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Provisional chapter

Current Concepts in Pancreatic Cancer

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Additional information is available at the end of the chapter

1. Introduction

Pancreatic cancer is one of the most lethal malignancies, ranking as the fourth leading cause of death from cancer in the United States. Despite a variety of improved diagnostic and therapeutic approaches over the past several decades the mortality rate has not significantly improved. There is wide variation in the therapeutic approach to pancreatic cancer based upon multiple factors such as the stage at presentation, patient's coexisting medical comorbidities, etc. and at times the optimal treatment strategy is still controversial.

2. Epidemiology

Cancer of the exocrine pancreas was diagnosed in 45,220 patients in the United States in 2013. Underscoring its fatal nature, during the same year, 85% of patients (38,460) died from this disease [2]. Thus, despite only comprising 3% of all new cancer diagnoses, pancreatic cancer accounted for 6-7% of all deaths related to cancer [2]. Over the past 10 years, the similar incidence and the death rates emphasize that most pancreatic cancers are fatal as a result of late stage at diagnosis (Figure 1) [2-12]. Although, the gap between the yearly incidence and mortality of pancreatic cancer has slightly widened over the past ten years, most patients diagnosed with cancer will succumb to this deadly disease (Figure 2).

The average age at diagnosis is 60 to 65 years. The etiology of pancreatic cancer is not known, but several risk factors have been identified. For instance, men have a slightly higher incidence compared to women (Relative Risk [RR] 1.35) and Black men have a 30-40% higher rate in incidence compared to White men [13]. Cigarette smoking is the best well-recognized environmental risk factor for the development of pancreatic cancer. Current smokers have a RR of

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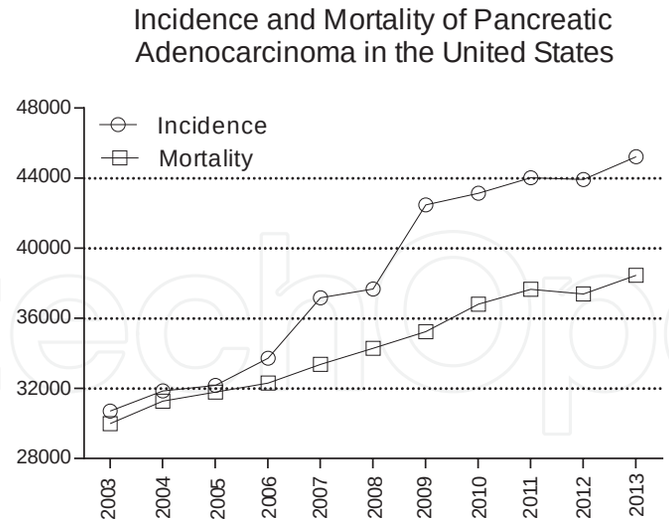


Figure 1. Incidence of Adenocarcinoma of the pancreas in the United States over the past ten years.

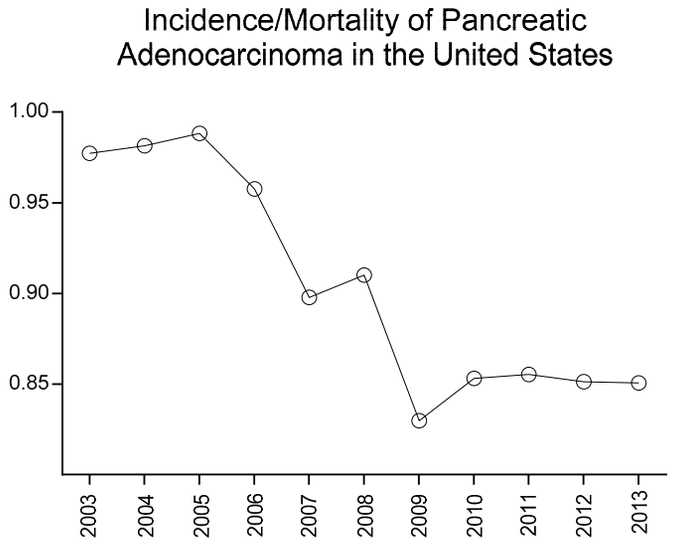


Figure 2. The incidence divided by the mortality in the Unites States over the past.

up to 3.6 compared to non-smokers and smoking is estimated to contribute to 25% as an etiology of pancreatic cancer [14;15]. Other risk factors for pancreatic cancer include: diabetes, obesity, Helicobacter *pylori* infection, non-O blood group and chronic pancreatitis [16-20].

Most forms of pancreatic cancer are sporadic. However, familial pancreatic cancer accounts for 5-10% of all pancreatic cancers [21]. Data from the National Familial Tumor Registry demonstrates that the risk of pancreatic cancer of the pancreas is 18-fold higher if two first-degree relatives are involved and 57-fold higher if three first-degree family members are affected [22]. This risk is conferred by an increased risk in several recognized genetic syndromes caused by germline mutations leading to familial syndromes. For instance Peutz-Jeghers Syndrome results from a germline mutation of the *STK11* gene. Affected individuals have a 132-fold increased risk for pancreatic cancer [23]. Familial Atypical Mole Multiple

Melanoma Syndrome patients with a germline mutation of the *CDKN2A* gene have a 46-fold increased risk for the development of pancreatic cancer. Individuals with mutations of the *PRSS1* gene have an increase in trypsin activity, which in turn causes chronic inflammation of the pancreas. These patients suffer from hereditary pancreatitis and have a 50-fold increase risk of pancreatic cancer [23]. Other genetic syndromes that confer a higher risk include cystic fibrosis (CTFR gene mutation), Fanconi Anemia, familial breast or ovarian cancer (BRCA2 gene mutations), familial adenomatous polyposis (*APC* gene mutations), Li-Fraumeni syndrome (*p53* gene mutation) and Lynch II syndrome (MLH1 gene mutation) [24].

3. Pathology

Pancreatic ductal carcinomas arising from the exocrine pancreas is the most common type accounting for 95% of these tumors. Two- thirds of these tumors occur in the head of the pancreas and have an aggressive behavior [25]. The vast majority of malignancies of the pancreas are infiltrating ductal adenocarcinomas and the term pancreatic cancer generally refers to adenocarcinoma of the pancreas. Pancreatic cancer can originate from each of the cell types that form the pancreas. For instance, neuroendocrine tumors arise from the pancreatic islet cells. Unlike ductal adenocarcinoma, many of the endocrine tumors are benign. Small subsets are endocrine carcinomas and make up around 1% of pancreatic cancers. Pancreatic cystic neoplasms include a group of tumors having varying malignant potential. Uncommonly, extrapancreatic tumors can metastasize to the pancreas and have been reported from renal cell carcinoma, non-small cell lung cancer, sarcoma, melanoma, and bladder cancers (Figure 3) [26].

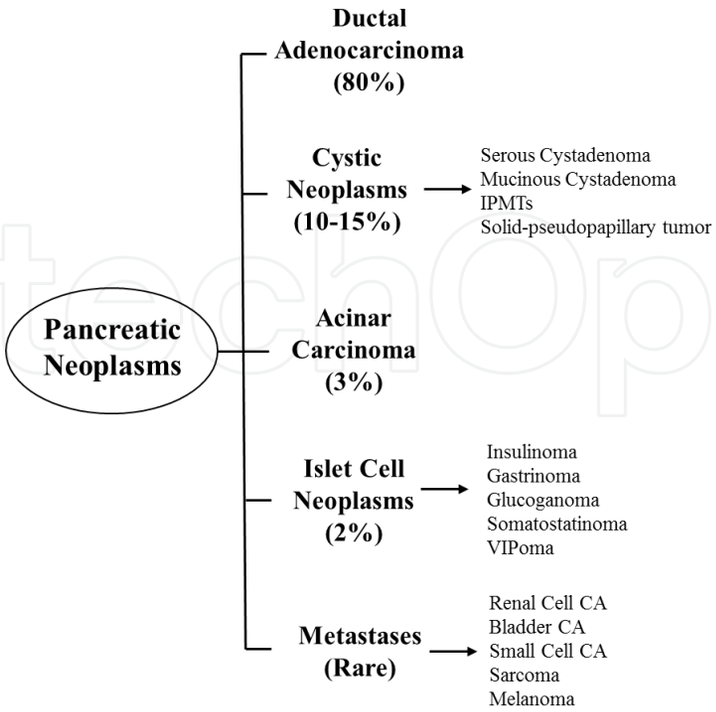


Figure 3. Incidence of malignancies of the pancreas.

Current pancreatic cancer models are similar to that of colon cancer, in which there is a progression from precancerous lesions to invasive carcinomas. Pancreatic cancer evolves from normal ductal epithelium, to pancreatic intraepithelial neoplasms/ductal lesions, to invasive adenocarcinomas [27;28]. The ductal epithelium undergoes changes that are characterized by PanIN-1A. Changes continue to accumulate and lead to PanIN-3, which denotes carcinoma *in situ* (Figure 4). This evolution is associated with the acquisition of a large number of genetic alterations that function through a small number of signaling processes and pathways. The stepwise acquisition of genetic abnormalities leading up to invasive ductal adenocarcinoma is now well characterized and includes mutations in *KRAS2*, inactivation of *p16*, *p53*, *PDX1*, and *SMAD4* [29].

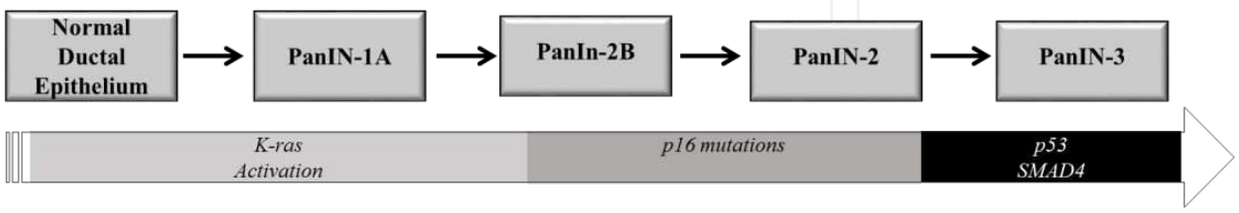


Figure 4. Progression of normal epithelium to pancreatic cancer and genes involved in the pathogenesis of sporadic pancreatic cancer.

Comprehensive genetic analysis of pancreatic cancer specimens demonstrated that the most frequent genetic abnormality in invasive pancreatic adenocarcinomas is activation of KRAS2 oncogene, which was present in more than 90% of pancreatic cancers [28]. *KRAS2* mutations are thought to be acquired early in the development of pancreatic cancer as they are found in a large number of ductal lesions and become more prevalent as these lesions progress to invasive adenocarcinoma [27]. In addition to *KRAS2* mutations, several other pathways in cellular signaling have been found to be altered in 67-100% of the tumors. These pathways include: TGF β, JNK, Integrin, Wnt/Notch, Hedgehog, control of G1/S phase transition, apoptosis, DNA damage control, small GTPase, invasion, and homophilic cell adhesion [30].

Histologically, poorly formed glands are present in a dense fibrotic background within the pancreatic parenchyma and sprinkled inflammatory cells. Some of the tumor cells might show some mucin production. Perineural invasion is often seen and can help with the diagnosis in well-differentiated tumors. Other features of malignancy include nuclear pleomorphism, occasional large nuclei and multiple large nucleoli (Figure 5).

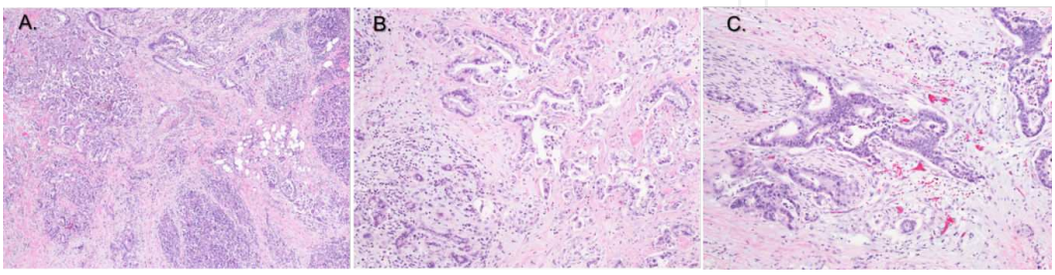


Figure 5. H&E stains of normal and adjacent ductal adenocarcinoma 40X (panel A). Panel B demonstrates invasive adenocarcinoma (100X). Perineural invasion is demonstrated in panel C.

4. Clinical features

4.1. History

Currently there are no established screening tests for pancreatic cancer. The vague and nonspecific symptoms in pancreatic cancer contribute to its delay in diagnosis. The location of the tumor within the pancreas dictates some historical features and clinical presentation. The stage of the disease is also important. Because most pancreatic tumors are located in the head of the pancreas and present at an advanced stage, clinical findings suspicious for pancreatic cancer must be rapidly addressed to exclude this lethal diagnosis.

Patients with lesions of the head of the pancreas present with painless jaundice and weight loss, which might be accompanied with anorexia and weakness [31]. The frequency of presenting symptoms in 1175 patients with adenocarcinoma of the pancreas was: 2/3 painless jaundice, ½ weight loss, and about 1/3 abdominal pain [32]. Obstructive cholestasis might lead to dark urine, light stools and pruritus. Distention of the pancreatic capsule causes vague epigastric and/or back pain that poorly localizes to the location of the tumor. Obstruction of the pancreatic duct or perineural invasion also causes pain, but this is less specific and poorly localized. Ten percent of patients have symptoms attributed to cholelithiasis and will have undergone recent cholecystectomy prior to the diagnosis of pancreatic cancer. Similarly, obstruction of the pancreatic duct might lead to acute pancreatitis [13, 33]. Uncommonly, large tumors might present with symptoms of duodenal obstruction such as nausea and vomiting or symptoms associated with a gastrointestinal bleed [31].

Systemic manifestations are more usual in patients with lesions of the body and tail of the pancreas such as weight loss and anorexia [31]. Constant pain is attributed to tumor invasion of the celiac and mesenteric plexuses and occurs with advanced disease. Eight weeks is a typical mean duration of symptoms. New-onset diabetes mellitus may be an initial presenting symptom in patients with pancreatic cancer and glucose intolerance occurs in 15%-20% of these patients. Depression, increased abdominal girth, and a history of panniculitis are rare, but might accompany a diagnosis of pancreatic cancer [31, 34].

4.2. Physical examination

The physical examination for patients with pancreatic cancer is unyielding. Since two-thirds of pancreatic adenocarcinomas occur in the head of the pancreas, the most common presenting physical finding is evidence of obstructive cholestasis. Painless jaundice in an older patient has been attributed a hallmark of physical findings necessitating careful exclusion of pancreatic cancer. The examiner must investigate for signs of weight loss such as temporal wasting as well as careful interrogation of lymph node basins [31].

Hepatomegaly, ascites or a palpable gallbladder (Courvoisier's sign/law) may be present in some patients with advanced pancreatic cancer. Courvoisier's sign is more likely to be present in patients with pancreatic cancer compared to calculi disease [35]. Physical findings in patients with disseminated disease include supraclavicular lymphadenopathy (Virchow's node). However, pancreatic cancer usually does not metastasize to the supraclavicular nodes and only a few cases have been reported [36]. Cutaneous metastasis in the periumbilical area (Sister

Mary Joseph's nodule) [37] and peritoneal seeding (Blumer's shelf) are also rarely found with pancreatic metastatic disease. Migratory thrombophlebitis (Trousseau's sign), which is evidence of intravascular thrombosis, may occur in patients with advanced pancreatic cancer as well as other advanced cancers resulting from a hypercoagulable state from malignant disease [38].

5. Staging

The AJCC staging system, based on the TNM stage, is most often used staging system for pancreatic cancer. The tumor stage describes the size of the primary tumor, vascular structure involvement and any direct extension of the tumor outside of the pancreas. The nodal stage assesses the presence or absence of any regional lymph node involvement. The metastasis stage describes the presence or absence of any distant disease (Table 1).

(a)	**Primary Tumor (T)**		
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ (includes lesions classified as PanInIII classification)		
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension		
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension		
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or superior mesenteric artery		
T4	Tumor invades the celiac axis or the superior mesenteric artery (unresectable primary tumor)		
(b)	**Regional Lymph Nodes (N)**		
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
(c)	**Distant Metastasis (M)**		
M0	No distant metastasis		
M1	Distant metastasis		
(d)	**Anatomic Stage/Prognostic Groups**		
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Table 1. TNM staging system for pancreatic cancer

Common sites of metastatic disease often include the liver, peritoneal cavity, and lungs [39]. The anatomic staging roughly correlates with whether or not the tumor is resectable. Those tumors with Stage IA to IIB are considered resectable. Tumors designated as Stage IV are unresectable and those designated as stage III can be borderline resectable or unresectable. The NCCN classification system which divides tumors into resectable, borderline resectable or unresectable categories may be more applicable clinically [40].

6. Diagnostic evaluation

Routine laboratory analyses are rarely abnormal and if abnormal they lack specificity for a diagnosis of pancreatic cancer. Evidence of extrahepatic obstruction may be revealed by increased levels of serum alkaline phosphatase, bilirubin and gamma-glutamyl transferase with possible mild elevations in hepatic aminotransferases [31]. Hypoalbuminemia and anemia may be present in patients with advanced disease. Mild coagulopathy can be seen in patients with obstructive jaundice. Poor flow of bile acids in the small bowel in these patients decreases vitamin K absorption resulting in depletion of vitamin K dependent clotting factors over time. Elevated pancreatic enzymes (elevated amylase and lipase) associated with acute pancreatitis can rarely be the first manifestation of pancreatic cancer [41].

There are no accurate or reliable serum markers to aid in the diagnosis of pancreatic cancer. Low sensitivity and cross-reactivity with other tumors have prevented the clinical use of carcinoembryonic antigen (CEA), fetoprotein, and pancreatic oncofetal antigen in the diagnosis of pancreatic cancer. Carbohydrate antigen 19-9 levels (normal <37 units/mL) has been the most useful commercially available test. However, the sensitivity of CA 19-9 ranges from 70% to 92% and the specificity is poor (68% to 92%) [42]. The accuracy of CA 19-9 in the diagnosis of pancreatic cancer is excellent when combined with ERCP, abdominal CT, or abdominal US [43]. High levels of CA 19-9 have been associated with poor prognosis and tumor unresectability [43]. CA 19-9 is also useful in monitoring the response of therapeutic interventions. As the CA 19-9 requires the presence of Lewis blood group antigen (a glycosyl transferase enzyme) to be expressed, this serum marker is of no value in 10% of the population who is negative for this antigen [44, 45].

7. Conventional imaging modalities

Imaging studies are essential in the management of pancreatic cancer. The most important goal of imaging is to determine tumor resectability. Involvement of adjacent vessels (superior mesenteric vein, portal vein, and superior mesenteric artery), nodal involvement and distant metastatic lesions are paramount in selecting treatment options. The investigation of most patients with pancreatic cancer generally begins with a right upper quadrant ultrasound to evaluate jaundice.

7.1. Abdominal ultrasound

Abdominal ultrasound (US) examination reliably detects extra-hepatic and intra-hepatic ductal dilatation. However, accurate identification of a pancreatic mass may be compromised by operator experience, bowel gas interference, or obesity, and does not provide information regarding tumor involvement of the vascular structures or lymph node involvement. In advanced disease, ascites and liver metastases (>1 cm) may be seen by abdominal US.

7.2. Computed Tomography

Computed tomography (CT) has been used routinely for evaluation of pancreatic cancer over the last few decades. However, since the advent of triple phase (noncontrast, arterial, and portal venous) helical multidetector row CT (MDCT) with thin cuts (1 mm slices) through the pancreas along with coronal three dimensional reconstruction (pancreatic protocol), it has become the gold standard initial test for the diagnosis and staging of all pancreatic cancers. The sensitivity for lesions greater than 2 cm is 100% [46]. While the false positive rate is low, it might occur in the setting of focal chronic pancreatitis or autoimmune pancreatitis. The advantage of CT is its wide availability, non-invasive approach, non-operator dependent and easily reproducible images. It is also deliberately used in conjunction with ^{18}F-fluorodeoxy-glucose positron emission tomography (PET)/CT for surveillance imaging post treatment.

7.3. Endoscopic ultrasound

Endoscopic ultrasound (EUS) transmits high-frequency sound waves through the upper GI tract to detect abnormalities in the pancreas (Figure 6). The accuracy of EUS is operator dependent and it is not yet available at many community hospitals. At experienced centers, EUS has been shown to have a similar (or better) sensitivity and specificity for the diagnosis of pancreatic cancer to that of MDCT [47]. Being a dynamic test, it can distinguish subtle abnormalities such as pancreatic duct strictures and small neuroendocrine tumors. Not uncommonly, it can detect small (<1cm) pancreatic cancers, which would escape detection by MDCT. EUS can also evaluate malignant as well as pre-malignant cystic lesions such as intra-ductal papillary mucinous neoplasms with its characteristic findings of intramural nodules and communication with the main pancreatic duct.

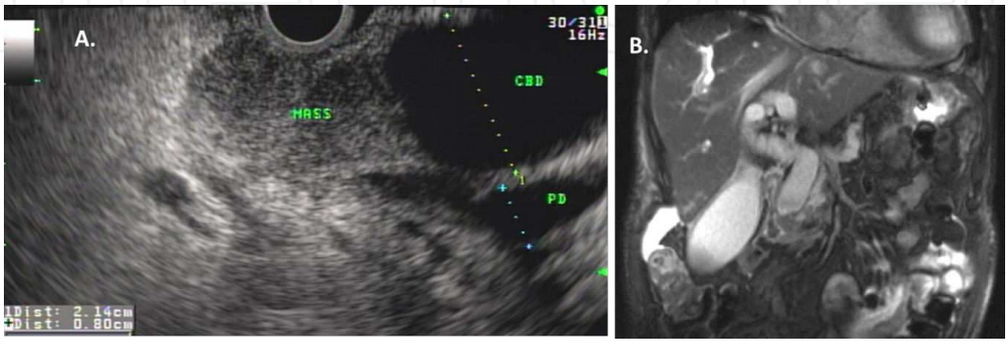


Figure 6. Malignant biliary obstruction from mass in head of pancreas causing CBD and PD dilation (double-duct sign) US (A). MRCP in (B) Note the distended gallbladder, seen in patients with malignant biliary obstruction (Courvoisier's sign)

Due to the high sensitivity of EUS in detecting small lesions, it is widely used to screen patients with familial pancreatic cancer or other hereditary syndromes [48]. EUS has the advantage of allowing sampling of the tumor mass, regional nodes, liver lesions, ascites and malignant cyst fluid, as well as assessing tumor resectability during diagnostic evaluation (Figure 7). In one study, the sensitivity, specificity, and accuracy of EUS-FNA for diagnosis of a pancreatic malignancy were 91%, 100%, and 92%, respectively. No mortalities were reported in this analysis and morbidity was only 2% [49]. Recently, the EUS-FNA needles have been employed to introduce sophisticated probes directly into the pancreatic lesions for diagnostic needs, as well as deliver therapeutic approaches such as local injections of cytotoxic agents and probe based application of radiofrequency ablation.

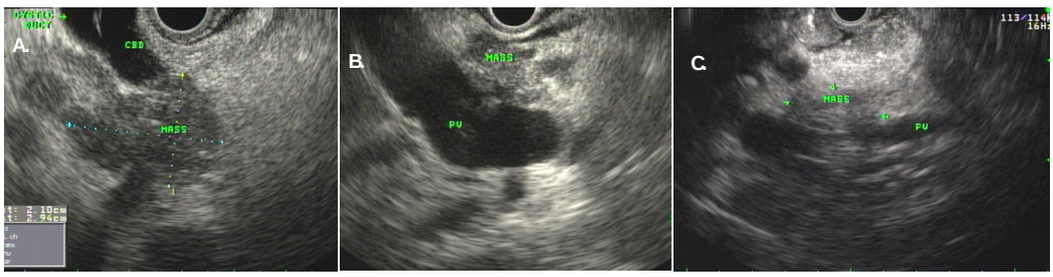


Figure 7. Mass in head of pancreas causing biliary obstruction (note both cystic duct and common bile duct are dilated)-A; The portal Vein PV-B and PV confluence (C).

EUS is not without limitations in the evaluation of patients with pancreatic cancer. In some cases pancreatic cancer might be indistinguishable from focal chronic pancreatitis (with or without focus of ductal adenocarcinoma), pancreatic intraepithelial neoplasms-PanINs, and patients with autoimmune pancreatitis. The ability of EUS alone in differentiating these from malignant lesions can be challenging and thus a multimodality diagnostic evaluation becomes necessary along with the history and physical exam findings. Tissue sampling for pathological evaluation might also be challenging with EUS as fine needle aspiration provides scant aspirate and core biopsies (by pro-core needles) might not give adequate histological architecture needed to make an accurate diagnosis. Further limitations of EUS are the result of anatomical constraints such as tumors located in the uncinate process because the acute angle of the echoendoscope in the second portion of the duodenum makes this location challenging for FNA sampling.

7.4. Endoscopic retrograde cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) has been used historically to allow direct visualization of the duodenum and ampulla, as well as delineation of the biliary and pancreatic ductal systems. ERCP may also be used to obtain "brush" samples for cytology and intra-ductal biopsies in order to increase diagnostic yield, especially in situations where EUS-FNA results are inconclusive. However, ERCP remains an invasive test with potential risks such as post ERCP-pancreatitis, which might result from injecting contrast to delineate a suspected malignant pancreatic duct stricture. Hence, the usefulness of ERCP as a primary

diagnostic modality for pancreatic cancer has significantly decreased since the introduction of endoscopic ultrasonography. Currently, ERCP is not favored as an initial test for the diagnosis of adenocarcinoma of the pancreas. On the other hand, ERCP is generally reserved for therapeutic indications such as palliating patients with obstructive jaundice from pancreatic cancer with metastatic or locally advanced disease who are not candidates for resection. These patients benefit from biliary sphincterotomy and/or stent placement (Figure 8). Routine stenting of patients with resectable pancreatic cancer, however, has not shown clear benefits in patients that might be considered candidates for resection as this might lead to unjustified complications [50]. A new role of ERCP is evolving as a means to access the pancreatic duct for endoscopic pancreatic imaging and therapeutics.

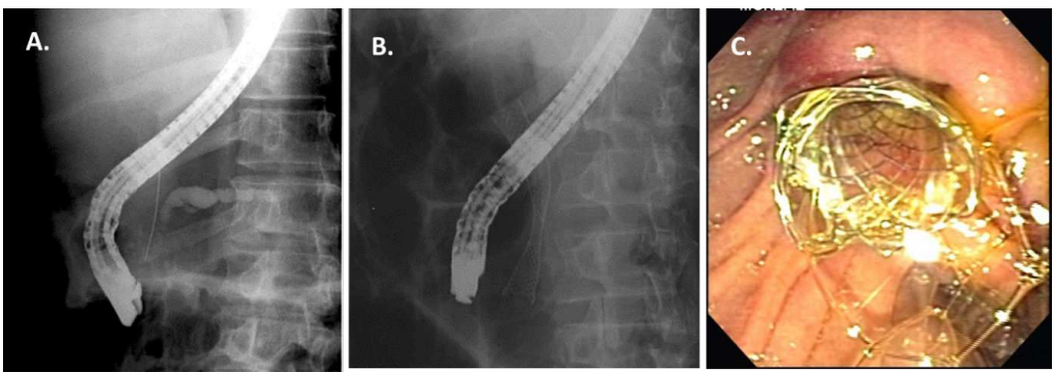


Figure 8. Malignant pancreatic stricture causing upstream pancreatic duct dilation. Note that the wire was advanced into the bile duct during ERCP to place biliary stent for palliation of obstructive jaundice (A). Placement of metallic biliary stent for palliation of obstructive jaundice in a patient with unresectable pancreatic cancer [fluoroscopic picture (B); endoscopic picture (C)]

7.5. Magnetic resonance cholangiopancreatography

Magnetic resonance cholangiopancreatography (MRCP) is better than CT in outlining the anatomy of biliary and pancreatic tree and can provide useful information in patients who have suspected biliary or pancreatic strictures. It can also provide a road map for future endoscopic therapy. MRI of the pancreas can provide valuable information about solid tumors of the pancreas as well as cystic neoplasms, and is generally comparable to MDCT in determining resectability (Figure 6) [51].

Centers without personnel experienced with EUS-FNA rely on percutaneous fine-needle aspiration (FNA) of pancreatic masses to establish a diagnosis. CT-guided percutaneous FNA performed by interventional radiologist carries a theoretical risk of malignant seeding of the needle tract, but no convincing data has proven this theory conclusively. The CT guided approach is technically easier for masses in the tail of the pancreas rather than the head. A negative result on tissue diagnosis with a suspicious mass on CT scan does not preclude surgical intervention. This approach can be helpful in patients who are considered poor candidates for any endoscopic intervention due to underlying co-morbidities and individuals who have unresectable disease.

7.6. Exploratory laparoscopy

Reportedly, 20% to 40% of patients staged by CT, MRI, ERCP or EUS will have undetected disseminated disease during exploratory laparoscopy. The use of laparoscopy has proponents that span usefulness [52-54] to an entirely unnecessary procedure. The main argument against its use emanates from the currently available non-invasive image modalities, which in the view of some clinicians eliminates the need for a further invasive procedure [55]. Laparoscopic exploration for patients with pancreatic lesions is best used selectively rather than routinely and may have a larger role in resectable tumors of the body and tail of the pancreas [56;57]. Selective criteria for patients with pancreatic cancer include tumors larger than 3 cm, a CA 19-9 level above 100 U/ml, and questionable imaging findings.

8. EUS combined modalities

There has been recent interest in mucosal imaging (as discussed below), but none has yet been accepted in the standard of care in diagnosing pancreatic cancer. Narrow band imaging technology uses light of specific blue and green wavelengths to enhance the detail of certain aspects of the surface of the mucosa. This technology has made it possible to visualize the wall of the pancreatic duct with the help of a small catheter inserted into the pancreatic duct ('pancreatoscopy') [58].

Optical endomicroscopy using a small diameter probe advanced into the pancreatic duct, at the time of ERCP or EUS, allows real time microscopic imaging of the epithelial lining of the pancreatic duct and pancreatic cyst wall. This allows direct high yield targeted tissue sampling in the region of interest. Two modalities used in this fashion include confocal laser endomicroscopy (CLE) [59;60] and high resolution microendoscopy [59;61]. On the other hand, optical coherence tomography uses infrared light to scan areas beneath the mucosal lining of the duct but the field of view is limited to only a few millimeters making evaluation of the entire pancreatic duct difficult and time consuming [62].

During intraductal ultrasound (IDUS), a mini-ultrasound probe is advanced into the main pancreatic duct to evaluate the wall of the pancreatic duct in indeterminate pancreatic strictures. This allows diagnosis of early pancreatic cancers and outlines margins of IPMNs before surgical resection [63;64]. IDUS is not widely used in United States due to the risk of pancreatitis associated with the procedure and inability to obtain tissue for pathological examination [65]. Another modality using EUS, contrast enhanced EUS, utilizes intravenous contrast to highlight the echogenicity and enhancement of a lesion [66]. In a recent meta-analysis, the pooled sensitivity of contrast-enhanced EUS for the differential diagnosis of pancreatic adenocarcinomas was 94% (95% CI, 0.91-0.95), and the specificity was 89% (95% CI, 0.85-0.92) [67].

EUS elastography allows quantitative analysis of tissue stiffness and helps differentiate pancreatic cancers from benign conditions such as chronic pancreatitis. In one study, the sensitivity and specificity for detecting pancreatic malignancies was 100% and 92.9% respectively [68]. Three-dimensional reconstruction and spectrum analysis using EUS has shown promising results, and will likely be used more often in the future [69].

9. Novel diagnostic imaging modalities

Because pancreatic cancer might metastasize at an early stage, an ideal imaging modality is one that would predict the biological behavior of the tumor. Understanding the molecular aspects of pancreatic cancer has facilitated use of investigational modalities in this area. Imaging agents such as peptides that bind to specific factors on the surface of pancreatic tumors have been developed and include: plectin 1 (Plec 1), integrin $\alpha_v\beta_6$, cathepsin E and claudin-4 [70-73]. Early studies have shown promising results, but more work is needed before routine clinical use.

A similar approach, but by interrogating normal tissue has also been investigated. Montet *et al.* demonstrated that as pancreatic tumors do not express receptors for bombesin, a bombesin peptide-coupled nanoparticle (BN-CLIO[Cy5.5]) can be used to image normal pancreas and hence, differentiate it from pancreatic tumors [74]. Similarly, a novel concept of microbubbles, small gas –filled microspheres, has been used in preliminary studies to image the peri-tumoral vasculature with the assistance of ultrasound. Moreover, this technology can also be used as a vehicle to deliver anti-cancer therapies [75].

10. Treatment

10.1. Surgical intervention

Surgery offers the only possibility for long term survival, however the majority (>85%) of patients with pancreatic cancer will present with unresectable or metastatic disease [76]. Removal of all disease offers the patient the only chance of long-term survival. Those who undergo surgical resection have a disappointing ~20% 5-year survival. Over the years it has become clear that the indications for surgical intervention have been substantially widened. Typically, the current criteria dictates possible resection for tumors stage I-A to II-B [77]. There are no randomized trials that assess resectability criteria to guide surgical intervention. In the absence of controlled trials, the best recommendations emanate from consensus guidelines [40, 78, 79]. It is practical to classify pancreatic tumors into one of three categories following diagnostic imaging [77]:

i. **Resectable Tumors**: These are tumors localized to the pancreas. In this case, there is no evidence of SMV or portal vein involvement of any kind. A plane of dissection indicated by a fat pad between the SMA, celiac axis, and hepatic artery and the pancreas has to be identified by CT scan as well as absent involvement of the SMV and portal vein [40, 78]. These patients should proceed with surgical intervention.

ii. **Borderline Resectable Tumors**: There is a dynamic criteria for resection of these tumors that continues to change based on the ability of specialized centers to perform complex arterial/venous/portal resection and reconstruction [79]. These tumors include those that have (A) Severe SMV-portal impingement (unilateral or bilateral), (B) SMA/celiac artery involvement, but less than 180°, (C) Hepatic artery involvement with the possibility of reconstruction, and (D) SMV occlusion or involvement with

the possibility of reconstruction [40, 77]. These patients should undergo surgical intervention at the discretion of highly specialized pancreatic cancer centers, undergo neoajuvant treatment, and/or enrollment in clinical trials.

iii. **Unresectable Tumors**: These are tumors in which distant or extensive lymph node metastatic disease has been identified. Involvement of vasculature beyond resection or malignant ascites are also considered contra-indications for resection (i.e. major venous thrombosis of the portal vein or SMA that extends for several centimeters or circumferential encasement of the SMA) [78]. Resectability is best determined preoperatively rather than intraoperatively. These patients are candidates for chemotherapeutic interventions and enrollment in clinical trials as well as palliative interventions depending on degree of the disease.

According to a consensus statement by the American Hepato-Pancreato-Biliary Association, tissue obtained via EUS guided FNA is only required prior to surgery if neoadjuvant chemo-radiation is indicated. However, if there is sufficient evidence for pancreatic adenocarcinoma based on history, physical exam, and diagnostic modalities; no tissue is required in good surgical candidates prior to surgical intervention [78].

11. Surgical intervention for tumors of the pancreatic head

Extirpation of pancreatic tumors at the head of the pancreas require pancreatic and duodenal resection as well as common bile duct re-implantation with reconstruction. The pacreatico-duodenectomy procedure (Figure 9) was first described in 1909 by Walter Kausch. Twenty six years later, the success with the procedure in three patients was reported at the American Surgical Association by Allen O. Whipple and Parson. The pancreaticodudenectomy procedure then became widely performed and it is commonly referred to as the Whipple procedure. Although, it's original description was a two-stage operative approach, it was rapidly modified [80]. The commonly known one-stage Whipple operation is credited to Trimble's group from John Hopkins in 1941 [81]. The drastic increase in the number of operations performed today is represented by the experience at Mass General where between 1940 and 1950, twenty pancreaticoduodenectomies were performed; while, between 2005-2011 813 were described (~125 per year) [82].

Technical considerations for standard pancreaticoduodenectomy (PD) have been reviewed extensively [83]. The proposed lines of resection are shown in (Figure 9). The general exploration of the abdomen includes careful inspection of the peritoneal surfaces and liver for metastases, which can be more accurately determined by intra-operative liver ultrasonography. Suspicious lymph nodes need to be submitted for frozen section histology to evaluate for metastatic disease. The presence of peritoneal implants and liver metastases render the patient incurable. Similarly, histologically proven metastases in lymph nodes accessible during the initial abdominal exploration makes the chance of cure highly remote.

Following abdominal exploration, the right colon is mobilized and retracted medially; a technique known as the Cattell-Braasch maneuver. The lesser sac is entered and posterior

attachments of the stomach are divided. The superior mesenteric vein is identified by tracing the middle colic vein proximally, or after Kocherization by following the sweep of the duodenum medially. The gallbladder is mobilized and the common hepatic duct and gastroduodenal arteries are divided. These maneuvers allow exposure of the anterior surface of the portal vein. The portal vein and superior mesenteric vein are carefully separated from the overlying pancreas. The stomach (or duodenum in cases of pylorus-preserving pancreaticoduodenectomy [PPPD]), small bowel, and pancreas are then divided sequentially. The uncinate process is liberated from its retroperitoneal attachments to complete the dissection. Gastrointestinal continuity is re-established by a pancraticojejunostomy (or pancreaticogastrostomy), choledocojejunostomy, and gastrojejunostomy (or duodenojejunostomy in the case of PPPD). Anastomoses are done in sequence: pancreas, then bile duct, then stomach (or duodenum in the case of PPPD) (Figure 9).

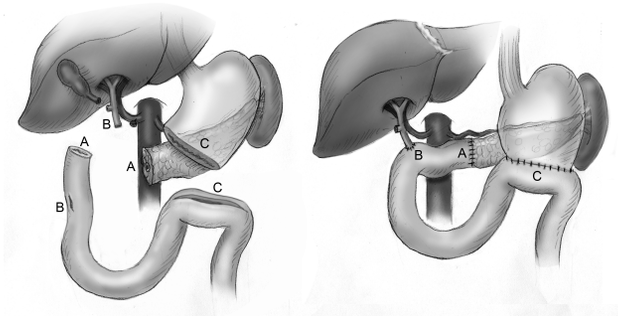


Figure 9. Lines of resection of the typical pancreaticodoudenectomy. Reconstruction is performed in order from A to C.

PPPD is a modification of the standard Whipple procedure in which the entire stomach, including the pylorus, and 2 cm to 3 cm of the duodenal cuff, are preserved. This modification retains the entire stomach as a reservoir and may prevent the development of postgastrectomy syndromes, marginal ulceration, and enterogastric reflux. PPPD is touted to result in shorter operative times, less blood loss, and fewer transfusions. PPPD was first described by Dr. Warshaw in 1981 and has been the largest variation of the procedure since the one-stage approach was introduced in clinical practice [83]. However, delayed gastric emptying without much further benefit has led to a change back to the gastrojejunostomy approach in some centers, but this remains a point of controversy [84, 85].

Pancreaticojejunostomy may be performed as an end to-end "dunking" procedure, an end-to-side anastomosis between pancreas and jejunum, or an end-to-side duct-to-mucosa anastomosis. A duct-to mucosa anastomosis may be performed over a stent and left in place for pancreatic ducts less than 5 mm. The primary theoretical advantage of duct-to-mucosa pancreaticojejunostomy is long-term patency. Pancreaticogastrostomy (PG) is performed in an end-to-side fashion. There is no evidence that the type of pancreatic-enteric anastomosis affects the rate of pancreatic fistula. Because pancreatic fistulas remain the most serious complication of the operation, a pancreaticogastrostomy (PG) instead of a pancreaticojejunostomy (PJ) has been performed by some surgeons. Randomized controlled trials (n=3) have not shown a difference in complications with these two approaches. However, thirteen non-randomized observational clinical studies have been in favor of PG [86]. Further studies are needed to clarify these findings.

The biliary and pancreatic anastomoses are drained and jejunostomy (for feeding) and gastrostomy (for decompression) tubes are placed prior to closure. Routine placement of feeding and decompression tubes is paramount in the postoperative management of patients following a pancreaticodudodenectomy.

Total pancreatectomy for pancreatic cancer is rarely performed. Total pancreatectomy had been proposed to obtain superior tumor margins and provide a more extensive lymph node dissection. In practice, total pancreatectomy is associated with increased postoperative mortality and no change in survival compared to standard pancreaticodudenectomy. Postoperative diabetes is extremely difficult to manage in patients undergoing total pancreatectomy. Similarly, extensive lymph node dissection does not improve survival and leads to a higher complication rate [87].

Fifteen percent of pancreatic adenocarcinomas occur in the body and the tail of the pancreas. Because these tumors typically do not cause biliary obstruction, its diagnosis is not made until the disease is advanced and unresectable. Only 5% to 7% of individuals with adenocarcinoma of the body or the tail of the pancreas undergo resection and their survival is much worse compared to patients with adenocarcinoma of the head of the pancreas [77]. Distal pancreatectomy with splenectomy is reserved for rare instances when the tumor located in the body or the tail of the pancreas is resectable.

11.1. Laparoscopic Pancreaticoduodenectomy

While the formidable Whipple remains one of the most complex abdominal operations performed today, at some centers it has become common practice where several open operations are performed in a week at Johns Hopkins or Mass General. With the continued advancement in laparoscopic technique and popularity of this approach to surgical intervention, there has been a rapid acceptance of more advanced laparoscopic approaches to patients with cancer. The first total laparoscopic pancreaticoduedenectomy was described by Gagner and Pomp in 1994 and constitutes one of the most advanced laparoscopic procedures today [88;89]. Between the time it was first described to 2009, 146 laparoscopic pancreaticoduodenectomies were performed worldwide. A large series has been reported by Palanivelu and colleagues which included 45 pancreaticoduodenectomies between 1998 and 2010 of which 18 were for pancreatic adenocarcinoma [90]. Another large report from the U.S. included 65 cases of laparoscopic pancreaticoduodenectomy and documented a morbidity of 42% and a mortality of 1.5% [89]. A more recent review reported 10 case series totaling 150 totally laparoscopic pancreaticoduodenectomies. In this review, mortality and morbidity have been comparable to the open approach. Operative time for this cohort has been 483 minutes and length of hospital stay 14.1 days [91]. The leading authors on these studies have concluded that the laparoscopic Whipple is feasible and safe. However, in the absence of controlled trials this approach remains experimental.

11.2. Robotic pancreaticoduodenectomy

The first pancreaticoduodenectomy was described in 1909 by Kausch. In 1935 AO Whipple described three successful cases via a two-stage approach [80]. One-stage Whipple was

introduced in 1941 by Trimble [81]. No major variations occurred in technique until preservation of the pylorus was introduced by Warshaw in 1981 [85]. These changes in operative technique were not as radical as the introduction of the minimally invasive approach. The laparoscopic pancreaticoduodenectomy was introduced by Gagner and Pomp in 1994 [88]. Almost 100 years later, the first human robotic surgery was described by Himpens in 1997 [92] and the first robotic pancreaticoduodenectomy is credited to Giulianotti in 2000 [93]. While several limitations still exist, robotic surgery is the most innovative technology brought to the operating room in the last century.

A recent systematic review of the robotic approach demonstrated that up to date, 203 patients have had an intention to treat approach to a pancreaticoduodenectomy [94]. While the technical approach is wide and not clearly defined, the number of reported cases appears to be increasing over the past few years. In Cirocchi's review, the conversion rate was 14%, overall morbidity 58% and reoperation occurred in 7.3% of the cases [94]. Totally robotic technique has been reported by several surgeons [93;95-98]. While oncologic operations (R0) have been performed with similar morbidity and mortality to the open Whipple, the innovative nature of this approach makes it highly experimental and should only be undertaken in specialized centers. Similarly, cost analysis must be addressed in subsequent studies.

12. Outcomes

In the United States, there has been a substantial increase in the number of pancreaticoduodenectomies performed. The average age of patients undergoing surgical intervention has also increased from 1991 to 2005. Similarly, more patients with a higher index of comorbidities underwent Whipples during this time. In spite of this, perioperative morbidity remained unchanged (53%) and 30-day mortality decreased from 6% to 3% in this cohort of patients [1].

The mortality rate in high volume centers performing pancreaticoduodenectomies is 2-4% [99]. However, perioperative morbidity remains substantially high (15% to 50%) even at high volume centers [100]. In patients undergoing resection for cure and treated with neoadjuvant chemoradiation, the 5-year survival is still disappointingly low (10% to 20%) [101-106]. In a study using the Surveillance, Epidemiology, and End Results-Medicare data inclusive of 2,461 patients investigating outcomes and use of adjuvant therapy between 1991 and 2005 in the USA, the median survival of patients treated for cure was 14 months, the 1-, 3-, and 5- year survival was 53.2%, 19.7%, and 12.6%, respectively. This study, demonstrated that the use of adjuvant chemoradiotherapy led to a 2 month increase in overall survival [1]. A study from Johns Hopkins examining temporal variation in morbidity and mortality following pancreaticoduodenectomy found a magnificent decrease in mortality to 4% (1981-1986) from 24% (1969-1980) with an accompanying decrease in morbidity from 59% to 36% during the same periods. The 5-year survival in patients with pancreatic cancer was 18% [107]. Thus, while the number of patients undergoing pancreaticoduodenectomy has increased with a variable decrease in complications, the overall mortality has not improved in most high volume centers [108].

13. Morbidity

Postoperative complications occur in 25-50% of patients following this operation. Delayed gastric emptying, even with standard definitions by the International Study Group of Pancreatic Surgery, occurs in a wide range of 14% to 45% and constitutes the most common complication following pancreaticoduodenectomy [109-111]. Erythromycin or metoclopramide may reduce the incidence of gastric emptying by only 37% [112]. Thus, a jejunostomy tube for prolonged postoperative feeding as well as a gastrostomy tube for postoperative decompression should be routinely employed during pancreaticoduodenectomy.

Pancreatic fistula (defined as the output of more than 50 cc of amylase-rich fluid) accompanies 5%-30% of cases [113-117] and is directly responsible for up to 20% of postoperative deaths [115;117], which constitutes the most serious complication of pancreaticoduodenectomy. Pancreatic fistula indicates disruption of the pancreatic-enteric anastomosis and occurs at the same rate regardless of anastomosis (i.e. pancreaticogastrostomy *vs.* pancreaticojejunostomy), modified drainage strategies, or somatostatin administration [118].

Disruption of biliary and gastric anastomoses are rare and less serious. Patients with pancreatic fistula may be completely asymptomatic if it is a controlled fistula and the output is well captured by the drain. These patients do well with a clear liquid diet, enteral nutrition through a jejunostomy tube, or parenteral nutrition. A CT scan should be performed to exclude abdominal fluid collections. The benefits of somatostatin in this setting are unclear. Diet may be progressively advanced as output decreases. Eighty percent of patients can be managed conservatively. An additional 10%-15% of patients with this complication respond well to percutaneous drainage.

Patients with sepsis or hemorrhage related to pancreaticoenteric anastomotic disruption necessitate immediate and aggressive intervention. Septic patients who do not respond to aggressive medical management within 48 hours should be explored. Hemorrhage associated with pancreatic fistulas can be managed with angiographic embolization. Patients who require operative exploration and have diffuse retroperitoneal hemorrhage and necrosis require completion pancreatectomy. The rare cases of hemobilia and hemopancreaticus are best diagnosed and treated angiographically.

Endocrine pancreatic function is rarely impaired and diabetes is unusual following pancreaticoduodenectomy. Exocrine pancreatic function, on the other hand, is affected to various degrees and in severe cases may require lifelong exogenous enzyme supplementation.

14. Neoadjuvant therapy

There are no randomized controlled trials that compare neoadjuvant to adjuvant therapy for patients with resectable disease. Potential benefits of neoadjuvant therapy include identifying those patients with occult metastatic disease thereby selecting patients who would probably not benefit from surgery. Another potential benefit is avoiding delay in chemotherapy for those patients who have postoperative complications or prolonged recovery. Conversely, the

response rates to neoadjuvant therapy are low (9-12%) which may allow for disease progression with the delay of surgery [119;120]. Since there is stronger data supporting adjuvant therapy, most centers prefer this approach over neoadjuvant therapy for patients with resectable disease.

Patients with borderline resectable cancer or locally advanced disease can be treated with neoadjuvant therapy with the goal of down-staging allowing for possible resection. Currently, there is no defined optimal neoadjuvant therapy for this population of patients supported by randomized controlled trials. The National Comprehensive Cancer Network recommends that patients with borderline resectable disease undergo a laparotomy followed by resection if possible or upfront neoadjuvant therapy. Available options for neoadjuvant therapy include FOLFIRINOX, gemcitabine, gemcitabine-based combination therapy, capecitabine or continuous infusion 5-FU [40]. It is suggested that chemoradiation should be reserved for patients who do not develop metastatic disease while receiving chemotherapy [40]. A meta-analysis showed that 31.6% of patients with initially borderline/unresectable tumors treated with neoadjuvant therapy were able to undergo resections. These patients had a median survival of 22 months which appears comparable to those patients with initially resectable disease [120].

15. Adjuvant therapy

Only about 15-20% of cases of pancreatic cancer are considered resectable. Even after resection the prognosis is poor with 5-year survival rates approximating 20% [121]. Systemic chemotherapy and radiation have been used adjuvantly to improve the survival rates. However the optimal choice of adjuvant therapy remains quite controversial. There have been several phase III studies evaluating therapy in the adjuvant setting; these are summarized in Table 2. The GITSG Trial compared concurrent 5-FU based chemoradiation with observation alone after resection. This study was closed early due to slow accrual and only had 49 patients enrolled at the time of analysis. The GITSG Trial showed an improved survival benefit (median survival 20 months *vs.* 11 months, p=0.03) favoring the concurrent chemoradiation group [122]. The GITSG study was followed up by the EORTC study which was similar in design, comparing 5-FU based concurrent chemoradiation to observation. The EORTC study demonstrated no survival advantage with adjuvant therapy. The 2-year survival was 26% *vs.* 34% for the observation and treatment arms respectively; this difference was not statistically significant [123]. The ESPAC-1 Trial had a 2 x 2 factorial design in which they compared concurrent chemoradiation, chemotherapy, chemoradiation followed by chemotherapy or observation. This study was only powered to compare the chemotherapy *vs.* no chemotherapy group and the chemoradiotherapy *vs.* no chemoradiotherapy group. The results showed a statistically significant improved median survival for those patients who received chemotherapy (20.1 months) compared to those patients who did not receive chemotherapy (15.5 months). Interestingly this study demonstrated a worse median survival for patients receiving chemoradiotherapy (15.9 months) compared to those patients that did not receive chemoradiotherapy (17.9 months) [124]. Three trials were done evaluating the efficacy of gemcitabine. The CONKO-001 trial compared adjuvant gemcitabine to observation. The trial showed a statistically significant improvement in median disease free survival of 13.4 months (gemcitabine

arm) compared to 6.9 months (observation arm). There was no difference in overall survival, but this was attributed to the fact that most patients in the observation arm received gemcitabine on relapse [104]. Two trials compared 5-FU with gemcitabine. In the RTOG 9704 study all patients received concurrent 5-FU based chemoradiation with either 5-FU or gemcitabine given before and after. The ESPAC-3 trial compared adjuvant 5-FU to gemcitabine without the use of radiation. Both of these studies showed no survival advantage for one arm over the other. However in the RTOG 9704 study those patients stratified to the gemcitabine arm did have a greater proportion of T3 or T4 disease which may account for no improvement in survival. The ESPAC-3 trial did demonstrate that gemcitabine was associated with fewer adverse events [104;124]. The treatment practice for these patients can be quite variable. Some advocate for adjuvant chemotherapy alone without radiotherapy based on the EORTC and ESPAC-1 trials. Others continue to advocate for radiotherapy given the high risk of local failure and the benefit seen in the GITSG study. The dose of radiation given in these studies would be considered suboptimal by today's standards which the supporters of radiotherapy argue explains why the benefit was not seen in the EORTC and ESPAC-1 studies.

Trial	Intervention	Results	Conclusions
GITSG	Concurrent CRT (5-FU) ->maintenance 5-FU Observation	**Median Survival** 20 mos vs. 11 mos P=0.03	-Survival benefit of CRT followed by maintenance chemo
EORTC	Concurrent CRT (5-FU, 40Gy) Observation	**2-yr Survival** 34% vs. 26% P=0.099	-No statistically survival benefit observed
ESPAC-1	Observation Chemotherapy (5-FU/L) CRT (5-FU/L) CRT -> Chemo (5-FU/L)	**5-yr Survival** 10% (CRT) vs. 20% (no CRT) P=0.05 21% (chemo) vs. 8%(no chemo) P=0.009	-Adjuvant chemo has a survival benefit -CRT with a deleterious effect on survival
RTOG 9704	5-FU pre and post CRT Gemcitabine pre and post CRT	**Median Survival** 17.1 mos vs. 20.5 mos P=0.08	-No improvement of Gemcitabine over 5-FU
CONKO-001	Gemcitabine Observation	**Median DFS** 13.4 mos vs. 6.9 mos P<0.001 **Median Survival** 22.8 mos vs. 20.2 mos. P=0.005 (update from 2008)	-Gemcitabine improved DFS. -Updated survival data shows a benefit with Gemcitabine
ESPAC-3	5-FU Gemcitabine	**Median Survival** 23 mos vs. 23.6 mos P=0.39 **Serious Adverse Events** 14% vs. 7.5% P<0.001	-No difference in survival -Gemcitabine associated with less toxicity

Table 2. Phase III Adjuvant Therapy Trials

16. Metastatic disease

Systemic therapy for metastatic pancreatic cancer is aimed at minimizing disease-related symptoms and prolonging survival. For several years the standard of care was 5-fluorouracil (5-FU)-based combinations with an observed survival benefit over best supportive care. The median survival with 5-FU-based combinations on average approximates 6 months versus 3 to 4 months with best supportive care [125]. In 1996, gemcitabine was approved for treatment of metastatic pancreatic cancer after a phase III trial demonstrated a clinical benefit response of 23.8% for those in the gemcitabine group compared to only 4.8% in the 5-FU group (P=0.0022). Secondary endpoints evaluated in the trial included survival rate, which at 12 months was 18% for the gemcitabine arm and 2% for the 5-FU arm [126]. Several gemcitabine-based combinations have been investigated with the goal of further improving its therapeutic efficacy. Sun *et al.* performed a meta-analysis investigating gemcitabine-based combinations compared with gemcitabine monotherapy. The meta-analysis found that combination therapy provided a modest 1-year overall survival with a RR of 0.90 (P=0.04). However, this benefit with combination therapy was associated with more grade 3-4 toxicities including vomiting, diarrhea, neutropenia, anemia and thrombocytopenia. Based on subgroup analyses patients with a good performance status appeared to derive the most survival benefit from combination therapy [127]. The combination of gemcitabine and erlotinib was compared to gemcitabine alone in a phase III trial where a very modest improvement in median survival was observed (6.24 months *vs.* 5.91 months). In this study, 53% of samples were classified as EGFR positive. Interestingly EGFR status did not have any association with response or disease stability [128]. In 2011, Conroy *et al.* reported results of a randomized controlled trial of FOLFIRINOX compared to gemcitabine. The combination chemotherapy regimen improved the objective response rate from 9.4% in the gemcitabine group to 31.6% in the FOLIRINOX group (P<0.001). Median survival was also improved to 11.1 months in the FOLFIRNOX arm compared to 6.8 months in the gemcitabine arm (P<0.001). The combination chemotherapy, as seen with prior combination regimens, was associated with more adverse events [129]. Recently, the combination of nab-paclitaxel and gemcitabine was approved for first-line therapy in metastatic adenocarcinoma of the pancreas. Objective response rates were 23% and 7% in the nab-paclitaxel plus gemcitabine arm and single agent gemcitabine arms, respectively (P<0.0001). Progression free survival was also improved with a median PFS of 5.5 months in the combination arms compared with 3.7 months in the single agent arm (P<0.0001). There was also an observed median survival benefit of 8.5 months for the nab-paclitaxel plus gemcitabine arm while the single agent gemcitabine arm only had a median survival of 6.7 months (P<0.0001) [130] (Table 3).

17. Palliation

Palliation of pancreatic cancer patients may be the goal of operative exploration or may result from operative findings indicating unresectablility. Palliation can be performed

Study	Intervention	Results
Burris et al. 1997 Phase III	Gemcitabine 5-FU	**Clinical Benefit Response** 23.8% vs. 4.8% P=0.0022 **Median Survival** 5.65 mos vs. 4.41 mos P=0.0025
Moore et al. 2007 Phase III	Gemcitabine + Erlotinib Gemcitabine + Placebo	**Median Survival** 6.24 mos vs. 5.91 mos P=0.038
Sun et al. 2012 Meta-analysis	Gemcitabine monotherapy Gemcitabine combination therapy	**Objective Response Rate** RR, 0.72; 95% CI: 0.63-0.83 P<0.001 **1-yr Overall Survival** RR, 0.90; 95% CI: 0.82-0.99 P=0.04
Conroy et al. 2011 Phase III	FOLFIRINOX Gemcitabine	**Median Survival** 11.1 mos vs. 6.8 mos P<0.001 **Median PFS** 6.4 mos vs. 3.3 mos P<0.001
Von Hoff et al. 2013 Phase III	Nab-Paclitaxel + Gemcitabine Gemcitabine	**Median Survival** 8.5 mos vs. 6.7 mos P<0.0001 **PFS** 5.5 mos vs. 3.7 mos P<0.0001

Table 3. Selected studies for palliative chemotherapy in the metastatic setting

operatively and nonoperatively and this decision should be individualized depending on the overall status of the patient. Whether palliation is accomplished operatively or nonoperatively, relief of obstructive jaundice, duodenal obstruction, and back pain are the primary goals. About 65% to 75% of patients with pancreatic cancer will develop symptoms of obstructive jaundice [131]. In patients with obstructive jaundice endoscopic biliary stenting and surgical biliary bypass are palliative options. Endoscopic biliary stenting is associated with lower complication rates and shorter hospital stays while maintaining similar efficacy and overall survival compared with surgical bypass [132]. In the event that endoscopic management is not successful, external biliary drainage can be attempted. Duodenal obstruction develops in about 15% to 20% of patients with pancreatic cancer [133]. Traditionally duodenal obstruction had been palliated with gastrojejunostomy, but

with data showing similar efficacy with enteral stents, improved cost-effectiveness and shorter hospitalizations this option has become a viable alternative [134].

Most patients with pancreatic cancer, at some point in their disease course, will experience severe cancer-related pain. This pain can be a severely debilitating symptom leading to poor quality of life and decreasing performance status. In addition to systemic analgesics, regional celiac plexus nerve block is effective at alleviating pain [135]. In general, endoscopic palliative measures are preferred for those patients with known unresectable disease or those with a poor performance status. For patients who are discovered to have unresectable or metastatic disease on open exploration and expected to have a life expectancy of at least 3 to 6 months operative palliative measures (choledochojejunostomy, gastrojejunostomy and intraoperative chemical splanchnicectomy) can be considered for symptoms of obstruction and pain [136].

18. Conclusions

Multiple diagnostic and therapeutic modalities in the evaluation and treatment of pancreatic cancer have not resulted in a meaningful survival advantage in patients with pancreatic cancer. This dismal performance is primarily related to the inherent aggressive tumor biology of pancreatic adenocarcinoma. Early diagnosis and curative resection, when possible, holds promise for better survival but surgery in itself carries a definite morbidity and mortality, even in specialized centers. Hence, pancreatic adenocarcinoma should be managed at high volume centers in a multi-disciplinary setting and in light of proposed guidelines, until better treatment options are available in the future.

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