ARTICLE TITLE: Recent Progress in Pancreatic Cancer

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1. Summarize recent progress regarding pancreatic cancer risk factors, biology, diagnosis, and multimodality treatment.

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Supported by National Institutes of Health grants P30 CA06973 and P50 CA62924.

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AUTHOR DISCLOSURES
Michael A. Erdek, MD; Elliot K. Fishman, MD, FACR; Joseph M. Herman, MD, MSc; Daniel A. Laheru, MD; and Christopher L. Wolfgang, MD, PhD have no conflicts of interest to disclose.
Ralph H. Hruban, MD, and Alison P. Klein, PhD, MHS, receive royalty payments from Myriad Genetics for the PALB2 invention.

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Recent Progress in Pancreatic Cancer
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Pancreatic cancer is currently one of the deadliest of the solid malignancies. However, surgery to resect neoplasms of the pancreas is safer and less invasive than ever, novel drug combinations have been shown to improve survival, advances in radiation therapy have resulted in less toxicity, and enormous strides have been made in the understanding of the fundamental genetics of pancreatic cancer. These advances provide hope but they also increase the complexity of caring for patients. It is clear that multidisciplinary care that provides comprehensive and coordinated evaluation and treatment is the most effective way to manage patients with pancreatic cancer. CA Cancer J Clin 2013;63:318–348. ©2013 American Cancer Society.

Keywords: pancreatic neoplasms, molecular biology, radiology, radiation oncology, medical oncology

Introduction
The American Cancer Society estimates that 45,220 Americans will be diagnosed with pancreatic cancer in 2013, and that 38,460 will die from the disease.1 Despite decades of effort, the 5-year survival rate remains at only ~5%. There are no early detection tests and most patients with localized disease have no recognizable symptoms or signs; as a result, most patients are not diagnosed until late in their disease, after their cancer has metastasized to other organs.

Despite these grim statistics, we believe that there is real hope on the horizon. In this article we will review recent progress in pancreatic cancer, with emphasis on genetic advances and the multidisciplinary team approach to patient care. In the sections that follow, unless otherwise specified, “pancreatic cancer” will refer to ductal adenocarcinoma of the pancreas.

Risk Factors
Population and family-based studies have helped to establish that both environmental and inherited factors contribute to the development of pancreatic adenocarcinoma (Tables 1 and 2). The most common risk factor for pancreatic adenocarcinoma is cigarette smoking. Analyses of data from 12 case-control studies showed that current smokers have a 2.2-fold (95% confidence interval [CI] = 1.71-2.83) increased risk of pancreatic cancer compared with never-smokers.2 Approximately 25% of pancreatic cancers are attributable to cigarette smoking.3 The “fingerprint” of tobacco smoking can be seen in pancreatic cancers, as genetic analyses have shown that pancreatic cancers resected from smokers have more mutations than do pancreatic cancers from never-smokers.4 Importantly, smoking cessation reduces this risk.2 Risk estimates of 1.64 (odds ratio [OR],

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DISCLOSURES: Supported by National Institutes of Health grants P30 CA006973 and P50 CA62924. Dr. Hruban and Dr. Klein receive royalty payments from Myriad Genetics for the PALB2 invention.

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TABLE 1. Pancreatic Cancer Risk Factors

| RISK FACTOR                  | RISK ESTIMATE (95% CI) |
|------------------------------|------------------------|
| Current Cigarette Smoking    | OR = 2.20 (1.71-2.83)  |
| Past Cigarette Smoking       |                        |
| 1-10 years since quitting    | OR = 1.64 (1.36-1.97)  |
| 15-20 years since quitting   | OR = 1.12 (0.86-1.44)  |
| Diabetes Mellitus            |                        |
| <3 years                     | RR = 7.94 (4.70-12.55) |
| >10 years duration           | OR = 1.51 (1.16-1.96)  |
| BMI (>35 vs 18.9-24.9)       | OR = 1.55 (1.16-2.07)  |
| Heavy Alcohol (>6 drinks/day)| OR = 1.46 (1.16-1.83)  |
| Pancreatitis (>2 years)      | 2.71-fold (1.96-3.74)  |

BMI indicates body mass index; CI, confidence interval; OR, odds ratio; RR, relative risk.

95% CI = 1.36-1.97) have been reported for recent quitters (1-10 years) and of 1.12 (95% CI = 0.86-1.44) for individuals who quit smoking 15 to 20 years ago.2

Long-standing type 2 diabetes mellitus is also associated with an increased risk of pancreatic cancer, with patients with type 2 diabetes of >10 years duration having a 1.51-fold (95% CI = 1.16-1.96) increased risk of pancreatic cancer compared with nondiabetes.5 In addition, new-onset diabetes can be the first sign of pancreatic cancer.6 Up to 1% of new-onset adult diabetics are diagnosed with pancreatic cancer within 3 years of their diagnosis of diabetes, suggesting that new-onset diabetes could be a clue to the early diagnosis of pancreatic cancer in some people.6 Thus, long-standing diabetes is a risk factor for pancreatic cancer, and new-onset diabetes can be an early sign of the disease.

In the past several years, a number of studies have demonstrated that increased body mass index (BMI) is also associated with an increased risk of developing pancreatic cancer.7 This risk is independent of the risk of pancreatic cancer due to diabetes. An analysis of data from 12 cohort studies and 1 case-control study estimated that the risk of pancreatic cancer is 1.55-fold (95% CI = 1.16-2.07) greater for individuals with a BMI >35 compared to individuals with a BMI of 18.9 to 24.9.7 Although it has not been established, one would hope that significant weight loss in patients with an elevated BMI would help reduce some of this risk.

Other risk factors for pancreatic cancer include alcohol consumption and pancreatitis. Heavy alcohol consumption (>6 drinks per day) has been associated with an increased risk of pancreatic cancer with an OR of 1.46 (95% CI = 1.16-1.83) compared with light consumption (less than 1 drink per day).8 Low to moderate alcohol consumption does not appear to increase risk. Chronic pancreatitis also elevates risk of pancreatic cancer. An analysis of data from 10 case-control studies demonstrated that individuals with a history of chronic pancreatitis have a 2.71-fold (95% CI = 1.96-3.74) increased risk of pancreatic cancer.9 As was true for diabetes, pancreatitis can also be caused by pancreatic cancer and new-onset pancreatitis can therefore also be a sign of a pancreatic neoplasm.

Inherited Risk Factors
In addition to environmental risk factors, inherited genetic changes can be important risk factors for ductal adenocarcinoma of the pancreas (Table 2). Case-control and cohort studies have all demonstrated that individuals with a family history of pancreatic cancer are at an increased risk of developing pancreatic cancer themselves. Estimates from these studies range from a 1.9- to 13-fold increased risk.10-14 Family registries, in addition to population based studies, have helped to demonstrate the clustering of ductal adenocarcinoma of the pancreas in families and these registries have been used to quantify the risk of pancreatic cancer due to familial factors. One such registry is the National Familial Pancreas Tumor Registry (NFPTR) at Johns Hopkins (nfptr.org). Familial pancreatic cancer is defined as at least a pair of first-degree relatives diagnosed with pancreatic cancer in a family, and prospective studies of families enrolled in the NFPTR demonstrated a 6.8-fold (95% CI = 4.54-9.75) increased risk of pancreatic cancer in the first-degree relatives of familial pancreatic cancer patients compared to the general United States population.15 The standardized incidence ratio reached 17 (95% CI = 7.34-33.5) among individuals with 3 or more close relatives with pancreatic cancer.15 Data from the NFPTR also indicated that having a relative who developed pancreatic cancer at a young age is also associated with an increased risk of pancreatic cancer in familial pancreatic cancer families; however, risk did not vary with age in families with just a single pancreatic cancer.15 As if having an increased risk of pancreatic cancer was not bad enough, families in which there is a clustering of pancreatic cancer also have an increased risk of extrapancreatic cancers.16 Relatives of familial pancreatic cancer patients have an increased risk of dying from breast (1.66-fold, 95% CI = 1.15-2.34), ovarian (2.05-fold, 95% CI = 1.10-3.49), and bile duct cancers (2.89-fold, 95% CI = 1.04-6.39).16

Several germline genetic syndromes have been identified that are associated with an increased risk of ductal adenocarcinoma of the pancreas, these range from high-penetrance genes which are associated with high lifetime risk of pancreatic cancer, to low penetrance genes associated with only a slightly increased (<1.5-fold) risk of pancreatic cancer (Table 2).17 There are 3 important points to remember about these genetic syndromes. First, the risk
of pancreatic cancer can be quantified if one knows the gene responsible for the aggregation of pancreatic cancer in a family. Quantifying risk is important for the design of clinical trials to screen at-risk patients for early curable precancerous lesions. Second, all of these genes, with the exception of those associated with familial pancreatitis, not only increase the risk of pancreatic cancer, but they also increase the risk of extrapancreatic malignancies. This suggests that lives can be saved by screening for these extrapancreatic malignancies. Third, some of these syndromes have implications for therapy. For example, germline BRCA2 gene mutations increase the risk of pancreatic cancer, and cancers in which the BRCA2 gene has been inactivated appear to be sensitive to DNA cross-linking agents.

**BRCA2**

Inherited mutations in the BRCA2 gene are associated with a significantly elevated lifetime risk of breast, ovarian, prostate and pancreatic cancer. The prevalence of germline BRCA2 gene mutations in pancreatic cancer patients varies among different populations and is particularly high in individuals of Ashkenazi Jewish decent. Approximately 4% to 10% of Ashkenazi Jews with pancreatic cancer carry a germline BRCA2 mutation. The prevalence of BRCA2 gene mutations among pancreatic cancer patients also increases as the number of relatives they have with pancreatic cancer increases; 6% to 12% of pancreatic cancer patients from families in which 2 or more relatives have pancreatic cancer carry deleterious BRCA2 mutations, and 16% of patients from families in which 3 or more relatives have pancreatic cancer carry germline BRCA2 mutations. Although many of the pancreatic cancer families that are found to have deleterious BRCA2 mutations also report a family history of breast and/or ovarian cancer, a sizeable proportion of pancreatic cancer patients with germline BRCA2 mutations report no breast or ovarian cancers in their family. Clearly, the penetrance of these genetic changes is not complete. Several clinical trials are evaluating approaches to specifically target BRCA2-deficient pancreatic cancers.

**PALB2**

Germline mutations in the PALB2 (partner and localizer of BRCA2) gene have been reported in 1% to 3% of familial pancreatic cancer kindreds. The first observation of

### TABLE 2. Pancreatic Cancer Susceptibility Genes

| GENE/RISK GROUP        | RISK ESTIMATE (95% CI) | ESTIMATED LIFETIME PANCREATIC CANCER RISK |
|------------------------|------------------------|------------------------------------------|
| General Population     | 1                      | 0.96 (by age 80)                           |
| Familial Pancreatic Cancer |                       |                                          |
| Overall                | RR = 6.79 (4.54-9.75)  | Varies with youngest age of onset         |
| 3 or more first-degree relatives with pancreatic cancer | RR = 17.02 (7.34-33.5) |                                          |
| High Penetrance        |                        |                                          |
| BRCA2                  | RR = 3.51 (1.87-6.58)  | 3.36% (age 80)                           |
| PALB2                  | Elevated               |                                          |
| BRCA1                  | OR = 2.26 (1.26-4.06)  | 2.16% (age 80)                           |
| Mismatch Repair (HNPPC) | RR = 8.6 (4.7-15.7)    | 3.68% (1.45%-5.88%) (age 70)             |
| Hereditary Pancreatitis (PRSS1) | RR = 58 (23-105)    | 30-40% (age 70)                          |
| Peutz-Jeghers (STK11)  | RR = 132 (44, 261)     | 11%-32%                                 |
| Familial Melanoma (CDKN2A) | RR = 38 (10-97)   | 17% (age 75)                             |
| ATM                    | Elevated               |                                          |
| Low-Penetrance         |                        |                                          |
| ABO blood group        | OR = 1.20 (1.12-1.28)  | 1.15% (age 80)                           |
| 1q22.1 (rs3790844 T/C) | OR = 0.77 (0.71-0.84)  | 0.73% (age 80)                           |
| 13q22.1 (rs9543325 T/C) | OR = 1.26 (1.18-1.35)  | 1.2% (age 80)                            |
| 5p15.33 (rs401681 C/T) | OR = 1.19 (1.11-1.27)  | 1.10% (age 80)                           |

*Estimated based by multiplying general population risk by risk estimate.
CI indicates confidence interval; HNPCC = hereditary nonpolyposis colorectal cancer syndrome; OR, odds ratio; RR, relative risk.
PALB2 in familial pancreatic cancer kindreds was made by Jones et al using a whole-exome sequencing approach. Subsequent studies have replicated this finding. As is true for its binding partner BRCA2, mutations in the PALB2 gene are also associated with an increased risk of breast cancer, yet not all patients with pancreatic cancer who are found to have germline PALB2 mutations report a personal or family history of breast cancer. Just as pancreatic cancers harboring BRCA2 mutations appear to be sensitive to DNA cross-linking agents, so are pancreatic cancers harboring PALB2 mutations.

BRCA1

Unlike germline mutations in BRCA2 and PALB2 which have been consistently associated with an increased risk of pancreatic cancer, it is less clear if carriers of germline BRCA1 mutation are also at higher risk of pancreatic cancer. Although several studies have reported an increased risk of pancreatic cancer in BRCA1 carriers, including a large-scale study conducted by the Breast Cancer Linkage Consortium, which found a 2.26-fold (95% CI = 1.26-4.06) increased risk of pancreatic cancer in BRCA1 mutation carriers, other studies have not reported an increased prevalence of BRCA1 gene mutations in patients with pancreatic cancer.

The associations of germline BRCA2, PALB2 and possibly BRCA1 gene mutations with pancreatic cancer make it clear that a good family history, one that specifically asks about a family history of breast cancer, is important in the evaluation of patients with pancreatic cancer.

p16/CDKN2A

Germline mutations in the p16/CDKN2A gene are associated with a high lifetime risk of melanoma and the “familial atypical multiple mole melanoma syndrome” (Fig. 1), as well as an increased risk of pancreatic cancer. Individuals born with a mutation in the p16/CDKN2A gene have a 38-fold increased risk of developing pancreatic cancer. Studies of kindreds with a 19–base pair deletion in exon 2 of the p16/CDKN2A gene (the Leiden mutation) have estimated that these carriers have a 17% lifetime (by age 75) risk of developing pancreatic cancer. The association of germline mutations in the p16/CDKN2A gene with pancreatic cancer suggests that a careful skin examination for nevi and melanomas should be a part of the clinical evaluation of patients with pancreatic cancer. Importantly, lives can be saved by screening p16/CDKN2A gene mutation carriers and their relatives for early melanocytic lesions.

Lynch Syndrome

Lynch Syndrome is an autosomal dominant hereditary disease characterized by early onset colon cancer due to germline mutations in one of the DNA mismatch repair genes (hMSH2, hMLH1, hPMS1, hPMS2, or hMSH6/ GTBP). Patients with Lynch Syndrome also have an increased risk of endometrial, gastric, small intestinal, uterine, and pancreatic cancer. A recent study of 147 families containing a mutation in a mismatch gene reported an 8.6-fold (95% CI = 4.7-15.7) increased risk of pancreatic cancer compared with the general population. The pancreatic cancers that occur in these kindreds frequently have microsatellite instability (MSI) and a distinct poorly differentiated medullary histopathology as is seen in MSI-positive colorectal cancers. Notably, despite their poor differentiation, medullary cancers of the pancreas are associated with a good prognosis.

Hereditary Pancreatitis

Hereditary pancreatitis is a rare inherited form of pancreatitis in which the patients suffer repeated episodes of acute pancreatitis beginning in childhood, and which typically results in pancreatic insufficiency by early adulthood. Mutations in the cationic trypsinogen gene (PRSS1) cause an autosomal dominant form of hereditary pancreatitis, whereas mutations in the serine protease inhibitor gene (SPINK1) cause an autosomal recessive form of hereditary pancreatitis. Patients with hereditary pancreatitis have a remarkable 58-fold (95% confidence interval [CI] = 23-105) increased risk of developing...
pancreatic cancer and a lifetime risk (by age 70) of pancreatic cancer of 30% to 40%.\textsuperscript{47,48} Cigarette smoking has been shown to further increase this risk.\textsuperscript{48} Because the risk of pancreatic cancer is high, and the risk of cancer in patients with hereditary pancreatitis is confined to the pancreas, some of these patients choose prophylactic pancreatectomy. The risks and morbidity associated with total pancreatectomy are high, and such procedures should not be undertaken lightly.

**Peutz-Jeghers Syndrome**

Individuals with the Peutz-Jeghers syndrome, an autosomal dominant disorder characterized by hamartomatous polyps in the gastrointestinal tract and pigmented macules of the lips, buccal mucosa, and digits, have been shown to have an 11% to 32% lifetime risk of pancreatic cancer.\textsuperscript{49,50} Mutations in the \textit{STK11} gene explain more than 80% of Peutz-Jeghers cases. This risk of pancreatic cancer is high in patients with Peutz-Jeghers, and thus they would be a natural population to benefit from screening tests for early pancreatic neoplasia as such tests become available.\textsuperscript{19,51,52}

**Susceptibility Variants**

In addition to the above genetic mutations, which have been associated with a high lifetime risk of pancreatic cancer, several additional variants have been identified that are associated with a weak to modest increased risk of pancreatic cancer. For example, a single-nucleotide variant in the ABO blood group gene, rs505922, has been

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**TABLE 3. Pathology of the Major Neoplasms of the Pancreas**

| TUMOR TYPE                        | GROSS                                      | MICROSCOPY                                                                 | CLINICAL IMPORTANCE                                                                 |
|-----------------------------------|--------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Acinar cell carcinoma             | Large, soft, fleshy, solid masses          | Pyramidal cells neoplastic cells form small lumina. Expression of digestive enzymes can be demonstrated by immunolabeling. | Rare, fully malignant neoplasm. 15% associated with metastatic fat necrosis caused by the release of digestive enzymes into the bloodstream. |
| Invasive ductal adenocarcinoma     | Poorly defined, firm, solid, infiltrative masses | The neoplastic cells form glands and infiltrate tissues. Vascular and perineural invasion are common. Associated with a dense desmoplastic stroma. | Most common type of pancreatic cancer. Very poor prognosis.                         |
| Intraductal papillary mucinous neoplasm (IPMN) | Cystic tumors that arise in the larger pancreatic ducts. Finger-like papillae of neoplastic cells project into mucin-filled ducts | Papillae lined by mucin-producing neoplastic cells with varying degrees of dysplasia | IPMNs are detectable and curable noninvasive precursors to invasive pancreatic cancer. The challenge is not to over-treat low-grade IPMNs. |
| Mucinous cystic neoplasm (MCN)     | Cystic neoplasm that almost always arises in the tail of the pancreas. Cysts filled with mucin. | Mucin-producing neoplastic epithelium resting on ovarian-type stroma | Can progress to invasive cancer if untreated                                         |
| Pancreatic intraepithelial neoplasia (PanIN) | Microscopic lesions | Noninvasive epithelial proliferations in the smaller pancreatic ducts. Associated with lobulocentric atrophy. | PanINs are a curable noninvasive precursor to invasive pancreatic cancer, but most are too small to detect |
| Pancreatoblastoma                  | Large, soft, solid masses                  | Similar to acinar carcinoma but also have squamoid nests                   | More common in children than adults                                                 |
| Pancreatic neuroendocrine tumor (PanNET) | Well-demarcated and soft, solid masses    | Nests and trabeculae of relatively uniform cells with “salt and pepper” chromatin. Expression of neuroendocrine markers and hormones can be demonstrated by immunolabeling. | Some arise in the setting of a familial genetic syndrome. Aberrant hormone production can cause clinical syndromes. Fully malignant, with a 45% 10-year survival rate. |
| Serous cystadenoma                 | Cystic neoplasms with thin septa, and straw-colored fluid. Often have a central scar. | Clear cuboidal cells without atypia line cysts                           | Virtually always benign                                                            |
| Solid-pseudopapillary neoplasm     | Solid masses that undergo cystic change caused by hemorrhage and necrosis | Poorly cohesive cells surround delicate blood vessels                     | Most arise in young women. Low-grade malignant neoplasms.                         |
| Variants of ductal carcinoma (adenosquamous, colloid, medullary, undifferentiated, etc.) | Most are solid | Varies based on tumor type | Can be clinically important to recognize                                           |

IPMN indicates intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; PanIN, pancreatic intraepithelial neoplasia; PanNET, pancreatic neuroendocrine tumor; SCN, serous cystic neoplasm; SPN, solid-pseudopapillary neoplasm.
associated with a per-allele odds ratio of 1.20 for pancreatic cancer (95% CI = 1.12–1.28).53

Pathology

A number of clinically and pathologically distinct neoplasms arise in the pancreas. These neoplasms can be broadly divided pathologically into those that are typically solid and those that are usually cystic. This categorization parallels the primary radiologic appearances of these neoplasms, and it helps narrow the clinical differential diagnosis. Specific pathologic diagnoses within each of these 2 broad categories have important implications for patient management and prognosis (Table 3). The treatment recommendations in the “Treatment” section of this review are specific for invasive ductal adenocarcinoma (“pancreatic cancer”) and may not apply completely to some of the other tumor types that can arise in the pancreas.

Solid Tumors

The most common solid tumor is the invasive ductal adenocarcinoma, as the name suggests, form glands and infiltrate into tissues (Fig. 2A).54 Grossly, these cancers are usually solid and firm, and send tongues of neoplastic cells far beyond the main tumor. Microscopically, almost all invasive ductal adenocarcinomas invade nerves and spread along perineural spaces. These cancers also have a proclivity to invade lymphatic spaces and small veins, and in so doing to spread to regional lymph nodes and to metastasize to the liver. As a result, by the time most invasive ductal adenocarcinomas are diagnosed, they have spread beyond the gland and are not amenable to surgical resection.

Another important histologic feature of invasive ductal adenocarcinomas of the pancreas is that these cancers elicit an intense desmoplastic reaction.54–56 This desmoplastic reaction is composed of fibroblasts, inflammatory cells, endothelial cells, and a complex extracellular matrix, and is associated with significantly increased interstitial fluid pressure within the tumor. This elevated interstitial fluid pressure has been hypothesized to be an impediment to perfusion of the tumor, explaining the low attenuation seen on contrast-enhanced imaging, and the elevated pressure may serve as an obstacle to the diffusion of therapeutic agents.55 The desmoplastic reaction associated with pancreatic cancer has to be taken into account when designing therapeutic regimens, because even the best agents will not be effective if they do not reach the neoplastic cells.57 Some have also suggested that the desmoplastic reaction can be exploited therapeutically. For example, the albumin in nab-paclitaxel (albumin-bound paclitaxel) may bind to SPARC, a protein expressed at high levels in the desmoplastic stroma, increasing the delivery of paclitaxel to the neoplastic cells.58,59 Cell-matrix interactions could also be targeted therapeutically, and some investigators are testing novel approaches to remodeling the tumor microenvironment, such as enzymatic digestion of stromal hyaluronan.55

Several clinically important variants of ductal adenocarcinoma of the pancreas have been described. Adenosquamous carcinoma has, in addition to neoplastic cells with ductal differentiation, a significant component with squamous differentiation.54,60 Adenosquamous carcinomas are particularly aggressive cancers with an extremely poor prognosis, however, patients with an adenosquamous carcinoma may still benefit from surgical resection.60,61

Colloid carcinoma is a mucin-producing epithelial neoplasm composed of neoplastic cells “floating” in pools of mucin embedded in the stroma.54 These invasive carcinomas almost always arise in association with intraductal papillary mucinous neoplasms (IPMNs), and colloid carcinomas are associated with a better prognosis than invasive ductal adenocarcinomas.62 Some of the improved prognosis associated with colloid carcinomas may be related to their tendency to present clinically at a lower stage than invasive ductal adenocarcinomas that did not arise in association with an IPMN.63

FIGURE 2. (A) Histopathology of a Ductal Adenocarcinoma of the Pancreas. Note the atypical glands embedded in the desmoplastic stroma. (B) Intraductal papillary mucinous neoplasms (IPMNs) are characterized by an intraductal growth of neoplastic mucin-producing cells that typically form papillae (both hematoxylin and eosin stain).
Medullary carcinoma is composed of poorly differentiated cells with a syncytial growth pattern, and characterized by pushing borders, extensive necrosis, and an associated lymphocytic inflammatory cell infiltrate. As described earlier, some medullary cancers arise in patients with the Lynch syndrome, and not surprisingly, some medullary carcinomas are microsatellite unstable, and patients with these cancers are more likely to have a family history of cancer. Patients with medullary cancers have a better prognosis than do patients with invasive ductal adenocarcinomas, despite the poor differentiation of the neoplastic cells in medullary carcinomas.

Signet ring carcinoma is composed of individual neoplastic cells each with a prominent mucin globule, imparting a “signet ring” appearance to the cells. Although signet ring cell carcinomas can arise in the pancreas, clinicians should be aware that cancers with this morphology more commonly arise in the stomach or breast, and these latter 2 cancers can metastasize to the pancreas and mimic a pancreatic primary.

Undifferentiated carcinomas and undifferentiated carcinomas with osteoclast-like giant cells are extremely aggressive carcinomas associated with a very poor prognosis.

Perhaps because the prognosis for invasive ductal adenocarcinoma is so poor, significant emphasis has been placed on understanding the potentially curable noninvasive precursor lesions that give rise to these cancers. Extensive histologic and genetic studies have helped establish that a small microscopic lesion, called pancreatic intraepithelial neoplasia (PanIN), can be a precursor to invasive pancreatic cancer. Although most PanINs are too small to be detected using currently available imaging technologies, abnormal DNA shed from PanINs can be detected in the duodenal fluid and even in the stool, raising the possibility of a gene-based early detection test for PanINs the future. In addition, the pancreatic parenchyma immediately surrounding PanIN lesions is often fibrotic and atrophic, a finding called “lobulocentric atrophy.” When PanINs are multifocal, as can be seen in individuals with a strong family history of pancreatic cancer, the associated multiple foci of lobulocentric atrophy can produce histologic changes of chronic pancreatitis, and these changes can be detected by endoscopic ultrasonography, suggesting another possible approach to the early detection of curable PanIN lesions.

Pancreatic neuroendocrine tumors (PanNETs) are the second most common type of solid neoplasm of the pancreas. PanNETs are less aggressive than invasive ductal adenocarcinomas, but they are fully malignant with a 10-year survival rate of only 45%. Although not as common as ductal adenocarcinomas, these neoplasms are clinically important for 2 reasons. First, some arise in the setting of a genetic predisposition syndrome such as the multiple endocrine neoplasia 1 (MEN-1) and von Hippel Lindau (VHL) syndromes. PanNETs arising in these settings cannot be managed in isolation, instead the entire patient has to be considered as other neoplasms may dominate the patient’s course. Second, some PanNETs produce endocrine hormones that are released into the bloodstream, producing a clinical syndrome (such as insulinomas, glucagonomas, and so forth). These are designated functional PanNETs, and the prognosis and management of functional PanNETs is usually determined by the specific clinical syndrome produced.

Grossly, PanNETs are usually well-demarcated, soft, and solid neoplasms. Microscopically, the neoplastic cells form nests or trabeculae, and the neoplasms are characteristically richly vascular. This rich vascularity explains the proclivity of PanNETs to enhance with contrast. Tumor grade and stage are the most important prognosticators, with grade determined by the proliferation rate of the neoplastic cells, and stage by the size and extent of the tumor.

Surgery is the treatment of choice for patients with a localized PanNET, and there are a variety of treatment options for patients with metastatic or progressive disease. For example, the tyrosine kinase inhibitor sunitinib and the mammalian target of rapamycin (mTOR) pathway inhibitor everolimus have both been reported to significantly improve progression-free survival in patients with advanced PanNETs.

Acinar carcinoma and pancreatoblastoma are rare usually solid tumors, and both are composed of neoplastic cells with differentiation along the lines of exocrine enzyme production. Pancreatoblastomas also have a component of squamous nests. Unfortunately, both acinar cell carcinoma and pancreatoblastoma are associated with a poor prognosis.

Cystic Neoplasms

With recent improvements in and the increasing use of cross-sectional imaging such as computed tomography (CT) scanning, more and more people are being diagnosed with cystic lesions in their pancreas. For example, in one series, pancreatic cysts were identified in 2.6% of more than 2800 CT scans performed on patients without pancreas-related symptoms. Many of these cysts are neoplastic cysts, and some will progress to invasive carcinoma if left untreated. Cystic neoplasms of the pancreas therefore represent a unique opportunity to treat pancreatic neoplasia before an invasive cancer develops. Unfortunately, because cystic tumors of the pancreas are so common and many are entirely benign, pancreatic cysts also present a significant risk for over-treating patients.
There are 4 main cystic neoplasms of the pancreas. Intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) are noninvasive mucin-producing neoplasms. IPMNs, by definition, involve the larger pancreatic ducts (Fig. 2B), whereas MCNs usually arise in the tail of the gland and the cysts of MCNs do not communicate with the pancreatic duct system. Some IPMNs and MCNs progress over years from lesions with low-grade dysplasia and few genetic abnormalities, to lesions with high-grade dysplasia, to invasive carcinomas with complex genetic changes. The clinical goal in managing these patients is to resect high-risk lesions such as IPMNs and MCNs with high-grade dysplasia, and to observe, and not over treat, those with low-grade dysplasia. Patients who have had an IPMN resected are at risk for developing an invasive cancer in the remnant of their pancreas and should be followed carefully.

Solid-pseudopapillary neoplasms (SPNs) are low-grade malignant neoplasms composed of poorly cohesive cells. SPNs almost always arise in younger women, and are best treated surgically. Serous cystic neoplasms (SCNs) are almost always benign, and are composed of uniform glycogen-rich cuboidal cells which form small cysts filled with straw-colored fluid. Most SCNs can be safely followed clinically and need not be resected unless they are large or cause symptoms.

Molecular Biology

Cancer is fundamentally caused by inherited (germline) and acquired (somatic) mutations in cancer-causing genes. The germline changes associated with ductal adenocarcinoma of the pancreas were discussed earlier. The exomes of ductal adenocarcinoma and of all of the most common types of tumors of the pancreas have been completely sequenced, providing unprecedented insight into the somatic mutations in these neoplasms (Table 4). This insight, in turn, will almost certainly change the way these neoplasms are clinically managed, and form the basis for new approaches to the early detection and treatment of pancreatic neoplasia.

The sequencing of infiltrating ductal adenocarcinomas of the pancreas revealed that 4 genes, KRAS, p16/CDKN2A, TP53 and SMAD4, are each somatically altered in > 50% of the cancers. KRAS, an oncogene on chromosome 12, is activated by point mutation in 95% of invasive ductal adenocarcinomas. The protein coded for by the KRAS gene is a small GTPase that plays an important role in cell signaling through the mitogen-activated protein kinase (MAPK) and other pathways. The point mutations in KRAS occur early in pancreatic neoplasia, and almost exclusively target 3 codons (codons 12, 13, and 61), making them relatively easy to identify and, suggesting that KRAS mutations could form the basis for gene-based tests to detect early curable pancreatic neoplasia.

The p16/CDKN2A gene, a tumor suppressor gene on chromosome 9p, is inactivated in ~ 95% of pancreatic cancers. The protein product of the p16/CDKN2A gene, p16, plays an important role in the regulation of the cell cycle and loss of p16 function in pancreatic cancer is believed to promote unrestricted cell growth.

The TP53 tumor suppressor gene on chromosome 17p is inactivated in 75% of pancreatic cancers. TP53 codes for the p53 protein, and p53 plays an important role in cellular stress responses, particularly by activating DNA repair, inducing growth arrest and triggering cell death (apoptosis). Loss of p53 function, through mutation of the TP53 gene, therefore promotes pancreatic neoplasia through the loss of a number of critical cell functions.

The fourth major gene that is somatically targeted in pancreatic cancer is the SMAD4 (previously designated DPC4) tumor suppressor gene on chromosome 18q. The protein product of the SMAD4 gene, Smad4, functions in the transforming growth factor beta (TGFβ) cell signaling pathway. SMAD4 gene mutations in pancreatic cancer are associated with poor prognosis and with more widely metastatic disease.

In addition to these 4 major genes, several genes are somatically mutated in pancreatic cancer at lower frequencies. They include MLL3, TGFBR2, FBXW7, ARID1A, AIRID2, and ATM. ATM is particularly interesting because it is a possible therapeutic target as cancers which have genetically inactivated ATM may be particularly sensitive to radiation damage and to poly(ADP) ribose polymerase (PARP) inhibitors.

In addition to changes in the DNA sequence, the expression of a number of genes in pancreatic cancer is altered by epigenetic mechanisms such as aberrant methylation. The expression of these aberrantly methylated genes is often downregulated, as can be seen with p16/CDKN2A. Other genes are hypomethylated and overexpressed in pancreatic cancer. DNA methylation in a cell can be chemically altered, and it has been suggested that the aberrant methylation in pancreatic cancer could be targeted therapeutically or used as a marker for early detection.

In addition to studies of DNA changes, a number of investigators have studied changes in gene expression in pancreatic cancer. The list of genes abnormally overexpressed in pancreatic cancer is large, and includes proteins such as mesothelin, trefoil factor 1, prostate stem cell antigen, claudin 4, and several of the S100-related proteins. These overexpressed genes are potentially clinically important for 2 reasons. First, some, such as mesothelin, are potentially targetable therapeutically. Second, some, such as those
that are secreted, could form the basis for a clinical test for the detection of pancreatic cancer. Of interest, Wang et al have suggested that one could integrate our understanding of the genes that are genetically altered with those that are expressed in pancreatic cancer to develop a test that detects mutant proteins shed by the cancers.

### TABLE 4. Genetic Alterations in Common Neoplasms of the Pancreas

| TUMOR TYPE          | GENE(S)            | PREVALENCE OF THE ALTERATION | COMMENT                                                                 |
|---------------------|--------------------|------------------------------|-------------------------------------------------------------------------|
| Acinar cell carcinoma | APC                | 15%                          |                                                                         |
|                     | CTNNB1 (beta-catenin) | 5%                           |                                                                         |
| Invasive ductal adenocarcinoma | KRAS            | 95%                          | KRAS mutations occur early, and KRAS mutations may be a target for early detection |
|                     | p16/CDKN2A         | 95%                          |                                                                         |
|                     | TP53               | 75%                          |                                                                         |
|                     | SMAD4              | 55%                          | SMAD4 loss associated with poor prognosis and widespread disease        |
|                     | MLL3, TGFBR2, FBXW7, ARID1A, ARID2, and ATM | <5% | Some of these, such as ATM, may be targetable therapeutically |
| IPMN                | KRAS               | 80%                          |                                                                         |
|                     | RNF43              | 75%                          | RNF43 is a marker of mucin-producing tumors because it is present in both IPMNs and MCNs |
|                     | GNAS               | 60%                          | GNAS is a marker of IPMNs. GNAS and/or KRAS mutations are present in >95% of all IPMNs |
|                     | p16/CDKN2A         | Varies dependent on histologic grade |                                                                         |
|                     | TP53               | Varies dependent on histologic grade | Associated with higher grade lesions                              |
|                     | SMAD4              | Varies dependent on histologic grade | Associated with higher grade lesions                              |
|                     | PIK3CA             | 10%                          |                                                                         |
| MCN                 | KRAS               | 75%                          |                                                                         |
|                     | RNF43              | 40%                          | RNF43 is a marker of mucin-producing tumors, present in IPMNs and MCNs  |
|                     | p16/CDKN2A         | Varies dependent on histologic grade |                                                                         |
|                     | TP53               | Varies dependent on histologic grade | Associated with higher grade lesions                              |
|                     | SMAD4              | Varies dependent on histologic grade | Associated with higher grade lesions                              |
| Pancreatoblastoma   | Imprinted region on chromosome 11 | 85% | Same region is targeted in hepatoblastoma and Wilms tumors                   |
|                     | CTNNB1 (beta-catenin) | 55% |                                                                         |
|                     | APC                | 10%                          |                                                                         |
| PanNET              | MEN1               | 45%                          |                                                                         |
|                     | DAXX or ATRX       | 45%                          | Associated with ALT+                                                   |
|                     | TSC2, PTEN, and PIK3CA (mTOR pathway genes) | 15% | Potentially targetable therapeutically with everolimus |
| SCN                 | VHL                | 50%                          | Among the cystic tumors of the pancreas, VHL loss is specific for SCN   |
| SPN                 | CTNNB1 (beta-catenin) | 95% | Immunolabeling for beta-catenin is useful diagnostically               |

ALT+ indicates alternative lengthening of telomeres; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; PanNET, pancreatic neuroendocrine tumor; SCN, serous cystic neoplasm; SPN, solid-pseudopapillary neoplasm
MicroRNAs are small noncoding RNA molecules that regulate gene expression. As such, microRNAs can serve as master switches in cells, turning on and off the expression of a number of genes in concert. Several microRNAs are aberrantly expressed in pancreatic cancer, and, because microRNAs tend to be long-lived, these abnormally expressed microRNAs could serve as markers for pancreatic cancer.96-98

The molecular alterations that characterize invasive ductal adenocarcinoma can be used as tools to study other lesions in the pancreas. For example, as discussed earlier, PanINs are thought to be precursor lesions to infiltrating ductal adenocarcinomas. The genetic changes in PanINs have been extensively studied and, as one would expect in a bona fide precursor, PanINs harbor many of the same changes as have been identified in invasive cancers.65 KRAS and p16/CDKN2A mutations appear to occur early, in PanINs with low- to intermediate-grade dysplasia, while TP53 and SMAD4 mutations appear to be late events, occurring in PanINs with high-grade dysplasia and in invasive cancer. These findings not only help establish PanINs as noninvasive precursors to invasive pancreatic cancer, but they are also useful in designing early detection tests. For example, because KRAS mutations occur early and are present in most PanINs, they could be used as markers for the presence of a PanIN, but they would not provide information on histologic grade. By contrast, the presence of TP53 or SMAD4 gene mutations would suggest that a high-grade precursor or an invasive carcinoma is present.

The exomes (all known coding genes) of the 4 most common cystic neoplasms of the pancreas, IPMN, MCN, SPN and SCN, have also recently been sequenced, and each tumor type appears to have its own specific mutational profile (Table 4).90,91 KRAS, TP53, and RNF43 mutations are found in the mucin-producing tumors (IPMN and MCN); GNAS mutations are relatively specific for IPMNs; VHL mutations are specific for SCN; and CTNNB1 (beta-catenin) alterations are specific for SPNs. The identification of cyst-type specific mutations is very exciting because it suggests that the genetic analysis of cyst fluid collected at the time of endoscopic ultrasound (EUS) could be used to classify cyst type.99 The challenge will be to identify markers of the degree of dysplasia.

The exomes of pancreatic neuroendocrine tumors (PanNETs) have also been sequenced and the results are dramatic.78,100 In addition to MEN1, a known tumor-suppressor gene which is inactivated in 45% of PanNETs, DAXX or ATRX are altered in 45%, and mTOR pathway genes are targeted at least 15% of PanNETs. DAXX and ATRX mutations have been associated with “alternative lengthening of telomeres,” establishing a new cancer pathway in PanNETs.100 The mTOR pathway gene mutations are particularly interesting because the drug everolimus targets the mTOR pathway and everolimus has been shown to be effective in some patients with PanNETs.73,101,102 Although it still needs to be validated in clinical trials, it is reasonable to hypothesize that PanNETs with genetic mutations in an mTOR pathway gene may be particularly sensitive to everolimus, whereas patients with PanNETs that lack an mTOR pathway activation could be spared the side effects of a drug that may be less effective for them. This is an exciting potential opening of the door to individualized therapy in which the optimal therapy for a patient with a PanNET is based on the genetic changes in their tumor.

Thus, analyses of molecular alterations at the DNA, RNA and protein levels have identified alterations specific for the various tumors of the pancreas (Table 4). Some of these alterations are candidate early detection markers, and others have the potential to form the basis for the rational selection of patient specific therapies.

**Signs and Symptoms**

Unfortunately, most pancreatic cancers present nonspecifically and are not diagnosed until late in the course of the disease, after the cancer has already spread to other organs. Common symptoms include pain, particularly epigastric pain that radiates to the back, unexplained weight loss, jaundice, clay-colored stools, nausea, and in <10%, migratory thrombophlebitis (Trousseau’s syndrome).54

As noted earlier in the section on risk factors, patients with pancreatic cancer sometimes present with new-onset diabetes mellitus or with signs and symptoms of chronic pancreatitis. Of interest, depression is common in patients with pancreatic cancer, and in some instances the diagnosis of depression is established before the patient is found to have the cancer.103 This observation suggests that the cancers are producing a factor that induces the depression.

![FIGURE 3. CT of Pancreatic Cancer. A resectable pancreatic cancer with a well-defined fat plane around the superior mesenteric artery (arrow).](image)
The radiologic diagnosis of pancreatic cancer has improved significantly with enhancements in the sensitivity of imaging technologies. Multidetector computed tomography (MDCT) (Figs. 3 and 4A,B), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) can all be used to visualize the tumors. CT and MRI have comparable sensitivities and specificities, and both have the advantage that they can also be used to stage the neoplasm, and as described below, 3-dimensional reconstructions can provide detailed information on the relationship of the tumor to nearby vessels. The gold standard for establishing a diagnosis is pathology, and tissues can be sampled at the time of EUS. Positron emission tomography (PET) imaging also has a role in selected instances.104

Clinical Staging

Once a diagnosis of pancreatic cancer has been established, the next step is careful staging, as stage will determine treatment. The American Joint Committee on Cancer (AJCC) staging system, which includes the TNM classification, is the most widely used system to stage pancreatic cancer.105,106 This system has undergone recent revisions to emphasize the importance of resectability of the cancer and it has been optimized to stratify survival by stage. Resectable stages include AJCC Stages I and II, and the subset of Stage III that is defined as borderline resectable. The unresectable categories include the subset of Stage III that is defined as locally advanced (unresectable), and Stage IV (metastatic). The staging workup focuses on defining the relationship of the tumor to large vessels and on identifying extraregional metastatic disease and, when done properly, predicts the ability to perform a margin-negative resection.

The presence of clinically apparent extraregional metastasis is classified as Stage IV and is a contraindication to an attempt at a curative resection. Frequent sites of extraregional disease are the liver, peritoneum, and lung, and these sites are not accurately assessed by physical examination. Palpable supraclavicular, periumbilical, or pelvic nodes do occur, but are uncommon. Thus, the identification of extraregional metastases relies heavily on imaging studies and the selective use of staging laparoscopy.

In the absence of metastatic disease, the relationship of the tumor to the adjacent major vascular structures defines resectability.107 These vessels include the superior mesenteric artery (SMA), the celiac axis, and the superior mesenteric and portal veins (SMV-PV). Patients who do not have vessel involvement or who have only focal involvement of the SMV-PV confluence are considered to be resectable, whereas patients whose cancers involve arteries or have more extensive involvement of the SMV-PV confluence are classified as clinical Stage III. As detailed below, the extent of involvement determines the further subclassification of Stage III into borderline resectable or locally advanced.107

Abutment (defined as less than 180-degree involvement), of the celiac axis (celiac, common hepatic, replaced hepatic, or proper hepatic arteries) or SMA is considered Stage III borderline resectable (Figs. 4A and 5).106,107 Although resection of Stage III borderline tumors is likely to be technically feasible, the probability of a positive margin is high and neoadjuvant therapy is recommended for this group of patients with the intent of sterilizing the margin of viable cancer cells. Greater than 180-degree involvement of any of these arteries is defined as encasement and is considered Stage III locally advanced or unresectable (Figs. 4B and 6). Resection of these cancers is either not possible or would result in a R2 (where some visible tumor could not be removed) resection. Rarely, exceptions are made in which short-segment encasement of the common hepatic artery is resected en bloc and reconstructed or, as will be
discussed in greater detail later, in which focal involvement of the celiac artery and proximal common hepatic artery is resected with an Appleby’s procedure. In these rare cases, patients are typically treated with neoadjuvant chemotherapy and radiation prior to resection.

In contrast to the arterial side, resectability on the venous side depends on the prospect of resecting and reconstructing the vessel. Tumors that focally involve the SMV-PV confluence can be reconstructed because the PV and SMV can be reanastomosed. As a result, these tumors are considered to be resectable. In contrast, tumors that involve a large segment of the portal vein high in the porta hepatis or inferior on the superior mesenteric vein in the area of confluence of multiple tributaries are not technically reconstructable and are considered to be Stage III locally advanced (Fig. 7).

A contrast-enhanced thin-slice CT scan of the chest, abdomen, and pelvis is the primary modality for the clinical staging of patients with pancreatic cancer and can accurately identify metastatic disease and local tumor relationships. Using this technology, the ability to predict a margin-negative resection (R0) is on the order of 73%. Three important features should be noted on CT. The absence of vessel involvement is defined by the presence of a fat-plane separating the tumor from the vessels (Fig. 3). Abutment of a vessel is defined by loss of the fat-plane with less than 180 degrees of involvement (Figs. 4A and 5), whereas encasement is defined as greater than 180 degrees (Figs. 4B and 6).

Patients who undergo R2 resection have a median survival less than 12 months which is no better than patients with locally advanced disease who do not have their tumors resected. Patients with vascular encasement by CT should therefore not undergo surgical exploration unless they respond to neoadjuvant therapy.
**Treatment**

Pancreatic cancer is a complex disease, and patients with ductal adenocarcinomas (referred to in this section as “pancreatic cancer”) are best treated by a multidisciplinary team (see, for example, pathology.jhu.edu/pc). As outlined in Figure 8, the optimal treatment first and foremost depends on careful accurate staging. Patients with Stage I/II disease should undergo surgical resection followed by adjuvant therapy. Neoadjuvant therapy should be considered in this patient population but is controversial, whereas patients with Stage III borderline resectable cancers should undergo neoadjuvant therapy prior to resection. Patients with stage III locally advanced disease should be treated with chemotherapy and/or chemoradiotherapy. A vast majority of these patients eventually develop metastatic disease; however, select patients can still be considered for surgical resection. Patients with Stage IV and good performance status may receive systemic therapy and those with poor overall health should be given supportive therapy.

**Localized Disease: Stage I/II and Stage III Borderline Resectable**

Although the best chance of long-term survival for patients with localized pancreatic cancer is through complete resection of the primary lesion, the systemic nature of pancreatic cancer at diagnosis, the impact of pancreatectomy on quality of life and the relatively low chance of long-term survival must all be taken into account when selecting patients who will most benefit from surgery. Because most patients have locally invasive and micrometastatic disease at the time of surgery, the risk of both local and systemic recurrence following a potentially curative operation is high. The operations necessary to resect pancreatic cancer are associated with significant morbidity in 40% to 60% of patients and mortality in the 2% to 3% range. Moreover, complete recovery to a normal quality of life can take 2 to 3 months even in the absence of complications. In addition, long-term survival is uncommon. The median...
survival reported for resected pancreatic cancer ranges from 17 to 27 months, and the 5-year survival is approximately 20%.116 Taken together, these points underscore the importance of the multidisciplinary approach in the care of patients with pancreatic cancer regardless of stage.113 The purpose of this section is to provide a surgical perspective on the management of pancreatic cancer with an emphasis on patient selection and recent advances in pancreas surgery.

**Patient Selection for Surgery**

Several factors, in addition to stage, need to be considered in the selection of patients who will benefit from pancreatectomy.117 These include the patient’s overall health, their tumor biology and the use of neoadjuvant therapy. Often these 3 factors impact on each other and should be considered collectively in formulating a management plan. It cannot be emphasized enough that this is best achieved through patient evaluation by a multidisciplinary team.113

Significant comorbidities can influence the ability of a patient to tolerate a major pancreatectomy.117 Typical comorbidities in patients presenting with pancreatic cancer include cardiac disease, chronic obstructive pulmonary disease (COPD) and dementia. Moreover, cachexia and malnutrition that result from the cancer itself are common and can be further debilitating. Patients with poor overall health as a result of comorbid conditions and advanced age (>75 years) are not likely to benefit from pancreatectomy and may be harmed by the further debilitation and immunosuppression brought on with these operations.117 A classification system proposed by Katz et al takes this into account and classifies patients with poor overall health as “medically borderline” regardless of tumor-vessel relationships.118

Another consideration in selecting patients for resection is “tumor biology.” This is a term used to describe the relative propensity of a patient’s tumor toward metastatic spread or locally aggressive behavior. Because no validated biomarkers are currently available to predict clinical behavior, the assessment of tumor biology is subjective. Indicators of aggressive biology include extensive metastatic disease at diagnosis, locally infiltrative tumors and rapid progression over time. Unvalidated markers include serum CA19-9 levels and tumor SMAD4 gene status.85,86,119 Patients with significantly elevated CA19-9 levels often do worse than those with low levels, and patients with tumors that have a wild-type SMAD4 gene have been reported to have a lower propensity for widespread metastases than do those with loss of SMAD4.85 In general, patients with aggressive tumor biology are unlikely to benefit from local therapy such as surgical resection even if they have an early-stage tumor. Patients with localized but suspected biologically aggressive tumors may benefit from neoadjuvant therapy to control micrometastatic disease or at the very least allow assessment of biological behavior over time.

**Neoadjuvant Therapy for Localized Disease**

Neoadjuvant therapy remains controversial in the treatment of pancreatic cancer. It does have the advantage of downstaging some locally advanced patients and sterilizing the margin of borderline resectable patients allowing them to undergo a surgery with a higher likelihood of an R0 resection.114,120 In fact, 15% to 40% of patients with initially borderline or unresectable tumors can eventually undergo surgery. Neoadjuvant therapy also has the advantage that it will spare the 15% to 35% of patients who develop metastatic disease the risks and stress of a major operation; as metastases develop they would no longer be considered for surgery.118,121,122 Neoadjuvant therapy also guarantees that almost all patients will receive some form of chemotherapy or radiation because they do not have any postoperative complications and recovery to overcome prior to starting therapy. Studies show that 73% to 100% of patients are able to complete the majority of their neoadjuvant regimens.114,120,123-126 If radiation is given as part of the neoadjuvant regimen, it can be delivered to a smaller volume (tumor plus 1-2 cm) thus allowing for escalation of radiation dose to the tumor and resulting in less toxicity by decreasing the radiation exposure of adjacent normal organs.

Although neoadjuvant therapy is attractive for the reasons described above, surgery is required for a cure and neoadjuvant therapy delays patients’ potentially curative surgery. Simply put, there are no randomized trials favoring neoadjuvant over adjuvant therapy. Therefore, at this time resectable patients are usually taken to surgery immediately and subsequently given adjuvant therapy, and neoadjuvant therapy is usually reserved for borderline resectable patients. The decision of whether to use neoadjuvant therapy followed by surgery, or surgery first followed by adjuvant therapy should be made in a multidisciplinary manner to achieve the timeliest and most coordinated treatments.113

There are no clear protocols established for neoadjuvant therapy; however, most centers use similar regimens as for locally advanced/unresectable disease. The combination of 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin (a regimen referred to as FOLFIRINOX), the combination of gemcitabine, docetaxel, and capcitabine (a regimen referred to as GTX), and gemcitabine alone are possible chemotherapy regimens that are typically followed by continuous infusion 5-FU, capcitabine, or gemcitabine-based chemoradiation to 45 to 54 Gy in 1.8 to 2.5 Gy fractions or 36 Gy in 2.4 Gy fractions.115,120,121,126-128
Surgery should be performed within 6 to 8 weeks following completion of neoadjuvant therapy. Further delays lead to increased radiation-induced fibrosis, more challenging operations, longer operating times, and sometimes increased length of stay. An additional 2 to 3 cycles of adjuvant chemotherapy should be considered based on multidisciplinary evaluation of the tumor pathology.129,130

Surgery for Localized Disease

The required operation for a given patient depends on the location of their tumor. Cancers arising in the head of the pancreas require a pancreaticoduodenectomy (Whipple operation), whereas those in the tail require a distal pancreatectomy with an en bloc splenectomy.131 Lesions located in the neck and body may require a pancreaticoduodenectomy, distal pancreatectomy or, rarely, a total pancreatectomy.111,132 Other partial resections, such as central pancreatectomy or enucleations do not result in an adequate lymphadenectomy and are not considered to be a potentially curative resection for pancreatic cancer. With the emergence of nonoperative biliary decompression, endoscopically directed therapies, such as duodenal wall stents and nonoperative celiac plexus blocks, the need for elective surgical palliation has dramatically decreased.

Pancreaticoduodenectomy

The pancreaticoduodenectomy has 3 broad phases: 1) exploration to assess for occult extraregional spread not identified on preoperative imaging; 2) resection of the tumor (Fig. 9);

FIGURE 9. The Organs Resected in a Pancreatoduodenectomy (PD) Include a Portion of the Stomach, the Entire Duodenum, the Proximal 20 to 30 cm of Jejunum, the Common Bile Duct, Gallbladder, the Head and Uncinate of the Pancreas Along With the Associated Regional Lymph Nodes. In the pylorus-preserving version of the PD, the duodenum is divided just beyond the first portion and the stomach and pylorus are preserved. Illustration by Corinne Sandone. © Johns Hopkins University; used with permission.

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FIGURE 10. Illustrations of Standard (A) and Pylorus-Preserving (B) Pancreatoduodenectomies (PD). Three anastomoses are necessary to reestablish gastrointestinal function. In the typical reconstruction shown here, the end of the pancreas and end of the common hepatic duct are connected to the same limb of jejunum. Downstream from this, the stomach is connected to the jejunum in a standard PD (A) or for a pylorus-preserving version, the duodenum is connected to the jejunum (B). Illustration by Corinne Sandone. © Johns Hopkins University; used with permission.
and 3) reconstruction of the pancreaticobiliary and intestinal tracts (Fig. 10A,B).

The operation begins with a careful inspection of the peritoneal surface for occult cancer implants. The liver is inspected both visually for surface lesions and by palpation for deeper lesions. Intraoperative ultrasonography may be used to assess the liver parenchyma. Patients at high risk for peritoneal dissemination based on CT findings or significantly elevated serum CA19-9 should undergo these initial steps laparoscopically. The second phase is the resection of the head of the pancreas, duodenum, distal common bile duct and gallbladder (Fig. 10). In a standard pancreaticoduodenectomy the stomach is divided proximal to the antrum, and in a pylorus preserving pancreaticoduodenectomy the first portion of the duodenum is transected distal to the pylorus (Fig. 9). In tumors that involve the SMV-PV, the SMV-PV can be divided and resected en bloc with the specimen. The PV and SMV are then reconstructed (Fig. 11).

Optimal patient selection by a multidisciplinary team has made even more extensive resections possible in appropriate patients. For example, if the cancer involves the common hepatic artery in the region of the gastroduodenal artery (GDA), the cancer can be resected by removing the involved segment of artery en bloc with the specimen and performing an end-to-end reconnection of common and proper hepatic arteries (Fig. 12).

In the third phase of the pancreaticoduodenectomy, the enteric, biliary, and pancreatic continuity are re-established with 3 anastomoses: pancreaticojejunostomy, hepaticojejunostomy, and gastrojejunostomy for a standard pancreaticoduodenectomy (Fig. 10A) or pancreaticojejunostomy, hepaticojejunostomy, and duodenojejunostomy for the pylorus-preserving version (Fig. 10B).

**Distal Pancreatectomy**

In a distal pancreatectomy, the distal pancreas and spleen are removed en bloc. Cancer of the body of the pancreas can be the most difficult lesion to manage surgically and is usually resected through a distal pancreatectomy. By virtue of this location, extension of the tumor superiorly beyond the pancreas often results in involvement of the celiac trunk, common hepatic artery and base of the splenic artery at its take-off from the celiac trunk (Fig. 13A). Growth slightly to the right and posteriorly will involve the medial wall of the PV or SMV and may also infiltrate the junction of the splenic vein with the PV–SMV confluence. In these patients, considerable complexity is added to a distal pancreatectomy. The determination of resectability in these patients is based on the extent of involvement of the celiac axis.

In a variation of the standard distal pancreatectomy, cancers involving the celiac artery and proximal common hepatic artery can be resected using an Appleby procedure (Fig. 13). Patients have to be carefully selected for this operation which involves the en bloc resection the body and tail of pancreas along with the celiac artery, proximal common hepatic artery, and splenic artery. Hepatic arterial blood supply is then dependent on retrograde flow from the GDA to the proper hepatic artery. This operation also

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**FIGURE 11.** Focal Tumor Involvement of the Portal Vein–Superior Mesenteric Vein Confluence. Note that the tumor invades the vessel in a location that does not involve numerous small tributaries of the superior mesenteric vein (SMV) nor does it extend high on the portal vein. Because there is a single target vessel (dark lines) above and below the necessary region of resection, this is considered to be resectable. The inset shows a primary anastomosis of the portal vein (PV) and SMV after en bloc resection of the vessel with the splenic vein tied off. Illustration by Corinne Sandone. © Johns Hopkins University; used with permission.

**FIGURE 12.** (A) Short-Segment Encasement of the Common Hepatic Artery (CHA). (B) Although arterial encasement is most often considered to be locally advanced, short segment encasement of the common hepatic artery is amenable to resection and primary anastomosis. Illustration by Corinne Sandone. © Johns Hopkins University; used with permission.
important oncological parameters such as margin status and lymph node counts are also comparable to standard pancreatectomy.\textsuperscript{138,140} The benefits of minimally invasive pancreatectomy are, however, less clear than they are for other general surgical procedures. Wound complications such as surgical site infections do appear to favor minimally invasive pancreatectomy, but length of stay has not been reduced significantly.\textsuperscript{140} Moreover, in contrast to minimally invasive colectomy for colon cancer, no high-quality studies exist that compare long-term disease-specific outcomes between minimally invasive and open pancreatectomy. In theory, the reduction of wound complications and reduced impact on immune function seen with minimally invasive surgery does have the potential to improve disease-specific survival. In particular, fewer wound complications may increase the number of patients who are able to undergo adjuvant therapy. With the ever-increasing use of minimally invasive pancreatectomy the importance of this approach in the management of patients with pancreatic cancer will become clear.

**Surgical Complications**

Through the 1970s, the mortality rate associated with a pancreaticoduodenectomy was as high as 30%. This has been reduced to less than 2% over the subsequent 3 decades.\textsuperscript{116} Results have been shown to be significantly better at high-volume centers.\textsuperscript{142} However, the morbidity rate associated with the pancreaticoduodenectomy has remained between 30% and 45%, even at high volume centers.\textsuperscript{142} The most common postoperative morbidity complication is delayed gastric emptying, occurring in 15% of patients, followed by wound infection (8%), pancreatic fistula (5%), cardiac morbidity (4%), abdominal abscess (4%), cholangitis (2%), sepsis (2%), bile leak (2%), and several other complications occurring in less than 2% of patients.\textsuperscript{116}

**Minimally Invasive Surgery**

Minimally invasive surgery is used extensively in general surgery for a variety of procedures including antireflux procedures, bariatric surgery, hernia repairs, colectomies and cholecystectomy. The benefits of minimally invasive approaches in these instances include less scarring, less postoperative pain, less wound complications, and an earlier return to normal activity.

As a result of the complexity of most pancreatectomies, minimally invasive approaches to pancreas surgery have lagged behind other areas of general surgery in terms of widespread acceptance; however, in recent years, minimally invasive approaches have been applied to pancreatic resections and most pancreatic cancer operations can now be performed laparoscopically or robotically.\textsuperscript{137-141} Access to the abdomen is gained through small ports placed through the abdominal wall, and early published series have shown that minimally invasive pancreatic operations can be performed safely and with similar outcomes to the standard approach.\textsuperscript{139,140} Important oncological parameters such as margin status and lymph node counts are also comparable to standard pancreatectomy.\textsuperscript{138,140} The benefits of minimally invasive pancreatectomy are, however, less clear than they are for other general surgical procedures. Wound complications such as surgical site infections do require a total gastrectomy, because the blood supply to the stomach is compromised.

**Outcomes of Surgery**

In one of the largest series reported of pancreaticoduodenectomies for pancreatic adenocarcinoma, the median survival was 18 months and the 5-year survival was 18%.\textsuperscript{116} Factors that negatively affected survival included tumor size of greater than 3 cm (hazard ratio [HR] = 1.6; \(P < .001\)), positive resection margin (HR = 1.6; \(P < .001\)), histological grade (HR = 1.6; \(P < .001\)), and regional lymph node metastases (HR = 1.3; \(P = .05\)).

**Adjuvant Therapy**

Although surgery offers the only chance of cure, the majority of patients who undergo resection will still recur locally near the superior mesenteric artery margin or distantly (liver, lung, peritoneum). Adjuvant therapy is therefore indicated to decrease the risk of locoregional and metastatic recurrence (Table 5). Adjuvant therapy is typically started 1 to 2 months after surgery to allow the patient to recover from the side effects or complications associated with surgery. Although no regimen has been proven substantially more effective than others, 6 months of adjuvant therapy with a 5-FU–based or gemcitabine-based chemotherapy is an appropriate standard option. The integration of approximately 6 weeks of 5-FU- or gemcitabine-based...
chemoradiation (CRT) (45 Gy directed to the tumor bed, surgical anastomoses (pancreaticojejunostomy), and peri-pancreatic nodes with an additional 5 to 15 Gy boost to the tumor bed) during this 6-month period is an option and may be more favored for R1 (microscopically positive) resections and when the risk of locoregional recurrence is higher (the debate surrounding radiation therapy for pancreatic cancer will be discussed in detail later in this review). The appropriate sequencing of chemoradiation therapy in the adjuvant setting is unclear. Because more than 70% of patients will recur with distant disease, systemic chemotherapy is usually given first to be followed by CRT if there are no radiographic or clinical concerns for metastatic recurrence after chemotherapy is completed.

The benefit of adjuvant systemic chemotherapy was evaluated in the Charité Onkologie (CONKO)-001 trial in which 354 patients were randomized to either observation or adjuvant gemcitabine given intravenously (IV) for a total of 6 cycles. Disease-free survival (DFS) and overall survival (OS) were 6.9 months and 20.5 months for the observation arm, and 13.4 months and 24.2 months for the treatment arm, respectively. Similarly, the European Study Group for Pancreatic Cancer (ESPAC)-3 phase 3 trial randomized 1088 patients to bolus 5-FU daily with folinic acid for 5 days every 4 weeks or gemcitabine weekly for 3 weeks every 4 weeks for 6 cycles total. The OS was 23.0 months in the 5-FU group and 23.6 months in the gemcitabine group, with higher rates of stomatitis and diarrhea in the 5-FU group and higher rates of hematologic toxicity in the gemcitabine group, but without any difference in quality of life. Taken together, the CONKO and ESPAC trials establish both 5-FU and gemcitabine as effective options for adjuvant chemotherapy. Unfortunately, the median OS for patients with resected pancreatic cancer is still approximately 20 to 22 months.

### The Controversy Over Radiation Therapy

The role of adding radiation therapy in the adjuvant setting is controversial. The Gastrointestinal Tumor Study Group (GITSG) trial in the 1980s was the first trial to show a survival benefit for adjuvant chemoradiation. In this trial, patients with resected pancreatic cancer were randomized to either observation or chemoradiation. Chemoradiation included a 40-Gy split course of radiation with a 2-week break after 20 Gy, given with concurrent bolus 5-FU (500 mg/m² on days 1 to 3 of each 20-Gy course of RT), followed by additional weekly 5-FU for 2 years or until progression. The median OS was 20

### Table 5. Selected Key Adjuvant Studies

| STUDY (YEAR) | TREATMENT | 1-y SURVIVAL (%) | 2-y SURVIVAL (%) | 5-y SURVIVAL (%) | DFS (mo) | MEDIAN SURVIVAL (mo) |
|--------------|-----------|-----------------|-----------------|-----------------|---------|---------------------|
| GITSG (1985), N = 43 | Observe vs Chemorad | 49 vs 63 | 15 vs 42 | 14 vs 4 | < < vs 16 | 11 vs 20 (P = .01) |
| EORTC 40891 (1999), N = 218 | Observe vs Chemorad | 53 vs 65 | 23 vs 37 | 22 vs 25 | NR | 12.6 vs 17.1 (pancreas only, P = .099) |
| JHH retrospective (2006), N = 452 | Observe vs Chemorad | NR | 32 vs 44 | 15.4 vs 20.4 | NR | 14.4 vs 21.2 (P < .001) |
| ESPAC-1 (2004), N = 289 | 2 × 2 design | Observe vs Chemo | NR | 38 vs 45 | 11 vs 29 | ChemoXRT: 10.7 | 17 vs 16 |
| CONKO-1 (2007), N = 354 | Observe vs Chemo | 72 vs 72 | 42 vs 47 | 11 vs 22 | 6.9 vs 13.4 (P < .001) | 20 vs 22 (P = .06) |
| RTOG-9704 (2008), N = 538 | Gem–5-FU/XRT vs 5-FU, 5-FU/XRT | 69 vs 65 | 35 vs 39 | 20 vs 20 | NR | 20.6 vs 16.9 (P = .03) |
| ESPAC-3 (2009), N = 1030 | Gem vs SFU | 70 vs 70 | 40 vs 40 | NR | 14.3 vs 14.1 | 23.6 vs 23 |
| JHH and Mayo Clinic Retrospective (2010), N = 1272 | Observation vs Chemorad | 58 vs 80 | 34.6 vs 44.7 | 16.1 vs 22.3 | 15.5 vs 21.1 (P < .001) |
| ACOSOG (2011), N = 89 | 5-FU CI, IFN/cisplatin + XRT | 80 | 60 | NR | 14.1 | 25.4 |
| CapRI (2012), N = 110 | 5-FU/cis/XRT + IFN followed by 5-FU vs 5-FU | 85 vs 80 | 60 vs 55 | 25 vs 25 | 15.2 vs 11.5 (P = .61) | 32.1 vs 28.5 (P = .49) |

ACOSOG indicates American College of Surgeons Oncology Group; CaPRI, Combined Chemoradioimmunotherapy for Pancreatic Adenocarcinoma; CI, continuous infusion; CONKO, Charité Onkologie; DFS, disease-free survival; EORTC, European Organization for Research and Treatment of Cancer; ESPAC, European Study group for Pancreatic Cancer; 5-FU, 5-fluorouracil; GITSG, Gastrointestinal Tumor Study Group; IFN, interferon; JHH, Johns Hopkins Hospital; RTOG, Radiation Therapy Oncology Group; XRT, external beam radiation therapy.
months in the treatment arm compared to 11 months in the observation arm. The European Organization for Research and Treatment of Cancer (EORTC) trial randomized patients to observation or to chemoradiation with 40-Gy split course given identically to the GITSG trial, with continuous infusion 5-FU (25 mg/kg/day) during the first course of radiation therapy, and for 0, 3, or 5 days of the second course (depending on toxicities). Although the OS was 12.6 months in the observation arm compared to 17.1 months in the treatment arm, this difference was not statistically significant, however unlike the GITSG trial patients did not receive maintenance chemotherapy. A third trial, ESPAC-1, put the use of chemoradiation into question when it compared adjuvant chemoradiation, chemotherapy, both, or neither. Patients were randomized to either 20 Gy total of radiation with bolus 5-FU over 2 weeks, bolus 5-FU daily for 5 days that was repeated every 4 weeks for a total of 6 cycles, chemoradiation followed by chemotherapy, or observation. With approximately 71 patients in each arm, median OS rates were 13.9 months, 21.6 months, 19.9 months, and 16.9 months, respectively. Patients who received radiation had a median OS of 15.9 months compared to 17.9 months for those who did not receive radiation, suggesting that radiation was detrimental. However, there was a great deal of nonadherence within this trial. Only 70% of patients randomized to receive chemoradiation received the prescribed dose of radiation (50% of the violations due to patient decision not to receive assigned treatment), and only 50% of patients randomized to receive chemotherapy received the full course of chemotherapy (33% of violations due to patient decision not receive assigned treatment). As with trials previous to this trial, a split-course radiation regimen was used, and the quality assurance for the radiation therapy was lacking with no centralized review of the radiation fields. Finally, it is worth noting that patients in the chemoradiation arm received only 2 cycles of 5-FU during radiation, whereas patients in the chemotherapy and chemoradiation followed by chemotherapy arms received ≥ 6 cycles of 5-FU. Not surprisingly, the results of this study have been criticized highly based on the perceived weaknesses in trial design and the quality of radiation delivery.

Improvements in the delivery of radiation therapy now offer hope. The increased use of more 3-dimensional (3D) conformal planning has led to more focused radiation fields, and it has now become feasible to deliver higher doses of continuous chemoradiation without increasing toxicities. Using these more modern approaches, 2 high-volume surgical centers, Johns Hopkins University and the Mayo Clinic, reported on a large series of patients who had undergone surgical resection for pancreatic cancer and received postoperative CRT with a median dose of 50.4 Gy. Independently, both studies found that chemoradiation was associated with improved survival and increased locoregional control compared to surgery alone. These 2 studies were combined (n = 1092) and propensity scores were created and a matched pair analysis was performed to control for patient and treatment related variables. Again, adjuvant chemoradiation was found to provide a statistically significant survival benefit (median survival 21.1 months) compared to surgery alone (15.5 months, P < .001). In the match pair analyses, the benefit of chemoradiation was seen in margin-positive or margin-negative patients and node-positive disease.

In an effort to improve on chemoradiation therapy, several studies have examined the use of agents other than 5-FU. The benefit of adding gemcitabine to 5-FU based chemoradiation was examined in RTOG 9704, a multicenter, randomized controlled phase 3 study. The final analysis included 451 patients (388 pancreatic head tumors) and incorporated 5-FU or gemcitabine before and after 5-FU based chemoradiation. Notably, this trial used a continuous course of chemoradiation, and prospective central quality review was instituted for the first time. A 5-year update of the trial demonstrated a trend toward improved survival (P = .08) for those patients (pancreatic head tumors only) who received gemcitabine. Reported local failure rates were 25% for the gemcitabine arm and 30% for the 5-FU arm, much improved from the earlier studies which used a lower radiation dose, suggesting that an increased radiation dose is more effective in preventing local recurrence. The primary mode of failure remained distant metastasis, occurring in > 70% of patients, which highlights the need for better systemic therapies.

**Novel Adjuvant Therapy Approaches**

Smaller trials have also looked at other systemic therapies in the adjuvant setting (Table 5). The combination of interferon-alpha, cisplatin and 5-FU with chemoradiation had a median OS of 32 months compared to 28.5 months in the standard arm of 5-FU alone. Erlotinib is being studied in the adjuvant setting and can be safely combined with gemcitabine as well with concurrent capecitabine and chemoradiation. Immunotherapy is also being evaluated in the adjuvant setting. In a phase 2 trial of 5-FU based chemoradiation combined with a pancreatic cancer vaccine of irradiated granulocyte-macrophage colony stimulating factor (GM-CSF) transfected allogeneic whole-cell tumor lines, the median OS was 24.8 months and patients who demonstrated a CD8+ T cell response to mesothelin had a higher likelihood of remaining disease free. K-Ras mutant vaccines and MUC1 peptide-loaded dendritic cell vaccines also have shown early promising results.

In summary, a growing body of evidence-based medicine has established a role for systemic chemotherapy in the adjuvant setting. The role of chemoradiation is less clear,
but newer technologies such as intensity modulated radiation therapy (IMRT) or stereotactic body radiation therapy (SBRT) use multiple, modulated beams of radiation that are likely to be safer and more effective than older radiation techniques. IMRT and SBRT can limit the dose to normal structures (bowel, kidneys, and liver) and deliver higher doses of radiation to the tumor bed (Fig. 14) than traditional methods.¹⁶¹ The incorporation of both modern radiation therapy and combination chemotherapies such as FOLFIRINOX (oxaliplatin, leucovorin, irinotecan, and 5-FU), which has shown promising results in the metastatic setting, is currently being tested in the adjuvant setting.¹⁶²

Locally Advanced Pancreatic Adenocarcinoma

For patients with locally advanced pancreatic adenocarcinoma, the median survival in most historical studies ranges from 8 to 12 months.¹²⁷,¹⁶³-¹⁷¹ Standard radiation therapy includes total doses of 50 to 54 Gy in 1.8 to 2.0 Gy fractions with concurrent chemotherapy (often 5-FU or gemcitabine), but some radiation therapy regimens can be delivered over shorter intervals (Fig. 14).¹²⁷,¹⁶³,¹⁷²-¹⁷⁴

More contemporary studies using aggressive induction systemic therapy and/or dose escalated radiation therapy using 3D conformal, IMRT, or SBRT have reported improvements in treatment related toxicity and survival.¹²⁷,¹⁷⁵ Nevertheless, a majority of patients with locally advanced or metastatic pancreatic cancer are not curable, and multidisciplinary treatment that optimizes patient selection while balancing disease control, toxicity, and quality of life (QOL) is paramount.

The order in which chemo- and radiation therapy are given to patients with locally advanced disease can be important. Many patients (~20%) who receive upfront chemoradiation will be found to have metastases soon after their therapy is completed.¹¹⁵ Furthermore, patients who receive upfront chemoradiation are likely to experience more toxicities than patients who receive chemotherapy alone, and these toxicities may interfere with subsequent chemotherapy needed to prevent and/or delay metastatic disease. An attractive alternative approach is therefore to start with several cycles of chemotherapy (1 to 4 months) and then to restage the patient. Patients who have no evidence of metastatic disease on restaging, and who have a good performance status, would then be consolidated with chemoradiation. This strategy selects those patients who are more likely to benefit from chemoradiation, and has been shown to prevent or delay loco-regional progression which could result in pain (celiac plexus involvement) or duodenal obstruction. Studies have also shown that CRT-based control of local progression can prevent the development of metastatic disease and improve survival when compared to chemotherapy alone.¹⁷¹,¹⁷⁶

Several modern single phase 2 studies have reported impressive increases in median survival by incorporating more aggressive chemotherapy (multiple agents), radiosensitizers and/or targeted agents during the induction phase of treatment and/or in conjunction with radiation therapy.¹⁶⁹,¹⁷⁷-¹⁸² For example, S-1 is a combination of tegafur (a prodrug converted to fluorouracil), gimeracil (an inhibitor of an enzyme which degrades fluorouracil), and oteracil (an inhibitor of fluorouracil phosphorylation in the gastrointestinal tract that acts to decrease toxicities).¹⁶⁴ In a study by Sudo et al, S-1 (oral, twice daily) was given concurrently with radiation (50.4 Gy) and followed with S-1 maintenance in patients with locally advanced pancreatic adenocarcinoma (N = 34).¹⁶⁴ Toxicity rates were acceptable (Grade 3-4), and outcomes were promising, with a median OS of 16.8 months and a 1-year survival rate of 70.6%. Although the results are encouraging, S-1 is currently not available in the United States. These single-arm treatment studies, however, have all been small, and future study is needed.
Agents directed against the human epidermal growth factor receptor (EGFR) are among the best studied targeted agents in pancreatic cancer.\textsuperscript{157} A phase 1 study examined the role of erlotinib (small molecule inhibitor of EGFR) with concurrent chemoradiation, and the results were promising, with partial responses seen in 35% of patients.\textsuperscript{170} Crane et al reported a multicenter phase 2 study in which patients with locally advanced pancreatic adenocarcinoma were treated with 2 months of induction cetuximab (antibody targeting EGFR), gemcitabine, and oxaliplatin, followed by concurrent capecitabine and cetuximab with RT (50.4 Gy) and maintenance gemcitabine and cetuximab therapy.\textsuperscript{127} Median OS was 19.2 months (95% CI = 14.2-24.2 months), and 1-year, 2-year, and 4-year actuarial OS rates were 66.0%, 25.02%, and 11.3%, respectively. Gastrointestinal toxicity was 32% and 10% for grades 2 and 3, respectively. In this study, Smad4 (Dpc4) expression was determined from pretreatment fine-needle aspirations and was found to correlate with patterns of recurrence. Cancers with Smad4 inactivation were more likely to recur distantly whereas Smad4 intact cancers tended to recur locally ($P = .016$).

Selection of the optimal area to radiate is critical (Fig. 14). The standard of care is to deliver a radiation field encompassing only the tumor plus a small margin to account for microscopic disease (clinical tumor volume = CTV) and tumor movement secondary to breathing, bowel distension, and set up error (planning treatment volume = PTV). By not treating elective nodal regions, the smaller margin around the tumor can: 1) allow for the escalation of radiation dose to the tumor above 54 Gy; 2) limit the dose delivered to the bowel and stomach in the field, thus decrease toxicity; and 3) allow for a shorter course of radiation, such as can be achieved with stereotactic body radiation therapy (Fig. 14).\textsuperscript{183-186} Overall, results of recent studies indicate that the use of intensity modulated radiation therapy and fractionated stereotactic body radiation therapy provide a promising means of intensifying treatment without adding excessive toxicity.\textsuperscript{104,187,188}

**Treating Metastatic Disease**

In the last few decades of the Twentieth Century, 5-FU was the standard of care for the treatment of advanced pancreatic cancer. A meta-analysis of trials performed between 1970 and 2003 demonstrated that 5-FU was superior to best supportive care (Table 6).\textsuperscript{189} In 1997, a randomized phase 3 trial demonstrated a survival benefit for gemcitabine (dose at 1000 mg/m$^2$ weekly for 7 weeks with a 1-week break followed by cycles of 3 weeks on/1 week off) over bolus 5-FU with a median survival of 5.65 months as compared to 4.41 months, and 1-year survivals of 18% versus 2%.\textsuperscript{190}Gemcitabine also had a superior clinical benefit response described as improvement in pain, performance status or weight in 24% of the patients versus 5% in the 5-FU group.\textsuperscript{190} Both gemcitabine and 5-FU were well tolerated with similar toxicities. On the basis of this trial, gemcitabine was approved by the Food and Drug Administration for pancreatic cancer and gemcitabine became the standard of care. Fixed-dose gemcitabine, given at a fixed rate of 10 mg/m$^2$/minute, is an alternative to the standard regimen described above as the prolonged exposure with the fixed rate dosing leads to an increased intracellular gemcitabine triphosphate concentration, however it did not lead to a statistical improvement in overall survival as compared to gemcitabine standard dose and infusion.\textsuperscript{191,192}

Numerous gemcitabine-based combinations have been tested and these combinations can be considered in patients with good performance status (ECOG 0-1).\textsuperscript{193,194} Gemcitabine combined with capecitabine in a phase 3 trial did not result in a statistically significant improvement in overall survival compared to gemcitabine alone.\textsuperscript{195} Capecitabine has also been studied alone and it does provide clinical benefit response, although capecitabine could be considered as an alternative to single-agent gemcitabine in patients with moderate performance status.

The combination of gemcitabine and platinum (DNA-binding alkylating agents) has not shown improved efficacy in general. Gemcitabine plus oxaliplatin or gemcitabine in combination with cisplatin showed no statistically significant improvement in survival in phase 3 trials, although the results may have trended in that direction.\textsuperscript{165,196,197} Selected subgroups of patients may, however, benefit. For example, retrospective analyses have suggested that patients with inherited \textit{BRCA1} or \textit{BRCA2} gene mutations and/or a family history of pancreatic, breast, or ovarian cancer may respond to gemcitabine-platinum combinations with longer median survivals compared to patients who were not given a platinum.\textsuperscript{198} This sensitivity to platinum is thought to be a result of the fact that the BRCA1/2 protein complex is needed to repair DNA cross-linking damage, the very type of damage that platinum is thought to induce.\textsuperscript{27,31}

The addition of docetaxel and capecitabine to gemcitabine (in a regimen referred to as GTX) has demonstrated good activity. Phase 2 trials and a retrospective review have demonstrated disease control rates of 63% to 80% with median survival for locally advanced patients of 25 months and for metastatic patients of 11 months.\textsuperscript{128} The most common toxicities were neutropenia, diarrhea and hand/foot syndrome. Although these are smaller trials, GTX is a commonly used first-line therapy for patients with good performance status who want another option for combination therapy.
A phase 1/2 trial published in 2011 demonstrated exciting results when gemcitabine was combined with nab-paclitaxel (albumin-bound paclitaxel) as first-line therapy for metastatic pancreatic cancer patients. As discussed earlier, this combination makes sense as it has been suggested that nab-paclitaxel binds SPARC in the stroma of pancreatic cancer helping to deliver the paclitaxel.58,59 Gemcitabine was given at the standard dose of 1000 mg/m² and nab-paclitaxel (maximum tolerated dose was 125 mg/m²) weekly for 3 weeks on, repeated every 4 weeks. Median OS was 12.2 months with tolerable toxicity and a negative PET-CT at 3 months was a predictor for good response.59 A much-anticipated phase 3 study of gemcitabine with or without nab-paclitaxel demonstrated only a less than 2-month improvement in survival from the addition of nab-paclitaxel (8.5 months versus 6.7 months) with more side effects in the nab-paclitaxel group.199 Clinicians will need to weigh the small benefit from nab-paclitaxel with its toxicity and cost.

Gemcitabine has also been tested in combination with several different targeted therapies, and the combination with erlotinib improved OS, albeit minimally. A phase 3 randomized trial demonstrated a statistically significant improvement in OS from 5.91 months with single-agent gemcitabine to 6.24 months with gemcitabine plus erlotinib.200 Erlotinib was approved by the Food and Drug Administration (FDA) after this trial and can be considered as first-line therapy in patients with good performance status, although again, one needs to weigh the small benefit of this agent versus the toxicity and cost. The addition of cetuximab to gemcitabine, and of bevacizumab (vascular endothelial growth factor [VEGF] inhibitor) to gemcitabine both demonstrated no survival benefit and an increase in toxicities in phase 2 and 3 trials.166,201

The newest combination regimen for patients with metastatic pancreatic cancer is FOLFIRINOX.162 FOLFIRINOX was initially described in France as oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 180 mg/m², 5-FU bolus 400 mg/m² on day 1 followed by a 46-hour continuous infusion of 5-FU (2400 mg/m²) repeated every 2 weeks. When 342 patients were randomized, disease control rate and median OS were 70% and 11.1 months in the FOLFIRINOX arm compared with 51% and 6.8 months in the gemcitabine arm.162 Although there were more grade 3 and 4 toxicities in the FOLFIRINOX arm, quality of life was not different. FOLFIRINOX has therefore been recommended as an option for first-line therapy in patients with a good performance status (ECOG PS = 0-1); however, the doses are usually reduced and adjusted when given in the United States because of the greater toxicity seen here.

### TABLE 6. Key Metastatic Pancreatic Cancer Studies

| STUDY                  | CHEMO                  | RR       | MS (mo) | 1-y SURVIVAL (%) |
|-----------------------|------------------------|----------|---------|-----------------|
| Burris et al (1997),190 N = 126 | 5-FU vs Gem            | NR       | 4.4 vs 5.6 (P = .0025) | 2 vs 18        |
| Rocha Lima et al (2003),235 N = 342 | Gem ± Irinotecan    | 4.4 vs 16 | 6.6 vs 6.3 | 22 vs 21        |
| Heinemann et al (2003),236 N = 195 | Gem ± Cisplatin       | 8 vs 10.2 | 6 vs 7.6 (P = .12) | 22 vs 26        |
| Tempo et al (2003),198 N = 92   | Gem ± Gem (Fixed rate) | 9.1 vs 5.9 | 5 vs 8 (P = .013) | 9 vs 29         |
| O’Reilly et al (2006),237 N = 340 | Gem ± exatecanc     | 6.3 vs 8.2 | 6.2 vs 6.7 (P = .52) | 21 vs 23        |
| Richards et al (2004),238 N = 565 | Gem ± Pemtrexed     | 9.1 vs 18.3 | 6.3 vs 6.2 (P = .85) | 21 vs 20 (P = .72) |
| Louvet et al (2005),199 N = 313  | Gem vs Gem (FDR + Oxaliplatin) | 17.3 vs 26.8 (P = .04) | 7.1 vs 9 (P = .13) | 28 vs 35        |
| Cunningham et al (2009),195 N = 533 | Gem ± Capecitabine  | 14 vs 7 (P = .008) | 7.4 vs 6 (P < .05) | 26 vs 19        |
| CALGB (2009),239 N = 259          | Gem/Cis               | 11       | 6.7     |                 |
|                        | Gem (FDR)             | 14       | 6.4     |                 |
|                        | Gem/irinotecan        | 12       | 6.4     |                 |
|                        | Gem/irinotecan        | 12       | 7.1     |                 |
| Conroy et al (2011),162 N = 343  | Gem vs FOLFIRINOX    | 6.8 vs 11.1 (P < .0001) | 17 vs 36        |
| Moore et al (2005),200 N = 569   | Gem ± erlotinib      | 8.7 vs 7.9 (P = .8) | 6.4 vs 5.9 (P = .025) | 26 vs 20        |
| Kindler et al (2007),201 N = 602 | Gem ± bevacizumab   | 13.1 vs 11.3 | 6 vs 5.7 | NR              |
| Philip et al (2007),196 N = 735  | Gem ± cetuximab      | 14 vs 12 | 6 vs 6.5 (P = .14) | NR              |
| Von Hoff et al (2013),199 N = 861 | Gem ± nab-paclitaxel | 8.5 vs 6.7 |         |                 |

Cis indicates cisplatin; 5-FU, 5-fluorouracil; FDR, fixed dose rate; Gem, gemcitabine; MS, median survival; NR, not reached.
Second-line treatment is not very well established, partially because many of the patients are not strong enough to undergo further treatment. Patients with an adequate performance status who progressed on a gemcitabine-based regimen should be treated with a 5-FU-based regimen, and vice versa. Single-agent capecitabine is well tolerated and can be considered in patients with moderate performance status. Capecitabine and oxaliplatin (referred to as CAPOX or XELOX), provided 28% of patients with disease control with median overall survival of 23 weeks in a second-line phase 2 trial.²⁰²,²⁰³ Capecitabine plus erlotinib was reasonably tolerated and partial responses were seen in 10%.²⁰⁴ Modified 5-FU and oxaliplatin (FOLFOX) and 5-FU and irinotecan (FOLFIRI) regimens can also be considered as second-line options with the former demonstrating a 2-month survival advantage over best supportive care.

If patients recur after resection and adjuvant therapy, biopsy can be considered. If the disease relapse is locoregional only, chemoradiation can be performed if no prior radiation was given. In regards to chemotherapy, if relapse occurs > 6 months after completion of adjuvant therapy, the same regimen can be considered. If relapse occurs earlier, a different regimen should be chosen. Metastatectomy can be considered in very fit patients who have isolated metastases. Although resection of liver metastases have shown mixed results in terms of improving survival as compared to a palliative procedure only, pulmonary and brain metastatectomy have improved survival in a carefully selected group of patients.²⁰⁵

### Future Therapies

The future for the development of new treatments is promising as there has been significant progress in the understanding of the genetics and molecular biology of pancreatic cancer.³¹,⁷⁹ Several attempts have been made to target the genetic changes specific to pancreatic cancer. The KRAS gene is the most appealing target, because it is mutated in the vast majority of pancreatic cancers; however, inhibitors targeting the Kras protein itself have been largely unsuccessful. More recent strategies have focused on targeting downstream pathways such as MEK, ERK and AKT.²⁰⁶,²⁰⁷ Very promising are therapies targeting the rarer genetic alterations in pancreatic cancer. As discussed earlier, cancers in which either BRCA2 or PALB2 is biallelically inactivated appear to be uniquely sensitive to DNA cross-linking agents such as mitomycin C, and to PARP inhibitors.²¹,³¹ Similarly, although the evidence in pancreatic cancer is lacking, one would predict that pancreatic cancers with inactivating ATM mutations may be particularly sensitive to radiation damage and to PARP inhibitors.⁸⁸

We can easily imagine a scenario in the not-too-distant future in which all patients with pancreatic cancer will have their tumor DNA sequenced and information gleaned from the genetic changes in their cancer will be used to individualize their care.

In addition, much has been learned about the supportive tumor-stromal cell environment that is thought to not only influence the development of pancreatic cancer progression but which also supports mechanisms for resistance to effective treatment given its inherent protective properties.²⁰⁸,²⁰⁹ This includes the complex relationship between inflammation and the immune suppressive tumor microenvironment in pancreatic cancer. Targeting this environment is an exciting area only slowly being explored. Already, there are new treatment opportunities targeting small molecules that can reverse immune suppression, as well as immunotherapy approaches that activate the immune system.¹⁵⁸,²¹⁰

Another exciting new area is the targeting of cancer-specific cell metabolism including pathways associated with glucose/glutamine metabolism as well as mechanisms associated with the altered metabolic pathways or amino acid supply.²¹¹-²¹⁶

### Pain Assessment and Treatment

Patients with pancreatic cancer frequently present with pain as the initial symptom of their disease, with nearly 75% of patients suffering from pain at the time of diagnosis.²¹⁷ It is important for the practitioner to manage a patient’s pain appropriately while other therapies such as chemotherapy, radiation therapy, or surgery are being carried out. Consultation with a physician with specific expertise in pain medicine is often helpful both in the outpatient clinic and multidisciplinary clinic settings.

The initial assessment of pain includes evaluating the intensity, frequency, duration, exacerbating and/or alleviating factors, and a comprehensive history of current and previous pain medications along with documentation of any side effects encountered on these medications. Once obtained, this pain history and concomitant physical examination allows the health care team to make appropriately guided decisions regarding the potential implementation of pharmacologic, procedural, or surgical pain therapy.

Opioids are the mainstay of pharmacologic therapy for pancreatic cancer pain. Initial therapy may consist of a short-acting agent such as morphine or oxycodone. A sustained-release opioid, along with a short-acting opioid for breakthrough pain, may work better for those patients with constant pain or those who encounter difficulties with sleep secondary to pain. Common side effects of opioids include sedation, constipation, pruritis, nausea, and testosterone suppression in those on long-term therapy. Constipation is commonly addressed with stool softeners or bowel motility-promoting agents.
The most common and effective procedural intervention for pancreatic cancer pain is celiac plexus block. The celiac plexus is formed by the coalescence of the greater, lesser, and least splanchnic nerves in the vicinity of the celiac trunk and provides visceral innervation from the pancreas and its surrounding structures (Fig. 15). Patients who may benefit most from a celiac plexus block are those who have pain refractory to escalating doses of opioids or those who suffer debilitating opioid-mediated side effects. Patients whose pain is relieved by diagnostic celiac plexus block may undergo subsequent celiac plexus neurolysis, with careful patient selection maximizing therapeutic outcomes. Although initial celiac plexus neurolysis yields >3 months relief in most patients, disease progression often mitigates the efficacy of repeat procedure, and may indicate the need for more-invasive therapy.

Intrathecal delivery of analgesic agents is helpful in patients whose pain is poorly controlled by less invasive means (Fig. 16). Typically, a temporary percutaneous catheter is placed and the effectiveness of treatment is assessed and the dose optimized over several days. Subsequently, a pump and catheter system is surgically implanted to deliver opioid and/or adjuvant analgesic agents directly into the cerebrospinal fluid. Randomized, controlled studies have delineated the benefit of this therapeutic modality, not only for pain control, but particularly in minimizing the toxicities of systemically administered opioids.

Ongoing consultation with a pain specialist is advised to optimize an integrated approach to pharmacologic, procedural, and surgical pain care for the patient with pancreatic cancer. Reassurance given to the patient that his or her pain care is paramount during their care, regardless of the stage and severity of their disease, is essential in a process where the emphasis is often more focused on palliation rather than cure.

Depression

Approximately 10% to 20% of patients with pancreatic cancer suffer from depression, and patients who are depressed are less likely to have their cancers managed optimally than are patients who are not depressed.
Notably, although it is often assumed that this depression is caused by the psychological burden of the diagnosis of a life-threatening cancer, in fact, depression can precede the diagnosis of pancreatic cancer.\textsuperscript{103} This latter observation raises the possibility that pancreatic cancers provide a factor or factors that contribute to depression.\textsuperscript{103} Regardless of its etiology, the immense suffering depression causes and its prevalence make it clear that patients should be screened for depression, and adequately treated if they have it.\textsuperscript{103,223,224}

End of Life

Although it is natural for health care providers to focus on prolonging life, helping a patient and their family through the difficult transitions that come all too often with pancreatic cancer are equally important. A detailed discussion of palliative care is beyond the scope of this review, but practitioners are encouraged to include a palliative care expert as a part of their multidisciplinary team.\textsuperscript{115}

The Importance of Multidisciplinary Care

It should be clear from this review that pancreatic cancer is a complex disease and that this complexity is best managed clinically by a multidisciplinary team of health care providers working in concert to deliver the best individualized care for their patients.\textsuperscript{113} Indeed, a recent analysis of the Multidisciplinary Pancreatic Cancer Clinic at Johns Hopkins (pathology.jhu.edu/pc) showed that 25% of the patients referred to the clinic had a significant change in their diagnosis or treatment.\textsuperscript{113} In addition, a large number of patients who went through the clinic elected to participate in research studies including clinical trials and the National Familial Pancreas Tumor Registry. The advantages of multidisciplinary care go beyond this, because these clinics build cohesion and communication within the team, helping to ensure the highest quality care even after the patient leaves the clinic to pursue specific treatments.

Summary and Conclusions

Pancreatic cancer is a complex and highly lethal disease that is best treated in the multidisciplinary setting. Although the survival statistics are currently bleak, there are a number of bright spots on the horizon, including individualized therapies and the prevention of an invasive pancreatic cancer by improvements in the management of cystic lesions of the pancreas.

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