Multidisciplinary Standards of Care and Recent Progress in Pancreatic Ductal Adenocarcinoma

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Abstract: Despite tremendous gains in the molecular understanding of exocrine pancreatic cancer, the prognosis for this disease remains very poor, largely because of delayed disease detection and limited effectiveness of systemic therapies. Both incidence rates and mortality rates for pancreatic cancer have increased during the past decade, in contrast to most other solid tumor types. Recent improvements in multimodality care have substantially improved overall survival, local control, and metastasis-free survival for patients who have localized tumors that are amenable to surgical resection. The widening gap in prognosis between patients with resectable and unresectable or metastatic disease reinforces the importance of detecting pancreatic cancer sooner to improve outcomes. Furthermore, the developing use of therapies that target tumor-specific molecular vulnerabilities may offer improved disease control for patients with advanced disease. Finally, the substantial morbidity associated with pancreatic cancer, including wasting, fatigue, and pain, remains an under-addressed component of this disease, which powerfully affects quality of life and limits tolerance to aggressive therapies. In this article, the authors review the current multidisciplinary standards of care in pancreatic cancer with a focus on emerging concepts in pancreatic cancer detection, precision therapy, and survivorship.

Keywords: cachexia, epidemiology, health outcomes, pancreatic neoplasms, screening and early detection

Background and Epidemiology

Pancreatic cancer has the poorest prognosis of any common solid malignancy, with a 5-year overall survival (OS) rate of approximately 10%.1 Although this represents a modest improvement in survival, the absolute number of individuals who die of this disease continues to rise. In 2020, it is estimated that 57,600 people will be diagnosed with and 47,050 deaths will be attributed to pancreatic cancer in the United States, recently eclipsing breast cancer as the third leading cause of overall cancer death.2 The median age at diagnosis of pancreatic cancer is 70 years.1,3 Incidence rates during 2013 through 2017 were higher among males than females (14.9 and 11.6 cases annually per 100,000 persons, respectively), as were mortality rates (12.7 and 9.6 deaths annually per 100,000 persons, respectively).1,3 Incidence and mortality rates during this period were highest for blacks (15.3 cases and 13.3 deaths annually per 100,000 persons, respectively), followed by non–Hispanic whites (13.1 cases and 10.9 deaths annually per 100,000 persons, respectively), with lower rates among Hispanics, and especially among Asian/Pacific Islanders and American Indian/Alaska Natives.1 Lost earnings from person-years of life lost from pancreatic cancer in 2015 are estimated to be over $6 billion.4 Both incidence rates and mortality rates increased by an average of 0.3% per year during the past decade.1 Underlying these trends is a combination of an aging population, longer expected lifespan, and the public health pandemics of obesity and diabetes.
Approximately 95% of pancreatic cancers are exocrine cell tumors, most commonly pancreatic ductal adenocarcinomas (PDAC). Endocrine pancreatic cancers are generally more indolent tumors with a more favorable prognosis, as reviewed elsewhere. There are 4 fundamental challenges that underlie the high mortality of PDAC. First, the pancreas is situated deep within the upper abdomen, seated behind the stomach and between the aorta and its major upper abdominal branches. Not only does this shield growing tumors from detection but, because the cancer often grows around and encases these vessels, only 15% to 20% can undergo surgical resection, which is the foundation of curative treatment. Second, PDAC exhibits an aggressive biology characterized by early metastasis. Greater than 50% of patients have distant metastatic disease on presentation, and the majority of patients who undergo resection will develop metastases within 4 years of surgery, suggesting the de facto presence of micrometastases in patients with apparently localized tumors. Third, the physiologic effects of PDAC can dramatically weaken patients, limiting their ability to withstand aggressive treatment. The wasting syndrome of cachexia is present in up to 80% of patients with PDAC at diagnosis, and this may be further complicated by exocrine and endocrine pancreatic dysfunction. Cachectic patients exhibit poor treatment tolerance, as evidenced by decreased survival after pancreatectomy or chemotherapy. Finally, PDAC exhibits resistance to many antineoplastic therapies, with rapid progression and low rates of pathologic complete response even with the most effective systemic agents and radiotherapy. Indeed, fewer than 3% of patients who present with metastatic disease are alive after 5 years, whereas this number jumps to over 70% in patients with localized, stage IA disease. The impact of these challenges is reflected in the prognostic factors predicting poorer survival: advanced tumor (T) classification, the presence of nodal metastasis or distant metastasis, the presence of macroscopic or microscopic residual disease after resection, high histologic grade, invasion of major blood vessels, and poor performance status.

Presentation

Although most patients are symptomatic at presentation, symptoms of PDAC are often nonspecific, leading to a median delay between presentation and diagnosis of >2 months. The most commonly reported symptoms are fatigue (86%), weight loss (85%), anorexia (83%), jaundice (56%), nausea (51%), abdominal pain (79%), diarrhea (44%), pruritis (32%), and steatorrhea (25%). Clinical signs of PDAC, including jaundice (55%), hepatomegaly (29%), cachexia (13%), epigastric mass (9%), or ascites (5%), are much less common. This can make it difficult for primary care and front-line physicians to know when it is appropriate to escalate a workup, as there is no specified diagnostic algorithm for PDAC. The development of any of these symptoms in the context of newly diagnosed diabetes, a family history of PDAC, or a history of recurrent or chronic pancreatitis should alert the managing physician to strongly consider PDAC in the differential diagnosis.

Risk Factors and Early Detection

Despite the poor prognosis of PDAC overall, data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program underscore the impact of earlier detection on outcomes. For example, an analysis of SEER data between 2010 and 2016 shows that, although only 2.9% of patients with PDAC who had distant metastases survived ≥5 years, approximately 39.4% of patients who had localized disease survived for that duration. Patients with PDAC <1 cm who were diagnosed by endoscopic ultrasound (EUS) had even higher 5-year survival rates (reaching approximately 70%) for patients with no obstructive symptoms or detectable mass on computed tomography (CT), whereas a more recent study from the United States of individuals at high risk for PDAC undergoing longitudinal surveillance has demonstrated that resecting advanced preneoplastic lesions is essentially curative. These findings reiterate the importance of earlier detection of PDAC, possibly even at the stage of carcinoma in situ (aka pancreatic intraepithelial neoplasia 3 [PanIN-3]).

Nonetheless, the US Preventive Services Task Force (USPSTF), an expert body charged with making recommendations for screening and other clinical preventive services for the nation, has recently reaffirmed its longstanding recommendation of discouraging screening for PDAC in the general population, concluding, with moderate or high certainty, that such a screening service has no net benefits or
that the benefits are outweighed by the harms, thus giving the service a failing “D” grade.29 On one hand, the USPSTF guidelines sound counterintuitive in light of the aforementioned impact of earlier detection of PDAC on stage-specific survival. On the other hand, there is compelling rationale against screening the general population for PDAC. At an incidence rate of approximately 13 cases per 100,000 adults,3 PDAC is still relatively uncommon. In contrast, the incidence rates of 2 cancers for which general population screening is recommended by the USPSTF—breast cancer and colorectal cancer—are approximately 69 and 38 cases per 100,000 adults, respectively.30-33 This suggests that even a “perfect” PDAC biomarker with a sensitivity of 100% (ie, not a single cancer being missed) and a specificity of 99% (1 false-positive of 100 abnormal tests), would only have a positive predictive value close to 1%,34,35 leading to a large number of individuals undergoing unnecessary imaging tests or potentially harmful procedures and adding greatly to health care costs and patient morbidity. To circumvent this pitfall, the USPSTF has excluded defined cohorts that are at average risk for PDAC from its screening recommendation. In the following paragraphs, we discuss some of these high-risk cohorts and other emerging paradigms in early detection.

Approximately 10% of patients with PDAC harbor a pathogenic germline mutation in a cancer-predisposing gene, of which BRCA2 and ATM are the 2 most common candidates, followed by BRCA1, PALB2, CDKN2A/p16, and LKB1/STK11; the mismatch repair genes (hMLH1, hMSH2, and hPMS2); and other rarer variants (Table 1).36-46 Of note, only one-half of patients with a deleterious germline mutation report an overt family history of PDAC, in light of which the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) recently updated their guidelines to recommend universal germline mutation testing for all patients diagnosed with PDAC (instead of only those with a suspicious family history).46,47 This has the added benefit of identifying patients with BRCA1/BRCA2 mutations who might benefit from poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor therapy (see below).48 The first-degree relatives of positive index cases can then be approached for testing done of the pathogenic mutation of interest (a process known as cascade testing), and the ready availability of relatively inexpensive blood-based and saliva-based multigene panels has greatly simplified the process.49 Asymptomatic germline mutation carriers represent a rich pool of high-risk individuals for cancer interception, and, in fact, this subset has been explicitly excluded from the USPSTF recommendations against screening in the general population at average risk.29 There is currently no broad consensus on how to conduct longitudinal surveillance of germline mutation carriers, including the optimal imaging modalities to use in this population, although a recent international consortium has suggested some overall guidelines that can be pursued within an academic research setting.17 Nonetheless, retrospective data from 2 of the largest familial PDAC registries have shown the impact of longitudinal surveillance on outcomes, with the majority (75%-90%) of incident cancer cases being diagnosed at a resectable stage, which, in turn, translated into disease-specific survival >3 years.17,30

A separate subgroup of patients, those with pancreatic cysts, may benefit from early detection efforts as well. Pancreatic cysts are categorized as inflammatory (including pancreatic pseudocysts) and noninflammatory (including mucinous and nonmucinous lesions).51 Mucinous cysts of the pancreas are comprised of 2 distinct entities—intraductal papillary mucinous neoplasms and mucinous cystic neoplasms—and both are considered bona fide precursor lesions of PDAC.52 In contrast to microscopic PanINs, which are the most common (approximately 90%) precursor subtype associated with an invasive adenocarcinoma,53 the macroscopic (cystic) precursors can be readily imaged using CT or magnetic resonance imaging (MRI) scans and thus are amenable to longitudinal surveillance for progression to cancer. Notably, retrospective studies on imaging data have shown

| SYNDROME                          | GENE          | RELATIVE RISK       | REFERENCES                  |
|-----------------------------------|---------------|---------------------|-----------------------------|
| Familial atypical multiple mole  | CDKN2A        | 13-Fold to 39-fold  | Hu 2018,27                  |
| melanoma (FAMMM)                  |               |                     | Potjer 2015,30               |
|                                   |               |                     | Goldstein 200446            |
| Familial breast and ovarian       | BRCA1 and BRCA2 | 2-Fold and 3-9 fold | Hu 2018,27                  |
|                                   |               |                     | Iqbal 201240                |
| Fanconi anemia, breast cancer     | PALB2         | Unknown             | Petersen 201641             |
| Familial adenomatous polyposis    | APC           | 5-Fold              | Giardiello 199342           |
| Lynch syndrome                    | MLH1, MSH6, MSH2, PMS2, EPCAM | 9-Fold to 11-fold | Hu 2018,43                  |
|                                   |               |                     | Kastanios 200943            |
| Peutz-Jeghers syndrome            | STK11/LKB1    | 132-Fold            | Giardiello 200044           |
| Hereditary pancreatitis           | PRSS1         | 53-Fold             | Lowervels 199745           |
| Li-Fraumeni syndrome              | TP53          | 7-Fold              | Hu 201847                  |
| Ataxia-telangiectasia             | ATM           | ~3-Fold             | Hu 201847                  |

Table 1. Pancreatic Cancer Susceptibility Genes and Estimated Risk
that as much as 2% to 3% of the general population might harbor asymptomatic pancreatic cysts, and this number rises to >10-fold higher in elderly individuals. This man-made epidemic in pancreatic cysts can be attributed to the tens of millions of abdominal scans that are conducted each year in the United States for unrelated causes. Given that no more than 5% to 10% of PDACs annually arise in the backdrop of a cystic lesion, the vast majority of these asymptomatic pancreatic cysts are essentially benign and can be followed with conservative surveillance. The importance of early detection in patients who have cysts is underscored by data indicating that patients with noninvasive cystic lesions are usually cured upon surgical resection, whereas those with an invasive component can see their 5-year survival drop by ≥50%. Therefore, identifying the minor subset of mucinous cysts that have progressed to either high-grade dysplasia or PDAC, or that harbor an intrinsic biological potential for progression during the patient’s lifetime, is of paramount importance. However, based on SEER data, a cyst detected incidentally on MRI has a 17 in 100,000 chance of being a ductal cancer, indicating a very elevated number needed to surveil to prevent one premature death. Despite this, several international societies have published largely overlapping recommendations on cyst surveillance. The evidence driving these recommendations is derived from case series and retrospective reports, and graded as “very low quality”; thus it is unclear that the benefits of imaging surveillance outweigh potential harms. A compendium of clinical and imaging-based criteria has been suggested by various expert bodies (reviewed by van Huijgevoort and colleagues) that can support the clinician in their management decision making, but all have various shades of imperfections, resulting in some cases of both overtreatment and missed cancer diagnoses. Recently, molecular testing of endoscopically aspirated pancreatic cyst fluid for molecular biomarkers of mucinous cysts, as well as progression to cancer, have been implemented in the clinical domain and have resulted in improved performance over the clinical/imaging criteria alone.

The application of machine-learning algorithms toward designing an integrated approach to cyst classification will result in further accuracy in predicting underlying biology and improved management.

A third high-risk subset for PDAC are patients with chronic pancreatitis, most commonly secondary to chronic alcohol dependence, smoking, hypertriglyceridemia, diabetes, or renal failure. Approximately 5% of patients with chronic pancreatitis of 20 years’ duration will progress to PDAC, and concomitant smoking enhances the risk of neoplastic progression. Patients with sporadic chronic pancreatitis are currently not recommended to undergo PDAC surveillance under the USPSTF screening guidelines. However, the USPSTF recommendation against screening does not apply to a rare subset of patients with so-called hereditary pancreatitis secondary to germline mutations in the PRSS1 gene, which encodes for cationic trypsinogen.

The mutation renders trypsin resistant to inactivation, resulting in recurrent episodes of acute pancreatitis beginning in childhood. These patients have an approximately 50-fold higher lifetime risk of PDAC, again demonstrating the intimate link between inflammation and cancer.

Although the aforementioned risk factors cumulatively affect approximately 15% to 20% of patients diagnosed with PDAC annually, the majority still fall under the category of what would be considered as sporadic cancer (Table 2). How do we enable early detection in individuals with no apparent clinical risk factor such as cysts or family history? One can certainly implement public health approaches such as smoking avoidance and cessation and maintaining a healthy body mass index, because both of these modestly affect approximately 15% to 20% of patients diagnosed with PDAC, thereby raising the lifetime risk of PDAC. The use of genome-wide association studies, in which thousands of polymorphisms across the genome are compared in cases versus controls, has enabled the identification of multiple susceptibility alleles in PDAC, such as alleles within the ABO blood group genes and the gene-encoding telomerase reverse transcriptase (TERT). In contrast to the deleterious germline mutations described above (BRCA1/BRCA2, ATM, etc), these variant alleles individually only have a very modest effect on lifetime risk, but their cumulative risk could become appreciable. The incorporation of predisposing allelic information into a so-called polygenic risk score could then identify individuals at the highest quartile of lifetime risk who could be enrolled into longitudinal surveillance programs. In the past decade, the emergence of new-onset hyperglycemia or frank diabetes has been identified as the presenting symptom of an otherwise asymptomatic PDAC in up to one-half of all patients. The deregulation in glucose homeostasis is a paraneoplastic syndrome caused by the underlying PDAC, which can

### Table 2. Risk Factors for the Development of Pancreatic Cancer

| FACTOR                  | RELATIVE RISK | REFERENCES                      |
|-------------------------|---------------|----------------------------------|
| Tobacco smoking         | 1.7-Fold to 2.6-fold | Iodice 2008, Lynch 2009, Whitmore 1985 |
| Obesity                 | 1.1-Fold to 1.5-fold | Anslan 2020, Renehan 2008 |
| Diabetes                | 1.5-Fold to 2-fold | Andersen 2017 |
| Family history          | 1.7-Fold to 2.3-fold | Amundadottir 2004, Hemminki & Li 2003, Jacobs 2009 |
| Chronic pancreatitis    | 13.3-Fold      | Raimondi 2010 |

*Smoking appears to increase the risk of pancreatic ductal adenocarcinoma in women more than in men (see Andersson 2016 and Muscat 1977).*
start to appear as early as 36 months before clinical diagnosis and is accompanied by changes in subcutaneous adipose tissue. Circulating factors, including antigen and microRNA panels, show promise in discriminating patients with early PDAC from controls or individuals with benign pancreatic conditions, offering the promise of liquid biopsy approaches toward the early detection of PDAC. In addition, recent data have established that alterations in the gut and pancreatic microbiome directly promote pancreatic oncogenesis and influence survival, indicating that changes in fecal microbial composition may also help identify disease development. In a cancer interception paradigm of the future, one can envision a pipeline wherein asymptomatic individuals are identified at higher than average lifetime risk for PDAC based on a combination of polygenic risk score, family history, smoking history, and body mass index, and are enrolled into a risk-reduction program for PDAC (which includes guidance on lifestyle modification) and a surveillance program for individuals for whom benefit is anticipated to exceed harm. The onset of hyperglycemia or frank diabetes, as well as a catalog of longitudinally structured data readily available from the electronic medical record would then trigger additional workup, such as imaging studies, in these high-risk individuals, eventually leading to earlier diagnosis of PDAC at a resectable stage and improved long-term survival.

**Diagnosis and Imaging**

**Diagnostic Workup**

The diagnosis of PDAC cannot be made based on symptoms and signs alone. Patients presenting with jaundice or epigastric pain should be evaluated with complete blood count, blood chemistry panel, and liver function tests, including serum aminotransferases, alkaline phosphatase, and bilirubin. These values can help assess the extent of cholestasis (bilirubin), liver metastasis (alkaline phosphatase), hepatitis (aminotransferases), and nutritional status (albumin, prealbumin). Those with epigastric pain should also have serum lipase measured to evaluate for acute pancreatitis. The tumor marker sialylated Lewis’ blood group antigen CA 19-9 is frequently used in the workup for PDAC. In symptomatic patients, the sensitivity and specificity of CA 19-9 range from 70% to 90%, but the positive predictive value of elevated CA 19-9 in asymptomatic patients was only 0.9%, making it inadequate as a diagnostic in this population. Its limited utility is based on elevations in benign pancreaticobiliary diseases, cancers other than PDAC, and the fact that 5% to 10% of the population do not express Lewis antigens. Emerging data suggest that the combination of serum CA 19-9 with additional biomarkers, such as MUC5AC or thrombospondin-2, improves the specificity of serum testing, offering potential for a future blood-based diagnostic approach. Serum CA 19-9 levels are closely related to tumor size, and the degree of elevation in CA 19-9 is associated with prognosis. In a study of patients with apparently localized disease, values >130 units/mL predicted occult, unresectable disease and were prognostic for survival among >1500 patients with resectable cancers. Although patients with apparently localized PDAC and high levels of CA 19-9 are commonly recommended for staging laparoscopy and neoadjuvant therapy, ASCO guidelines do not specify a cutoff value of CA 19-9 to be used in this manner. Because elevations in serum CA 19-9 can be induced by either tumor production or cholestasis, CA 19-9 should be remeasured after stent placement in patients with biliary obstruction to estimate true tumor burden, accounting for its 4-day to 8-day half-life. Serial monitoring of CA 19-9 is commonly used to track response to therapy in patients who present with elevated CA 19-9. A failure in CA 19-9 normalization after surgery is associated with poor survival and is thought to represent occult metastatic disease. Similarly, declining CA 19-9 during systemic therapy correlates with improved patient survival, although it is unclear what magnitude of decline is most prognostic. Rises in CA 19-9 after a nadir can represent treatment failure and often precede imaging evidence of recurrent or progressive cancer. Serum CA 19-9 changes are not considered to be a substitute for imaging evidence of treatment response or recurrence. In some tumors, additional cancer-specific biomarkers, such as carcinoembryonic antigen or CA 125, are elevated and can also be used to track response to therapy and recurrence. Because these markers are elevated in only a subset of patients with PDAC, their utility in diagnosis is limited.

**Imaging Techniques**

CT is the first-line imaging modality for the initial evaluation of suspected PDAC and is preferred over MRI because of its lower cost and widespread availability. Both CT and MRI have comparable sensitivity in the detection of PDAC, ranging from 76% to 96% for CT and from 83% to 94% for MRI. MRI is usually reserved as a second-line imaging modality in patients with contraindications to CT (e.g., severe iodinated contrast allergy or renal insufficiency). MRI is also used as a problem-solving tool in cases with equivocal CT features and for the characterization of indeterminate liver lesions. Position emission tomography/CT has been shown to detect extrapancreatic metastatic disease that was not detected based on traditional staging examination. Although not recommended as part of routine staging, position emission tomography/CT may be considered in patients at high-risk of extrapancreatic metastases. The primary role of EUS is to guide needle biopsies to confirm the diagnosis of PDAC. In select cases, EUS may be helpful in...
detecting a small pancreatic mass that may be difficult to observe on CT or MRI and thus is the preferred imaging modality in some early detection surveillance programs.\textsuperscript{28,105,106} The reported accuracy in determining tumor resectability ranges from 73\% to 87\% for CT and from 70\% to 79\% for MRI.\textsuperscript{103} CT offers superior spatial resolution and is less susceptible to respiratory motion artifacts than MRI, which is essential in demonstrating the critical relationship between the tumor and adjacent vasculature. The accuracy of PDAC detection and staging critically depends on the appropriate imaging protocol, postprocessing technique, and experience of radiologists.

The pancreatic cancer CT protocol, endorsed by both the Society of Abdominal Radiology and the American Pancreatic Association, states that CT examination should be performed with intravenous contrast (>300 mg iodine per mL) at an injection rate of 3 to 5 mL/second with scans obtained at pancreatic parenchymal phase (40-50 seconds) and portal venous phase (65-70 seconds). A neutral or low-Hounsfield-unit oral agent should be administered. The data set should be obtained with submillimeter slice thickness, reconstructed into 0.75-mm to 3-mm axial slices, with multiplanar reconstruction, and 3-dimensional (3D) reconstruction to allow for full assessment of vascular involvement.\textsuperscript{107} Cinematic rendering is a recently described 3D rendering technique that can provide photorealistic detail, and has the potential to improve visualization of tumor-vessel relationships (Figs. 1 and 2).\textsuperscript{108}

**Staging Systems**

The American Joint Committee on Cancer (AJCC) stages PDAC based on a TNM staging system. The revised eighth edition of the AJCC manual addressed some of the criticisms of earlier versions with changes to the T and lymph node (N) categories.\textsuperscript{109} T categories are mostly based on tumor size. T4 is defined as tumor with arterial involvement regardless of size. N categories are further classified in the eighth edition based on the absence of lymph node involvement (N0) and the number of regional lymph nodes involved (1-3 for N1 and $\geq$4 for N2), rather than only the
absence (N0) or presence (N1) of lymph nodes. The primary goal of the AJCC system is to provide prognostic information, rather than guiding management. Several organizations have issued management guidelines. NCCN guidelines classify the resectability of localized PDAC based on preoperative imaging findings into resectable, borderline resectable, and locally advanced disease and are summarized in Table 3. Arterial abutment (<180 degrees) is considered borderline resectable, whereas arterial encasement (≥180 degrees) is usually considered locally advanced (exception noted below) (Fig. 2). Venous abutment, encasement, or thrombosis are considered borderline resectable, as long as the venous segment is reconstructable. Unreconstructable venous involvement is considered locally advanced (Fig. 3). However, in other guidelines, the presence of celiac artery encasement is considered unresectable.

**Principles of Multidisciplinary Treatment**

**Metastatic Disease Therapy: An Evolving Treatment Paradigm**

Metastatic disease represents the most common clinical presentation of PDAC. Historically, gemcitabine was the standard of care for the first-line treatment of metastatic disease based on a 5.65-month improvement in median OS compared with 5-fluorouracil (5-FU). Major studies establishing standard-of-care first-line therapy for PDAC are listed in Table 5. In 2011, the phase 3 PRODIGE 4/ACCORD 11 trial (Research Partnership in Digestive Oncology [PRODIGE] 4/Concerted Actions in Colorectal and Digestive Cancers 11 Combination Chemotherapy as First-Line Therapy in Treating Patients With Metastatic Pancreatic Cancer [fluorouracil, leucovorin, irinotecan, and oxaliplatin versus gemcitabine for metastatic pancreatic cancer]; ClinicalTrials.gov identifier NCT00714631) showed a survival benefit of combination chemotherapy over gemcitabine, with a 10-month improvement in median OS compared with gemcitabine (5-FU). Therefore, the first-line treatment of metastatic PDAC has evolved to combination chemotherapy, which is now considered the standard of care. Combination regimens involve the use of at least two agents from different classes of drugs, including fluoropyrimidines, platinum agents, and targeted therapies such as EGFR inhibitors and PD-1/PD-L1 blockers.

**Table 3. National Comprehensive Cancer Network Criteria for Defining Resectability of Pancreatic Ductal Adenocarcinoma at Diagnosis**

| Resectability Status | Arterial Involvement | Venous Involvement |
|----------------------|----------------------|-------------------|
|                      | Celiac Artery        | SMA               | Common Hepatic Artery | Portal Vein/SMV |
| Resectable           | None                 | None              | None                   | None            |
| Borderline Resectable| ≤ 180°               | ≤ 180°            | Solid tumor contact without extension into CA or hepatic artery bifurcation | ≤ 180° contact without contour irregularity |
| Locally Advanced     | > 180° (head/uncinate) | > 180°            | None                   | > 180°          |

Abbreviations: CA, celiac artery; GDA, gastroduodenal artery; IVC, inferior vena cava; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein. 

**Table 4. Comparison of Resectability Criteria Among Organizations**

| VESSEL INVOLVEMENT | NCCN 2019 | MDACC | ACTO | AHPBA/SSAT/SSO |
|---------------------|-----------|-------|------|---------------|
| CA abutment (≤180 degrees) | Borderline | Borderline | Borderline | Borderline |
| CA encasement (>180 degrees) | Borderline (head/uncinate); locally advanced | Borderline (body/tail); locally advanced | Unresectable | Unresectable |
| SMA abutment (≤180 degrees) | Borderline | Borderline | Borderline | Unresectable |
| SMA encasement (>180 degrees) | Locally Advanced | Unresectable | Borderline | Borderline |
| CHA abutment or encasement | Borderline | Borderline | Borderline | Borderline |
| PV/SMV encasement (>180 degrees) or abutment (≤180 degrees) with contour abnormality | Borderline | Borderline | Borderline | Borderline |

Abbreviations: ACTO, Alliance for Clinical Trials in Oncology; AHPBA, American Hepato-Pancreato-Biliary Association; CA, celiac artery; CHA, common hepatic artery; MDACC, The University of Texas MD Anderson Cancer Center; NCCN, National Comprehensive Cancer Network; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; SSAT, Society for Surgery of the Alimentary Tract; SSO, Society for Surgical Oncology.
NCT00112658) demonstrated an improved median OS and median progression-free survival (PFS) in patients who received FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) compared with those who received gemcitabine as first-line therapy for metastatic PDAC (median OS: 11.1 months vs 6.8 months [hazard ratio (HR), 0.57; \( P < .001 \)]; median PFS: 6.4 months vs 3.3 months [HR, 0.47; \( P < .001 \)]).\(^{122}\) FOLFIRINOX now embodies standard first-line therapy for fit patients. The combination of gemcitabine plus nanoparticle albumin-bound (nab)-paclitaxel represents another first-line therapy for the disease. The phase 3 MPACT trial (A Randomized Phase III Study of Weekly ABI-007 Plus Gemcitabine Versus Gemcitabine Alone in Patients With Metastatic Pancreatic Cancer [ClinicalTrials.gov identifier NCT00075684]; ±, with or without; MS, median survival; NS, not significant.)

### TABLE 5. Trials Evaluating Chemotherapy for Metastatic Pancreatic Cancer

| TRIAL | NO. | CHEMOTHERAPY | MS | \( P \) |
|-------|-----|--------------|----|--------|
| Cullinan 1985\(^{114}\) | 144 | 5-FU vs 5-FU + Dox vs 5-FU + Dox + mitomycin | 5.5 mo vs 5.5 mo vs 4.5 mo | NS |
| Burris 1997\(^{113}\) | 126 | 5-FU vs Gem | 4.4 mo vs 5.6 mo | .0025 |
| Tempero 2003\(^{115}\) | 92 | Gem vs Gem (fixed rate) | 5 mo vs 8 mo | .013 |
| Heinemann 2006\(^{116}\) | 195 | Gem ± cisplatin | 6.0 mo vs 7.5 mo | .015 |
| NCIC-CTG PA.3 (Moore 2007\(^{117}\)) | 569 | Gem ± erlotinib | 5.9 mo vs 6.2 mo | .038 |
| Cunningham 2009\(^{118}\) | 533 | Gem ± capecitabine | 6.2 mo vs 7.1 mo | .08 |
| CALGB 80303 (Kindler 2010\(^{119}\)) | 602 | Gem ± bevacizumab | 5.9 mo vs 5.8 mo | .95 |
| SWOG S0205 (Philip 2010\(^{120}\)) | 745 | Gem ± cetuximab | 5.9 mo vs 6.3 mo | .23 |
| PRODIGE 4/ACCORD 11 (Conroy 2011\(^{121}\)) | 342 | Gem vs FOLFIRINOX | 6.8 mo vs 11.1 mo | .0001 |
| MPACT (Von Hoff 2013\(^{122}\)) | 861 | Gem ± nab-paclitaxel | 6.7 mo vs 8.5 mo | .001 |

**Abbreviations:** 5-FU, 5-fluorouracil; Dox, doxorubicin; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; Gem, gemcitabine; nab-paclitaxel, nanoparticle albumin-bound paclitaxel; CALGB 80303, phase 3 trial of the Cancer and Leukemia Group B Trial 80303 (gemcitabine plus bevacizumab vs gemcitabine vs placebo in patients with advanced pancreatic cancer); MPACT, A Randomized Phase III Study of Weekly ABI-007 Plus Gemcitabine Versus Gemcitabine Alone in Patients With Metastatic Adenocarcinoma of the Pancreas (ClinicalTrials.gov identifier NCT00844649); NCIC-CTG PA.3, a phase 3 trial of the National Cancer Institute of Canada Clinical Trials Group (erlotinib plus gemcitabine alone in advanced pancreatic cancer); PRODIGE 4/ACCORD 11, Research Partnership in Digestive Oncology 4/Concerted Actions in Colorectal and Digestive Cancers 11 (Combination Chemotherapy as First-Line Therapy in Treating Patients With Metastatic Pancreatic Cancer [fluorouracil, leucovorin, irinotecan, and oxaliplatin versus gemcitabine for metastatic pancreatic cancer]; ClinicalTrials.gov identifier NCT00112658); SWOG S0205, Southwest Oncology Group Trial S0205 (A Phase III Randomized Open-Label Study Comparing Gemcitabine Plus Cetuximab [IMC-C225] Versus Gemcitabine as First-Line Therapy of Patients With Advanced Pancreas Cancer; ClinicalTrials.gov identifier NCT00075684); ±, with or without; MS, median survival; NS, not significant.
considered the more challenging, but perhaps more effective, regimen.

Second-line therapy primarily consists of doublet therapy using the alternative pyrimidine backbone to what was used in the first-line setting. Patients receiving FOLFIRINOX for first-line therapy are commonly transitioned to gemcitabine plus nab-paclitaxel as second-line therapy based on findings of the MPACT study.\(^{123,124}\) In contrast, patient receiving gemcitabine plus nab-paclitaxel in the first-line setting generally are treated with FOLFIRINOX, FOLFOX (5-FU and oxaliplatin), or 5-FU plus nanoliposomal irinotecan.\(^{121,124-126}\)

These additional options are important for patients with impaired performance status or those who exhibit dose-limiting toxicities precluding FOLFIRINOX treatment. FOLFOX has been evaluated in several trials demonstrating a median PFS of approximately 3.5 months.\(^{124,125}\) However, the randomized phase 3 PANCREOX study (Randomized Study With Oxaliplatin in Second Line Pancreatic cancer; ClinicalTrials.gov identifier NCT01121848), which compared second-line FOLFOX versus infusional 5-FU/leucovorin found that FOLFOX was associated with similar PFS but worse OS and toxicity than the comparison arm, calling into question the advantage of adding oxaliplatin in this setting.\(^{125}\)

The randomized phase 3 NAPOLI-1 trial (Study of MM-398 With or Without 5FU/LV, Versus 5FU/LV in Patients With Metastatic Pancreatic Cancer; ClinicalTrials.gov identifier NCT01494506) demonstrated an improved OS of 6.1 months associated with nanoliposomal irinotecan treatment compared with 4.2 months for 5-FU (HR for death, 0.67; \(P = .012\)). The use of 5-FU as the control versus FOLFOX is a common criticism of this study, which may be unwarranted given the PANCREOX results.\(^{126}\)

The addition of new combinations of cytotoxic chemotherapies is being evaluated as an optimization strategy. The results of a phase 1b/2 study of gemcitabine, nab-paclitaxel, and cisplatin as first-line therapy demonstrated the safety of the regimen while providing early evidence of potential clinical benefit, with a remarkable PFS of 10.1 months.\(^{127}\) Although these results suggest increased efficacy with the addition of platinum, these data should be interpreted with caution in the absence of phase 3 data.

### Maintenance Therapy

The improved outcomes associated with multimodality chemotherapy have led to prolonged exposure of patients to chemotherapy-related toxicities. The PANOPTIMOX-PRODIGE 35 trial (First-Line Metastatic Pancreatic Cancer: FOLFIRINOX ± LV5FU2 in Maintenance Versus Firgem [PANOPTIMOX]-PRODIGE 35; ClinicalTrials.gov identifier NCT02352337) phase 2 study was designed to evaluate the role of using a strategy of abbreviated FOLFIRINOX plus maintenance 5-FU or sequential gemcitabine and FOLFIRI3 (5-FU, folinic acid, and irinotecan) versus continuous FOLFIRINOX until disease progression to mitigate oxaliplatin-induced neuropathy.\(^{128}\) Treatment with alternating gemcitabine and FOLFIRI3 demonstrated inferior clinical outcomes compared with the FOLFIRINOX regimens. Patients treated with FOLFIRINOX were randomly assigned to continuous treatment for 6 months or 4 months followed by 5-FU maintenance with reintroduction of FOLFIRINOX at disease progression. The primary endpoint of the study was 6-month PFS. Treatment with the FOLFIRINOX regimens resulted in equivalent 6-month PFS and OS. Patients treated with maintenance 5-FU therapy experienced increased grade 3 and 4 neurotoxicity, which may be reflective of a higher cumulative oxaliplatin dose in these patients. Retrospective single-institution data out of Germany report 11-month PFS in patients receiving maintenance FOLFIRI, delivered after 4 months of FOLFIRINOX.\(^{129}\) Importantly, these studies demonstrate that maintenance therapy is a viable treatment strategy that is not associated with inferior clinical outcomes compared with continued therapy until disease progression.

The POLO study (Olaparib in BRCA Mutated Pancreatic Cancer Whose Disease Has Not Progressed on First Line Platinum-Based Chemotherapy; ClinicalTrials.gov identifier NCT02184195) was a phase 3 study that addressed the role of maintenance targeted therapy in a biomarker-selected patient population. Patients with metastatic PDAC harboring deleterious germline BRCA1 or BRCA2 mutations who had not progressed on first-line platinum-based chemotherapy were randomized to receive either the PARP inhibitor olaparib or placebo as maintenance therapy.\(^{48}\) Olaparib maintenance therapy produced a median PFS of 7.4 months versus 3.8 months in the placebo group (HR, 0.53; \(P = .004\)) but did not improve the median OS.\(^{48}\) Although this represents the first trial supporting molecular-guided therapy for PDAC, interpretation of this study was limited both by low patient numbers and by comparison against a no-treatment control arm, which is not standard of care. However, the POLO trial has led to US Food and Drug Administration approval of olaparib for maintenance therapy in patients with germ-line BRCA-mutant disease.

### Precision Oncologic Approaches to Pancreatic Cancer

With the increased analysis of the genomic signatures of PDAC, PDAC has been reliably classified into 2 distinct molecular subtypes: basal/quasimesenchymal or classical. The classical subtype is characterized by an epithelioid phenotype, whereas the basal/quasimesenchymal subtype
has a mesenchymal phenotype that has a propensity to metastasize.\textsuperscript{30-112} The COMPASS trial (Study of Changes and Characteristics of Genes in Patients With Pancreatic Cancer for Better Treatment Selection; ClinicalTrials.gov identifier NCT02750657) demonstrated that patients with the classical subtype demarcated by high levels of GATA6 expression by RNA sequencing or RNA in situ hybridization in baseline tumor specimens have a higher response rate to FOLFIRINOX therapy, leading to an improved median PFS.\textsuperscript{133} Consistent with these findings, acquired resistance to FOLFIRINOX was associated with the development of basal phenotype upon FOLFIRINOX exposure.\textsuperscript{134,135} Prospective studies are now required to confirm these observations. If these observations hold true, the choice of chemotherapy may be determined by the predominant molecular phenotype of the tumor.

Patients with either germline or somatic deleterious mutations resulting in homologous DNA repair deficiency (HRD) represent another important subset of patients who are likely to require specific therapies. Patients who have HRD comprise >15% to 20% of patients with metastatic PDAC.\textsuperscript{36,136} As outlined previously, these patients may be specifically sensitive to PARP inhibition. The PARP inhibitor rucaparib has demonstrated clinical activity as a single agent in patients who have advanced, metastatic PDAC with both germline and somatic mutations in BRCA1/BRCA2.\textsuperscript{137} In addition, there are several small-molecular inhibitors in development targeting various aspects of the homologous DNA repair pathway. Combination strategies incorporating multiple agents targeting the HRD pathway in combinations with PARP inhibition are in development.\textsuperscript{138} In addition to these effects, PARP inhibition possesses radiosensitizing properties.\textsuperscript{139} Platinum drugs induce double-strand DNA breaks, resulting in increased sensitivity of HRD pancreatic tumors to this class of chemotherapy. Consistent with this observation, a randomized phase 2 study of gemcitabine plus cisplatin with or without veliparib as first-line therapy in patients with HRD demonstrated response rates of 74% and 65%, respectively, and a median OS of 16 months and 15 months, respectively.\textsuperscript{140}

PDAC harboring microsatellite instability represents approximately 1% of patients afflicted with the disease.\textsuperscript{141} However, it is important for all patients to be tested for microsatellite instability because 40% of patients who have microsatellite instability respond to immune checkpoint inhibition and derive improved survival from this therapy.\textsuperscript{142,143} This paradigm of tailoring therapeutic approaches to the molecular vulnerabilities of each cancer is known as precision medicine. For PDAC, in which so few agents demonstrate clinically meaningful activity, precision medicine approaches hold substantial promise. In support of precision medicine in PDAC, a recent publication on the Know Your Tumor program found that patients with actionable molecular alterations who received matched molecular therapies had significantly longer median OS than patients who received unmatched therapies (2.58 years vs 1.51 years; HR, 0.42 $[P = .0004]\)\textsuperscript{144} Furthermore, that study demonstrated the feasibility of molecular assessment on biopsy samples in real time. As capacity for molecular testing improves, such precision approaches may become the standard for the subset of patients with actionable molecular drivers.

### Investigational Therapeutic Approaches

#### Treatments Targeting the Tumor Microenvironment

The PDAC tumor microenvironment consists of a complex network of cells, including cancer-associated fibroblasts, immune cells, and endothelial cells, plus a dense extracellular matrix.\textsuperscript{145-148} The inhibitory immune checkpoint programmed death ligand–1 (PD-L1) is expressed on myeloid cells within the tumor microenvironment and on tumor cells.\textsuperscript{149} High expression of PD-L1 expression in PDAC predicts a poor prognosis, yet immune checkpoint blockade (ICB) has been a largely ineffective therapeutic strategy. Anti–CTLA4 inhibition with ipilimumab or tremelimumab, either as a single agent or in combination with gemcitabine and anti–PD-L1 (BMS-936559 or durvalumab), demonstrated no evidence of clinical activity.\textsuperscript{150-153} Combined CXCR4 and ICB is currently under investigation as an approach to overcome immune exclusion of effector T cells based on preclinical data linking CXCR4 blockade to tumor infiltration of effector T cells.\textsuperscript{154,155} CD40 agonism represents another promising approach of ICB. CD40 is a component the costimulatory cascade resulting in upregulation of MHC class I and costimulatory molecules and skewing of myeloid cells to a tumoricidal phenotype.\textsuperscript{156-159} A phase 1 study of the CD40 agonist APX005M in combination with gemcitabine and nab-paclitaxel with or without nivolumab demonstrated early evidence of clinical benefit with a partial response rate of 58%.\textsuperscript{160} Finally, ionizing radiation can induce immune priming through the production of toxic nucleotide adducts, enhancing intratumoral antigen presentation by dendritic cells.\textsuperscript{161-162} An initial evaluation of this hypothesis has been conducted in 25 patients with metastatic PDAC by combining radiotherapy plus nivolumab and ipilimumab, with overall response rate of 14% and a median PFS of 2.5 months on interim analysis.\textsuperscript{163} The value of this approach will be further tested in future studies.

The extracellular matrix, comprised of a collagenous matrix and glycosaminoglycans such as hyaluronic acid (HA), is not inert—specifically, HA promotes metastasis and
PDAC initiation. Recombinant human pegylated hyaluronidase (peg-PH20) was developed as an extracellular matrix-targeted strategy. Phase 2 or 3 studies evaluating peg-PH20 in combination with both FOLFIRINOX and gemcitabine plus nab-paclitaxel in patients with metastatic PDAC expressing high HA levels by immunohistochemistry failed to demonstrate the benefit of adding peg-PH20 to either chemotherapy backbone. In fact, the combination of peg-PH20 with FOLFIRINOX led to excessive toxicity. Stroma modification remains a challenging therapeutic approach; however, recent work evaluating angiotensin receptor blockade using losartan in patients with locally advanced pancreatic cancer shows therapeutic promise (see below).

Treatments Targeting Metabolism and Autophagy

PDAC arising from PanIN is characterized by activating mutations in KRAS. The ensuing mitogen-activated protein kinase (MAPK) activation results in a hypermetabolic state characterized by increased glycolysis as well as increased metabolic plasticity through altered glutamine metabolism, dependence on oxidative phosphorylation, and metabolite scavenging through the process of macropinocytosis. Autophagy is a cellular process designed to allow cells to use cellular components as an alternative fuel source in response to cellular stress. Autophagy is integral for PDAC oncogenesis and proliferative capacity. Recently, 2 independent research teams demonstrated that MAPK activation regulates PDAC dependency on autophagy. Therefore, phase 1 clinical trials are now ongoing or in development to evaluate combining either MEK or ERK inhibitors with the autophagy inhibitor hydroxychloroquine (ClinicalTrials.gov identifiers NCT04132505 and NCT03825289).

Resectable Pancreatic Cancer Surgery

Surgical resection is currently the only means to achieve long-term survival in patients with PDAC. Although only 15% to 20% of patients present with resectable disease, the increasing use of neoadjuvant therapies and advances in surgical techniques have broadened the pool of patients who are eligible for surgical resection. The goals of care for patients with resectable PDAC are increasing the likelihood of margin-negative (R0) resection, decreasing procedural morbidity and mortality, preventing metastatic spread, and improving the patient’s quality of life (QOL). As surgical quality, perioperative care, and systemic therapies have improved, the ultimate goal is to determine the optimal timing and sequencing of high-quality surgery in the appropriate patient as part of a multimodality treatment plan.

A step-by-step review of pancreatectomy is beyond the scope of this review, but key steps to emphasize include: 1) a thorough exploration of the abdomen to rule out metastatic disease; 2) biopsy and examination by frozen section of any suspicious lesions outside of the field of resection; and 3) careful management of the surgical margin to ensure adequate tumor clearance, with the uncinate or retroperitoneal margin the margin most at risk. Careful dissection along the periadvential plane of the superior mesenteric artery mitigates the risk of a positive margin at this location during a pancreaticoduodenectomy (Fig. 4).

Although mortality rates from pancreatectomy have fallen significantly and are below 2% in numerous high-volume centers worldwide, elevated morbidity remains common and still affects the delivery of adjuvant therapy in up to 40% of patients. It is recommended that patients seek out high-volume centers with multidisciplinary expertise to optimize their treatment plan and increase opportunities for clinical trial participation. The use of minimally invasive pancreatic resection has been expanding in the last decade. Excellent outcomes in some studies have been reported; however, others cite safety concerns, particularly for the use of minimally invasive pancreaticoduodenectomy. In all cases, it is clear that implementation of rigorous dedicated training programs and experience with open pancreatic surgical techniques are needed to ensure the safe use of these techniques in clinical practice and to determine whether they will improve longer term oncologic outcomes.

Pathology

Rigorous pathologic assessment is essential for accurate prognosis as well as for determining the appropriate adjuvant treatment plan. Despite guidelines from the College of American Pathologists and the NCCN on standard protocols for the pathologic analysis of PDAC surgical specimens, this practice remains inconsistent because of both vagueness in the protocols and variable degrees of adherence across institutions. Protocols for specimen orientation and inking should be well established between the surgeon and pathologist to ensure clear definition of key margins, generally using different colored inks (specific recommendations can be found in the reports by Tempero et al and the College of American Pathologists). The definition of involved margins are variable across institutions, with most centers in the United States defining a positive margin as tumor-on-ink, whereas in Europe margins are called positive if tumor cells fall within 1 mm of the inked margin. Such inconsistency may help to explain the broad variation in reported R0 resection rates across studies. This distinction is significant for determining prognosis because resection margin distance correlates closely with locoregional failure and survival. The pathology report should also include maximal tumor diameter (for staging), histologic subtype, tumor grade, and the presence of lymphovascular or perineural invasion. For those patients who have undergone neoadjuvant therapy, there are multiple histopathologic systems to evaluate treatment response. Unlike other solid tumor types, the
relation between neoadjuvant treatment effect and prognosis is less clear in PDAC, possibly owing to the lack of standardization in this practice (as reviewed by Kang et al193). The most important prognostic factors for patients who have undergone curative-intent resection are the presence of lymph node metastasis and the ratio of positive lymph nodes to total lymph nodes.194,195 Because the number of negative lymph nodes and the total lymph node count influence stage-based survival prediction, the College of American Pathologists recommends microscopic evaluation of at least 12 lymph nodes for pancreatectomy specimens.185,196,197 Some groups advocate for reporting the involvement of specific lymph node groups, such as the hepatic artery lymph nodes; however, the prognostic value of this practice remains controversial in light of contradictory data from retrospective studies.198-200

**Adjuvant Chemotherapy**

The median OS of patients with localized PDAC who are treated with surgery alone is from 11 to 20 months.7,8,201 Currently, both the NCCN and ASCO recommend 6 months of adjuvant systemic chemotherapy for all patients who undergo pancreatectomy.102 Multiple randomized studies demonstrated consistent improvement in median OS and disease-free survival (DFS) using a variety of fluoropyrimidine-based chemotherapies. In general, the selection of chemotherapeutic agents has closely followed those found to be superior in the metastatic setting. The evolution of adjuvant chemotherapy regimens is outlined in Table 6.7,8,175,201-204 More recently the PRODIGE 24 trial (Phase III Trial of Adjuvant mFOLFIRINOX vs Gemcitabine in Patients With Resected Pancreatic Ductal Adenocarcinoma) demonstrated an improved DFS for modified FOLFIRINOX (mFOLFIRINOX) treatment of nearly 9 months compared with gemcitabine (HR, 0.58; 95% CI, 0.46-0.73 [P < .001]), establishing it as a standard of care in fit patients.7 Unfortunately, the combination of gemcitabine with nab-paclitaxel failed to meet its primary endpoint of improved DFS in the APACT trial (Nab-Paclitaxel and Gemcitabine vs Gemcitabine Alone as Adjuvant Therapy for Patients With Resected Pancreatic Cancer; ClinicalTrials.gov identifier NCT01964430).204 Tolerance of adjuvant therapy remains a limitation, with patients commonly receiving <50% of the planned dose.7,8,203,204 This observation is a reflection of exposure to significant chemotherapy-related toxicity in patients experiencing substantial postpancreatectomy morbidity. This has led many centers to move toward a total neoadjuvant approach to systemic therapy, as discussed below.

**Radiation**

Although the role of systemic therapy in the adjuvant setting for resected PDAC has been well validated, the value

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**FIGURE 4.** The Whipple Procedure (Pancreatectoduodenectomy) for Resectable Pancreatic Ductal Adenocarcinoma in the Head of the Pancreas. (A) The normal anatomic relationship of the pancreas and surrounding structures. (B) A diagram of a pancreatic head mass (white) surrounding the pancreatic and bile ducts (shown in green). (C) Standard resection for pancreatectoduodenectomy, to include the head of the pancreas, duodenum, distal common bile duct, distal stomach, and gallbladder. (D) Reconstruction to reconnect the pancreas, common bile duct, and stomach to the gastrointestinal tract.
Another report was presented as an abstract.
with maximum prescription doses constrained entirely by the tolerance of radiosensitive endoluminal organs (stomach, duodenum, and jejunum). An example of the dose distribution in the adjuvant setting is shown in Figure 5. As a result, standard radiation prescriptions in the adjuvant setting consist of daily treatments over the course of 5 or 6 weeks to a total dose of 50 to 54 gray (Gy). Given this and other factors, neoadjuvant regimens consisting of targeted pancreatic tumor delivery of radiation while maximizing normal tissue avoidance are attractive. These approaches are discussed in more detail below.

**Total Neoadjuvant Therapy**

Patients undergoing upfront surgical resection plus adjuvant chemotherapy experience 5-year OS rates of 25% to 50% because of high rates of systemic relapse. On the basis of this premise, neoadjuvant approaches have been tested in resectable PDAC with the following possible advantages: upfront treatment of occult micrometastases, avoiding unnecessary resection for rapidly progressing tumors, improved likelihood of margin-negative resection, and improved chemotherapy delivery compared with postresection adjuvant therapy. In the absence of clear guidelines, current clinical criteria for considering neoadjuvant therapy in resectable PDAC are large primary tumors, high CA 19-9 levels (＞1000 U/mL), and peripancreatic lymph node involvement or equivocal radiographic features suggestive of more advanced disease. Several randomized clinical trials are underway to more comprehensively define the role of neoadjuvant compared with adjuvant therapies in resectable patients, with an ultimate goal to most effectively target micrometastatic disease.

Results from the randomized phase 3 PREOPANC-1 trial (Preoperative Radiochemotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Study Protocol for a Multicentre Randomized Controlled Trial; the Netherlands National Trial Register identifier NTR3709) in patients with resectable and borderline resectable PDAC suggest that patients had longer survival if gemcitabine-based therapy was given in the neoadjuvant versus the adjuvant setting. In that study, 246 patients were randomized to immediate surgery and then 6 cycles of adjuvant gemcitabine (arm A) versus preoperative chemoradiotherapy, consisting of 3 courses of gemcitabine (the second course combined with radiotherapy to 36 Gy in 15 fractions), followed by surgery and 4 cycles of adjuvant gemcitabine (arm B). Among patients who underwent resection, the study demonstrated an OS benefit from arm A at a median of 35.2 months versus 19.8 months for arm B (P = .029), although the intention-to-treat analysis revealed only a trend toward improved survival. These results are supported by a propensity score–matched analysis of adult patients with resected stage I or II PDAC from the National Cancer Database (2006–2012). Neoadjuvant therapy followed by resection had a significant survival benefit compared with upfront resection (median survival, 26 months vs 21 months [P < .01]), further supporting the consideration of offering neoadjuvant therapy to resectable patients. As in the adjuvant setting, the role of radiation in the neoadjuvant approach to resectable disease remains controversial in the absence of phase 3 trials directly comparing neoadjuvant treatment approaches with or without radiation. A randomized clinical trial (The [Cost]-Effectiveness of Neoadjuvant FOLFIRINOX Versus Neoadjuvant Gemcitabine Based Chemoradiotherapy and Adjuvant Gemcitabine For (Borderline) Resectable Pancreatic Cancer [PREOPANC-2]; The Netherlands National Trial Register identifier NTR7292) is underway investigating whether neoadjuvant chemotherapy with FOLFIRINOX improves survival compared with neoadjuvant gemcitabine-based chemoradiotherapy with borderline resectable PDAC. By using a different approach of neoadjuvant systemic therapy, a randomized prospective trial (Southwest Oncology Group Trial S1505 [SWOG]; Combination Chemotherapy or Gemcitabine Hydrochloride and Paclitaxel Albumin-Stabilized Nanoparticle Formulation Before Surgery in Treating Patients With Pancreatic Cancer That Can Be Removed by Surgery; ClinicalTrials.gov identifier NCT02562716) was conducted evaluating perioper-
neoadjuvant mFOLFIRINOX versus gemcitabine/nab-paclitaxel (12 weeks presurgery and 12 weeks postsurgery in both arms) in patients with resectable PDAC. The trial has completed accrual, and results should be forthcoming in the near future. The added value of this study will be a direct comparison of the performance of these 2 regimens and perhaps some interpretable data regarding genomic signatures that may help predict therapeutic responses.

Borderline Resectable Treatment Paradigm

Patients with borderline resectable pancreatic cancer (BRPC) have no evidence of metastatic disease but are less likely to undergo resection with negative margins because of close proximity to or direct involvement of venous and/or arterial structures. The goal of the treatment approach is to maximize the chance at a margin-negative resection. Although no randomized studies have provided specific guidance regarding the optimal treatment paradigm, several prospective phase 2 studies have demonstrated the feasibility and efficacy of a total neoadjuvant approach consisting of neoadjuvant chemotherapy followed by radiation or chemoradiation. Patients who do not show distant progression or local invasion precluding surgery then undergo surgical exploration and resection.

The single-arm Alliance for Clinical Trials in Oncology (Alliance) A021101 trial (Chemotherapy and Radiation Therapy Before Surgery Followed by Gemcitabine in Treating Patients With Pancreatic Cancer; ClinicalTrials.gov identifier NCT01821612) enrolled 23 patients with BRPC who underwent treatment with neoadjuvant mFOLFIRINOX and neoadjuvant chemoradiotherapy (50.4 Gy in 28 fractions) before definitive surgical resection. Fifteen of 23 patients (68%) underwent resection with an impressive 93% R0 resection rate, and neoadjuvant treatment was not found to preclude resection. Investigators at Massachusetts General Hospital conducted a phase 2 trial evaluating the R0 resection rates in patients who received 8 cycles of FOLFIRINOX plus short-course or long-course neoadjuvant chemoradiation with capecitabine. R0 resection rates for patients who underwent resection was 97%, with a median PFS of 48.6 months and 2-year OS rate of 72%, far surpassing previously published historical outcomes. Furthermore, several retrospective studies have shown high R0 resection rates (88%-96.7%) with low toxicity, and one study in particular showed improvement in local control and OS with the integration of neoadjuvant chemoradiation compared with neoadjuvant chemotherapy alone. In a modern cohort of patients with BRPC at The University of Texas MD Anderson Cancer Center who underwent either neoadjuvant chemotherapy (31 patients) or neoadjuvant chemoradiation (227 patients), patients who received neoadjuvant chemoradiation had significantly improved R0 resection rates (91% vs 79%), histologically lymph node–positive resection rates (3% vs 23%), and locoregional recurrence rates (16% vs 33%), with a nonsignificant OS difference (33.6 months vs 26.4 months). Although early data suggest the importance of integrating both neoadjuvant chemotherapy and chemoradiation into the treatment paradigm for PDAC, large prospective trial data are lacking.

Chemotherapy

The selection of chemotherapeutic agents in BRPC follows the same rationale used in the resectable and metastatic settings. Typically, patients receive ≥2 to 6 months of neoadjuvant chemotherapy before proceeding to radiation, chemoradiation, or directly to surgery, if there is no evidence of distant metastasis. If the full 6 months of chemotherapy are not delivered preoperatively, the balance is commonly offered after surgery. The goals of therapy are to improve resectability by downstaging the primary tumor, reduce micrometastasis, and avoid surgery in patients with aggressive metastatic biology. The only randomized data supporting this approach come from the PREOPANC-1 study discussed above, which enrolled both resectable and borderline resectable patients and demonstrated improved OS and DFS when gemcitabine and chemoradiation were delivered before surgery compared with upfront resection. NCCN guidelines now recommend neoadjuvant chemotherapy for all patients with borderline resectable PDAC. The ongoing SWOG-S1505 and Alliance A021501 trials are evaluating 3 or 4 months of upfront chemotherapy, whereas a completed phase 2 study out of Massachusetts General Hospital used a total neoadjuvant approach in patients who did not progress after 4 months of systemic therapy. The overall treatment goals and approach are similar among most centers that use neoadjuvant therapy for these patients, although, in the absence of level 1 data, there is little consensus regarding optimal timing and sequencing of treatment.

Radiation

The goal of neoadjuvant radiation or chemoradiation in patients with BRPC is to increase the number of patients who can receive R0 resections and improve durable locoregional control. Most commonly, standard fractions of 1.8 to 2 Gy daily are delivered for 5 or 6 weeks to the tumor, the tumor-vessel interface, and the regional lymph node basins. For patients with BRPC, targeted dose escalation of regions of the tumor abutting the vessel has been shown to be feasible and safe and may improve surgical resection rates and survival. Because there is a definable tumor volume, radiotherapy in the neoadjuvant setting may also allow for the safe delivery of hypofractionated regimens consisting of larger daily radiation doses in fewer treatments and a more convenient and less costly treatment consisting of...
5 to 15 fractions. This approach was used in the aforementioned PREOPANC-1 study, which included patients with BRPC. The effectiveness of hypofractionation in PDAC has not been compared against that of conventional fractionation in a randomized fashion.

The use of stereotactic body radiotherapy (SBRT), in which a smaller tumor and tumor-vessel interface volume is treated in ≤5 fractions, is increasing nationally. Because of small margins and rapid dose fall-off, SBRT requires added measures to ensure target delineation, motion management, and daily imaging to verify that the treatment can be delivered safely and effectively (Fig. 6). Initial single-institution studies of SBRT in locally advanced disease indicated survival that approximated standard-of-care treatment and very few grade >3 toxicities. Neoadjuvant SBRT was included as an arm in the ongoing prospective Alliance trial A021501, which is evaluating neoadjuvant FOLFIRINOX for patients with BRPC. The American Society for Radiation Oncology clinical practice guidelines provide a conditional recommendation to treat patients who have borderline resectable pancreatic cancer with either conventional or hypofractionated radiotherapy as part of a neoadjuvant treatment regimen including chemotherapy, generally limiting the use of SBRT to patients who have smaller tumors located ≥1 cm from a gastrointestinal mucosal margin and with no evidence of nodal involvement.

**Surgery**

The challenge to achieve a margin-negative resection at pancreatectomy in increased when the tumor is adherent to or invading critical blood vessels. The addition of vascular resection and reconstruction adds to the technical complexity of the procedure. The most critical aspects of vascular resection and reconstruction in this setting are having high-quality preoperative imaging to develop an operative game plan and to have a surgeon or surgical team experienced in both pancreatic and vascular surgery. Given the increased risk of perioperative complications and the complex nature of these operations, they should be performed only in high-volume pancreatic centers and by surgeons with the appropriate level of expertise to deal with the added complexity and morbidity that may accompany these types of cases. The relative value of superior mesenteric vein/portal vein resection and/or reconstruction has been clearly shown. Because of increased surgical experience, venous resection and reconstruction are now safe and standardly performed in high-volume centers. In 2 meta-analyses comparing survival for patients who underwent pancreaticoduodenectomy with or without vein resection, no differences in survival were observed. Furthermore, across several studies, patients who undergo pancreatectomy with vein resection are reported to have increased survival compared with those who do not undergo resection or have a R2 resection performed. Generally, margin status is a predictor of survival.

**Locally Advanced Pancreatic Cancer Treatment Paradigm**

Locally advanced pancreatic cancer (LAPC) accounts for 30% of newly diagnosed cases and is considered surgically unresectable because of local involvement of adjacent critical blood vessels. Current guidelines for LAPC recommend enrollment in clinical trials where available or, in the absence of clinical trials, nonoperative treatment through a multidisciplinary approach. Currently, because this disease is generally considered incurable, the standard of care is very similar to that for patients who have metastatic disease, based around at least 6 months of chemotherapy. At this time, there are no randomized data supporting the inclusion of local therapy in these patients, but more studies are re-evaluating this question for patients who complete chemotherapy with no evidence of distant metastatic disease. We review these approaches below.

**Chemotherapy**

Chemotherapy forms the backbone of the therapeutic approach to LAPC because many patients will never convert to resectability, and the risk of distant progression is very high.
in this population. The goals of therapy are to control disease progression, reduce symptoms, and maintain QOL. For a subset of patients, chemotherapy may assist in shrinking the local tumor and converting unresectable to resectable disease. First-line therapy, similar to in the metastatic and resectable settings, has shifted toward the use of FOLFIRINOX or gemcitabine plus nab-paclitaxel, despite the absence of randomized data in the locally advanced setting. The recommendation to use these regimens are based on retrospective data or extrapolated from the MPACT and PRODIGE 4/ACCORD 11 studies discussed above. A recent meta-analysis suggested a potential survival benefit of FOLFIRINOX in patients with LAPC. Furthermore, results from the phase 2 SCALOP study (A Multi-Centre Randomized Study of Induction Chemotherapy Followed by Capecitabine /Nelfinavir/ With High or Standard Dose Radiotherapy For Locally Advanced Non-Metastatic Pancreatic Cancer) and the phase 3 LAP07 study (A Randomised Multicentre Phase III Study in Patients With Locally Advanced Adenocarcinoma of the Pancreas; Gemcitabine With or Without Chemoradiotherapy and With or Without Erlotinib), each of which investigated single-agent chemotherapy, reported progression in the majority of patients, reinforcing the importance of more aggressive combination chemotherapy. Therefore, all patients with LAPC should be strongly considered for upfront combination chemotherapy unless it is precluded by performance status or toxicity. In these patients, dose adjustments or less toxic chemotherapy regimens may be considered.

Radiation
Although LAPC represents an ideal opportunity to achieve local tumor control using radiotherapy, its role in unresectable pancreatic cancer is controversial because, historically, technological limitations and organ tolerance prevented ablative dose delivery to a central abdominal organ. The LAP07 trial randomized 450 patients initially to gemcitabine alone versus gemcitabine plus erlotinib followed by randomization, if there was no progression, to the same chemotherapy or chemoradiotherapy. Chemoradiotherapy was delivered at 54 Gy in 30 fractions to the pancreas and peripancreatic nodal basins with concurrent capecitabine using basic 3D-conformal radiotherapy and revealed no improvement in OS despite decreased rates of local progression (32% vs 46%), thereby removing radiotherapy from the treatment algorithm. Perhaps these results should not be surprising because the delivered dose was inadequate for tumor ablation. Despite the equivocal results of LAP07, current ASCO guidelines include a strong recommendation to follow chemotherapy with localized chemoradiation or SBRT in patients who have stable disease after 6 months of chemotherapy or those who cannot tolerate further chemotherapy because of toxicities.

Multiple technological advancements, including 4D-motion management, improved image guidance, and the implementation of intensity-modulated radiotherapy and proton therapy, have allowed for minimizing unwanted dose in normal tissues (ie, liver, small bowel, stomach). Early studies of ablative (biologically effective dose (BED) >100) SBRT reported excellent tumor control but evidence of increased acute and late gastrointestinal toxicities. Using either high-dose conventional fractionation or a hypofractionated approach (15 fractions) to a BED from 77.2 to 97.9 Gy has resulted in published 3-year and 5-year OS rates of 35% and 18%, far exceeding historical controls. Furthermore, using MRI-guided radiotherapy, treating to a BED >70 Gy significantly improved OS in a small cohort (median OS, 8.8 months in the conventional-dose group vs not reached in the high-dose cohort). Fractionation should be selected based on the safe delivery of an ablative dose to maximal tumor volume; tumors that closely appose the bowel may require increased fractionation, whereas those with more clearance may be amenable to shorter courses. Ablative doses of 75 Gy in 25 fractions, 67.5 Gy in 15 fractions, and 50 Gy in 5 fractions each allow for the delivery of a BED of approximately 100 Gy and show evidence of efficacy in appropriately selected populations (Fig. 7). Ongoing prospective trials, such as panCRS (Phase III FOLFIRINOX [mFFX] ± SBRT in Locally Advanced Pancreatic Cancer; ClinicalTrials.gov identifier NCT01926197) and a phase 1/2 dose-escalation trial for pancreatic SBRT with the radioprotector GC4419 (Dose Escalation Trial of Stereotactic Body Radiation Therapy [SBRT] in Combination With GC4419 in Pancreatic Cancer; ClinicalTrials.gov identifier NCT03340974) are further evaluating the efficacy and safety of pancreatic SBRT in patients with locally advanced disease. Importantly, these approaches should only be used at centers with technology for and experience in delivering ablative therapy under image guidance.

Alternatively, radiation may play an important role in converting unresectable patients into surgical candidates, as with BRPC. In a recent phase 2 single-arm study out of Massachusetts General Hospital, optimizing neoadjuvant treatment response with neoadjuvant FOLFIRINOX, l-o-sartan, and chemoradiotherapy (conventional fractionation with 5-FU or capecitabine for the majority of patients) resulted in an unprecedented 69% R0 resection rate and a median OS of 33 months in those who underwent resection (42 patients). A key determinant in the selection of radiation approaches will be the likelihood of resectability because those patients with persistent extensive vascular involvement after neoadjuvant chemotherapy may be more likely to benefit from an ablative rather than neoadjuvant dose and fractionation. In the absence of high-quality evidence supporting the use of radiation to downstage or
definitively treat locally advanced disease, current American Society for Radiation Oncology clinical guidelines provide conditional recommendation for each of these practices.  

Surgery

As surgical outcomes of pancreatectomy performed in combination with vascular reconstruction have improved, and as neoadjuvant combination regimens have become more effective, there has been increased interest in defining patients with LAPC who may benefit from a more aggressive surgical approach. After neoadjuvant therapy, it may be difficult to accurately assess treatment response, with studies showing resection rates ranging from 12% to 60%. Although some of these patients (approximately 10%-25%) may demonstrate downstaging to a borderline resectable or resectable category after neoadjuvant treatment, it has been increasingly appreciated that imaging may not be reflective of surgical candidacy because of the presence of fibrotic changes that persist after effective treatment. As such, there has been considerable development and use of more advanced surgical approaches to increase the number of patients with LAPC who may be considered surgical candidates. In general, these operations are longer in duration and are associated with increased blood loss and higher morbidity and mortality, in particular when resection of the celiac artery or the superior mesenteric artery, either alone or in combination with venous reconstruction, is performed (Fig. 8). In several recent single-center series, it has been shown that some of these patients can successfully undergo R0 resection, and patients in this subgroup may experience improved survival compared with those who receive nonsurgical treatment.  

The definition of resectability for LAPC varies among surgeons and at different centers, depending on the level of expertise and willingness to undertake these complex procedures. Given the morbidity and mortality associated with pancreaticoduodenectomy and complex vascular reconstruction, careful patient selection is warranted, and these cases should be managed in the setting of significant clinical expertise. In the absence of clear guidelines, the administration of 4 to 6 months of neoadjuvant therapy and documentation of the absence of disease progression, stable or improving CA 19-9 levels, and good Eastern Cooperative Oncology Group performance status (≤1) should occur before considering surgical resection.

Posttreatment Surveillance

According to NCCN guidelines, after completing both local and systemic therapy, patients are followed every 3 to 6 months for the first 2 years and every 6 to 12 months thereafter. Patients should be evaluated with a history and physical examination focused on symptoms, specifically weight loss, anorexia, fatigue, and pain. Laboratory tests may be ordered as clinically indicated, although most physicians will follow complete blood count, blood chemistries, and liver function tests because these can indicate long-term sequelae of therapy or new metastatic disease. Imaging surveillance includes chest CT and CT or MRI studies of the abdomen and pelvis with contrast to identify recurrence or metastasis. As described above, in appropriate patients, CA 19-9 can be used to track therapy response and recurrence, although this is considered a category 2B recommendation. Patients exhibiting recurrence with good performance status should be considered for clinical trials, if available, or the next appropriate line of systemic therapy. If not already engaged, supportive (or palliative) care should be introduced at this time, given the poor prognosis and high disease-related and treatment-related morbidities associated with recurrence.

Survivorship and Patient Resilience

Although cure remains the top priority for research and practice, the high mortality of PDAC calls for the increased use of supportive care in the management of this disease.
As one example, venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is highly prevalent in patients with PDAC and contributes to both morbidity and mortality. Two large randomized studies, the FRAGEM trial (A Phase II Study of Chemo-Anticoagulation [Gemcitabine-Dalteparin] Versus Chemotherapy Alone [Gemcitabine] for Locally Advanced and Metastatic Pancreatic Adenocarcinoma; ClinicalTrials.gov identifier NCT00462852) and CONKO-004 (Oncology Charity Trial 004: Pilot Study of Intensified Chemotherapy and Simultaneous Treatment With Heparin in Out-patients With Pancreatic Cancer; ClinicalTrials.gov identifier NCT01945879), randomized unselected patients with unresectable or metastatic PDAC to chemotherapy with or without the addition of a low-molecular-weight heparin anticoagulant at higher than standard prophylactic dosing—FRAGEM used dalteparin at a dose of 200 IU/kg daily for 4 weeks before reducing to 150 IU/kg daily for a further 8 weeks, whereas CONKO-004 used enoxaparin at a dose of 1 mg/kg daily. Both studies reported concomitant reductions in VTE risk and mortality without a significant increase in bleeding events. ASCO guidelines recommend VTE prophylaxis with low-molecular-weight heparin or, based on recent reports demonstrating effectiveness and safety with factor Xa inhibitors, apixaban or rivaroxaban for patients with a Khorana score ≥2, which includes all patients with PDAC.

Regardless of cancer stage and patient prognosis, early introduction to expert supportive care improves the social, psychological, and physical well-being of patients; decreases the intensity of medical interventions at the end of life; and ultimately improves survival. Indeed, whereas systemic therapies have a modest impact on final survival outcomes, modern chemotherapy combinations do significantly improve symptoms such as pain, sleep disturbance, appetite, gastrointestinal distress, and emotional functioning. Collectively, the many dimensions of the patient experience and perception of health during PDAC treatment is captured in patient-related outcome measures within the broader concept of health-related QOL (HRQOL), and measurement of this index is an important part of research and clinical care in this patient population.

As described in previous sections, the initial presenting symptoms of PDAC are vague and inconsistent. Some symptoms are primarily caused by local invasion and distortion of normal anatomy (eg, abdominal pain, jaundice), but many are because of a conserved systemic response to illness. This sickness response consists of several stereotypical behaviors and metabolic adaptations that serve to protect the host from acute survival challenges such as infection and trauma. Lethargy, anorexia, fever, and catabolism of muscle are beneficial to the host in the short term but, in the setting of chronic disease, become maladaptive. In particular, a constellation of
Fatigue is a common symptom in patients with cancer, and numerous etiologies are proposed (for a recent review, see Thong et al.285). However, specific data in the PDAC population are rare, with most studies reporting high levels of fatigue both at presentation and throughout treatment.285 Various interventions for cancer-related fatigue have been proposed, ranging from counseling-based therapy to pharmacotherapy (e.g., corticosteroids, methylphenidate), but none have produced a definitive benefit in this patient population. Some evidence suggests that mindfulness techniques and exercise may benefit patients, but available data indicate that benefits are modest and inconsistent.286

Although the association between mood disorders, fatigue, and cognitive decline and PDAC has been extensively documented, it was often assumed that these were secondary to both the psychological impact of the diagnosis itself and the overall toxicity of PDAC treatment. However, it is now apparent that these are often presenting symptoms with this diagnosis, demonstrating that the cancer has independent detrimental effects on the brain.287-289 Furthermore, these symptoms are collectively the most significant drivers of declines in HRQOL and are independently predictive of survival in patients with PDAC.290,291 Although the true prevalence of mood disorders in patients with PDAC is controversial, it is likely far higher than in the healthy population, with rates ranging from one-third to one-half of patients being reported in some studies.292,293 Clinicians should be sensitive to these comorbidities and routinely implement screening for and, if present, treatment for depression.294

Emerging technologies such as electronic patient-reported outcomes hold promise as more efficient and standardized ways to assess HRQOL and deliver supportive care. Future clinical care and research will also benefit from the advent of modern methods for recording patient-reported symptoms in real time, particularly when combined with more objective measures of daily activity (e.g., actigraphy devices). Several studies have demonstrated the efficacy of these electronic methods to improve patient symptoms, reduce health care costs, and improve OS in other cancer types, suggesting that these technologies will also benefit the population of patients with PDAC.295-297

Conclusions
As we enter the third decade of the 21st century, the story of PDAC is 1 of 2 competing narratives. On one hand, the progress in PDAC outcomes continues to lag far behind the survival gains made in other solid tumors. Despite being relatively uncommon, PDAC is expected to become the second leading cause of cancer death by the end of the decade.298 The vast majority of patients diagnosed with PDAC in 2020 will die of the disease. On the other hand, 5-year survival among all patients has eclipsed double digits for the first time. Led by improvements in the effectiveness of systemic therapy, an increase in the proportion of patients with early-stage disease, and stage-specific treatment paradigms, a true separation in expected survival is widening between patients with resectable cancer and those with locally advanced or metastatic disease. Moving forward, efforts are focusing on surveillance approaches and imaging innovations to improve the early detection of PDAC, thereby increasing the proportion of patients...
diagnosed with curable, localized disease. Simultaneously, advances in systemic therapy led by the implementation of precision oncology and an increasing focus on QOL outcomes promise to improve both lifespan and health span in patients with both localized and metastatic disease. Together, fueled by these innovations, we may be on the cusp on meaningfully changing outcomes in PDAC.

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