cisplatin resulted in a higher response rate (26.4% vs. 11.0%) and time to tumor progression (5 vs. 2 months) but no significant differences in median or 1-year survival. The combination arm resulted in higher hematologic toxicity. The preliminary results from a phase III randomized clinical trial have also been presented.¹⁹⁴ The trial enrolled a total of 198 patients with advanced or locally advanced PC. The combined gemcitabine-cisplatin regimen resulted in a statistically significant prolongation of time to tumor progression from 2.5 to 6.4 months, with no significant improvement in the objective response rate or overall survival.

Gemcitabine-Oxaliplatin Combinations

The combination of gemcitabine with oxaliplatin has been reported in two published phase II studies. The GERCOR (Oncology Multidisciplinary Research Group) cooperative group assessed the efficacy and toxicity of a biweekly regimen of oxaliplatin, 100 mg/m², and gemcitabine, 1000 mg/m² administered as a 10-mg/m² fixed-dose-rate infusion in patients with advanced or locally advanced PC.¹⁹⁶ Sixty-four patients were treated, and 30% of them achieved an objective response. Symptom improvement was noticed in 40% of the patients. The median survival and 1-year survival were 5.3 months and 36%, respectively. Overall, the treatment was very well tolerated, with fewer than 15% of the patients having grade 3 to 4 toxicity. The second study was conducted by the North Central Cancer Treatment Group cooperative and enrolled 47 patients in a regimen of oxaliplatin, 100 mg/m² on day 1, and gemcitabine, 1000 mg/m² on days 1 and 8, with cycles repeated every 3 weeks, a regimen based on a prior phase I study conducted by the same group.^{197,198} The overall response rate was 10.9%, and the median survival was 6.2 months. In a preliminary report of a phase III study, the combination of gemcitabine-oxaliplatin using the GERCOR regimen described above resulted in an increase in progression-free survival from 4 to 6 months.¹⁹⁹ The study, however, included two variables: the addition of oxaliplatin and the use of a fixed-dose-rate infusion rather than the conventional 30-minute infusion, making it difficult to determine which one is responsible for the apparent improvement. Based on these data, ECOG 6201 is comparing standard gemcitabine, with fixed-dose-rate infusion gemcitabine, with the gemcitabine-oxaliplatin combination as developed by the GERCOR group. This study will provide definitive data with regard to the relative merits of adding oxaliplatin to gemcitabine, as well as the dosing schedule of gemcitabine.

TABLE 29.3-17. Gemcitabine-Cisplatin Combinations in Advanced Pancreatic Cancer

Author	Gemcitabine Dose/ Schedule	Cisplatin Dose/ Schedule	Phase	No. of Patients	Response Rate (%)	CBR (%)	Median Survival (Mo)	1-Y Survival (%)
Brodowicz et al., 2000 ¹⁸⁹	1000 mg/m ² d 1, 8, 15 q4wk	35 mg/m ² d 1, 8, 15 q4wk	II	16	31	NR	9.6	NR
Heinemann et al., 2000 ¹⁹⁰	1000 mg/m ² d 1, 8, 15 q4wk	50 mg/m ² d 1 and 15 q4wk	II	41	11.4	NR	8.2	27
Philip et al., 2001 ¹⁹¹	1000 mg/m ² d 1, 8, 15 q4wk	50 mg/m ² d 1 and 15 q4wk	II	42	26	NR	7.1	19
Colucci et al., 2002 ¹⁹²	Arm A: 1000 mg/m ² weekly \times 7; 1 wk rest; d 1, 8, 15 q4wk	Arm A: None	II	44	9.2	49	5	11
	Arm B: 1000 mg/m ² weekly \times 7; 1 wk rest, d 1, 8, 15 q4wk	Arm B: 25 mg/m ² weekly \times 7, 1 wk rest; d 1, 8, 15 q4wk		53	26.4 (P = .02)	53	7.5	11.3
Cascinu et al., 2003 ¹⁹³	1000 mg/m ² d 1, 8 q3wk	25 mg/m ² d 1, 8 q3wk	II	45	9	24	5.6	NR
Heinemann et al., 2003 ¹⁹⁴	Arm A: 1000 mg/m ² d 1, 8, 15 q4wk	Arm A: None	III	100	8	NR	6	NR
	Arm B: 1000 mg/m ² d 1 and 15 q4wk	Arm B: 50 mg/m ² d 1 and 15 q4wk		98	10.2	NR	7.6 (P = .1)	NR

CBR, clinical benefit response; NR, not reported.

Gemcitabine-Docetaxel Combination

The combination of gemcitabine and docetaxel was developed based on early reports suggesting that docetaxel was very active as a single agent in patients with PC.¹⁴⁰ Cascinu et al.²⁰⁰ from the GISCAD (Italian Group for the Study of Digestive Tract Cancer) reported a phase I/II study of docetaxel, 70 to 80 mg/m² on day 8, and gemcitabine, 1000 mg/m² on days 1 and 8 every 21 days. The maximum tolerated dose of the regimen was 70 mg/m² docetaxel, with higher doses resulting in dose-limiting hematologic toxicity. Eighteen patients were treated in the phase II portion of the study, with only one partial response (5.5%) and a median survival of 5.4 months, which resulted in early termination of the study. Jacobs²⁰¹ conducted a phase II study of docetaxel, 75 mg/m² on day 1, and standard gemcitabine, 1000 mg/m² on days 1, 8, and 15 every 28 days. The regimen had to be modified to a weekly docetaxel schedule of 40 mg/m² on days 1 and 8, with gemcitabine, 1000 mg/m², administered the same days every 21 days, because grade 2 to 3 hematologic toxicity developed in 13 of the first 18 patients. Overall, seven patients achieved a partial response, for a median time to progression of 5.25 months. The combination of gemcitabine-docetaxel (gemcitabine, 800 mg/m² on days 1 and 8, and docetaxel, 85 mg/m² every 3 weeks) has been compared to cisplatin-docetaxel (cisplatin, 75 mg/m² on day 1, and docetaxel, 75 mg/m² on day 1 every 21 days) in a randomized phase II study conducted by the EORTC.²⁰² Preliminary data from this study indicate that the regimens are equally effective, with a response rate of 16% and a median survival of 7.6 and 7.1 months, respectively. The combination of docetaxel-gemcitabine is currently one of the experimental arms of CALGB 89904, a phase III randomized clinical trial in which patients with advanced PC are randomized to treatment with fixed-dose-rate gemcitabine (10 mg/m²/min × 150 minutes on days 1, 8, and 15 every 28 days), gemcitabine-cisplatin (gemcitabine, 1000 mg/m² on days 1, 8, and 15, and cisplatin, 50 mg/m² on days 1 and 15), gemcitabine-docetaxel (gemcitabine, 1000 mg/m² on days 1 and 8, and docetaxel, 40 mg/m² on days 1 and 8 every 21 days), or gemcitabine-irinotecan (gemcitabine, 1000 mg/m² on days 1 and 8, and irinotecan, 100 mg/m² on days 1 and 8).

Gemcitabine-Topoisomerase I Inhibitor Combination Studies

The topoisomerase inhibitor most widely studied in PC is irinotecan. In a phase I study of gemcitabine combined with irinotecan, the maximum tolerated dose of the drugs was 1000 mg/m² gemcitabine and 100 mg/m² irinotecan on days 1 and 8 every 21 days.²⁰² A subsequent phase II study with this regimen showed a 20% objective response rate in 45 patients treated, and 30% of the patients had a greater than 50% reduction in CA 19-9 levels.²⁰³ Median and 1-year survival were 5.7 months and 27%, respectively. These results are very similar to those obtained by Stathopoulos et al.²⁰⁴ using a different regimen in which patients received gemcitabine, 1000 mg/m² on days 1 and 8, and irinotecan, 300 mg/m² on day 8, with cycles repeated every 21 days.²⁰⁴ A total of 60 patients were treated, reporting an objective response rate of 24.7%, median survival of 7 months, and 1-year survival of 22.5%. Despite these encouraging results, a phase III randomized trial that compared gemcitabine with gemcitabine plus irinotecan using the day 1 and 8 schedule mentioned above in a total of 360 patients with locally advanced or advanced PC failed to demonstrate a survival

benefit for the combination.²⁰⁵ Patients treated with the combination had a higher response rate of 16.1% versus 4.4% ($P = .001$) but similar time to tumor progression (3.5 to 3.0 months; $P = .352$) and survival (6.3 vs. 6.6 months; $P = .789$). Toxicity was similar in the two groups, with patients treated with the combination arm having a higher occurrence of diarrhea (19% vs. 2%) and the groups having similar quality-of-life scores. As mentioned earlier, CALGB 89904 is currently testing the gemcitabine-irinotecan combination in a phase III study. Phase II and III studies of other topoisomerase inhibitors such as exatecan and rubitecan are also being conducted, but results are not available.

Gemcitabine-Antifolate Combinations

The two antifolates that have been studied in combination regimens in PC are raltitrexed and pemetrexed. The combination of raltitrexed (3 mg/m² as a 15-minute infusion on day 1 and gemcitabine, 1000 mg/m² on days 1 and 8 every 21 days) was tested in 25 patients with advanced or locally advanced PC.²⁰⁶ Three partial remissions (12%) occurred, and the median survival of the entire cohort was 6.1 months. Pemetrexed is synergistic with gemcitabine *in vitro*, and in a phase I study the combination was well tolerated.²⁰⁷ A subsequent phase II study combining gemcitabine, 1250 mg/m² on days 1 and 8, with pemetrexed, 500 mg/m² on day 8 with folic acid and vitamin B₁₂ supplementation, enrolled 42 patients.²⁰⁸ The response rate was 15%, median survival was 6.5 months, and 1-year survival was 29%. Based on these results, a multicenter phase III study targeting a sample size of 520 patients has been completed.^{209,210}

Other Combination Chemotherapy Regimens in Pancreatic Cancer

The anthracycline epirubicin has single-agent activity in patients with PC, which, in a randomized trial, was similar to a 5-FU-based combination.²¹¹ Several phase II studies have explored the activity of epirubicin in combination with gemcitabine. Neri et al.²¹² administered epirubicin, 20 mg/m² on days 1, 8, and 15, with gemcitabine, 1000 mg/m² on days 1, 8, and 15, every 4 weeks to 44 patients with locally advanced or metastatic pancreatic adenocarcinoma, or both. The overall response rate was 25%, and the median survival was 10.9 months. A total of 12 of 27 (44.4%) eligible patients attained a CBR. Other gemcitabine-based combinations that have been tested in phase II studies included gemcitabine-celecoxib and gemcitabine-flutamide.^{167,213}

Few studies have evaluated three or more drug combination regimens in PC. Reni et al.²¹⁴ published a phase II study of gemcitabine, 600 mg/m² on days 1 and 8; cisplatin, 40 mg/m² on day 1; epirubicin, 40 mg/m² on day 1; and continuous-infusion 5-FU, 200 mg/m² on days 1 to 28. A total of 49 patients were treated in the study, with a response rate of 58%, median survival of 10 months, and 1-year survival of 39%. Twenty-eight percent and 51% of the cycles were complicated by grade 3 and 4 thrombocytopenia and neutropenia, respectively. Several other triple- and quadruplet-drug combinations have also been reported.

NEW DRUGS IN PANCREATIC CANCER

During the last few years, an increasing number of new drugs, many of them targeted to specific alterations in malignant cells, have been tested in PC, as well as in other tumors. The rationale

TABLE 29.3-18. Studies with Novel Drugs in Advanced Pancreatic Cancer

Novel Agent	Author	Gemcitabine Dose/ Schedule	Novel Drug Dose/ Schedule	Phase	No. of Patients	Response Rate (%)	Median Survival (Mo)	1-Y Survival (%)
MMPI	Rosemurgy et al., 1999 ²²⁶	—	Marimastat, 5–75 mg PO b.i.d., 10–25 mg PO/d	I	64	NR	5.3	21
MMPI	Evans et al., 2001 ²¹⁷	—	Marimastat, 10–100 mg PO b.i.d. ^a	II	130	—	3.8	—
MMPI	Bramhall et al., 2001 ²¹⁸	Arm A: 1000 mg/m ² weekly × 7; 1 wk rest; d 1, 8, 15 q4wk	Arm A: — Arm B: marimastat, 5 mg b.i.d	III	103 104	26 3	5.6 3.7	19 14
		Arm B, C, D: —	Arm C: marimastat, 10 mg b.i.d. Arm D: marimastat, 25 mg b.i.d.		105 102	3 3	3.5 4.2	14 20
MMPI	Bramhall et al., 2002 ²¹⁹	1000 mg/m ² weekly × 7; 1 wk rest; d 1, 8, 15 q4wk	Arm A: marimastat, 10 mg b.i.d. Arm B: placebo	III	120 119	11 16	5.5 5.5	NR NR
MMPI	Moore et al., 2003 ²²⁰	Arm A: 1000 mg/m ² weekly × 7; 1 wk rest, d 1, 8, 15 q4wk	Arm B: BAY12-9566, 800 mg PO b.i.d.	III	139 138	6 0.9	6.59 3.74 (P<.001)	25 10
Angiogenesis inhibitor	Kindler et al., 2003 ²²¹	1000 mg/m ² d 1, 8, 15 q4wk	Bevacizumab, 10 mg/kg IV, days 1 and 15	II	30	27	Not reached	53 ^b
FTI	Cohen et al., 2003 ²²³	—	Tipifarnib, 300 mg PO b.i.d.	II	20	0	4.8	NR
FTI	Van Cutsem et al., 2002 ²²⁴	1000 mg/m ² weekly × 7; 1 wk rest; d 1, 8, 15 q4wk	Arm A: tipifarnib, 200 mg PO b.i.d. Arm B: placebo	III	688	NR	6.4 6.1	27 24
FTI	Lersch et al., 2001 ²²⁵	Arm A: 1000 mg/m ² weekly × 7; 1 wk rest; d 1, 8, 15 q4wk	Arm B: lonafarnib, 200 mg PO b.i.d.	II	30 33	3 6	4.4 3.3	NR
EGFR	Safran and Schwartz, 2001 ²²⁷	1000 mg/m ² weekly × 7; 1 wk rest; d 1, 8, 15 q4wk	Trastuzumab, 2 mg/kg/wk ^c	II	23	24	7.5	24
	Abbruzzese et al., 2001 ²²⁸	1000 mg/m ² weekly × 7; 1 wk rest; d 1, 8, 15 q4wk	Cetuximab, 250 mg/kg/wk ^d	II	41	12.5	6.7	33

EGFR, epidermal growth factor receptor; FTI, farnesyltransferase inhibitor; MMPI, matrix metalloproteinase inhibitor; NR, not reported

^aNinety percent of the patients received 25-mg dose.

^bActuarial estimated.

^cLoading dose of 4 mg/kg/wk.

^dLoading dose of 400 mg/kg/wk.

to develop these drugs in PC comes from better understanding of the biologic basis of the disease that has made possible the identification and validation of some of these targets in PC. In addition, the poor prognosis of patients with this disease, and the evidence from clinical trials discussed above that conventional chemotherapy may have reached a plateau with regard to improving outcome, has also motivated an aggressive evaluation of new drugs in PC.²¹⁵ Table 29.3-18 summarizes the key features of selected studies conducted with novel drugs in PC.

Matrix Metalloproteinase Inhibitors

The matrix metalloproteinase (MMP) inhibitors are a group of closely related proteases, which are dysregulated in the majority of human neoplasms including PC. The increased activity of these enzymes has been related to tumor growth, progression, invasion, generation of blood vessels, and metastasis. Several inhibitors of the MMPs have been developed as anticancer

agents, and two of them, marimastat and BAY12-9566, have been more extensively studied in PC.²¹⁶

Marimastat is a hydroxamate peptidomimetic broad-spectrum inhibitor of the MMP family, including MMP 1, 2, and 9. In phase I studies in PC, dosages from 10 to 25 mg orally twice a day were well tolerated. In a large phase II study that enrolled 113 patients, 90% of whom were treated with 25 mg once a day, a 30% decline or stabilization in the tumor marker CA 19-9 was reported, with a median survival of 3.8 months.²¹⁷ Arthralgias, the most common toxicity encountered with marimastat, developed in 29% of the patients. The efficacy and toxicity of marimastat at dosages of 5, 10, and 25 mg twice a day were compared to those of gemcitabine in a phase III study. Patients treated with gemcitabine had a longer progression-free survival of 3.8 months versus 1.9 to 2.0 months for the marimastat-treated group ($P = .001$).²¹⁸ Overall survival was also better for gemcitabine and significantly worse for patients treated with marimastat at doses of 5 and 10 mg, whereas no statistically sig-

nificant differences were observed in overall survival with the 25-mg twice-a-day dose. A subset analysis in this study showed that the benefit of gemcitabine was restricted to patients with advanced disease and that those with locally advanced tumors benefited from marimastat, supporting the hypothesis that these drugs may be more active in situations of early disease. Finally, the combination of gemcitabine with marimastat was tested against gemcitabine alone in a randomized phase III study, with no improvement in any parameter of outcome in the combined-treatment group.²¹⁹

The second MMP inhibitor extensively studied in PC is BAY12-9566, a peptidomimetic inhibitor specific for the MMPs 2 and 9. The drug was compared in a phase III study to single-agent gemcitabine.²²⁰ Of a planned sample of 350 patients, 270 were enrolled, after an interim analysis demonstrated that patients treated with gemcitabine had a significantly better time to tumor progression (3.5 vs. 1.6 months; $P < .001$) and overall survival (6.59 vs. 3.74; $P < .001$). Quality-of-life analysis also favored gemcitabine. In summary, these studies suggest that current MMP inhibitors do not have relevant antitumor activity in patients with advanced PC. Whether or not these drugs or newer-generation analogs will be effective in earlier stages of PC remains to be determined.

Angiogenesis Inhibitors

The angiogenesis inhibitor that appears most promising in PC is bevacizumab, a recombinant, humanized monoclonal antibody against the vascular endothelial growth factor, which is a growth factor that has been implicated in PC progression in several preclinical studies. Bevacizumab has been studied in combination with gemcitabine in a phase II study in patients with PC.²²¹ Patients with advanced or locally advanced PC received gemcitabine, 1000 mg/m² on days 1, 8, and 15 every 28 days, and bevacizumab, 10 mg/kg intravenously on days 1 and 15. Results on the first 26 evaluable patients have been reported, with a response rate of 27%, median time to tumor progression of 6 months, and estimated 1-year survival of 53%. Correlative studies suggest that patients with higher baseline levels of vascular endothelial growth factor tend to have poorer outcomes.

Inhibitors of the Ras Oncogene

Mutations in the oncogene Ras are the most frequent genetic abnormality in PC. Because Ras must be farnesylated to be active (a posttranslational modification mediated by the enzyme farnesyltransferase), inhibitors of this enzyme have been developed as potential Ras inhibitors.²²² Two of these farnesyltransferase inhibitors, tipifarnib and lonafarnib, have been studied in disease-oriented studies in PC. Tipifarnib was tested in a single-agent phase II study in patients with advanced PC, administered at a dosage of 300 mg orally twice a day.²²³ Twenty patients were treated, with no objective responses and a median survival of less than 5 months. Correlative studies conducted in peripheral blood mononuclear cells demonstrated partial inhibition of the target farnesyltransferase enzyme. In parallel to this study, a randomized phase III study compared the combination of tipifarnib plus gemcitabine versus gemcitabine plus placebo in patients with advanced PC²²⁴; 688 patients were treated, without demonstrating any improvement in out-

come in those given tipifarnib plus gemcitabine. Lonafarnib was evaluated in a randomized phase II study in comparison to gemcitabine.²²⁵ The 3-month progression-free survival rate for patients treated with lonafarnib was 23%, compared to 31% for gemcitabine, and the median overall survivals were 3.3 months and 4.4 months, respectively. Two partial responses occurred in patients treated with lonafarnib, and one partial response was observed in the gemcitabine-treated group.

Inhibitors of the Epidermal Growth Factor Receptor Family of Receptors

Pharmacologically, the inhibitors of the epidermal growth factor receptors (EGFR) belong to two broad classes of drugs: monoclonal antibodies against the extracellular domain of the receptor and small-molecule inhibitors of the intracellular TK domain. The studies conducted in PC have mainly tested the combination of these drugs with gemcitabine.

Several studies have evaluated monoclonal antibodies. Safran and Schwartz²²⁷ reported a phase II study of trastuzumab, a monoclonal antibody that targets the Her-2 receptor, in combination with gemcitabine in patients with PC. Up to 21% of PCs are Her-2 positive, and preclinical studies have shown that inhibition of Her-2 signaling with trastuzumab is associated with antitumor effects in PC models. Patients with Her-2-positive pancreatic adenocarcinoma received gemcitabine, 1000 mg/m² weekly for 7 consecutive weeks followed by 1 week of rest and then weekly for 3 weeks every 4 weeks, and trastuzumab, 2 mg/kg/wk after an initial loading dose of 4 mg/kg. Data on 23 patients have been reported thus far. Five patients had a partial response (response rate 24%), and the median survival and 1-year survival were 7.5 months and 24%, respectively. Nine of 18 evaluable patients (50%) have had greater than 50% reduction in CA 19-9. Abbruzzese et al.²²⁸ conducted a phase II study of gemcitabine and cetuximab, a monoclonal antibody against the EGFR in EGFR-positive PC patients. Forty-one patients were treated in the study. The overall response rate was 12.5%, with a median survival of 6.7 months and 1-year survival of 33%.

The second clinically relevant classes of agents that inhibit the EGFR are small-molecule inhibitors of the receptor TK. Several of these agents are currently in clinical development. Two of these compounds, EKB-569 and erlotinib, have been specifically developed for PC. EKB-569, an irreversible inhibitor of the EGFR and of the Her-2 receptor, has completed a phase I study in combination with gemcitabine. Furthermore, a randomized phase III study of gemcitabine plus erlotinib or placebo has completed enrollment.

TREATMENT RECOMMENDATIONS

The standard treatment for patients with advanced PC remains single-agent gemcitabine. This strategy is also appropriate for patients with locally advanced disease, although these individuals are commonly managed with combined modality approaches. Either a conventional 30-minute or fixed-dose-rate gemcitabine infusion is appropriate, based on existing data. Combinations of gemcitabine with other agents, such as cisplatin, irinotecan, oxaliplatin, and fluoropyrimidines, have not resulted in improvement in survival or quality of life in studies available thus far. Such combinations should not be considered standard of care at the present time, although this could change as the results of

randomized studies become available. Because the main effect of chemotherapy in PC is symptom palliation, this should be the primary criterion to guide chemotherapy treatments. More recently, the serum marker CA 19-9 has been used as a predictor of clinical and radiologic response. Finally, considering the poor outcome of patients treated with conventional treatments, enrollment in clinical trials testing new treatment strategies should be encouraged.

IMMUNOTHERAPY

Immunotherapy has the potential to provide non-cross-resistant mechanisms of antitumor activity that can be integrated with surgery, radiation, and chemotherapy. A major advantage of immune-based therapies is their ability to specifically target the transformed tumor cell relative to the normal cell of origin. As a result, minimal and less severe nonspecific toxicities are expected when compared with other PC treatment modalities. Immunotherapy is extensively discussed elsewhere in this text.

ANTIGEN-BASED VACCINES

A few candidate pancreatic antigens recognized by B and T cells have already been identified and fall into several categories, including reactivated embryonic genes (carcinoembryonic antigen), mutated oncogenes/suppressor genes (*k-ras* and *p53*), altered mucins (MUC1), and overexpressed tissue-specific genes (*HER-2/neu* and *Gastrin-17*). Viral vector, protein, and peptide vaccines using some of these antigens have been tested in phase I and II clinical trials. Although T-cell responses have been observed, they have not yet been correlated with clinical regressions.^{229,230}

Mutated *k-ras* vaccines have been the most extensively studied peptide/protein-based vaccine approach in patients with pancreatic adenocarcinoma. In the largest study, patients with either resected or advanced pancreatic adenocarcinoma were intradermally administered a 17 amino acid peptide containing either the specific *k-ras* codon 12 mutation (resected disease) or a mixture of four *k-ras* peptides containing the four most common mutations (advanced disease). Human granulocyte-macrophage colony-stimulating factor (GM-CSF; 40 g) was administered intradermally 15 minutes before peptide vaccination. Patients were vaccinated weekly for 4 weeks and were given booster injections at weeks 6 and 20. Peptide vaccination was well tolerated in all 48 patients. Of the 48 vaccinated patients, 43 were evaluable for induction of immune response. A positive delayed-typed hypersensitivity (DTH; measured as less than 5 mm induration 48 hours after vaccination) was observed in 21 of 43 evaluable patients. In addition, the peptide vaccine elicited a positive mutated *k-ras*-specific proliferative T-cell response in the peripheral blood of 17 of 43 evaluable patients. Mean survival of patients after resection was 25.6 months. In the group with advanced disease, stable disease was seen in 11 of 34 evaluable patients. An immune response (defined as either a positive DTH or a proliferative T-cell response) was observed in 20 of the 34 treated patients, including all 11 patients demonstrating stable disease. The median survival in the group that demonstrated an immune response was 148 days, versus 61 days in the group that did not demonstrate an immune response ($P = .0002$).

WHOLE TUMOR CELL VACCINES

Whole tumor cell vaccine approaches involve the use of autologous or allogeneic tumor cells to stimulate an immune response. However, studies aimed at dissecting antitumor immune responses have confirmed that most tumors are not naturally immunogenic. A preclinical model suggests that the failure of the immune system to reject spontaneously arising tumors is unrelated to the absence of sufficiently immunogenic tumor antigens. Instead, the problem is derived from the immune system's inability to respond appropriately to these antigens.²³⁰ These findings have led to the concept that a tumor cell can become more immunogenic if engineered to secrete immune activating cytokines.

The results of a phase I study testing irradiated allogeneic pancreatic tumor cell lines transfected with GM-CSF as adjuvant treatment administered in sequence with adjuvant chemoradiation in patients with resected pancreatic adenocarcinoma have been reported.²³¹ Fourteen patients with stage 2 or 3 disease received an initial vaccination 8 weeks after pancreaticoduodenectomy. This was a dose-escalation study in which three patients each received 1×10^7 , 5×10^7 , and 1×10^8 , and five patients received 5×10^8 vaccine cells. Study patients were jointly enrolled in an adjuvant chemoradiation protocol for 6 months. After the completion of adjuvant chemoradiation, patients were reassessed, and those who were still in remission were treated with three additional vaccinations given 1 month apart at the same original dose that they received for the first vaccination. Few toxicities were observed. Systemic GM-CSF levels were measured to assess the longevity of vaccine cells at the immunizing site. Serum GM-CSF levels could be detected for up to 96 hours after vaccination. Postvaccination DTH responses to autologous tumor cells were observed in one of three patients receiving 1×10^8 and in two of four patients receiving 5×10^8 vaccine cells. Follow-up studies are ongoing.

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SECTION 4

Cancer of the Liver

Primary tumors of the liver represent one of the most common malignancies worldwide. The annual international incidence of the disease is some 1 million cases, with a male to female ratio of approximately 4:1. In the United States, approximately 15,400 new tumors of the liver and biliary passages are diagnosed each year, with 12,300 deaths estimated annually.¹ Approximately one-half of these tumors are of the gallbladder, a third are tumors of the intrahepatic and extrahepatic biliary ducts, and the remainder are primary hepatocellular carcinomas (HCCs), accounting for 4000 to 6000 cases per year in the United States.^{2,3}

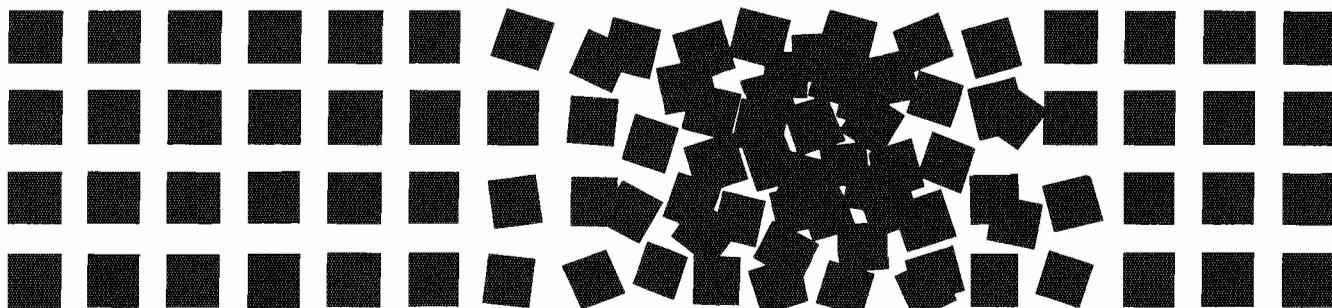
The death rates in males in low-incidence countries such as the United States are 1.9 per 100,000 per year, in intermediate-incidence areas such as Austria and South Africa they range from 5.1 to 20.0, and in high-incidence areas such as Asia (China and Korea) they are as high as 23.1 to 150 per 100,000 per year. The incidence of HCC in the United States is currently thought to be around 3 per 100,000 persons, with significant gender, ethnic, and geographic variations.⁴ The highest rate was in Hawaii

at 4.5 and the lowest was in Utah at 1.0 patients per 100,000 population. These numbers for the United States are rapidly increasing and may be a gross underestimate.⁴⁻⁸ There are thought to be around 4 million chronic hepatitis C virus (HCV) carriers alone in the United States. Approximately 10% of them, or 400,000, are likely to develop cirrhosis. Of these, it is estimated that around 5%, or 20,000, may develop HCC. Add to this the two other common predisposing factors—hepatitis B virus (HBV) infection and chronic alcohol consumption—and 60,000 new HCC cases annually seem possible. There appears to be evidence for increasing incidence of HCV-based HCC (Fig. 29-4). Because most HCC patients have a multiyear history of hepatitis B, hepatitis C, or alcohol abuse and cirrhosis, possibly the death certificates record the chronic liver failure, rather than HCC, as a cause of death. Since the last edition of this text, better imaging studies have become available to further define intrahepatic spread of hepatic malignancies, liver transplantation has been increasingly applied and its role better defined, and new treatment methods such as yttrium 90 (⁹⁰Y) microspheres have become available. The twin problems of major derangements in hepatic physiology associated with many neoplasms of the biliary tree, and the associated high incidence of recurrence of most of these tumors, will require new basic information about hepatobiliary biology and the tumors arising from them to allow significant progress. It is likely that future advances in the management of these malignancies will be dependent in part on immunization strategies for HBV and HCV, as well as develop-

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