17 - 88 Pancreatic Cancer

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Pancreatic Cancer Pancreatic cancer is the third leading cause of cancer-related mortality in the United States, with >66,000 Americans diagnosed and >51,000 dying from the disease each year. Pancreatic cancer is projected to be the second leading cause of death from cancer in the United States by 2030. Worldwide, pancreatic cancer is the eleventh most common can cer, with about half a million diagnoses per annum. Pancreatic cancer is the most lethal human cancer, with an overall 5-year survival of 13%. However, that situation is changing. In particular, (1) an enhanced understanding of the pathobiology and genomic landscape of pancre atic cancer is steadily giving rise to new therapeutic opportunities, (2) the integration of multimodality therapy for patients with localized disease has improved outcomes, and (3) increasingly more molecularly defined groups of patients are eligible for targeted therapy beyond cytotoxic therapy. ■ ■EPIDEMIOLOGY Pancreatic cancer accounts for 3% of all new cancer cases in the United States and ~8.3% of all deaths from cancer in the United States. The lifetime risk of developing pancreatic cancer is ~1.7%; however, the incidence has been increasing about 1.1% per year overall, but notably in people <55 years of age, it has been increasing 2.36% per year in women and 0.62% per year in men. Pancreatic cancer is more common with increasing age and slightly more common in men than in women. The 5-year survival rate for all stages has increased from 3% in 1975 to 13% in 2024. The latest information from the U.S. Surveil lance, Epidemiology, and End Results (SEER) database predicts that the 5-year survival is about 44% for patients with localized pancreatic cancer, 16% for those with regional disease, and 3.2% for patients with metastatic disease. Pancreatic cancer is more common in developed countries (although it tracks with the prevalence of smoking). The inci dence is highest in Eastern (e.g., Hungary and Slovakia) and Western (e.g., Germany) Europe and North America followed by other areas in Europe, Australia, New Zealand, and Southcentral Asia. ■ ■RISK FACTORS Age is one of the strongest risk factors for pancreatic cancer with median age at diagnosis of 71 years (the disease is most frequently diagnosed in the 65–79 age group; for men, 65–69; for women, 75–79). The number of new cases per 100,000 persons and the number of deaths per 100,000 persons are higher for males and for black people of both sexes. People who have a non-O blood type are at higher risk of developing pancreatic cancer. Environment The greatest risk factor for pancreatic cancer is cigarette smoking. The risk correlates with the increased number of cigarettes smoked and persists for at least 10 years following smoking cessation. Twenty-five to 30% of pancreatic cancers are believed to be caused by smoking. Exposure to cadmium as part of cigarette smoking or via exposure to welding, soldering, or dietary exposure has been weakly associated with an increased risk of pancreatic cancer. Dietary factors

may contribute to risk, acknowledging confound ing issues; however, high intake of fat or meat (particularly well-done barbequed meat) are risk factors. High intake of citrus fruits and veg etables are associated with a decreased risk of pancreatic cancer. Coffee and low-to-moderate alcohol consumption are not associated with an increased risk for pancreatic cancer, although consumption of sugary carbonated drinks has been associated with elevated risk. Hereditary Factors, Genetics, and Screening Hereditary fac tors account for 10–16% of all pancreatic cancers. Family members of patients with pancreatic cancer and selected individuals with certain pathogenic germline variants should seek participation in an early

detection program with genetic counseling, definition of risk, and if appropriate, periodic magnetic resonance imaging (MRI) screening and endoscopic ultrasound of the pancreas, ideally enrolled on a pro spective registry. Table 88-1 summarizes the various germline variants along with familial cancer syndromes where there is known to be an increased risk for pancreatic cancer. For an average-risk individual (without any known predisposing factors), there is currently no recom mended screening.

Knowing that an individual carries a BRCA1/2 or PALB2 germline variant or any of the above mutations requires referral of that person to an early detection or high-risk screening clinic. For patients with a BRCA1/2 or PALB2 pathogenic germline variant, a poly(ADP-ribose) polymerase (PARP) inhibitor should be considered (see below) as part of treatment for metastatic pancreatic cancer. Other pathogenic germline variants are under study to determine their increased risk of pancreatic cancer, including CFTR, PRSS2, CDK4, FANCC, APC, ATM, BRIP1, BRCA1, EPCAM, MEN1, MLH1, MSH2, MSH6, NF1, PMS2, SMAD4, TP53, TSC1, TSC2, and VHL. Some of these variants are also associated with pancreatic neuroendocrine tumors (Chap. 89). In addition to recognized genetic syndromes from single gene vari ants, other individuals without any of these identifiable germline vari ants may be at higher risk for this cancer. For example, a family history of pancreatic cancer is associated with increased risk based on the number of affected relatives. Having one first-degree relative with pan creatic cancer, one’s risk for developing the disease is increased 4.6-fold, having two first-degree relatives increases the risk 6.4-fold, and three or more first-degree relatives confers a 32-fold increased risk. The risk is also increased if a relative developed pancreatic cancer at <55 years old and is further compounded by smoking. CHAPTER 88 Pancreatic Cancer Medical Conditions Chronic pancreatitis that is nonfamilial is associated with an increased risk of pancreatic cancer (2.3–16.5-fold increase). Risk is also increased in people with chronic pancreatitis associated with cystic fibrosis or tropical pancreatitis. A clear association exists between diabetes mellitus (both type 1 and type 2) and pancreatic cancer. Whether this is a causal association or whether the diabetes is the result of the cancer is not exactly clear. Newonset (particularly with concomitant weight loss) or unexpected wors ening of type 2 (or type 3c) diabetes may be associated with pancreatic cancer, and research programs are evaluating screening in otherwise healthy individuals in this setting. High body mass index (BMI) is considered a risk factor for pancre atic cancer. A high BMI of ≥30 is associated with a doubling of pancre atic cancer risk. As obesity is a risk factor for diabetes, the contribution of obesity alone is unclear. Interestingly, patients with severe obesity TABLE 88-1 Germline Mutations, Familial Cancer Syndromes,

and Fold Risk of Pancreatic Cancer ESTIMATED INCREASED RISK (FOLD) OF PANCREATIC CANCER FAMILIAL CANCER SYNDROME GERMLINE MUTATION BRCA2 a Familial breast/ovarian cancer and

others 3.5–10 PALB2 (partner and localizer of BRCA2) Familial breast cancer and others ~Sixfold p16/CDKN2A Familial atypical multiple mole melanoma (FAMMM) 15–22 STKII (LKB1) Peutz-Jeghers syndrome 76–140 PRSS1 or SPIN11b Hereditary (familial) pancreatitis

ATM Ataxia-telangiectasia 6c MLH1, MSH2, MSH6, PMS2 Heredity nonpolyposis colorectal syndrome or Lynch syndromed 9–36 aParticularly common in individuals with Ashkenazi Jewish heritage. bForty percent chance of pancreatic cancer by the age of 70. cCalculated at age 70. dVery important because this is associated with microsatellite instability, which is a marker for response to immune checkpoint blockade.

who undergo a bariatric intervention experience a reduction in the incidence of gastrointestinal cancers, including pancreatic cancer, by

> 30% in the first 3 years (along with a decrease in their hemoglobin A1c and blood glucose level). Physical inactivity also has been associated with an increased risk of pancreatic cancer.

Other Considerations Most patients with pancreatic cancer relate that they have had developing symptoms over months to years before diagnosis. Efforts at early detection of the disease have not yet been fruitful, but this is an area of very active investigation. ■ ■PATHOLOGY AND MOLECULAR CONSIDERATION Location The posterior location of the pancreas in the abdomen is one of the issues that makes diagnosis more challenging (Fig. 88-1A). Pathology Cancers of the pancreas can be divided into neoplasms of the endocrine pancreas (Chap. 89) and those of the exocrine pan creas. The most common neoplasm of the exocrine pancreas and most lethal is ductal adenocarcinoma. These cancers arise in the head, body, or tail of the pancreas and are characterized by infiltrating desmoplas tic stromal reactions (Fig. 88-1B). Other subtypes of nonneuroendocrine pancreatic cancers include acinar cell carcinoma (tumors of the exocrine enzyme producing cell), colloid carcinoma, medullary carcinoma, adenosquamous carcinoma, and other rare subtypes. Each of these is different in behavior and in their molecular characteristics and often requires other specific types of treatment. Occasionally, metastases to the pancreas occur second ary to renal, breast, lung, and urothelial carcinomas, melanoma, lym phoma, and other malignancies. PART 4 Oncology and Hematology Molecular Characteristics The mutational landscape of pan creatic ductal adenocarcinoma is characterized by alterations in four genes that are commonly mutated or inactivated. The most common of these is the KRAS oncogene (mutations primarily in codon 12). It is increasingly important to identify the specific mutant KRAS allele as novel drugs targeting specific alleles now exist and others are in development. KRAS mutations are seen in 90–95% of pancreatic adenocarcinomas. A subset of pancreatic cancers is termed “KRAS Stomach Splenic artery Hepatic artery Portal vein Spleen Common bile duct Kidney Jejunum Pancreas Duodenum Superior mesenteric artery Superior mesenteric vein A FIGURE 88-1 A. Note the relationship of the pancreas to the major vessels of the retroperitoneum. B. Ductal adenocarcinoma of the pancreas (black arrows), with intense stromal component (white arrows). (Part A is courtesy of Mary Kay Washington, MD, PhD, Vanderbilt University. Part B is courtesy of Haiyong Han, PhD, Translational Genomics Research Institute [TGen].)

wildtype," where no alteration in KRAS is observed. This form of pancreatic cancer is more frequently observed in patients <55 years of age, and often other therapeutically actionable findings are identi fied in these cancers, including mutations in BRAF, rare oncogenic targetable fusions (e.g., NRG-1, NTRK1-3), or microsatellite instability. p16/CDKN2A mutation or epigenetic silencing is present in >90% of invasive pancreatic adenocarcinomas. TP53 is mutated in ~75% and DPC4/SMAD4 is mutated in about half of these tumors. As a reference point, the BRCA2 gene noted in Table 88-1 is mutated in 3.5–10% of pancreatic adenocarcinomas. Precursor Lesions Most pancreatic cancers are believed to arise from pancreatic intraepithelial neoplasia (PanINs), which have vary ing degrees of dysplasia designated as PanINs 1–3 (and constitute a progression model for pancreatic cancer). Genetic alterations become more frequent as the PanIN grade increases (e.g., grade 3). Most PanIN lesions will never progress to invasive malignancy. An alternate precursor lesion is an intraductal papillary neoplasm (IPMN), which is usually noninvasive. Unfortunately, even high-grade PanIN lesions are not detectable by currently available imaging modalities. In con trast, some pancreatic adenocarcinomas arise from noninvasive cystic epithelial precursor lesions. These lesions can be seen on magnetic resonance imaging (MRI) and computed tomography (CT) imaging, and thus detection may permit early diagnosis of pancreatic cancer. As compared to main pancreatic duct IPMN, a side branch duct IPMN is more likely to be noninvasive. MRI and endoscopic ultrasound are commonly used to assess malignant potential based on risk factors such as size, growth rate, main pancreatic duct size, and the presence of mural nodularity. One other rare pancreatic tumor is the mucinous cystic neoplasm; they may be seen as incidental findings on scans and are more com mon in the body and tail of the pancreas and tend to occur in women. These lesions are less likely to progress to malignancy. Clinical signs of concern include large size (>3 cm) and the presence of mural nodules and/or thickening. Even after rare progression to mucinous adeno carcinoma, they typically have a more favorable prognosis relative to typical ductal adenocarcinoma. B

A B C D E F FIGURE 88-2 Selected images from contrast-enhanced computed tomography (CT) in patients with locally advanced adenocarcinoma of the pancreas. A high-quality contrast-enhanced CT scan (arterial phase in panels A–C and portal venous phase in panels D–F) is required for optimal staging of pancreas cancer. Panel A demonstrates the typical features of adenocarcinoma of the pancreas on arterial phase axial CT scans (dotted outline) with tumor encasement of the superior mesenteric artery (white arrow). Note the dilatation of the common bile duct (red arrow). Panels B (magnified coronal) and C (sagittal) show reconstruction of CT images into additional orthogonal planes with exquisite details to confirm the unresectable nature of the tumor due to vascular encasement. Panel D demonstrates the typical features of adenocarcinoma of the pancreas on portal venous phase axial CT scans in a different subject. The dotted line outlines a pancreas cancer lesion in the pancreatic head, which is encasing the portal splenic confluence (dotted outline). Panels E (white arrow) and F show the pinched appearance of the portal splenic confluence by tumor abutment and invasion of the superior mesenteric vein (white arrow) on coronal and sagittal views. Note the presence of a stent in the common bile duct (red arrow) to help relieve biliary obstruction caused by the tumor. CA, celiac axis; SMA, superior mesenteric artery. ■ ■CLINICAL FEATURES History and Physical A classic presentation for a patient with pancreatic cancer arising in the head of the gland is "painless" jaundice. Jaundice is visually detectable with a bilirubin of >2 mg/dL, and pruritus may also occur due to bile salt deposition in the skin. However, pain is also common in newly diagnosed patients and is typically mid epigas tric (sometimes described as a "boring-like" pain) with radiation to the back (due to retroperitoneal

invasion of the splanchnic nerve plexus). The pain may be exacerbated by eating or lying flat. In the presence of jaundice, light stool color from the absence of bile occurs (steatorrhea also causes malodorous stools). Other signs include the onset of diabetes (particularly with concomitant weight loss) or hyperglycemia/elevated hemoglobin A1c in the preceding 1–2 years. The association of pancreatic cancer with depression remains controversial. In addition to jaundice, physical signs of pancreatic cancer include evidence of weight loss, including loss of muscle mass, and a palpable gallbladder in the setting of biliary obstruction (Courvoisier's sign). Migratory superficial thrombophlebitis and presentation with both deep venous and arterial thromboses can occur (Trousseau's syndrome). Signs of late-stage disease include a lymph node palpable in the supraclavicu lar fossa (usually on the left where the thoracic duct enters the subcla vian vein). This is referred to as Virchow's node. Occasionally, one can palpate subcutaneous metastases in the periumbilical area referred to as a Sister Mary Joseph's node—named after one of the operating room nurses from the Mayo Clinic who noted that when she prepped that area and felt those nodules, the patient often had peritoneal metastases. The history and symptoms noted above lead to imaging as the next step, including ultrasonography (jaundice) and CT or MRI. ■ ■DIAGNOSTIC WORKUP Imaging A key diagnostic tool is the use of a dual-phase con trast-enhanced CT using a pancreas cancer protocol, which allows

CHAPTER 88 Pancreatic Cancer arterial phase enhancement and portal venous phase enhancement and detailed visualization of tumor–blood vessel relationships to inform both resectability and staging. Figure 88-2 demonstrates such a CT scan (with vascular involvement). Figure 88-3 demonstrates the use of an 18F-glucose positron emission tomography (PET) scan that can aid in the detection of otherwise occult metastatic disease. FIGURE 88-3 Positron emission tomography scan demonstrating metastatic disease—baseline and after 6 weeks of chemotherapy with partial resolution of liver metastases.

Histologic Diagnosis A histologic (tissue) diagnosis is essential and should be obtained with a Tru-Cut biopsy needle (fine-needle aspi ration cytology is an acceptable but less preferred alternative). Obtain ing adequate tissue not only secures a histologic/cytologic diagnosis but also facilitates molecular testing (next-generation sequencing for genomic alterations including KRAS) and microsatellite status. Increas ingly subsets of patients based on genomic characterization are being identified and for whom therapies are available, making the need for adequate tissue sampling increasingly relevant to patient management.

A core needle (18- to 22-gauge) biopsy can be obtained via endo scopic ultrasound-guided technique for a tumor localized to the pan creas. To biopsy the liver or a lymph node, a larger (16- to 18-gauge) percutaneous needle biopsy by an interventional radiologist is typically undertaken. Serum Markers Before treatment and, ideally, once the bilirubin level has normalized (biliary obstruction is associated with elevated CA19-9), a serum sample should be obtained for level of CA19-9, carcinoembryonic antigen (CEA), and CA125 (can be helpful for the 8–15% of patients with nondetectable CA19-9–Lewis antigen nonse cretors). Trends of these tumor markers over time can inform thera peutic decision-making. ■ ■IMPORTANT IMMEDIATE CONSIDERATIONS

IN PATIENT CARE During the life cycle of this cancer, biliary tract obstruction is a fre quent occurrence for tumors arising in the head of the gland (and the attendant risk for sepsis from the biliary tree). A metallic biliary wall stent is typically placed endoscopically to alleviate jaundice and

pru ritus. If surgery is under consideration as the initial therapeutic step, biliary stent placement is not necessarily warranted; however, if neo adjuvant (preoperative) systemic therapy is planned, both a histologic/ cytologic diagnosis and placement of a biliary wall stent are required (where the latter is medically indicated). Of important note, all patients with localized pancreatic cancer require multidisciplinary evaluation by surgical, medical, and radiation oncology to optimize therapeutic decision-making. PART 4 Oncology and Hematology Patients with metastatic pancreatic cancer may have a hyperco agulable state and frequently have thrombophlebitis (Trousseau's sign) and deep vein thrombosis with pulmonary emboli and/or more rarely arterial thrombotic events. Anticoagulation using either a direct oral anticoagulant or low-molecular-weight heparin is required in these setting in the absence of a contraindication to anticoagulation. Control of pain or of active cancer-related symptomatology includ ing anorexia, weight loss, and malabsorption should be proactively treated. Pancreatic enzyme replacement therapy (PERT) is a critical measure to address symptoms of malabsorption, including abdominal cramping, bloating, steatorrhea, excess flatus, and weight loss. Early involvement of a supportive care team can help maximize symptom control, facilitate treatment readiness, and extend a better quality of life. ■ ■CLINICAL STAGING The clinical staging of pancreatic cancer according to the American Joint Commission on Cancer staging is presented in Table 88-2. Table 88-3 presents another clinical way to express extent of disease as well as therapeutic approaches (to be discussed later). For optimal staging, a laparoscopy is selectively indicated either before or at the time of definitive surgery. If metastatic disease is identi fied at laparoscopy, curative intent surgery is not undertaken. TREATMENT Pancreatic Cancer RESECTABLE DISEASE (10–20%) For all patients with localized pancreatic cancer, multidisciplinary evaluation should be undertaken. A standard approach for resect able disease (10–15% of patients; as defined in Table 88-3) is

upfront surgery. Neoadjuvant therapy (systemic therapy prior to surgery) is an option for patients with resectable disease. The ratio nales for preoperative chemotherapy include the following: (1) to control micrometastatic disease; (2) to assess tumor biology and response to the selected chemotherapy regimen (this allows patients with progressive disease to avoid nontherapeutic, morbid surgery); (3) to assure delivery of systemic therapy because therapy is better tolerated in the preoperative setting and is not subject to omission of drugs or altering doses due to delayed postoperative recovery; and (4) to achieve tumor downstaging to enhance the potential for a margin-negative surgical resection. The type of surgery for patients with tumors in the pancreatic head, neck, or uncinate process is typically a pancreaticoduodenectomy with or without pylorus preservation. For tumors in the body or tail, a distal subtotal pan createctomy and splenectomy are performed. These operations may be performed using a traditional "open" surgical technique or using minimally invasive techniques. Clinical and pathologic findings of the resection are defined as either an R0 resection (no macroscopic or microscopic disease left after surgery) or an R1 resection, which refers to microscopic residual disease at the surgical margin. An R2 resection refers to gross residual disease remaining after surgery and is a highly undesirable oncologic outcome. The best outcomes are achieved in patients with a small tumor (<2 cm), no lymph node involvement (N0), and R0 (stage I), in whom 5-year survival ranges from 50 to 90% depending on actual tumor size and grade. Overall, only a small fraction of tumors are diagnosed when stage I; however, a key goal of screening is to "stage migrate" and increase the proportion of tumors that are diagnosed as early stage I lesions. Several approaches are designed to maximize outcome for local ized pancreatic cancer. Postoperative Adjuvant Therapy A standard of care is 24 weeks of adjuvant treatment with the modified FOLFIRINOX regimen (folinic acid, 5-fluorouracil, irinotecan,

oxaliplatin). The median survival was 54 months for modified FOLFIRINOX compared to 35 months for gemcitabine alone (hazard ratio [HR] 0.64; 95% confidence interval [CI] 0.48–0.86; p = .003) in the definitive trial supporting this therapy. Main side effects included fatigue, gastro intestinal toxicity, myelosuppression, and neuropathy. Neoadjuvant Therapy A newer approach is the use of neoadjuvant chemotherapy (systemic therapy given before surgery) to shrink the tumor, eradicate micrometastatic disease, and normalize serum CA19-9 level. Neoadjuvant therapy is the standard approach for patients with borderline resectable or locally advanced disease. The role of radiation in the treatment of localized pancreatic cancer is controversial. LOCALLY ADVANCED DISEASE (25–30% OF PATIENTS) For patients with locally advanced disease (defined by tumor contact with arterial structures >180° and/or venous contact that does not permit resection/reconstruction), the median survival is poor (6–18 months). Complications from local disease progression can be significant and include pain, biliary and duodenal obstruc tion, vascular thromboses, varices, bleeding, and infection/sepsis. Typical treatment paradigms for locally advanced disease include systemic chemotherapy with or without radiation therapy. A pro portion of patients with locally advanced disease (~20%) may be rendered operable following neoadjuvant therapy. METASTATIC DISEASE (50–60% OF PATIENTS) The mainstay of treatment for metastatic pancreatic cancer is systemic chemotherapy. Several treatment regimens including FOLFIRINOX, gemcitabine, albumin-bound paclitaxel, and, more recently, NALIFIRINOX (nanoliposomal irinotecan, 5-fluorouracil, leucovorin, oxaliplatin; NAPOLI-3) have all demonstrated a survival advantage compared to prior standards in untreated metastatic pan creatic cancer. In a previously treated setting, liposomal irinotecan and infusional 5-fluorouracil and leucovorin (NAPOLI-1) regimen has been shown to improve survival. Predictors of outcome in the

TABLE 88-2 Definition of Primary Tumor (T) T CATEGORY T CRITERIA TX Primary tumor cannot be assessed T0 No evidence of primary tumor Tis Carcinoma in situ This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with

high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm

with high-grade dysplasia T1 T1a T1b T1c Tumor ≤2 cm in greatest dimension Tumor ≤0.5 cm in greatest dimension Tumor >0.5 cm and <1 cm in greatest dimension Tumor 1–2 cm in greatest dimension T2 Tumor >2 cm and ≤4 cm in greatest dimension T3 Tumor >4 cm in greatest dimension T4 Tumor involves celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size N CATEGORY N CRITERIA NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastases N1 Metastasis in one to three regional lymph nodes N2 Metastasis in four or more regional lymph nodes M CATEGORY M CRITERIA M0 No distant metastasis M1 Distant metastasis AJCC Prognostic Stage Groups WHEN T IS… AND N IS… AND M IS… THEN THE STAGE GROUP IS…. Tis N0 M0

T1 N0 M0 IA T1 N1 M0 IIB T1 N2 M0 III T2 N0 M0 IB T2 N1 M0 IIB T2 N2 M0 III T3 N0 M0 IIA T3 N1 M0 IIB T3 N2 M0 III T4 Any N M0 III Any T Any N M1 IV Source: Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging System (2023). TABLE 88-3 Extent of Disease and Therapeutic Approach DESIGNATION (MEDIAN SURVIVAL) THERAPEUTIC APPROACHES

1. Resectable (localized): (18–23 mo) Surgery followed by adjuvant therapy • mFOLFIRINOX or gemcitabine +/– • No solid tumor contact with celiac axis, hepatic artery, or superior mesenteric artery (SMA), contact with superior mesenteric–portal veins of <180° • Patent superior mesenteric–portal capecitabine or nab-paclitaxel Neoadjuvant chemotherapy followed by surgery veins • No extrapancreatic disease
2. Locally advanced: (6–18 mo) Chemotherapy Chemotherapy +/– radiation Evaluate for surgery following systemic therapy • Arterial involvement of >180° (superior mesenteric artery, others) • Venous occlusion (superior mesenteric vein [SMV] or portal) • No extrapancreatic disease
3. Metastatic: (6–12 mo) Chemotherapy with special consideration for tumors with specific targets (e.g., mismatch repair high, BRCA1/2, BRAF, etc.) Abbreviation: mFOLFIRINOX, modified FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (T Conroy et al: N Engl J Med 379:2395, 2018).

CHAPTER 88 Pancreatic Cancer metastatic setting include good physical functioning (performance status), favorable nutritional status, the absence of liver metastases, lung-only metastases, and the presence of select pathogenic germ line variants. Table 88-4 details combination regimens that have further improved survival modestly. Median overall survival ranges from 6 to 12 months. However, 1-year survival is improving, with subsets of patients whose survival with metastatic disease can reach a couple of years or longer. PATIENTS WITH A SPECIFIC MOLECULAR PROFILE IN

THEIR TUMOR/GERMLINE PARP inhibitors have activity in patients with pathogenic germline or somatic (tumor-based) BRCA2, BRCA1, or PALB2 (i.e., defective DNA repair proteins) variants. In addition, these tumors might be more sensitive to specific combinations of chemotherapy that include platinum agents (gemcitabine and cisplatin or FOLFIRI NOX). About 1% of pancreatic cancers have microsatellite insta bility, typically with high numbers of mutations in their tumors, due to deficient mismatch repair, and these tumors are likely to benefit from immune checkpoint blockade with anti-PD-1 (pem brolizumab, nivolumab) and anti-CTLA-4 inhibitors. KRAS muta tions occur ubiquitously in pancreatic cancer. Current treatment guidelines include drugs targeting KRAS G12C (~1% of pancreatic

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