REVIEW ARTICLE

MEDICAL PROGRESS

Pancreatic Cancer

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Deaths from pancreatic ductal adenocarcinoma, also known as pancreatic cancer, rank fourth among cancer-related deaths in the United States. In 2008, the estimated incidence of pancreatic cancer in the United States was 37,700 cases, and an estimated 34,300 patients died from the disease.[1] Pancreatic cancer is more common in elderly persons than in younger persons, and less than 20% of patients present with localized, potentially curable tumors. The overall 5-year survival rate among patients with pancreatic cancer is <5%.[1,2]

The causes of pancreatic cancer remain unknown. Several environmental factors have been implicated, but evidence of a causative role exists only for tobacco use. The risk of pancreatic cancer in smokers is 2.5 to 3.6 times that in nonsmokers; the risk increases with greater tobacco use and longer exposure to smoke.[3] Data are limited on the possible roles of moderate intake of alcohol, intake of coffee, and use of aspirin as contributing factors. Some studies have shown an increased incidence of pancreatic cancer among patients with a history of diabetes or chronic pancreatitis, and there is also evidence, although less conclusive, that chronic cirrhosis, a high-fat, high-cholesterol diet, and previous cholecystectomy are associated with an increased incidence.[4-7] More recently, an increased risk has been observed among patients with blood type A, B, or AB as compared with blood type O.[8]

Approximately 5 to 10% of patients with pancreatic cancer have a family history of the disease.[9] In some patients, pancreatic cancer develops as part of a well-defined cancer-predisposing syndrome for which germ-line genetic alterations are known (see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In addition, in some families with an increased risk of pancreatic cancer, a genetic rather than an environmental cause is suspected. The risk of pancreatic cancer is 57 times as high in families with four or more affected members as in families with no affected members.[10] The genetic bases for these associations are not known, although a subgroup of such high-risk kindred carry germ-line mutations of DNA repair genes such as *BRCA2* and the partner and localizer of *BRCA2* (*PALB2*).[11-13]

In recent years, there have been important advances in the understanding of the molecular biology of pancreatic cancer as well as in diagnosis, staging, and treatment in patients with early-stage tumors. Minimal progress has been made, however, in prevention, early diagnosis, and treatment in patients with advanced disease. This review summarizes recent progress in the understanding and management of pancreatic cancer.

THE BIOLOGY OF PANCREATIC CANCER

Data suggest that pancreatic cancer results from the successive accumulation of gene mutations.[14] The cancer originates in the ductal epithelium and evolves from premalignant lesions to fully invasive cancer. The lesion called pancreatic intraepithe-

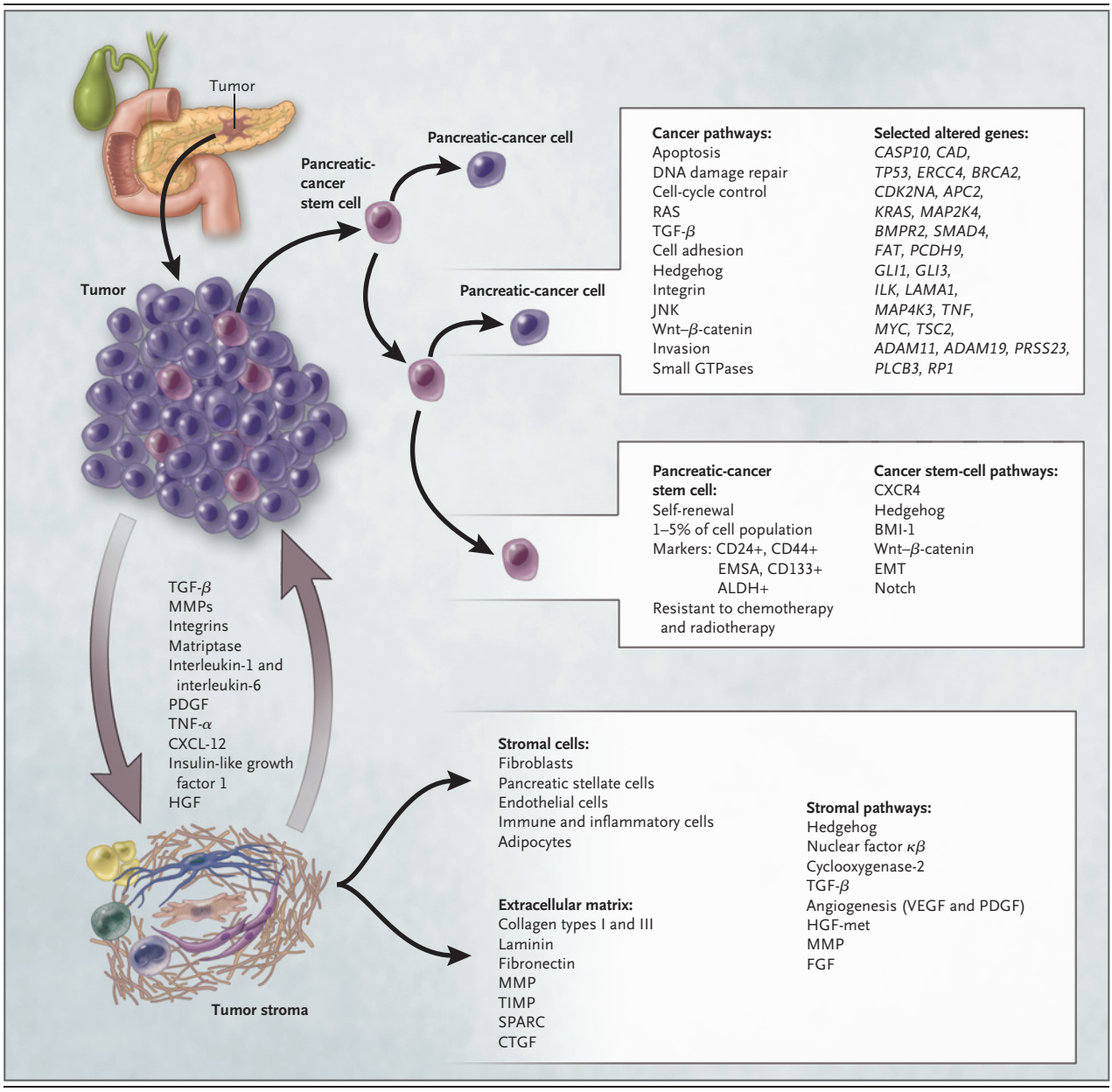
lial neoplasia is the best-characterized histologic precursor of pancreatic cancer.[15] The progression from minimally dysplastic epithelium (pancreatic intraepithelial neoplasia grades 1A and 1B) to more severe dysplasia (pancreatic intraepithelial neoplasia grades 2 and 3) and finally to invasive carcinoma is paralleled by the successive accumulation of mutations that include activation of the *KRAS2* oncogene, inactivation of the tumor-suppressor gene *CDKN2A* (which encodes the inhibitor of cyclin-dependent kinase 4 [*INK4A*]), and, last, inactivation of the tumor-suppressor genes *TP53* and deleted in pancreatic cancer 4 (*DPC4*, also known as the SMAD family member 4 gene [*SMAD4*]).[16] This sequence of events in pancreatic carcinogenesis is supported by studies in genetically engineered mouse models in which targeted activation of *Kras2* with concomitant inactivation of *Trp53* or *Cdkn2A*/*Ink4A* results in the development of pancreatic cancer that is identical to the cognate human disease.[17-19] Other premalignant lesions of the pancreas, which are less well characterized, include intrapancreatic mucinous neoplasia and mucinous cystic neoplasia.[20]

Almost all patients with fully established pancreatic cancer carry one or more of four genetic defects.[21] Ninety percent of tumors have activating mutations in the *KRAS2* oncogene. Transcription of the mutant *KRAS* gene produces an abnormal Ras protein that is "locked" in its activated form, resulting in aberrant activation of proliferative and survival signaling pathways. Likewise, 95% of tumors have inactivation of the *CDKN2A* gene, with the resultant loss of the p16 protein (a regulator of the G1–S transition of the cell cycle) and a corresponding increase in cell proliferation. *TP53* is abnormal in 50 to 75% of tumors, permitting cells to bypass DNA damage control checkpoints and apoptotic signals and contributing to genomic instability. *DPC4* is lost in approximately 50% of pancreatic cancers, resulting in aberrant signaling by the transforming growth factor β (TGF-β) cell-surface receptor. A recent comprehensive genetic analysis of 24 pancreatic cancers showed that the genetic basis of pancreatic cancer is extremely complex and heterogeneous.[11] In that study, an average of 63 genetic abnormalities per tumor, mainly point mutations, were classified as likely to be relevant. These abnormalities can be organized in 12 functional cancer-relevant pathways (Fig. 1). However, not all tumors have alterations in all pathways, and the key mutations in each pathway appear to differ from one tumor to another.

Figure 1 (facing page). Components of Pancreatic Cancer.

Pancreatic cancers are composed of several distinct elements, including pancreatic-cancer cells, pancreatic-cancer stem cells, and the tumor stroma. A recent analysis of 24 pancreatic cancers suggested that the mature pancreatic-cancer cell carries on average 63 genetic alterations per cancer; these alterations can be grouped in 12 core signaling pathways.[11] These results, if confirmed in larger studies, would indicate that pancreatic cancer is genetically very complex and heterogeneous. Thus, effective treatments will probably need to attack several targets (with combination regimens) and may require individualized therapy. A small group of cells (≤5%) appear to have cancer stem-cell features that render them capable of asymmetric division, enabling them to generate mature cells as well as cancer stem cells. These stem cells may be identified by the expression of specific membrane markers and can regenerate into full tumors on implantation in immunodeficient animals. Pancreatic-cancer stem cells are resistant to conventional treatment, but they have alterations in developmental pathways such as Notch, hedgehog, and wingless in drosophila (Wnt)–β-catenin that may result in new therapeutic targets. Pancreatic cancer is characterized by a dense, poorly vascularized stroma; this microenvironment contains a mixture of interacting cellular and noncellular elements. Autocrine and paracrine secretion of growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β) and cytokines results in continuous interaction between the stromal and cancer cells. Pancreatic stellate cells are a key cellular element in the stroma. They are characterized by the expression of desmin, glial fibrillary acidic protein, and intracellular fat droplets. On stimulation by growth factors, pancreatic stellate cells express α–smooth-muscle actin and produce abundant collagen fibers that contribute to tumor hypoxia. ALDH+ denotes aldehyde dehydrogenase, CTGF connective-tissue growth factor, CXCL-12 chemokine 12 ligand, EMSA electrophoretic mobility-shift assay, EMT epithelial-to-mesenchymal transition, FGF fibroblast growth factor, GTPase guanosine triphosphatase, HGF hepatocyte growth factor, HGF-met hepatocyte growth factor mesenchymal–epithelial transition factor, JNK Jun N-terminal kinase, MMP matrix metalloproteinase, SPARC secreted protein, acidic, cysteine-rich, TIMP tissue inhibitor of MMP, TNF-α tumor necrosis factor α, and VEGF vascular endothelial growth factor.

A characteristic of pancreatic cancer is the formation of a dense stroma termed a desmoplastic reaction (Fig. 1).[22,23] The pancreatic stellate cells (also known as myofibroblasts) play a critical role in the formation and turnover of the stroma. On activation by growth factors such as TGFβ1, platelet-derived growth factor (PDGF), and fibroblast growth factor, these cells secrete



collagen and other components of the extracellular matrix; stellate cells also appear to be responsible for the poor vascularization that is characteristic of pancreatic cancer.[24,25] Furthermore, stellate cells regulate the reabsorption and turnover of the stroma, mainly through the production of matrix metalloproteinases.[26] The stroma is not just a mechanical barrier; rather, it constitutes a dynamic compartment that is critically involved in the process of tumor formation, progression, invasion, and metastasis.[22,23] Stromal cells express multiple proteins such as cyclooxygenase-2, PDGF receptor, vascular endothelial growth factor, stromal cell–derived factor, chemokines, integrins, SPARC (secreted protein, acidic, cysteine-rich), and hedgehog pathway elements, among others, which have been associated with a poor prognosis and resistance to treatment. However, these proteins may also represent new therapeutic targets.[27,28]

The role of angiogenesis in pancreatic cancer remains controversial. Although early data suggested that pancreatic cancer is angiogenesis-dependent, as are most solid tumors, treatment

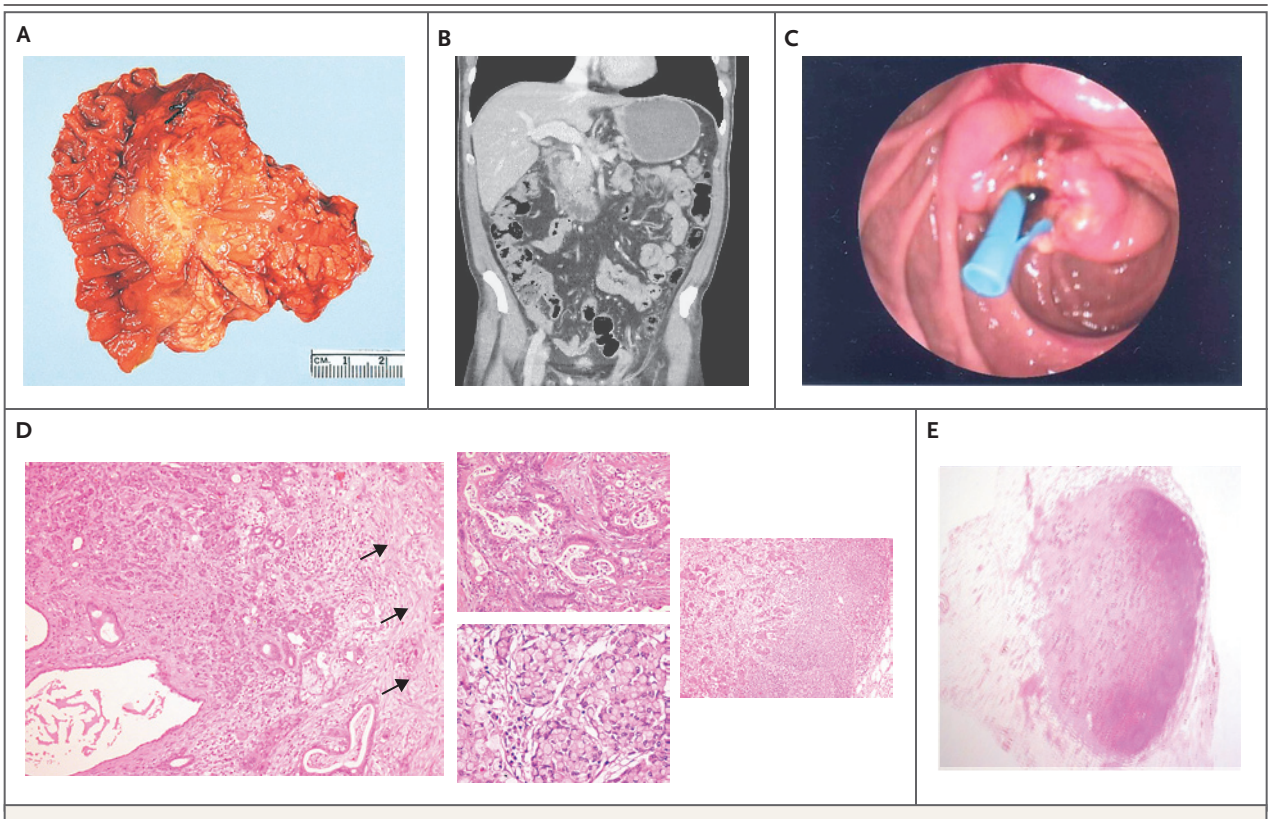


Figure 2. Pathological, Radiologic, and Histologic Features of Pancreatic Cancer.

Panel A shows a macroscopical view of a resected tumor affecting the head of the pancreas. Panel B shows a contrast-enhanced computed tomographic scan from a patient with a T3 pancreatic mass. The tumor invades the splenic superior mesenteric vein–portal vein axis. Panel C shows endoscopic retrograde cholangiopancreatographic imaging of a plastic stent through the ampulla of Vater in a patient with a tumor in the head of the pancreas. Panel D (hematoxylin and eosin) shows microscopical adenocarcinoma of the pancreas with abundant tumor stroma (black arrows). Smaller images show the tumor stroma at low, medium, and high magnification. Panel E shows a peripancreatic lymph node involved with metastatic adenocarcinoma (hematoxylin and eosin, high magnification). (Courtesy of Emilio de Vicente, M.D., and Elena Garcia, M.D.)

with angiogenesis inhibitors has failed in patients with pancreatic cancer. A recent study in a mouse model showed that targeting the stromal hedgehog pathway increases tumor vascularization, resulting in increased delivery of chemotherapeutic agents to pancreatic tumors and greater efficacy.[29]

In addition, a subgroup of cancer cells with cancer stem-cell properties such as tumor initiation have been identified within the tumor.[30,31] These cells, which compose just 1 to 5% of the tumor, are capable of unlimited self-renewal, and through asymmetric division, they give rise to more-differentiated cells (Fig. 1). Pancreatic-cancer stem cells are resistant to chemotherapy and radiation therapy, which may explain why these treatments do not cure the disease and why there is much interest in targeting these specific cells.[31,32]

CLINICAL PRESENTATION, DIAGNOSIS, AND STAGING

The presenting symptoms of pancreatic cancer depend on the location of the tumor within the gland, as well as on the stage of the disease. The majority of tumors develop in the head of the pancreas and cause obstructive cholestasis (Fig. 2A). Vague abdominal discomfort and nausea are also common. More rarely, a pancreatic tumor may also cause duodenal obstruction or gastrointestinal bleeding. Pancreatic cancer often causes dull, deep upper abdominal pain that broadly localizes to the tumor area.

Obstruction of the pancreatic duct may lead to pancreatitis. Patients with pancreatic cancer often have dysglycemia. Indeed, pancreatic cancer should be considered in the differential diagnoses of acute pancreatitis and newly diagnosed diabetes.

At presentation, most patients also have systemic manifestations of the disease such as asthenia, anorexia, and weight loss. Other, less common manifestations include deep and superficial venous thrombosis, panniculitis, liver-function abnormalities, gastric-outlet obstruction, increased abdominal girth, and depression.

Physical examination may reveal jaundice, temporal wasting, peripheral lymphadenopathy, hepatomegaly, and ascites. Results of routine blood tests are generally nonspecific and may include mild abnormalities in liver-function tests, hyperglycemia, and anemia.[2,21]

Evaluation of a patient in whom pancreatic cancer is suspected should focus on diagnosis and staging of the disease, assessment of resectability, and palliation of symptoms. Multiphase, multidetector helical computed tomography (CT) with intravenous administration of contrast material is the imaging procedure of choice for the initial evaluation.[33] This technique allows visualization of the primary tumor in relation to the superior mesenteric artery, celiac axis, superior mesenteric vein, and portal vein and also in relation to distant organs (Fig. 2B). In general, contrast-enhanced CT is sufficient to confirm a suspected pancreatic mass and to frame an initial management plan. Overall, contrast-enhanced CT predicts surgical resectability with 80 to 90% accuracy.[34] Positron-emission tomography can be useful if the CT findings are equivocal.

Some patients require additional diagnostic studies. Endoscopic ultrasonography is useful in patients in whom pancreatic cancer is suspected although there is no visible mass identifiable on CT. It is the preferred method of obtaining tissue for diagnostic purposes. Although a tissue diagnosis is not needed in patients who are scheduled for surgery, it is required before the initiation of treatment with chemotherapy or radiation therapy. Endoscopic retrograde cholangiopancreatography (ERCP) shows the pancreatic and bile-duct anatomy and can be used to guide ductal brushing and lavage, which provides tissue for diagnosis. The ERCP technique is especially useful in patients with jaundice in whom an endoscopic stent is required to relieve obstruction (Fig. 2C).[35] In patients who have large tumors, especially in the body and tail of the pancreas, as well as other indications of advanced disease such as weight loss, an elevated level of carbohydrate antigen 19-9 (CA 19-9), ascites, or equivocal CT findings, a staging laparoscopy can accurately determine metastatic and vascular involvement.[36]

There are many potential serum biomarkers for diagnosis, stratification of a prognosis, and monitoring of therapy.[37] CA 19-9 is the only biomarker with demonstrated clinical usefulness and is useful for therapeutic monitoring and early detection of recurrent disease after treatment in patients with known pancreatic cancer.[37-41] However, CA 19-9 has important limitations. It is not a specific biomarker for pancreatic cancer; the level of CA 19-9 may be elevated in other conditions such as cholestasis. In addition, patients who are negative for Lewis antigen a or b (approximately 10% of patients with pancreatic cancer) are unable to synthesize CA 19-9 and have undetectable levels, even in advanced stages of the disease. Although measurement of serum CA 19-9 levels is useful in patients with known pancreatic cancer, the use of this biomarker as a screening tool has had disappointing results.

Universal primary screening for pancreatic cancer is currently not recommended, given the tools available and their performance.[42] Single-institution studies focusing on surveillance of patients at high risk, such as those with a strong family history or cancer-predisposition syndromes, have used serial endoscopic ultrasonography and CT. Pancreatic lesions associated with benign intrapancreatic mucinous neoplasia or pancreatic intraepithelial neoplasia have been detected in approximately 10% of these high-risk patients. However, the cost-effectiveness of this approach is unclear, and its use is investigational.[43]

STAGING OF PANCREATIC CANCER

Pancreatic cancer is staged according to the most recent edition of the American Joint Committee on Cancer tumor–node–metastasis classification, which is based on assessment of resectability by means of helical CT.[44] T1, T2, and T3 tumors are potentially resectable, whereas T4 tumors, which involve the superior mesenteric artery or celiac axis, are unresectable (Table 1). Tumors involving the superior mesenteric veins, portal veins, or

Table 1. Staging of Pancreatic Cancer.*

Stage	Tumor Grade	Nodal Status	Distant Metastases	Median Survival†	Characteristics
				mo	
IA	T1	N0	M0	24.1	Tumor limited to the pancreas, ≤2 cm in longest dimension
IB	T2	N0	M0	20.6	Tumor limited to the pancreas, >2 cm in longest dimension
IIA	T3	N0	M0	15.4	Tumor extends beyond the pancreas but does not involve the celiac axis or superior mesenteric artery
IIB	T1, T2, or T3	N1	M0	12.7	Regional lymph-node metastasis
III	T4	N0 or N1	M0	10.6	Tumor involves the celiac axis or the superior mesenteric artery (unresectable disease)
IV	T1, T2, T3, or T4	N0 or N1	M1	4.5	Distant metastasis

* N denotes regional lymph nodes, M distant metastases, and T primary tumor.
† Data are from Bilimoria et al.[45]

splenic veins are classified as T3, since these veins can be resected and reconstructed, provided that they are patent.

MANAGEMENT OF EARLY DISEASE

Patients with pancreatic cancer are best cared for by multidisciplinary teams that include surgeons, medical and radiation oncologists, radiologists, gastroenterologists, nutritionists, and pain specialists, among others.[46,47] For patients with resectable disease, surgery remains the treatment of choice.[48] Depending on the location of the tumor, the operative procedures may involve cephalic pancreatoduodenectomy (the Whipple procedure), distal pancreatectomy, or total pancreatectomy. A minimum of 12 to 15 lymph nodes should be resected, and every attempt should be made to obtain a tumor-free margin. Data from several randomized clinical trials indicate that a more extensive resection does not improve survival but increases postoperative morbidity. Recent studies show that the results of vein resection and vascular reconstruction in patients with limited involvement of the superior mesenteric vein and portal vein are similar to the results in patients without vein involvement.[49] Poor prognostic factors include lymph-node metastases, a high tumor grade, a large tumor, high levels of CA 19-9, persistently elevated postoperative levels of CA 19-9, and positive margins of resection.[38,40,50,51]

Up to 70% of patients with pancreatic cancer present with biliary obstruction, which can be relieved by percutaneous or endoscopic stent placement. Decompression is appropriate for patients in whom surgery is delayed, such as patients who are treated with neoadjuvant therapy before resection or who are referred to other centers for treatment.[52] Patients with symptoms of cholangitis require decompression as well as antibiotic treatment before surgery.

Even if the tumor is fully resected, the outcome in patients with early pancreatic cancer is disappointing. The results of three large randomized clinical trials, summarized in Table 2 in the Supplementary Appendix, have established the role of postoperative treatment in patients with resected pancreatic cancer.[53-55] The results of the European Study Group for Pancreatic Cancer Trial 1 and Charité Onkologie 1 trial show that postoperative administration of chemotherapy with either fluorouracil and leucovorin or gemcitabine, a nucleotide analogue commonly used to treat advanced pancreatic cancer, improves progression-free and overall survival. In addition, the Radiation Therapy Oncology Group trial 97-04 showed that the combination of gemcitabine with fluorouracil administered as a continuous infusion and radiation therapy resulted in a trend toward increased overall survival, although the increase was not significant, among patients with tumors in the head of the pancreas. These results are similar to those of large single-institution series that incorporated radiation therapy.[56]

Notwithstanding differences in patient populations and therapies, the outcome in patients treated in these trials was similar, with a median survival of 20 to 22 months. Large tumor size, high differentiation grade, and involvement of the lymph nodes are risk factors for recurrent disease. The effect of positive resection margins, however,

is more controversial.[57] Thus, gemcitabine alone or gemcitabine in combination with fluorouracil-based chemoradiation can be considered the standard of care in this setting. The unequivocal demonstration that postoperative treatment improves the outcome in these patients is one of the most important advances that has been made in the management of pancreatic cancer.

An emerging strategy in patients with resectable pancreatic cancer is the use of preoperative (neoadjuvant) treatment. Nonrandomized, phase 2 studies suggest that this approach is at least as effective as postoperative treatment and may decrease the rate of local failures and positive resection margins after surgery.[58] These findings are particularly relevant for patients who have so-called borderline-resectable tumors with limited vascular involvement; in these patients, preoperative treatment may result in tumor-free resection margins.[59]

MANAGEMENT OF LOCALLY ADVANCED AND SYSTEMICALLY ADVANCED DISEASE

Approximately 30% of patients with pancreatic cancer receive a diagnosis of advanced locoregional disease, and an additional 30% of patients will have local recurrence of tumors after treatment for early disease. The treatment of patients with advanced locoregional disease is palliative; with current treatments, the median overall survival ranges only from 9 to 10 months. Management options range from systemic chemotherapy alone to combined forms of treatment with chemoradiation therapy and chemotherapy. A series of randomized trials conducted over the past two decades established that chemoradiation therapy was superior to radiation therapy alone in these patients.[60,61] The results of more recent studies, summarized in Table 3 in the Supplementary Appendix, suggest that chemotherapy is indeed the critical component in the treatment approach and that combined treatment with chemotherapy and chemoradiation therapy is an effective, though more toxic, approach. However, randomized clinical trials of such combined treatments have had low enrollment, precluding a firm conclusion.[60,62,63]

The majority of patients with pancreatic cancer either present with metastatic disease or metastatic disease develops in them, mainly in the liver and peritoneal cavity. The treatment of patients with advanced disease remains palliative, although these patients should be offered the opportunity to participate in clinical trials evaluating new treatments when available. A meta-analysis of published findings from clinical trials showed an improvement in survival among patients who received chemotherapy; these findings suggest that active treatment is beneficial.[61] For more than a decade, gemcitabine has been the treatment of choice on the basis of the results of the randomized trial of gemcitabine versus fluorouracil, summarized in Table 3 in the Supplementary Appendix.[64] Multiple new agents with diverse mechanisms of action in combination with gemcitabine have been tested in randomized clinical trials, with no improvement in outcome.[2,65,66]

The only agent that, in combination with gemcitabine, has shown a small, but statistically significant improvement in survival among patients with advanced pancreatic cancer is erlotinib, a small-molecule inhibitor of the epidermal growth factor receptor (EGFR) (Table 3 in the Supplementary Appendix).[67] As shown in other studies of agents targeting the EGFR, patients in whom drug-induced rashes developed had a better outcome. However, the high frequency of *KRAS2* mutations in pancreatic cancer probably limits the benefits of an EGFR inhibitor; this limitation is similar to that observed in other cancers such as colon cancer. As compared with erlotinib alone, the combination of gemcitabine and erlotinib has more toxicity, particularly gastrointestinal symptoms. Together with the rather modest improvement in survival, the toxicity of this combination has limited its wide acceptance as the standard of care. A recent meta-analysis of randomized trials showed that patients with minimal disease-related symptoms and otherwise good health may benefit from combination chemotherapy with gemcitabine and either a platinum agent or a fluoropyrimidine.[66,68] Thus, at the present time, the accepted treatment approach for patients with advanced disease is either gemcitabine given alone or gemcitabine combined with a platinum agent, erlotinib, or a fluoropyrimidine.

Once the disease progresses, there is no accepted standard of care; most patients at that point are too sick to receive any other treatment. In a highly selected group of patients with minimally symptomatic disease, second-line chemotherapy has modest efficacy, and it can be offered to patients with good functional reserve (i.e., pa-

Table 2. Commonly Used Treatment Regimens in Pancreatic Cancer.*

Drug	Mechanism of Action	Dose	Serious Toxic Effects Occurring in >10% of Patients	Reference
First-line therapy				
Gemcitabine (2′,2′-dFdC)	Nucleoside analogue metabolized to triphosphate moiety (dFdC triphosphate) by deoxycytidine kinase is incorporated into the nascent DNA and blocks DNA replication	1000 mg/m^2 given as 30-min IV infusion either weekly for 7 wk, followed by 1 wk rest, then weekly for 3 of every 4 wk; or weekly for 3 of every 4 wk	Neutropenia (26%), elevated alkaline phosphatase level (16%), thrombocytopenia (10%), elevated AST level (10%)	Burris et al.[64]
Fixed-dose infusion of gemcitabine	Prolonged exposure to gemcitabine increases accumulation of dFdC triphosphate	1500 mg/m^2 given as 10 mg/m^2/min IV infusion weekly for 3 of every 4 wk	Neutropenia (49%), thrombocytopenia (37%), anemia (23%), nausea and vomiting (21%)	Tempero et al.[71]
Gemcitabine plus oxaliplatin	Oxaliplatin is a diaminocyclohexano platinum analogue that binds and alkylates DNA	Gemcitabine: 1000 mg/m^2 given as 10 mg/m^2/min IV infusion on day 1 every other wk; plus oxaliplatin: 100 mg/m^2 given as 120-min IV infusion on day 2, every other wk	Neutropenia (20%), peripheral sensory neuropathy (19%), thrombocytopenia (14%), nausea (10%)	Louvet et al.[72]
Gemcitabine plus cisplatin	Cisplatin is a DNA-binding alkylating agent	Gemcitabine: 1000 mg/m^2 given as 30-min IV infusion every other wk; cisplatin: 50 mg/m^2 given as IV infusion every other wk	Nausea and vomiting (22%), anemia (13%), pain (12%), leukopenia (10%)	Heinemann et al.[73]
Gemcitabine plus capecitabine	Capecitabine is converted in the tumor to fluorouracil and inhibits thymidilate synthetase	Gemcitabine: 1000 mg/m^2 given as 30-min IV infusion weekly for 3 of every 4 wk; plus capecitabine: 1300 mg/m^2 daily, orally for 14 days every 3–4 wk, divided in two daily doses	Neutropenia (23%)	Bernhard et al.[74]
Gemcitabine plus erlotinib	Erlotinib is a small-molecule inhibitor of the epidermal growth factor receptor	Gemcitabine: 1000 mg/m^2 given as 30-min IV infusion, either weekly for 7 wk followed by 1 wk rest, then weekly for 3 of every 4 wk, or weekly for 3 of every 4 wk; plus erlotinib: 100 mg/day orally daily	Neutropenia (24%), infection (17%), fatigue (15%), elevated AST level (11%), thrombocytopenia (10%)	Moore et al.[67]

Second-line therapy				
Modified FOLFOX (combination regimen including oxaliplatin, fluorouracil, and leucovorin)	Fluorouracil is an inhibitor of thymidilate synthetase, and leucovorin potentiates the inhibition of thymidilate synthetase by fluorouracil	Oxaliplatin: 85 mg/m^2 given as 120-min IV infusion every other wk; leucovorin: 400 mg/m^2 on day 1, every other wk; and fluorouracil: 2000 mg/m^2 given as 46-hr infusion every other wk	Neutropenia (20%), asthenia (13%), vomiting (10%)	Li and Saif[75]
Modified FOLFIRI.3 (combination regimen of irinotecan with fluorouracil and leucovorin)	Fluorouracil is an inhibitor of thymidilate synthetase, and irinotecan is a topoisomerase I inhibitor; leucovorin potentiates the inhibition of thymidilate synthetase by fluorouracil	Irinotecan: 70 mg/m^2 given as 60-min IV infusion on day 1; leucovorin: 400 mg/m^2 given as given as 120-min IV infusion on day 1; and fluorouracil: 2000 mg/m^2 given as 46-hr IV infusion on day 1; and irinotecan: 70 mg/mg^2 given as 60-min IV infusion at the end of the infusion of fluorouracil, every 2 wk	Neutropenia (22%), vomiting (10%)	Li and Saif[75]
Oxaliplatin plus capecitabine	Oxaliplatin is a diaminocyclohexano platinum analogue that binds and alkylates DNA; capecitabine is converted in the tumor to fluorouracil and inhibits thymidilate synthetase	Oxaliplatin: 130 mg/m^2 given as 120-min IV infusion every 3 wk; and capecitabine: 2000 mg/m^2 daily, orally for 14 days every 3–4 wk, divided in two daily doses	Oxaliplatin: fatigue (13%), diarrhea (5%), vomiting (3%); capecitabine: hand–foot syndrome (3%), abdominal pain (3%)	Xiong et al.[69]
Capecitabine plus erlotinib	Capecitabine is converted in the tumor to fluorouracil and inhibits thymidilate synthetase; erlotinib is a small-molecular inhibitor of the epidermal growth factor receptor	Capecitabine: 2000 mg/m^2 daily, orally for 14 days every 3–4 wk, divided in two daily doses; and erlotinib: 150 mg orally daily	Capecitabine: diarrhea (17%), rash (13%), hand–foot syndrome (13%), mucositis (10%); erlotinib: fatigue (3%), elevated bilirubin level (3%), elevated alkaline phosphatase level (3%)	Kulke et al.[70]

* AST denotes aspartate aminotransferase; dFdC difluorodeoxycytidine; FOLFIRI.3 regimen of fluorouracil, leucovorin, and irinotecan; FOLFOX regimen of folinic acid, fluorouracil, and oxaliplatin; and IV intravenous.

Table 3. Selected Strategic Targets in Pancreatic Cancer.*

Target	Agent	Drug Class	Mechanism of Action	Trial Phase	Reference
SPARC	Nanoparticle albumin-bound paclitaxel	Cytotoxic agent	SPARC, expressed in cancer cells and stroma in the pancreas, binds nanoparticle albumin-bound paclitaxel, increasing local drug delivery	3	Li and Saif[75]
IGF-IR	MK 0646, AMG 479, R1507	Monoclonal antibody	Inhibits ligand binding activation of the IGF-IR and cell proliferation	3	Hewish et al.[78]
Death receptor	AMG 655, CS1008	Monoclonal antibody	Agonist antibodies to membrane death receptors induce apoptosis	2	Li and Saif,[75] Derosier et al.[79]
Mucin-1	90Y-hPAM4	Radioimmunoconjugate	Targets mucin-1 expressed in pancreatic-cancer cells and delivers radiation load	1–2	Gold et al.[80]
Hedgehog pathway	GDC-0449, IPI-926	Small-molecule inhibitor	Inhibits smoothened receptor, resulting in inhibition of cell proliferation; targets cancer stroma and cancer stem cells in the pancreas	1	Olive et al.,[29] Jimeno et al.[32]
c-kit, PDGFR, FGFR	Masitinib	Small-molecule inhibitor	Multikinase inhibitor targets c-kit, PDGFR, and FGFR3 and affects the FAK pathway; masitinib was shown to enhance the antiproliferative effects of gemcitabine in preclinical studies	3	Li and Saif[75]
MEK	AZD6244	Small-molecule inhibitor	Targets and inhibits MEK, decreasing cell proliferation	2	Chung et al.[81]
Src	AZD0530, dasatinib	Small-molecule inhibitor	Targets and inhibits Src kinase, resulting in inhibition of cell proliferation and invasion	2	Rajeshkumar et al.[77]
RAS	Sarilasib	Small-molecule inhibitor	Dislodges all forms of RAS from the plasma membrane, inhibiting RAS signaling	2	Haklai et al.[82]
PSCA	AGS-1C4D4	Monoclonal antibody	Binds membrane PSCA; specific mechanisms of cell killing undetermined	2	Wente et al.[83]
Mesothelin	MORAb-009	Monoclonal antibody	Binds membrane mesothelin; specific mechanisms of cell killing undetermined	2	Hassan et al.[84]
TNF-α	TNFerade	Gene therapy	Adenoviral gene therapy increases intratumoral concentration of TNF-α	3	Murugesan et al.[85]

* The abbreviation c-kit denotes stem-cell factor receptor; FAK focal adhesion kinase; FGFR fibroblast growth factor receptor; IGF-IR type I insulin-like growth factor receptor; MEK mitogen-activated protein kinase–extracellular-signal–regulated kinase, PDGFR platelet-derived growth factor; PSCA prostate stem-cell antigen; SPARC secreted protein, acidic, cysteine-rich; and TNF-α tumor necrosis factor α.

tients who are ambulatory and minimally symptomatic).[69,70] Table 2 lists commonly used first-line and second-line therapeutic regimens.

FUTURE DIRECTIONS

There is much room for improvement in all aspects of treatment for pancreatic cancer. Screening of high-risk persons by means of either innovative imaging methods or measurements of serum biomarkers for early diagnosis is critical.[42,43,76] A better understanding of the biology of pancreatic cancer is opening new avenues for treatment, and an increasing number of new targeted agents are in clinical development (Table 3). These agents include small-molecule inhibitors of oncogenes and signaling pathways such as RAS, Src, and MEK, monoclonal antibodies targeting cell-membrane proteins such as mesothelin and the so-called death receptors, and new nanotechnology and adenoviral agents. The recognition that the tumor microenvironment and cancer stem cells are critical components of pancreatic cancer has led to the development of agents, such as the hedgehog inhibitors, that target these components.[23,29,31,32] The availability of preclinical models that recapitulate the complexity of this disease will probably help in establishing priorities and strategies for the development of new treatments.[77,86] The complexity of the genome of pancreatic cancer indicates that it is a heterogeneous cancer and that methods to individualize therapy will be required.[11,87]

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