Chapter 11
Pancreatic Surgery in Patients with Cirrhosis

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Objectives

1. To develop an understanding of the considerations for management of pancreatic malignancies in the setting of cirrhosis or prior liver transplantation
2. To develop an understanding of the role of surgery and methods for selectively applying surgery to maximize overall and disease-specific survival for patients with cirrhosis or prior liver transplantation in the setting of pancreatic malignancies
3. To describe the relative frequency of incidental pancreatic cystic lesions and how to apply existing management algorithms to the population of patients with cirrhosis and prior liver transplantation
4. To describe the management principles for chronic pancreatitis in the setting of cirrhosis or prior liver transplantation and the selective indications for surgical interventions

Introduction

Surgical management of pancreatic disease is a challenging aspect of surgical practice. Even among experienced high-volume surgeons, complications and mortalities occur with a greater frequency than for most other operations in

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general surgery. With the exception of genetic or hereditary disorders and some pediatric malignancies, pancreatic disease is most commonly seen in advanced age groups throughout the world. The combination of medical comorbidities, technically challenging procedures, and high relative operative morbidities makes surgery for pancreatic disease in the general population a formidable proposition.

Within the spectrum of patients with pancreatic disease lies those with liver dysfunction, not an uncommon occurrence. Underlying liver dysfunction in the general population, recognized as an incidental finding during evaluation for other diseases, is common. Unfortunately, for those patients undergoing evaluation or planned surgical therapy for pancreatic disease who are found to have liver cirrhosis, the relative risk of any surgical procedure increases and their potential treatment options may also decrease. As will be noted later in this chapter, the incidental finding of cirrhosis in a patient with a pancreatic adenocarcinoma can drastically limit the presumed safety of some promising chemotherapeutic agents. Furthermore, given the already limited practice of appropriate referral to pancreatic surgeons for resectable pancreatic tumors, the concomitant diagnosis of cirrhosis may further worsen the referral of these patients for a potentially curative treatment.

Another common situation is the identification of pancreatic disease during the evaluation or treatment for liver cirrhosis. In the most frequent scenario, those patients who are being evaluated for liver transplantation or followed for liver transplant may be identified to have changes within their pancreas covering the spectrum from benign cystic disease and chronic pancreatitis to malignant masses. The challenge in these scenarios spans decisions to abort consideration of some treatment options, for example, liver transplantation versus consideration of treatment options for the pancreatic disease at some point during treatment of their liver cirrhosis. In the rare event, some patients may necessitate concurrent pancreatic and hepatic surgical therapies. The surgical decision-making for these patients must be deliberate and thoughtful due to the relative paucity of existing evidence. Evidence for management of these patients has only developed in a limited number of centers.

The purpose of this chapter is to discuss common surgical pancreatic diseases encountered in patients with either cirrhosis or a history of liver transplantation. The specific aims of the chapter will be to describe standard therapies for these common pancreatic diseases and methods from the authors' experience in applying these standards to this unique patient population. As mentioned earlier, the overall lack of reported experiences in this patient population has led surgeons to develop a wide variety of level III evidence-based practices. The approach described in this chapter attempts to identify those patients who can be managed with traditional standards of care and those who must have a more tailored treatment algorithm.

Main Ideas

Pancreatic Malignancies

Pancreatic Ductal Adenocarcinoma

The most common malignancy of the pancreas is ductal adenocarcinoma. This is the 12th most common malignancy is the United States with an estimated 53,000 new cases diagnosed per year. However, the mortality is disproportionately high compared to other malignancies and represents the third most common cause of cancer-related death in the United States. Unlike many cancer diagnoses, the overall incidence is also increasing over the past decade with a growth from 11.0 to 12.7 cases per 100,000 between 1993 and 2013.

The development of novel chemotherapeutic regimens in addition to significantly increased experience with surgical techniques has led to an overall improvement in the generally poor long-term survival of many pancreatic cancer patients. Historically 5-year overall survival for pancreatic adenocarcinoma was 3.6%; however, with newer therapies, this has improved to 7.6%. The most significant improvement in long-term survival has come in those with resectable localized disease which represents approximately 9–10% of all new pancreatic adenocarcinoma diagnoses. In these patients, the expected 5-year overall survival is estimated to be 29.3%, with significantly higher reported outcomes in those patients who are medically suitable for surgery. The addition of neoadjuvant or adjuvant therapies has also been reported to significantly improve overall survival for this subpopulation. In contrast, those patients with locoregional or locally advanced disease, lymph node invasion, or vascular invasion have a more limited 5-year overall survival estimated at 11.1%. The development of neoadjuvant therapies has played a particular role in prolonging survival in this subpopulation, as modern chemotherapy regimens have demonstrated newfound response rates not previously seen with historical regimens. Finally, those patients with metastatic disease represent the majority of patients presenting with pancreatic adenocarcinoma with approximately 52% presenting at this stage. Despite advances in the treatment for pancreatic adenocarcinoma in the past several decades, this subpopulation remains a significant challenge and is reflected by a 5-year overall survival of only 2.6%. More specifically, the median survival for a patient diagnosed with stage IV pancreatic adenocarcinoma is estimated to be only 4.5 months, as shown in Fig. 11.1.

In patients with underlying cirrhosis, pancreatic adenocarcinoma is more likely to occur than in the general population. As seen with cancers of hepatic origin, pancreatic adenocarcinoma occurs at a significantly higher likelihood in cirrhotic patients with alcoholic etiology as compared to other causes. In the United Kingdom, patients with cirrhosis were found to have an approximately ninefold increased risk for the development of pancreatic adenocarcinoma, except in

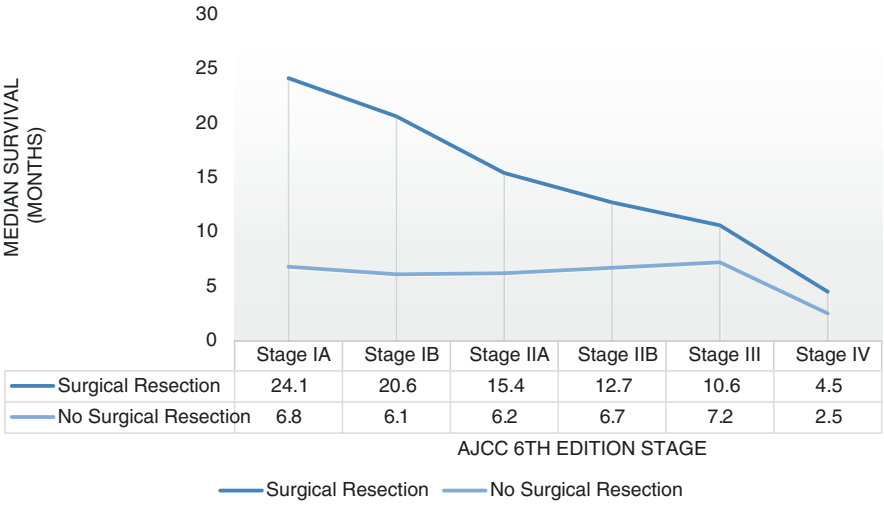

Fig. 11.1 Estimated median survival in months for patients diagnosed with pancreatic adenocarcinoma. The impact of surgical resection is demonstrated to be greatest in those patients who are diagnosed with local or resectable disease. The impact of neoadjuvant therapies in prolonging overall survival in those patients with borderline resectable or locally advanced disease has been demonstrated in multiple retrospective studies. Those patients with metastatic disease are most likely to have limited benefit from current therapies (Data derived from Bilimoria Karl Y, et al. Validation of the 6th edition AJCC pancreatic cancer staging system. *Cancer*. 2007;110(4):738–44)

patients with primary biliary cirrhosis who were not found to have an elevated risk. The relative risk for development of pancreatic adenocarcinoma in cirrhotics may be only partially attributable to a history of acute or chronic pancreatitis, of which the presence of chronic pancreatitis is associated with a markedly elevated risk for eventual pancreatic adenocarcinoma of 27% compared to 5%, respectively.

Three of the largest case series to date have reported on surgical outcomes for patients with Child's A and B cirrhosis with resectable pancreatic adenocarcinoma. These studies provide current evidence to support individual experiences for appropriate selection and anticipated outcomes in this population. In each series (El Nakeeb et al., Regimbeau et al., and Busquet et al.), the survival for patients who underwent resection demonstrated improved survival compared to historical outcomes; however, there were discordant findings regarding the comparison of outcomes to noncirrhotic patients. Specifically, Regimbeau et al. found that in their series the patients with cirrhosis had similar 3-year overall survival and disease-free survival (50% and 18%, respectively) compared to noncirrhotic patients (44% and 34%, respectively). In contrast, the series by El Nakeeb reported a decreased 3-year survival in the cirrhotic patients of 3% versus 19% with similar median survival of 19 months and 24 months, respectively. The likely rationale for this difference is the high rate of adjuvant therapy adherence by the cirrhotic

patients in the Regimbeau study of 76%, compared to 74% in noncirrhotic patients. This exemplifies the importance of adjuvant or neoadjuvant therapy in conjunction with surgery for the management of cirrhotic patients, similar to noncirrhotic patients.

Initial Evaluation and Staging Assessment

Critical to the determination of the management of pancreatic adenocarcinoma involves an accurate assessment of the resectability of the primary tumor and identification of metastatic disease. The classification of resectability of a pancreatic adenocarcinoma is currently divided into three groups: (1) resectable, (2) borderline resectable, and (3) locally advanced unresectable. Definitions for what tumor characteristics qualify in each group have variability based upon the criteria produced from each of the three main publications on the management of pancreatic adenocarcinoma. Table 11.1 details the criteria for determining the resectability of each primary tumor from each of the major published guidelines.

The key component of assessing the resectability comes through proper selection of diagnostic imaging. Based upon current guidelines, the recommended

Table 11.1 Published criteria for determination of the resectability of a pancreatic adenocarcinoma from the International Hepato-Pancreato-Biliary Association (IHPBA)/Society of Surgical Oncology (SSO)/Surgery of the Alimentary Tract (SSAT), National Comprehensive Cancer Network (NCCN), and MD Anderson Cancer Center (MDACC)

	AHPBA/SSO/SSAT	NCCN 2016	MDACC
Resectable	No venous or arterial abutment of SMV/PV or SMA or CHA/CA	No arterial abutment Abutment of SMV/PV	No arterial abutment Abutment of SMV/PV
Borderline resectable	Abutment/encasement/occlusion of SMV/PV Abutment of SMA/CHA Short-segment encasement of CHA No abutment of CA	Abutment/encasement/occlusion of SMV/PV Abutment of SMA/CHA or CA Encasement of CA (body/tail tumors only)	Encasement/occlusion of SMV/PV Abutment of SMA or CHA/CA or IVC Short-segment encasement of CHA
Unresectable	Unreconstructable SMV/PV Encasement of SMA Long-segment encasement of CHA Abutment of CA	Unreconstructable SMV/PV Encasement of SMA or first jejunal SMA branch Abutment of aorta	Unreconstructable SMV/PV Encasement of SMA or CA Long-segment encasement of CHA

Abutment is defined as less than or equal to 180° contact with the target vessel (variable definition including contour irregularity of the vessel). Encasement is defined as > 180° contact with the target vessel. *SMV* superior mesenteric vein, *PV* portal vein, *SMA* superior mesenteric artery, *CHA* common hepatic artery, *CA* celiac artery, *IVC* inferior vena cava

study should be either a multidimensional computed tomography (MDCT) using a pancreas-specific protocol of intravenous and oral contrast, or magnetic resonance imaging (MRI) using a pancreas-specific protocol of intravenous contrast. CT pancreas protocols based upon the American Pancreatic Association guidelines should be obtained using slice thickness no larger than 3 mm (goal of 0.5–1 mm), a pancreas parenchymal arterial phase and a portal venous phase, and neutral oral contrast in order to maximize the sensitivity for pancreatic masses. Similar guidelines for MRI pancreas protocols include maximal slice thickness of 6 mm on T1-weighted in-phase and opposed-phase gradient echo (GRE), T2-weighted fat-suppressed fast-spin echo (FSE), and diffusion-weighted imaging (DWI), as well as 2–3 mm thickness for pre- and post-gadolinium contrast T1-weighted fat-suppressed echo (phases: pancreas parenchyma, portal venous, equilibrium) and T2-weighted MRCP. A benefit of MRI imaging for staging is the improved resolution for subcentimeter hepatic metastases which can be most readily seen on DWI series with proper processing software. Recent retrospective studies have demonstrated the potential improved recognition of patients with these subcentimeter metastases not appreciated on traditional pancreatic CT imaging through MRI.

In the setting of combined chronic kidney disease with hepatic insufficiency, a decision to omit intravenous contrast can have a significant impact on the reliability of staging imaging. As mentioned previously, understaging due to failed identification of metastases or locally advanced disease may lead to an unfortunate decision to proceed with surgical resection in a patient population unlikely to benefit from the effort. An effort to ameliorate renal risks using precontrast volume expansion, N-acetylcysteine, or even temporary hemodialysis in selected patients should be made to allow proper imaging with intravenous contrast in the staging phase for all patients.

Other variables which have been assessed to attempt to improve accurate preoperative stratification of patients most likely to benefit from upfront surgical resection include serum CA 19-9 and CT/PET. Serum CA 19-9 is of particular interest in many pancreatobiliary tumors due to its common production by tumors of this cell lineage. CA 19-9 is a glycopeptide which is produced in a majority of pancreatic ductal adenocarcinoma patients, with the exception of approximately 10% of patients who lack the Lewis antigen and therefore are unable to produce CA 19-9 regardless of tumor burden. Unfortunately, CA 19-9 can be elevated with a range of hepatopancreatobiliary diseases including cirrhosis and biliary obstruction. Studies which have attempted to identify a role of elevated CA 19-9 have intentionally excluded patients with cirrhosis or underlying hepatopancreatobiliary diseases to avoid the risk for false positives. The role of CA 19-9 as a decision tool in the setting of cirrhosis is therefore not currently recommended. Additionally, CT/PET has been suggested in some small retrospective series to have a potential role of identification of metastatic pancreatic disease. These studies however have been limited to a significant false-positive rate with specific false positives identified in the liver and regional lymph nodes. Furthermore, in the setting of dysplastic nodules commonly seen in cirrhosis, additional false

positives in the liver would be expected due to their typically FDG-avid state on CT/PET. The decision-making ability of these adjunctive tests is therefore even more limited in the setting of cirrhosis patients and should not be used as a tool to differentiate treatment options for these patients with pancreatic adenocarcinoma.

A final consideration for pretreatment evaluation of pancreatic adenocarcinoma is the medical status of the patient. Significant experience has been gained in the surgical management of patients of greater ages and higher medical comorbidity risk within the past two decades. Current high-volume centers have demonstrated the feasibility of pancreatectomy procedures for pancreatic adenocarcinoma in these traditionally high-risk patient populations with near-equivalent morbidity and mortality. The main determinant that has been shown to be of importance in patient selection is the associated frailty assessment. Multiple methods have been described to report aspects of medical frailty across cardiovascular, pulmonary, and metabolic assessments. The ideal method to define frailty in the setting of ductal adenocarcinoma has yet to be determined. Further, in the setting of underlying cirrhosis or chronic immunosuppression for liver transplantation, the frailty of a patient may be the primary determinant for determining whether upfront surgery is appropriate. In these higher risk patients with surgically resectable tumors, a medical frailty assessment should be made to determine if neoadjuvant therapy is necessary to allow for an interval intervention to optimize frailty prior to any surgical intervention.

Neoadjuvant Therapy

The use of neoadjuvant therapy implies the intention to proceed with surgical resection following completion of the intervention. Development of neoadjuvant therapies occurred in response to the lack of patients with surgically resectable disease and overall lack of increased survival despite effective surgical resection. The intent of initial neoadjuvant therapies was to make locally advanced and unresectable tumors surgical candidates, given some survival benefit seen with resection. Subsequent advances in neoadjuvant therapy for borderline resectable and locally advanced tumors have been demonstrated mostly through retrospective or prospective observational studies. A limitation of a majority of these neoadjuvant therapy studies has been the lack of an intention-to-treat analysis demonstrating survival benefit from neoadjuvant therapy versus traditional upfront surgery with adjuvant therapy. More importantly, the role of neoadjuvant in the setting of resectable disease has yet to yield a demonstrable improvement in survival and therefore remains limited to clinical trials.

Within neoadjuvant therapies, the main applied interventions are chemotherapy alone, radiation with a chemotherapy agent as a radiosensitizing agent (chemoradiation), or a combination of the two modalities. Historical evaluation of radiation alone was demonstrated to have a limited role in the subset of locally advanced and

borderline resectable patients. The historical benefit seen in initial studies evaluating chemoradiation has more recently been questioned compared to the survival benefit seen with chemotherapy alone. In combined regimens of chemotherapy followed by chemoradiation, there has yet to be a demonstrated clear survival benefit by the addition of chemoradiation. Specifically, as applied to those patients with cirrhosis, the consideration for radiation field reduction and potential hepatotoxicity must be accounted for. Without a clear survival benefit and potential significant risk beyond those patients with well-compensated Child's A cirrhosis, the use of chemoradiation should likely be avoided unless a clear benefit can be demonstrated.

A major development for neoadjuvant therapies has been seen in recent years with modified FOLFIRINOX regimens to borderline resectable and locally advanced populations. The modified FOLFIRINOX regimen relies on a 25% dose reduction of irinotecan and 5-FU to reduce the high toxicity of the initial FOLFIRINOX regimens utilized in the study of metastatic pancreatic adenocarcinoma patients. Despite this dose reduction, the associated hepatotoxicity of irinotecan and oxaliplatin generally prevents the use of this regimen to cirrhotic patients beyond those with well-compensated Child's A class. Use of the modified FOLFIRINOX regimen in previously transplanted patients has not been evaluated to date, although the potential application would seem safe from a toxicity standpoint. Given the absence of alternative highly active chemotherapy regimens, the use of FOLFIRINOX may be warranted despite these hypothetical risks of liver injury. Another current regimen which has recently been demonstrated to yield significant survival advantages is the gemcitabine and nab-paclitaxel regimen. This regimen was demonstrated in the metastatic setting to improve overall survival from 6.6 months to 8.7 months in the MPACT trial and has also been extrapolated to the neoadjuvant setting more recently. Current evidence for this regimen in neoadjuvant setting is currently in development with ongoing studies to evaluate its efficacy. However, given the lack of underlying hepatotoxicity associated with gemcitabine and nab-paclitaxel, the use of this regimen may be preferred in the cirrhotic and liver transplantation population for neoadjuvant therapy.

Overall patients with borderline resectable or locally advanced pancreatic adenocarcinoma clearly have a survival benefit to neoadjuvant chemotherapy and possibly the addition of chemoradiation in well-selected patients. As has been shown, the implementation of neoadjuvant therapy is associated with an elevated likelihood to complete systemic and surgical therapies compared to upfront surgery. This benefit in particular is useful for those with cirrhosis who are prone to additional hepatic decompensation following a pancreatoduodenectomy, given the underlying perioperative risk for decompensation as well as progressive hepatic insufficiency from protein malabsorption associated with the reconstruction. As newer studies attempt to evaluate the benefit of patients with resectable pancreatic adenocarcinoma treated with modern neoadjuvant regimens, this pathway and its associated benefits may aid in the treatment of those cirrhosis patients who otherwise would be capable of undergoing surgical resection, but unfit to complete adjuvant therapy to yield the greatest survival benefit.

Pancreatectomy Procedures

Surgical management for pancreatic adenocarcinoma should be attempted in patients with resectable tumors and those with borderline resectable or locally advanced, who are anticipated to be capable of achieving an R0 resection. Given the inability to assess for venous or arterial invasion following neoadjuvant therapies using imaging studies and the unreliability of CA19-9 in predicting resectability, beyond the presence of metastases, those who have completed neoadjuvant therapy and are medically fit for surgery should be offered resection. General considerations for surgical resection of pancreatic adenocarcinoma should be the decision to use a diagnostic laparoscopy prior to proceeding with attempted resection. Historical rates of positive liver/peritoneal findings from diagnostic laparoscopy for pancreatic adenocarcinoma were up to 21% across all patients without radiographic peritoneal metastases. More modern imaging techniques however likely have led to this rate being lower, although many consider a diagnostic laparoscopy prior to resection as an important method to prevent unnecessary open exploration and potential resection. The use of diagnostic laparoscopy therefore remains an important component of surgical exploration for cirrhotic patients, given their inherent increased perioperative morbidity and mortality.

Standard resection principles for pancreatectomy should be applied regardless of the underlying liver function, as shown in Table 11.2. The technical procedure of performing a pancreatoduodenectomy or distal pancreatectomy and splenectomy is beyond the focus of this chapter. Standard resection techniques are appropriate to apply, and attention to oncological standards should be emphasized with avoidance of atypical resections or inadequate procedures simply due to underlying liver dysfunction or prior transplantation. One challenge in reported series of cirrhotic patients undergoing pancreatectomy is the risk for a lower lymph node yield. Reasons for this traditionally lower number of nodal tissue are likely due to concern for the risk of intraoperative hemorrhage with extensive dissection. With respect to the safety of venous resection in the setting of cirrhotic patients, small series have demonstrated the safety of venous resection in the setting of cirrhosis both with and without portal hypertension. Outcomes of these patients have led to increased intraoperative blood loss and operative duration, although this is not significantly different than is seen in noncirrhotic patients.

General factors likely to be encountered in the setting of cirrhosis include both anatomical and physiological changes. Anatomical changes which may alter the operative conduct and safety of the procedure relate to portal hypertension. In the setting of cirrhosis with portal hypertension, the development of engorged portal and mesenteric veins can obscure surgical planes with an increased propensity for hemorrhage. Dissection of the portal structures and superior mesenteric vein borders, which normally have small caliber vessels, is more likely to be of significant caliber and inadequately controlled with electrodissection techniques. The underlying pressurization of these vessels may cause the caliber to be inadequate for

Table 11.2 Standard recommendations for performance of a pancreaticoduodenectomy or distal pancreatectomy and splenectomy for pancreatic ductal adenocarcinoma

Surgical factor	Pancreaticoduodenectomy	Distal pancreatectomy and splenectomy
Target margin	R0	R0
En Bloc organ resection	Rare; acceptable if R0 obtained	Possible (up to 40%); Acceptable if R0 obtained
Vein resection	Common; should not be combined with arterial resection	Rare; can be combined with arterial resection
Arterial resection	Rare; should be avoided if gross invasion	Common; should be performed if no aorta involvement
Lymphadenectomy	Regional only	Regional only
Margin assessment	SMA (retroperitoneal/uncinate) Posterior PV groove Proximal PV Distal PV Pancreatic neck (transection) Common bile duct Anterior pancreas Proximal enteric Distal enteric	Proximal pancreatic (transection) Anterior peripancreatic (cephalad) Posterior peripancreatic (Caudad)
Minimally invasive approach	Possible noninferior oncological outcomes Highly selected patients only Technically challenging	Noninferior oncological outcomes Decreased length of stay

vessel-sealing bipolar technologies, which some surgeons prefer to employ along these margins. Furthermore, in the setting of portal vein or mesenteric obstruction leading to collateralization of portal venous branches, the lesser sac can be dangerously replaced with thin-walled venous structures. Entrance into the lesser sac and attempted mobilization of the pancreatic neck can produce significant hemorrhage if these overlying vessels remain pressurized. Current recommendations for patients with portal vein obstruction or thrombosis are against surgical resection, although a report on complex venous reconstruction and decompression of collateral veins has been reported in a highly selected group of 11 patients from the Medical College of Wisconsin group following neoadjuvant therapies. The implications for portal occlusion in this setting however were related to the underlying pancreatic cancer, and therefore how these outcomes apply to those patients with chronic cavernous changes is uncertain.

Other factors which are unique to patients who have underlying cirrhosis in pancreatic surgery are those relating to physiological alterations. As mentioned in other chapters, an underlying bleeding diathesis predisposes to significant increases in intraoperative hemorrhage. In a series of patients with both Child's A and B cirrhosis undergoing pancreaticoduodenectomy, El Nakeeb et al. reported a significant increase in operative blood loss as well as need for blood transfusion in the cirrhosis

subpopulation. Additionally, they identified the presence of portal hypertension as a significant factor associated with bleeding and need for transfusion. When controlled for portal hypertension (median 1000 mL), the operative blood loss and need for transfusion were similar between cirrhotic patients without portal hypertension (median 300 mL) and noncirrhotic patients (median 200 mL). This suggests that the bleeding diathesis may not be the major risk factor for hemorrhage in these patients compared to the anatomical changes associated with portal hypertension alone. Additionally, the development of ascites either preoperatively or postoperatively has the potential to impact surgical outcomes. Although not specifically evaluated in the existing series on cirrhotic patients, the presence of ascites has the potential to increase infectious complications which are clearly demonstrated to increase pancreatojejunostomy anastomotic leakage rates. Given the absence of level I or II evidence establishing a difference in the leak rate between pancreatogastrostomy and pancreatojejunostomy, no recommendation can be made for a preference of either anastomotic method.

In the setting of prior liver transplantation, the presence of prior surgical changes in the biliary and arterial supply to the liver requires unique attention to operative technique. One significant consideration is the method for biliary reconstitution in the setting of a prior hepatoenterostomy for liver transplantation. In these patients, the absence of regional nodal continuity makes meaningful nodal staging in the region of the hepatoduodenal ligament of lower impact on overall survival. The inherent risk for inadvertent devascularization of the transplanted extrahepatic biliary tree makes this dissection of potential risk beyond the potential benefit. Additionally, if a prior hepatoenterostomy has been performed in the Roux-en-Y fashion, the need to take down this anastomosis is of questionable benefit. Unfortunately, the presence of a short Roux limb or inability to gain adequate limb laxity to perform a pancreatic anastomosis proximal to the hepatoenterostomy makes it likely to require a takedown of the limb with re-formation of the hepatoenterostomy in traditional order with the pancreatojejunostomy. In the absence of a prior hepatoenterostomy, the standard reconstruction of the biliary continuity can be performed. Adequate resection of the extrahepatic common hepatic duct with limited dissection of the preserved duct to prevent regional biliary ischemia is important in this setting. Clearly thoughtful preoperative planning in consort with the transplantation team is essential in this setting.

Surgical outcomes following pancreatectomy for pancreatic adenocarcinoma are associated with a relatively high rate of overall morbidity but low mortality. Recent advances in perioperative management, preoperative optimization, and improved centralization have likely led to the reduction in severity of complications following pancreatoduodenectomy with a majority of complications consisting of Clavien I or II, whereas more serious complications such as those requiring reoperation are less frequent. Reported mortality across all patients undergoing pancreatoduodenectomy has been reported to be generally <5%. When evaluating the series by El Nakeeb, Regimbeau, and Busquets on cirrhotic patients undergoing pancreaticoduodenectomy, there is clearly an elevated risk for serious complications (Clavien III or higher). Factors which have been shown to be associated with

Table 11.3 List of medical and surgical factors which can be used to select appropriate surgical candidates for definitive pancreatectomy procedures for pancreatic adenocarcinoma

Acceptable for surgery	Not acceptable for surgery
Child's A cirrhosis	Child's B or C cirrhosis
Normal portal venous pressure (exception in those with prior TIPS or surgical shunt may be acceptable risk)	Portal hypertension
Patent or reconstructable portal/mesenteric vein	Unreconstructable portal/mesenteric vein or cavernous transformation
Low-volume medically controlled ascites	Uncontrolled or moderate or high-volume ascites
	Hepatopulmonary or portopulmonary syndrome
	Recent bleeding from esophageal varices
	Uncontrolled hepatic encephalopathy
	Medical noncompliance

an elevated risk among those with cirrhosis are portal hypertension and Child's B cirrhosis. For these reasons, surgical resection in these patients should be considered high risk for both pancreatectomy-related and cirrhosis-related complications. More specifically, the reported postoperative risk for hepatic decompensation following pancreaticoduodenectomy in patients with Child's B cirrhosis is approximately 36% compared to only 8% in Child's A cirrhosis patients. Mortality in those patients with Child's B was 50–55% compared to 4–9.5% in Child's A patients. The risk for hepatic decompensation in patients with portal hypertension is approximately 12.5% compared to 3.9% in those without. Mortality in patients with portal hypertension is similarly elevated at 9–25% compared to 4–7.8% in those without. Table 11.3 summarizes our recommendations for selection of patients with cirrhosis who are most likely to have an acceptable operative and perioperative risk profile for pancreatectomy for ductal adenocarcinoma.

Pancreatic Neuroendocrine Tumor (pNET)

Gastroenteropancreatic neuroendocrine tumors (GEP-NET) are a group of specialized tumors which are believed to originate from neural crest and endodermal cells in the gastrointestinal tract. Within this group of tumors exist pancreatic neuroendocrine tumors (pNET) which originate specifically from cells which differentiate into islets of Langerhans cells. Overall, GEP-NET are a rare group of tumors with an estimated incidence of about 0.02–0.08%. Within this group, pNET represents an even smaller incidence of about 0.005–0.01%. Of all pancreatic tumors, pNET represents approximately 1–10%, although the overall incidence of pNET is increasing, as with other GEP-NET.

pNET tumors are classified into whether they produce hormones capable of leading to clinically significant syndromes. Within pNET tumors, those which are non-

functional represent the significant majority of about 60–90%. With the increasing incidence of pNET over the past several decades, the prevalence of functional and nonfunctional pNET has remained approximately the same. There has however been an increasing incidence of diagnosed nonfunctional pNET lesions likely associated with increased imaging sensitivity and utilization. While there is a known increased risk for the development of pNET lesions with inherited genetic syndromes, the majority of pNET occur sporadically. Furthermore, even though there is a far greater percentage of functional pNET occurring in genetic syndromes, both the majority of functional pNET occur sporadically, and the majority of pNET in hereditary syndromes are nonfunctional. The known hereditary syndromes with associated elevated risk for pNET lesions are: Multiple Endocrine Neoplasia Type 1 (MEN1), von Hippel Lindau disease (VHL), von Recklinghausen's syndrome or Neurofibromatosis type 1, and tuberous sclerosis. The inherited syndrome with the greatest likelihood for the development of a pNET is MEN1, with approximately 50% developing a functional pNET and nearly 100% developing nonfunctional pNET during their lifetime.

Common to pNET lesions is the production of cellular products which aid in the surveillance and diagnosis of these tumors. Unlike neuroendocrine tumors of the midgut, a majority of pNET do not express serotonin or its similar metabolites. Rather, these tumors can be followed by measuring serum chromogranin A, pancreatic polypeptide, neuron-specific enolase, neurotensin, or protein S. Most often, the serial measurement of chromogranin A is sufficient as a marker for progressive or recurrent disease. In the setting of new pancreatic lesion of uncertain etiology, the elevation of chromogranin A and pancreatic polypeptide suggests the presence of a neuroendocrine tumor rather than adenocarcinoma, although it is not entirely specific for pancreatic origin.

There remains significant variability in the reporting and staging for pNET lesions. The best known predictors for survival in pNET involve the tumor size, grade, lymph node invasion, and presence of metastases which are reflected in most classification systems used. In the seventh edition of the AJCC staging system, however, the TNM classification for pNET is the same as that of adenocarcinoma. More importantly however are the recognition of the grading systems published by both the North American NeuroEndocrine Tumor Society (NANETS) and European NeuroEndocrine Tumor Society (ENETS) which classify tumors by grade: based upon the Ki-67 index, mitotic count, and level of differentiation. It is important to understand that with pNET lesions the survival is markedly prolonged compared to adenocarcinoma with median survival ranging from 14 to 112 months between stage IV and stage I, respectively. Therefore, the management of pNET in patients with cirrhosis must consider that the anticipated disease-specific survival related to the pNET is greater than that of the patient's underlying cirrhosis and other comorbidities without transplantation. In the setting of prior liver transplantation, the principles guiding therapy must be to intervene only on those lesions which have the greatest likelihood for eventual metastases, in order to prevent metastases to the liver which may impact the liver transplant function.

Management of Functional pNET

Functional pancreatic neuroendocrine tumors are often identified based upon their clinical symptoms which are either a constellation of a recognized syndrome or more commonly refractory symptoms. Of the clinical syndromes, the most common are shown in Table 11.4. As can be seen from Table 11.4, the most common functional pNET is an insulinoma. These tumors typically are singular with the exception of MEN1 patients who have approximately 10% likelihood of multifocal insulinoma lesions. Unlike almost all other pNET lesions, localization of insulinomas using somatostatin receptor scintigraphy is not reliable, given that only 30% of these lesions express the somatostatin receptors required for this modality. Historically, the use of arterial stimulation tests using calcium has been suggested to be the most sensitive method for identifying insulinomas, although a majority of these lesions can be readily identified on CT or MRI imaging using pancreatic protocols described earlier. The management of these lesions is generally enucleation, given the often benign clinical course. In the setting of cirrhosis or prior transplantation, this should only be attempted if a reasonable survival is anticipated related to the underlying medical conditions and well-compensated Child's A cirrhosis without portal hypertension. In those patients not suitable for local resection, insulin antisecretory agents can be used to minimize hypoglycemia events such as diazoxide.

Gastrinomas represent the second most common type of functional pNET. Unlike insulinomas, there is a higher rate of metastases in gastrinomas approaching 60% in some series. Further, a greater percentage (up to one-third) of patients with

Table 11.4 Summary of common clinical syndromes and their suspected hormonal mediators for functional pancreatic neuroendocrine tumors (pNET)

Syndrome	Incidence (per 100,000/ year)	Hormonal mediator	Clinical symptoms
Insulinoma	1–32	Insulin	Recurrent hypoglycemia
Gastrinoma (Zollinger-Ellison syndrome)	0.5–21.5	Gastrin	Pain Diarrhea Gastritis/ulcers/esophagitis
VIPoma (Verner-Morrison syndrome)	0.05–0.2	Vasoactive intestinal peptide	Diarrhea Dehydration
Glucagonoma	0.01–0.1	Glucagon	Rash Refractory hyperglycemia Weight loss
Somatostatinoma	<0.01	Somatostatin	Hyperglycemia Cholestasis Diarrhea

Overall, these functional tumors are estimated to represent about 10–40% of pNET lesions. Their incidence in patients with cirrhosis or prior transplantation is unreported, although likely follows similar to the general population

gastrinoma are likely to have the MEN1 syndrome. Despite the higher likelihood of progression to metastatic disease in gastrinoma, there remains a prolonged clinical course which can reach up to 90% of patients at 10 years. Localization is more challenging for these lesions due to the small diameter of many gastrinoma tumors. However, with the development of improved CT and MRI imaging in addition to EUS, up to 75% of lesions may be identified. More recently, a somatostatin-based CT/SPECT study has been developed which has shown higher sensitivity for identifying gastrinoma lesions and should be utilized to localize the tumor as the technology disseminates. As with insulinoma lesions, the ideal management for gastrinomas is enucleation and possibly tumor debulking in the setting of liver metastases. The likelihood for metastases, as well as the ability to control symptoms using proton pump inhibitors, makes the need for surgical resection less. Therefore, in patients with high surgical risk such as those beyond Child's A or with portal hypertension, the use of medical therapy alone would be adequate. In patients with a prior liver transplantation, if there is no demonstrated metastatic disease, these lesions can likely be followed until their risk for metastasis begins to increase. This would follow the existing guidelines for those patients with MEN1 who are not recommended for resection until the primary lesion reaches 2 cm in diameter, at which time the risk for metastases begins to increase. The challenge in the setting of resection for gastrinoma lesions is the need to perform a duodenotomy which has a greater likelihood for postoperative leak or fistula in the setting of immunosuppression. Therefore, if the lesion is clearly localized to the pancreas, this traditionally critical step should be excluded.

Management of Nonfunctional pNET

The presence of nonfunctional pNET lesions is of uncertain significance to those patients with cirrhosis or prior liver transplantation. The approach to management of pNET lesions is based primarily upon the size of the tumors, which predicts the likelihood for locoregional metastases. For those tumors which arise sporadically, they are often single with a variable risk for metastases depending on several factors. The ability to predict the presence of metastases in these sporadic tumors is mostly predicated on the size of the lesion, with those <1.0 cm diameter having a risk of metastases of about 4%. In this setting, the existing evidence is clear that resection for nonfunctional pNET is not warranted regardless of the clinical status of the patient. The risk for metastases increases with increasing size of the lesion and is generally warranted for patients with tumors >2.0 cm diameter, given the risk increases to >20% for locoregional metastases. The management of lesions between 1.0 and 2.0 cm is more uncertain with current guidelines from the European Neuroendocrine Tumor Society (ENETS) recommending observation for nonfunctional pNET unless the diameter is >2.0 cm. The management for a patient with underlying cirrhosis should utilize a more cautious approach than that proposed for the general population based upon the long survival associated with these

neuroendocrine tumors. Even in those patients with nonfunctional pNET lesions >2.0 cm diameter, the anticipated benefit with respect to survival is expected to be low. The survival of these patients would be limited to that of the underlying cirrhosis and other medical comorbidities. Although debulking techniques for metastatic disease can be used to improve overall survival for these nonfunctional pNET lesions as with functional tumors, the clinical benefit is even less clear in the setting of cirrhosis. Rather than a surgical approach, medical therapies should be utilized in the cirrhotic population, given the inability to tolerate the significant hepatic parenchymal loss that is often required with metastatic lesions to the liver.

Other Pancreatic Malignancies

Less common pancreatic malignancies may occur regardless of the status of a patient's hepatic status or prior liver transplantation. Less common primary tumors of the pancreas which are not clearly related to cirrhosis or prior liver transplantation are undifferentiated carcinoma, squamous-type carcinoma, colloid carcinoma, medullary carcinoma, pancreatoblastoma, solid pseudopapillary neoplasm, and acinar cell carcinoma. The management of each of these tumors should be similar to that of ductal adenocarcinoma with respect to determining suitability for resection. Unfortunately, many of these rare tumors are often diagnosed at a late stage as well, and therefore not surgical candidates, regardless of liver status. An exception is solid pseudopapillary neoplasms which are most often seen in young females and grow to large size without malignant features oftentimes. If a solid pseudopapillary neoplasm was suspected, the role of surgery could be significant as these tumors tend to compress adjacent structures including the superior mesenteric vein and portal vein which could produce a degree of portal insufficiency independently.

Additionally, pancreatic metastases which occur rarely can occur and represent approximately 5% of all pancreatic malignancies. The most common tumors which develop pancreatic metastases are renal cell carcinoma, sarcoma, and colorectal carcinoma. Experience with surgical resection for pancreatic metastases is limited, and the demonstrated survival benefit has only been through retrospective series. Therefore, in the presence of cirrhosis or prior liver transplantation, the role of pancreatectomy is unlikely to be justified. General recommendations for patients in this setting would be for systemic therapies for primary management of their disease rather than attempt a pancreatectomy with uncertain survival benefit.

Cystic Lesions of the Pancreas

Pancreatic cystic lesions are common findings which have become more prevalent with increasing quality of imaging and utilization in medical care. Among patients with underlying cirrhosis, the presumed incidence is believed to be similar to the baseline population, given the lack of any effect of liver disease on pancreatic cystic

lesions. A greater likelihood of identification of pancreatic cystic lesions occurs in cirrhotic patients due to the use of routine abdominal imaging with similar small slice thickness through the region of the liver which includes the pancreas. Among transplant evaluation patients, the reported incidence of pancreatic cystic lesions is approximately 3%, of which mucinous cystic lesions are thought to represent approximately half. Those patients who then undergo liver transplantation are similarly likely to have an incidental pancreatic cyst identified with an additional 3% identified following transplant for a cumulative incidence of 6% among cirrhotic patients who eventually undergo transplantation.

Of the numerous described types of cystic lesions of the pancreas, most can be broadly classified into either those which are neoplastic or those which are not. Of the nonneoplastic types of pancreatic cysts, the most common are associated with postinflammatory pancreatic pseudocysts following acute pancreatitis and pancreatic trauma. Pancreatic cysts in this setting are not true cysts, rather representing either pancreatic pseudocysts or walled-off necrosis as defined by the Revised Atlanta Classification. Management of these lesions will be discussed later under the Pancreatitis section. Neoplastic cysts can be then further subclassified into those with benign, variable, or malignant characteristic. Of the cysts which have near-uniform benign characteristics are serous cystadenoma, acinar cell cystadenoma, dermoid cyst, cystic hamartoma, and Von Hippel-Lindau associated cystic neoplasms. The management of these cysts does not typically involve resection or serial follow-up imaging. In the setting of identification of these cystic lesions in a cirrhotic or prior liver transplantation patient, there would be no further follow-up or intervention warranted.

Neoplastic mucinous cysts have either variable or malignant characteristics that are more concerning. Cysts with variable natural history include mucinous cystic neoplasms (MCN), intraductal papillary mucinous neoplasms (IPMN), cystic pancreatic neuroendocrine tumors, and solid pseudopapillary tumors. Similarly, cysts with defined malignant behavior are cystic ductal adenocarcinoma and cystic pancreatoblastoma. The management of these lesions will be discussed in the following subsections. In general, the risk for a malignant process must be evaluated in the context of these patients with cirrhosis or prior liver transplantation, as the risk of surgery and potential improved survival benefit compared to that of their baseline underlying medical conditions. More specifically, the therapy must not attempt to cure a disease, which is unlikely to be the cause of death of a patient.

Mucinous Pancreatic Cysts

Of the cystic lesions of the pancreas, approximately 30% are mucinous neoplasms. Within mucinous pancreatic cystic neoplasms are subclassifications, of which intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN) are the most common. IPMN is far more common compared to MCN among cystic lesions, representing 20% of all cystic lesions and 67% of all mucinous cystic lesions. The clinical significance of the mucinous cystic lesions of the pancreas is

their high relative risk for either the development of an invasive carcinoma within the cyst or development of a primary ductal adenocarcinoma in other regions of the gland. Variable reports have suggested the possibility that the carcinoma arising from either IPMN or MCN may behave in a more indolent fashion compared to pancreatic ductal adenocarcinoma. To date, there is molecular evidence which suggests the progression to IPMN or MCN with an associated invasive carcinoma that involves different cellular targets than those of pancreatic ductal adenocarcinoma. The relative rarity of these lesions with invasive carcinoma has made definitive evidence to support a clinical difference compared to ductal adenocarcinoma hard to definitively demonstrate. Furthermore, the lack of clear definitions until the Baltimore definitions reported in 2015 for cystic neoplasms has made characterization difficult, given the prior definitions used which led to confusion of malignancy and invasive terminology in reported series. One additional concerning feature for these neoplasms is the elevated relative risk for development of a concomitant or distinct pancreatic ductal adenocarcinoma. The risk for these concomitant ductal adenocarcinoma lesions is believed to be approximately 4% for a synchronous, and up to 11% when followed serially. Typical findings for these concomitant ductal adenocarcinomas are those of primary ductal adenocarcinomas such as progressive diabetes mellitus, jaundice, or elevated serum CA19-9.

Intraductal papillary mucinous neoplasms arise from ductal endothelial cells which can be located within either the: (1) main pancreatic duct (main duct type), (2) branches of the main pancreatic duct (branch duct type), or a combination of the two (mixed type). Papillary projections within the duct are seen, as these tumors grow within the duct unless there is an associated invasive component. The pattern of ductal involvement is one of the most predictive factors for determining risk for development of an invasive carcinoma, with the main duct type having a 40–50% likelihood at the time of resection. In comparison, the rate of invasive carcinoma in branch duct is 17%. Mixed-type tumors appear to have a similar risk for the development of an invasive carcinoma as the main duct type (about 45%), suggesting a possible biological mechanism of progression of a branch duct neoplasm to involvement of the main duct as the etiology of this mixed type. Histological subtypes of IPMN are also of clinical interest and consist of either gastric, intestinal, pancreatobiliary, or oncocytic. Of these subtypes, gastric is most commonly associated with the lowest risk for development of an invasive carcinoma and also to be of the branch duct type. In contrast, the intestinal and pancreatobiliary types are more often seen with progression to development of an invasive carcinoma and of the main duct type. The type of carcinoma (tubular vs. colloid) has also been shown to correlate with both the ductal involvement pattern and the histological subtype, which may account for the previously discussed potential difference in survival for these cancers.

Classification criteria for IPMN lesions as either main duct, branch duct, or mixed is based upon imaging characteristics. Imaging findings supportive of a main duct type are segmental or diffuse dilation of the main pancreatic duct (>9 mm diameter), whereas side branch appears as a cyst with communication to a nondilated main pancreatic duct. Findings of both ductal dilation and a side-branch cystic

lesion communicating with the main duct suggest a mixed type. Well-accepted criteria for standard patients have been adopted from two consensus conferences (Sendai and Fukouka). The most recent updated guidelines recommend resection of all main duct and mixed-type IPMN lesions due to the >50% risk for an invasive or malignant component.

In contrast, side-branch lesions are generally observed serially due to a limited yearly risk for development of malignancy (2–3% per year). Goals of monitoring are to identify features predictive of an underlying malignancy categorized as either high-risk stigmata (symptoms associated to the cyst, enhancing solid component, main duct >10 mm) or development of worrisome features (acute pancreatitis related to the cyst, size >3 cm, thickened/enhancing walls, main duct >5 mm, mural nodule, or change in the main duct with distal atrophy). If the high-risk stigmata develop, recommendations for resection are appropriate given the likely associated underlying malignancy. However, if only worrisome features develop while under surveillance, recommendations are for endoscopic ultrasound to better delineate noninvasive imaging findings from false-positive findings that are characteristic of IPMN lesions. Endoscopic ultrasound findings of a mural nodule, main duct involvement, or fine needle aspiration cytology with suspicious (high-grade dysplasia) or malignant cells warrant resection, given a similarly high relative risk for underlying malignancy. In the absence of these endoscopic findings or worrisome features, continued surveillance at intervals dependent on the size of the lesion with CT or MRI and endoscopic ultrasound can be continued, given a low relative risk of a malignancy.

The role of liver cirrhosis in the decision to proceed with pancreatic resection is currently uncertain. The guidelines which have been developed only recently and have not been demonstrated to lead to improved outcomes for patients with pancreatic mucinous cysts cannot be directly applied to the high-risk cirrhosis population. Predictive tools to determine the likelihood of an underlying malignancy in the setting of a mucinous cyst should be similarly applied to cirrhosis patients to allow for the most accurate assessment of risk for the patient. In the absence of clear markers for malignancy, the role of prophylactic pancreatic surgery must be balanced with the risk for decreased overall survival from the risks for major pancreatic surgery. The development of improved predictive methods may aid in this population. For example, the recent developments of combined molecular and pathological fluid analysis may eventually show an improved predictive ability for the risk of malignancy than prior evaluations limited by radiographic and cytology results alone.

Limited pancreatic resections have been proposed for high-risk medical patients to limit their overall surgical risk; however, these series have failed to definitively demonstrate a clear benefit. Of particular interest is that use of enucleation is associated with a higher risk for pancreatic fistula compared to traditional resection techniques. As mentioned earlier in the chapter, selection criteria for well-compensated Child's A cirrhosis patients without portal hypertension or other high-risk associated diagnoses from cirrhosis are likely at a relatively similar risk profile to the baseline population and can be considered for a traditional resection in the

setting of a high-risk mucinous cystic lesion, such as a main duct IPMN or MCN. However, in those patients with Child's B cirrhosis, portal hypertension, or other high-risk diagnoses, these patients are more likely to succumb to complications of surgery than benefit from the prophylactic surgery. Even in the setting of an associated pancreatic malignancy, the overall survival for these high-risk patients is unlikely to be increased by pancreatectomy. Thus, the role of pancreatic resection in cirrhosis patients must be clearly defined for the patient and more cautiously applied to this subpopulation than those with traditional ductal adenocarcinoma.

In evaluating the impact of chronic immunosuppression from liver transplantation, there has not been evidence suggesting that mucinous cystic lesions have a higher risk for progression or development of an invasive or malignant component. In a retrospective study of liver transplantation patients, Lennon et al. demonstrated no difference in the development of high risk or worrisome features compared to a control population (17.4% and 16.4%, respectively). Further, in this series, the only factor associated with development of progression of the lesion was early age of diagnosis which is similar to that seen in studies on normal patient populations. Of the patients in this series who developed high-risk or worrisome features, none of them underwent resection and were alive at a median follow-up of 32.9 months. In a similar series by Ngamruengphong et al. four patients were found either initially or on follow-up to have high-risk or worrisome features after liver transplant. In this series, a single patient underwent resection with no finding of malignancy. Of the three patients not undergoing resection, pancreatic malignancy was not found as a cause of death at the end of follow-up. These small series emphasize the recommendation that resection in liver transplant patients may have limited potential benefit. Without high-risk or worrisome features and an anticipated prolonged survival from other medical comorbidities, continued observation is warranted rather than upfront resection.

Chronic Pancreatitis

The overall incidence of chronic pancreatitis in the setting of cirrhosis has been reported to be as low as 3.8%. This reflects the different underlying pathophysiological mechanisms responsible for chronic pancreatitis than that of the cirrhosis. In this rare setting of concomitant chronic pancreatitis, the role of surgical intervention remains palliative as it is in the noncirrhotic population. Other therapies in the management of chronic pancreatitis are aimed at either minimizing the progression of the chronic pancreatitis or ameliorating the systemic effects of the disease. The impact of combined cirrhosis and chronic pancreatitis is yet to be studied due to the overall rarity of the disease. Furthermore, there is not a well-defined population of patients who have completed liver transplantation with chronic pancreatitis requiring surgical therapy to make strong evidence-based recommendations at the present time.

Medical Therapies for Chronic Pancreatitis

As the primary and most important management principle for chronic pancreatitis, medical management of the disease has multiple approaches. First, management of these patients should aim to identify the underlying cause of the chronic pancreatitis before proceeding with interventional therapies. As alcohol is the most common etiology for chronic pancreatitis in the United States, a thorough history for substance abuse is necessary. Lifestyle modifications play a critical role in decreasing the progression and control of pain symptoms for these patients. More importantly, any patient with concurrent underlying cirrhosis or prior liver transplant would be strongly encouraged to avoid any use of alcohol, tobacco, or illicit substance which could negatively impact both organ systems. Abstinence from alcohol alone has been demonstrated to decrease overall pain measures in up 50% of patients, although this is oftentimes not the only pain therapy required.

Other medical therapies which are important in these patients are the diagnosis and control of exocrine pancreatic insufficiency. As has been demonstrated in post-pancreatoduodenectomy patients, the development of exocrine pancreatic insufficiency can be independently responsible for progression of hepatic insufficiency. Correction of the insufficiency resolves around adequate dosing of pancreatic enzyme replacement therapy, with a typical dosing guide of 25–75,000 units per meal and 10–25,000 units per snack as an initial therapy. Monitoring for weight stabilization, resolution of steatorrhea, or normalization of fecal elastase are all appropriate measures suggested to demonstrate adequacy of treatment. In those patients who have developed hepatic insufficiency due to exocrine pancreatic insufficiency, treatment with enzyme replacement therapy has been shown to lead to significant improvement and prevention of progression of liver disease. Therefore, in the cirrhotic and prior liver transplant population who are found to have chronic pancreatitis, identification and prompt intervention are important treatment goals.

Pain management in those patients with chronic pancreatitis remains the most important aspect of their care. As is the case of patients without cirrhosis, this population should be managed in a step-up approach to pain medications. Nonnarcotic agents are initially started for control and titrated up, and eventually the addition of narcotic agents as needed for reasonable pain control. In the setting of frequent bleeding events, the use of nonsteroidal agents could be associated with increased risk for bleeding, and therefore these agents should be avoided. A potentially beneficial strategy in the pain management of these patients is the use of a differential nerve blockade and subsequent celiac plexus nerve blockade, if visceral pain is identified. Furthermore, if central pain is observed, the use of neuromodulator agents can be used to better control the central pain component of the disease.

Interventional Therapies for Chronic Pancreatitis

Of the interventional therapies available for chronic pancreatitis, the use of endoscopic therapies has potentially a greater role in the setting of cirrhosis, particularly those with Child's B or other high-risk factors. Although the durability for endoscopic therapies to either dilate an isolated obstructive lesion or perform extracorporeal lithotripsy is limited in series evaluating normal patients with chronic pancreatitis, those patients with cirrhosis should be directed through an endoscopic approach, except in the setting of a Child's A patient without other high-risk features including portal hypertension. In this selected group of patients, the use of well-selected surgical therapies may be appropriate. Surgical interventions for these patients should be chosen with the intent to avoid large pancreatectomy procedures with prolonged anesthesia requirements to limit unnecessary surgical complications and potential hepatic decompensation.

Procedures which may be appropriate and performed with limited morbidity and mortality in this population consist predominately of drainage procedures. In general, the use of drainage cystjejunostomy for isolated symptomatic pancreatic pseudocysts or lateral pancreatojejunostomy for well-defined main pancreatic duct proximal obstructive lesions can likely be performed with a low anticipated surgical complication rate. In the setting of portal hypertension, however, decompressive pancreatojejunostomy is contraindicated due to the development of collateral veins and a significant risk for bleeding in the Roux limb. Depending upon the medical status of a patient, the palliation achieved with these procedures can be significant and durable in relation to the anticipated overall survival of the patient. In general, the use of large resective procedures such as pancreatoduodenectomy should be avoided, given the elevated risk for complications in this population, unless there is an inability to differentiate chronic pancreatitis from pancreatic ductal adenocarcinoma.

Conclusions

Pancreatic disease is a frequent finding in patients with cirrhosis and prior liver transplantation. A variety of challenges facing surgeons in selecting appropriate therapies for these patients require extrapolation of evidence predominately from noncirrhotic and nonimmunocompromised patients. As is the recommendation for the management of pancreatic surgery across the globe, this patient population should be centralized to centers with expertise in both the management of pancreatic surgical disease and liver failure or transplantation. In conclusion, we believe that reasonable outcomes can be expected for pancreas-specific disease in the setting of cirrhosis or prior liver transplantation in high-volume centers when appropriately selected for either surgery or other therapies.

Recommended References

1. Busquets J, Pelaez N, Gil M, et al. Is pancreaticoduodenectomy a safe procedure in the cirrhotic patient? Cir Esp. 2016;94:385–91.
2. Darstein F, Konig C, Hoppe-Lotichius M, et al. Impact of pancreatic comorbidities in patients with end-stage liver disease on outcome after liver transplantation. Eur J Intern Med. 2014;25:281–5.
3. El Nakeeb A, Sultan AM, Salah T, et al. Impact of cirrhosis on surgical outcome after pancreaticoduodenectomy. World J Gastroenterol. 2013;19:7129–37.
4. Fuks D, Sabbagh C, Yzet T, Delcenserie R, Chatelain D, Regimbeau JM. Cirrhosis should not be considered as an absolute contraindication for pancreatoduodenectomy. Hepatogastroenterology. 2012;59:881–3.
5. Girometti R, Intini SG, Cereser L, et al. Incidental pancreatic cysts: a frequent finding in liver-transplanted patients as assessed by 3D T2-weighted turbo spin echo magnetic resonance cholangiopancreatography. JOP. 2009;10:507–14.
6. Lennon AM, Victor D, Zaheer A, et al. Liver transplant patients have a risk of progression similar to that of sporadic patients with branch duct intraductal papillary mucinous neoplasms. Liver Transpl. 2014;20:1462–7.
7. Macinga P, Kautznerova D, Fronek J, Trunecka P, Spicak J, Hucl T. Pancreatic cystic lesions in liver transplant recipients: prevalence and outcome. Pancreatology. 2016;3:S105.
8. Mejia J, Sucandy I, Steel J, et al. Indications and outcomes of pancreatic surgery after liver transplantation. Clin Transplant. 2014;28:330–6.
9. Ngamruengphong S, Seeger KM, McCrone LM, et al. Prevalence and outcomes of cystic lesion of the pancreas in immunosuppressed patients with solid organ transplantation. Dig Liver Dis. 2015;47:417–22.
10. Regimbeau JM, Rebibo L, Dokmak S, et al. The short- and long-term outcomes of pancreaticoduodenectomy for cancer in Child A patients are acceptable: a patient-control study from the Surgical French Association report for pancreatic surgery. J Surg Oncol. 2015;111:776–83.
11. Stauffer JA, Steers JL, Bonatti H, et al. Liver transplantation and pancreatic resection: a single-center experience and a review of the literature. Liver Transpl. 2009;15:1728–37.