Advances in Surgical Management of Pancreatic Diseases

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KEYWORDS

• Surgery • Pancreas • Minimally invasive • Pancreatic cancer • Chronic pancreatitis • Pancreatic fistula • Postoperative Morbidity Index • Pancreatic cystic neoplasm

KEY POINTS

- Preoperative risk stratification in pancreatic surgery allows rational selection of patients amenable for surgical therapy and prediction of postoperative morbidity.
- The Postoperative Morbidity Index is a novel tool that allows utility-based quantification of postoperative morbidity at the cohort level.
- Although minimally invasive pancreatectomy has been selectively applied at centers with expertise, there is insufficient evidence for its long-term equivalency or superiority compared with conventional open surgery.
- Borderline resectable pancreatic adenocarcinoma involves the regional mesenteric vasculature to a limited extent; resection for such tumors, although technically possible, is likely to result in positive surgical margins without preoperative therapy.
- The traditional paradigm of open pancreatic necrosectomy in infected pancreatic necrosis has been replaced by a surgical step-up approach, encompassing initial percutaneous drainage followed by minimally invasive approaches to necrosectomy.

INTRODUCTION

The surgical management of pancreatic diseases is rapidly evolving, encompassing advances in evidence-driven selection of patients amenable for surgical therapy, preoperative risk stratification, refinements in the technical conduct of pancreatic operations, and quantification of postoperative morbidity. These advances have resulted in dramatic reductions in mortality following pancreatic surgery over the last few

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decades, particularly at high-volume pancreatic centers.[1] Diagnosis, evaluation, and operative treatment of such patients are increasingly undertaken in a multidisciplinary format. Surgical decision making is complex and challenging, and requires an intimate understanding of disease pathobiology, host physiology, technical considerations, and evolving trends in the field. This article focuses on select key developments in the surgical management and perioperative principles associated with contemporary pancreatic surgery.

PREOPERATIVE RISK STRATIFICATION IN PANCREATIC SURGERY

Preoperative risk stratification has emerged as a critical decision-support tool in the pancreatic surgeon's skill set to estimate patients' risks of complications following pancreatectomy. This process is essential for patient-centered care, shared decision making with patients, and true informed consent. The ability to provide personalized risk estimates for patients undergoing pancreatectomy, or any other operation, has been revolutionized with the introduction of the American College of Surgeons (ACS) National Surgical Quality Improvement Project (NSQIP), which collects high-quality, standardized clinical data on preoperative risk factors and 22 rigorously defined postoperative complications from more than 500 hospitals in the United States.[2,3] Using this platform, a universal and procedure-specific risk calculator encompasses several preoperatively known variables (eg, age group, sex, steroid use, diabetes, smoking history, body mass index) to estimate a composite and complication-specific risk profile (http://www.riskcalculator.facs.org).[4]

This multi-institutional ACS-NSQIP data set has been used by several groups to develop risk prediction models capable of predicting postoperative morbidity and mortality following pancreaticoduodenectomy (PD)[5] and distal pancreatectomy (DP)[6]; the espoused benefits of these simple risk estimation systems include appropriate patient counseling and preoperative expectation management, allowing comparison of risk-adjusted outcomes between different institutions, and optimizing patient physiology before major pancreatectomy. However, these models are subject to limitations inherent in the ACS-NSQIP data set, including the inability to (1) determine pancreatectomy-specific complications (eg, delayed gastric emptying [DGE], postoperative pancreatic fistula [POPF], biliary leak/fistula), (2) ascertain complications beyond the 30-day accrual period, or (3) account for hospital-specific variations in pancreatic surgery volume and the corresponding impact on postoperative complications.[7]

Accordingly, a recently proposed preoperative risk prediction model for PD has drawn on multinational data from 4 high-volume European pancreatic centers. Aptly named the Preoperative Pancreatic Resection (PREPARE) score, this model effectively discriminated patients into low-risk, intermediate-risk, or high-risk for major complications (ie, Clavien-Dindo complication grades III and IV[8]) based on 5 physiologic variables (heart rate, systolic blood pressure, hemoglobin and albumin levels, American Society of Anesthesiologists [ASA] score) and 3 operative variables (whether surgery was elective or not, type of surgical procedure, and whether the origin of disease was pancreatic or not). Notably, this score accounted for clinically relevant POPF (CR-POPF), was not restricted to 30-day complication data, and prospectively validated the derived PREPARE score in 429 patients across the participating institutions.[9]

Recognizing the inability of the universal ACS-NSQIP registry to account for pancreatectomy-specific variables and effectively predict pancreatectomy-specific morbidity, the ACS has championed the initiation of a hepatopancreatobiliary (HPB)-centered module to better capture key outcomes in this population; the so-called Pancreatectomy Demonstration Project (PDP).[10] The ACS-NSQIP PDP

encompasses intraoperative variables such as pancreatic duct size, gland texture, need for vascular resection, method of pancreatic (eg, pancreaticojejunostomy vs pancreaticogastrostomy) or intestinal (eg, gastrojejunostomy vs duodenojejunostomy) reconstruction, use of intraoperative drain placement (discussed later), and use of minimally invasive approaches, while also accruing pancreatectomy-specific complications such as DGE, POPF, and need for postoperative percutaneous drainage.[11–14] This initiative promises to improve large-scale prediction of pancreatectomy-specific complications, provide risk-adjusted registries with HPB-specific data, facilitate multi-institutional clinical trials, and augment the quality improvement initiatives already underway in pancreatic surgery. These and other currently used risk assessment and prognostic modeling systems in pancreatic surgery are comprehensively reviewed elsewhere.[15]

QUANTIFYING THE MORBIDITY OF POSTPANCREATECTOMY COMPLICATIONS

Beyond the preoperative prediction of postoperative morbidity, pancreatic surgeons can now provide a quantitative analysis of the impact of those complications on patients. Such a quantitative instrument could serve as a benchmark for surgical quality and standardize research analysis of pancreatic resections across institutions. The Postoperative Morbidity Index (PMI) is the first such effort in quantifying postoperative morbidity at the cohort level.[16] The PMI combines 2 highly validated, publicly available systems: (1) the Modified Accordion Classification System,[17] in which numerical severity weights were stringently established by expert opinion for each of 6 complication severity grades; and (2) the ACS-NSQIP, which provides a uniform method for skilled data experts to identify 22 rigorously defined perioperative complications. Each ACS-NSQIP complication is assigned a utility-based Accordion severity weight ranging from 0.110 (grade 1/mild) to 1.00 (grade 6/death). PMI equals the sum of complication severity weights (total burden) divided by total number of patients; it can range along the utility scale from 0 (ie, no complication in any patient) to 1.00 (ie, all patients died of complications). It provides a population-level measure of the morbidity of a procedure irrespective of whether a patient experienced a complication in the series. As such, higher PMIs denote populations with greater average morbidity.[18–20]

The utility of the PMI in the assessment of complications was first shown for 5 common abdominal operations performed at a single institution.[16] Subsequently, using a cohort derived from 9 high-volume pancreatic centers, the PMI of the 3 most common pancreatic resections (PD,[20] DP,[18] and total pancreatectomy [TP])[19] have been established. The PMI improves on the imprecision of nonspecific or qualitative complication grading (eg, Dindo-Clavien classification), and reflects not only the occurrence of complications but also their impact on patients.[19] Perhaps most importantly, the PMI establishes that complications of one type (eg, pulmonary embolism) may have varying impacts across the severity spectrum in different patients.

However, a notable limitation of these iterations of the PMI model is that it is not yet risk-adjusted; it is unable to account for changes in patients' physiologic makeup or processes of postpancreatectomy care over time.[19] Moreover, disparities in patient risk between surgeons and institutions reinforce the need for comprehensive risk-adjusted modeling when assessing the impact of procedure-specific complications. Accordingly, efforts are underway to refine the PMI metric in order to achieve such risk adjustment.

PANCREATIC FISTULA PREDICTION AND MITIGATION STRATEGIES

POPF, which results from pancreatointestinal anastomotic disruption/leakage following PD, is a dominant contributor to post-PD morbidity and is often lethal.[21]

Although overall outcomes following PD have improved dramatically over the years, POPF rates remain high (up to 33%).[22] Although several studies have identified risk factors that reproducibly predict POPF, comprehensive risk modeling has only recently been made possible with the advent of a universal classification scheme for POPF, proposed by the International Study Group of Pancreatic Fistula in 2005.[23] This classification establishes definitions that delineate between purely biochemical POPFs (grade A) and those deemed clinically relevant (grades B and C). This framework has allowed the identification of distinct risk factors (ie, gland texture, pathology, duct diameter, and intraoperative blood loss) that have been incorporated into a validated metric for the prediction of CR-POPF following PD, known as the Fistula Risk Score (FRS).[24–26] This novel decision-support tool offers a weighted approach that assigns quantitative values to the presence of the aforementioned risk factors (**Table 1**).

Beyond the prediction of CR-POPF per se, strategies to mitigate the incidence and impact of CR-POPF have been proposed, including anastomotic stents, prophylactic somatostatin analogue therapy, autologous tissue patches, and tissue sealants.[27] Intraoperative juxtapancreatic drain placement is another common management strategy. Despite claims that drains are unnecessary because of their association with higher rates of POPF,[28,29] a recent randomized, controlled trial indicated that routine elimination of drain use in PD increases the severity and frequency of overall complications, resulting in an unacceptably high mortality.[30] Drawing on this same randomized patient cohort, McMillan and colleagues[27] used the FRS as a risk assessment tool to determine the effect of intraoperative drain placement on the incidence of CR-POPF. Patients with negligible/low FRS risk had higher rates of CR-POPF when drains were used (14.8 vs 4.0%). In contrast, there were significantly fewer CR-POPFs (12.2 vs 29.5%) when drains were used with moderate/high FRS patients; these particular patients who had a CR-POPF also had reduced 90-day mortality when a drain was used. These data suggest that assessment of patient risk at the time of operative reconstruction may allow a more selective strategy of intraoperative

Table 1
FRS for the prediction of CR-POPF after pancreaticoduodenectomy

Risk Factor	Parameter	Points
Gland Texture	Firm	0
	Soft	2
Pathology	Pancreatic adenocarcinoma or pancreatitis	0
	Ampullary, duodenal, cystic, islet cell, and so forth	1
Pancreatic Duct Diameter (mm)	≥5	0
	4	1
	3	2
	2	3
	≤1	4
Intraoperative Blood Loss (mL)	≤400	0
	401–700	1
	701–1000	2
	>1000	3
		Total 0–10 points

From Callery MP, Pratt WB, Kent TS, et al. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. J Am Coll Surg 2013;216(1):6; with permission.

drain use, particularly in patients with negligible/low risk of CR-POPF development. Adoption of this strategy, along with targeted, early drain removal, has decreased the CR-POPF rate from 12% to 4% at our institution (101 patients over the last year, Vollmer et al, unpublished data, 2015). Moreover, beyond drain management, the FRS has been useful in understanding the impact of other operative and perioperative techniques used during pancreatectomy.[31,32]

EXPANDING INDICATIONS FOR RESECTION OF PANCREATIC CYSTIC NEOPLASMS

Pancreatic cystic neoplasms (PCN), including main-duct (MD) or branch-duct (BD) intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN), are increasingly detected, owing in part to liberal application of, and technological improvements in, cross-sectional imaging techniques. IPMNs and MCNs span a spectrum of neoplastic transformation, and recommendations for resection or surveillance of these lesions are typically based on the preoperative risk stratification proposed in consensus guidelines from the International Association of Pancreatology (IAP) in 2006 (Sendai criteria),[33] and updated in 2012 (Fukuoka criteria).[34] Per the Fukuoka guidelines, resection is recommended in all surgically fit patients with MD-IPMN and MCN. In MD-IPMN, if the resection margin is positive for high-grade dysplasia, additional resection should be attempted in order to obtain at least moderate-grade dysplasia. In MCN less than 4 cm without mural nodules, minimally invasive pancreatectomy (discussed later) or parenchyma-sparing resections and DP with splenic preservation could be considered.[34]

For management of BD-IPMN, the 2012 guidelines also outlined worrisome features and high-risk stigmata; clinicoradiographic characteristics that add nuance to surgical decision making beyond consideration of cyst size alone. For instance, a BD-IPMN greater than 3 cm without high-risk stigmata (ie, obstructive jaundice from a pancreatic head lesion, enhancing solid component within cyst, or main pancreatic duct >10 mm in size) can potentially be observed without immediate resection. If worrisome features (ie, pancreatitis, thickened/enhancing cyst walls, MD 5–9 mm, nonenhancing mural nodule, or abrupt change in pancreatic duct caliber with distal pancreatic atrophy) are present, BD-IPMNs should be evaluated with endoscopic ultrasonography (EUS). Findings of positive cytology, definite mural nodule, and/or suspected MD involvement on EUS should drive the decision to resect. Lack of these features on EUS instead warrants close surveillance with MRI and EUS every 3 to 6 months.[34]

It deserves mention that these criteria are not intended to supplant clinical judgment or patient preference. For instance, younger (<65 years) fit patients with cyst size greater than 2 cm and concerning imaging/pathologic features, who may not otherwise fit resection criteria, may be considered for surgery because of the cumulative risk of malignancy over their anticipated lifespan. In addition, recent evidence indicates that caution should be exercised when managing BD-IPMNs greater than 3 cm expectantly. In a single-institution retrospective review of 543 patients with BD-IPMN, Sahora and colleagues[35] showed that although the risk of high-grade dysplasia in nonworrisome lesions less than 3 cm was only 6.5%, the risk increased to nearly 10% when the size threshold was increased to greater than 3 cm, with 1 of those cases representing invasive carcinoma. The investigators concluded that although expectant management of BD-IPMN using the original Sendai criteria is likely safe, larger lesions may harbor incipient or frank malignancy, even in the absence of worrisome features. Another robust recent series from our institution confirms the 3-cm size cutoff as highly relevant.[36] Ultimately, a personalized approach to surgical

resection of PCNs must entertain not only the risk of malignancy, presence of symptoms, and cyst size but also patient preferences; as such, balancing the risk of perioperative morbidity with the burden of prolonged surveillance is of utmost importance. Much remains to be achieved in establishing better, more precise prediction of the biological threat of these lesions. At select institutions, the management of PCNs occurs in a multidisciplinary group approach (so-called cyst clinic), similar to the manner in which pancreatic cancer is managed.

BORDERLINE RESECTABLE PANCREATIC DUCTAL ADENOCARCINOMA (PDAC)

There is growing recognition of borderline resectable PDAC as a distinct clinical entity, best conceptualized as tumors that involve the regional mesenteric vasculature (ie, superior mesenteric artery [SMA], common hepatic artery [CHA], superior mesenteric vein [SMV], and portal vein [PV]) to a limited extent; resection for such tumors, although technically possible, is likely to result in positive surgical margins (a highly negative prognosticator) without preoperative chemotherapy with or without radiotherapy (C ± RT).[37] Pioneering studies by the group from MD Anderson Cancer Center,[38] consensus guidelines from The Americas Hepatopancreatobiliary Association/Society for Surgery of the Alimentary Tract/Society of Surgical Oncology/National Comprehensive Care Network,[39,40] and more recently clinical trial protocols from the Alliance for Clinical Trials in Oncology Intergroup A021101 trial[37] have resulted in a contemporary definition for borderline resectable PDAC as localized tumors with 1 or more of the following: (1) interface between primary tumor and SMV-PV measuring greater than or equal to 180° of the circumference of the vein wall; (2) short-segment occlusion of the SMV-PV with normal vein above and below the level of obstruction that is amenable to resection and venous reconstruction; (3) short-segment interface (of any degree) between tumor and CHA with normal artery proximal and distal to the interface that is amenable to resection and arterial reconstruction; (4) an interface between the tumor and SMA/celiac trunk measuring less than 180° of the circumference of the artery wall.[37] Recently, an international consensus statement on this entity has also been derived.[41]

Surgical considerations for this disease entity have also evolved with growing understanding of its natural history; key elements of surgical decision making in this regard deserve mention. First, although margin-negative resection of the primary tumor (and its draining nodal basin) is critical, it is increasingly difficult to achieve de novo with increasing involvement of the major vascular structures. In this regard, rational application of preoperative C ± RT may select for patients with favorable tumor biology, and host physiology, who are most likely to benefit from aggressive local resection; by the same token, patients with rapid progression are spared the morbidity of major pancreatectomy. Second, in the cohort of carefully selected patients who complete preoperative therapy without progression (or perhaps tumor regression; so-called downstaging), aggressive surgical extirpation, with or without vascular resection, seems to be of benefit. Emerging data indicate that resection of the SMV-PV and CHA at the time of pancreatectomy is associated with acceptable perioperative morbidity and mortality[42]; however, SMA resection and/or reconstruction seems futile.[43,44] In addition, lack of sensitivity of radiographic staging (ie, Response Evaluation Criteria in Solid Tumors [RECIST]) seems to undercut the true efficacy of neoadjuvant C ± RT.[45] A recent single-institution study revealed that only 12% of 129 patients with borderline resectable PDAC had RECIST partial response, whereas only 1 patient (0.8%) was downstaged to resectable status, following neoadjuvant chemoradiotherapy. Despite these unfavorable radiographic indicators, R0 resection was possible in 66% of patients.[46]

In addition to standardization of radiographic and surgical criteria for resection, a multidisciplinary approach is critical to accurately determine the impact of preoperative therapy on borderline resectable PDAC and outcomes thereof; mechanisms to standardize these components (eg, surgical technique, chemotherapy regimens, radiotherapy field design) have been incorporated into the Intergroup A021101 trial, results from which are eagerly awaited. Notwithstanding, at this time there is no high-level evidence to support that neoadjuvant therapy for pancreatic cancer offers a survival benefit for either resectable or borderline resectable disease. This topic will continue to be a fertile, and necessary, area for future investigation and will mandate scrupulous study designs.

MINIMALLY INVASIVE PANCREATIC RESECTION

The advent of minimally invasive approaches (ie, laparoscopic or robotic-assisted laparoscopic) has revolutionized the surgical treatment of many benign and malignant conditions. Although initially sluggish, minimally invasive pancreatectomy (MIP) is increasingly gaining acceptance, particularly at specialized high-volume pancreatic centers. Although skeptics of MIP question the ability of these approaches to maintain oncologic integrity, proponents cite potential advantages associated with laparoscopy: (1) decreased inflammatory responses with less perioperative immunosuppression, which may translate into potential oncologic benefit[47]; (2) improved visualization (particularly with a robotic-assisted approach) and magnified view allowing more precise dissection; and (3) advanced degrees of freedom of technical maneuvers.[48] Controversy persists regarding efficacy of MIP versus open pancreatectomy, as well as which MIP platform is optimal.

The use of minimally invasive DP is increasing in surgical practice, with recent literature showing several benefits compared with its open counterpart.[48] Although adequately powered randomized trials comparing minimally invasive versus open DP are not currently available, several large retrospective comparative series have shown the feasibility, safety, and favorable outcomes associated with this approach.[49–51] Venkat and colleagues[49] performed a systematic review of 18 such studies, including 1814 patients (43% laparoscopic, 57% open). Although long-term oncologic outcomes could not be assessed, the laparoscopic approach was associated with equivalent rates of margin positivity, as well as decreased intraoperative blood loss, overall complications, surgical site infections, and duration of postoperative stay compared with an open approach. In a population-based cohort of 8957 patients from the National Inpatient Sample undergoing DP, just 382 (4.3%) underwent minimally invasive DP, indicating its relative lack of use thus far. On multivariable analysis, minimally invasive DP was associated with fewer overall complications and postoperative infections, as well as shorter duration of stay; no differences in rates of in-hospital mortality, concomitant splenectomy, or total costs were observed.[51] A recent single-institution experience suggested that robotic assistance for laparoscopic DP decreases the risk of conversion to an open resection, while maintaining equivalent outcomes compared with a purely laparoscopic approach; the investigators concluded that robotic assistance may broaden indications for minimally invasive DP, particularly for cancer.[50]

In contrast with minimally invasive DP, minimally invasive PD (MIPD) continues to lack widespread acceptance because long-term oncologic outcomes comparing MIPD with the open approach are lacking.[48] Although short-term outcomes (ie, duration of stay, blood loss, overall and pancreas-specific complications) seemed comparable with those achieved with the open approach when highly skilled specialists applied MIPD techniques (**Table 2**),[52,53,56] the intentional patient selection bias

Table 2
Selected series of minimally invasive PD reporting outcomes for at least 50 patients

Publication, Year	Patients (n)	Approach	Operative Time (min)	EBL (mL)	CR-POPF	DGE	LOS (d)	Mortality (%)
Palanivelu et al,[52] 2009	75	Lap	357	74	7	NR	8	1.3
Kendrick et al,[53] 2010	62	Lap	368	240	18	15	7	1.6
Giulianotti et al,[54] 2010	60	Robotic	421	394	21	5	22	3
Kim et al,[55] 2012	100	Lap	487	NR	6	2	20	1
Asbun et al,[56] 2012	53	Lap	541	195	10	11	8	6
Zeh et al,[57] 2012	50	Robotic	568	350	20	20	10	2
Zureikat et al,[58] 2013	132	Robotic	527	300	7	NR	10	1.5

Abbreviations: EBL, median estimated blood loss; Lap, laparoscopic; LOS, length of stay.

inherent in these early experiences limit assessment of equivalency or superiority of MIPD. Moreover, in addition to the technical complexity associated with MIPD,[48] there is no definitive evidence indicating that earlier postoperative recovery following MIPD mitigates the major morbidity of the operation or allows more timely initiation of adjuvant therapy. Based on existing data, it is therefore uncertain whether MIPD offers a substantial advantage compared with open PD beyond possibly restoring the functional capacity of patients to their premorbid states more rapidly. Moreover, significant concerns remain about the ability to generalize from these minimally invasive approaches given the lengthy learning curves necessary for proficiency (ie, as many as 250 cases).[58] Longitudinal follow-up and carefully controlled studies are needed to ascertain whether MIPD will remain a niche practice or garner broader adoption.

MINIMALLY INVASIVE PARADIGM FOR SURGICAL MANAGEMENT OF INFECTED PANCREATIC NECROSIS

Although most (~80%) patients with acute pancreatitis experience resolution of symptoms, the remainder progress to a more complicated course characterized by necrotizing pancreatitis with or without associated organ failure.[59] Approximately 30% of patients with necrotizing pancreatitis develop infected necrosis,[60] with in-hospital mortalities approaching 40% if organ failure ensues.[61] In general, although sterile asymptomatic pancreatic necrosis can be treated with supportive management, infected pancreatic necrosis remains a near-absolute indication for invasive intervention. Barring impending intra-abdominal sepsis and hemodynamic collapse, pancreatic necrosectomy in clinically stable patients, performed via open or minimally invasive approaches, should be postponed until the necrosis appears radiographically walled off; this typically correlates with an observation period of 4 to 6 weeks.[62]

The traditional paradigm of mandatory open pancreatic necrosectomy in infected necrosis has been replaced by a surgical step-up approach, championed in the randomized PANTER (PAncreatitis, Necrosectomy versus sTEp up appRoach) trial conducted by the Dutch Pancreatitis Study Group.[63] In this study, 88 patients were randomly allocated to either maximal necrosectomy via laparotomy (n = 45) or percutaneous catheter drainage (PCD) followed, if necessary, by video-assisted retroperitoneal debridement (VARD; n = 43). Both procedures were followed by continuous peritoneal lavage. The composite end point of major complications and/or death was observed less frequently in the step-up compared with the open necrosectomy cohort (40% vs 69%; $P = .006$).[63] In light of this groundbreaking study, PCD via a retroperitoneal and transperitoneal route is now considered the initial step in the contemporary treatment of infected necrosis per IAP/American Pancreatic Association consensus guidelines; drainage of purulent material under pressure mitigates ongoing sepsis and may postpone or even obviate necrosectomy (in up to 50% of patients). In some cases, drainage alone (without additive interventions) may suffice.[64]

If PCD fails, an array of minimally invasive options for necrosectomy has emerged, with growing evidence supporting their superiority to open necrosectomy with respect to procedural complications and resource use. These options include sinus tract necrosectomy, VARD, retroperitoneoscopic necrosectomy, endoscopic transluminal drainage and necrosectomy, and laparoscopic transgastric necrosectomy.[65] VARD, the best studied of these options, involves removal of loosely adherent and visible necrosis under videoscopic guidance from a left-sided retroperitoneal approach, wide catheter drainage, and postoperative lavage until the effluent is clear.[66] In a multicenter prospective cohort study by Horvath and colleagues,[67] VARD was technically feasible in 60% of patients requiring necrosectomy (ie, failing PCD alone), was

associated with a favorable complication profile compared historically with open necrosectomy (6% hemorrhage, 10% enteric fistulas), and did not result in any mortalities. However, 16 of 31 patients (52%) requiring necrosectomy ultimately underwent open necrosectomy because of the presence of a centromedial peripancreatic collection with inferior extension into the mesenteric root; a significant negative predictor for successful VARD.

A minimally invasive alternative to VARD is endoscopic transluminal drainage/necrosectomy, particularly if the infectious nidus lies in close proximity to the gastric or duodenal lumen. The peripancreatic collection is accessed via EUS guidance, and serially dilated with balloon dilators; fully covered self-expandable metallic stents may be used to reinforce the fistula tract. Once access is gained, necrosectomy may be performed with various instruments (eg, snares, nets, baskets).[65] Typically, multiple attempts are required for complete debridement. A pilot randomized trial (PENGUIN [Pancreatitis Endoscopic Transgastric vs Primary Necrosectomy in Patients with Infected Pancreatic Necrosis]) in 22 patients comparing endoscopic necrosectomy with VARD suggested an attenuated proinflammatory postprocedure response (measure by systemic interleukin-6 levels) and lower rates of complications/death in the endoscopic cohort.[68] To validate this question on a larger scale, the Dutch multicenter TENSION (Transluminal endoscopic step-up approach versus minimally invasive surgical step-up approach in patients with infected necrotising pancreatitis) trial (SRCTN09186711) is randomizing patients to either endoscopic transluminal drainage (if necessary) followed by (if necessary) endoscopic necrosectomy versus PCD followed by (if necessary) VARD. The primary end point is a composite of major complications and death.[69]

A recently proposed novel surgical option is laparoscopic transgastric necrosectomy, which uses 2 to 3 laparoscopic ports to achieve necrosectomy via a wide cyst-gastrostomy cavity. A retrospective report of 21 patients from Worhunsky and colleagues[70] revealed that complete debridement in a single operation was possible in almost all cases; more importantly, none of the patients required additional surgery, developed pancreatic/enteric fistulae, or experienced wound complications. Larger-scale studies comparing this and other minimally invasive techniques are planned, and will inform best practices in this rapidly evolving arena of pancreatic surgery.

EMERGING SURGICAL OPTIONS FOR THE MANAGEMENT OF CHRONIC PANCREATITIS

The irreversible process of chronic pancreatitis (CP) results in intractable pain, progressive endocrine and exocrine insufficiency, and (in a minority of patients) PDAC. Surgical management of CP must be tailored to the unique anatomic determinants of disease, encompassing (1) drainage procedures (ie, longitudinal pancreatojejunostomy) in patients with pancreatic ductal dilatation with (Frey procedure) or without (Puestow procedure) pancreatic head involvement; (2) formal resections in localized disease with small duct pancreatitis (eg, Whipple PD, Beger duodenum-sparing pancreatic head resection, or DP); and (3) total pancreatectomy with or without autoislet transplantation (TP-AIT).[71] Consensus guidelines indicate that TP-AIT is indicated for the treatment of intractable pain in patients with impaired quality of life (QOL) caused by CP (or recurrent acute pancreatitis) in whom medical, endoscopic, or prior surgical therapy have failed.[72] Patients with known genetic predisposition to CP (eg, hereditary pancreatitis caused by mutations in *PRSS1*, *SPINK1*, or *CFTR* genes) are given particular consideration for TP-AIT because of the low likelihood of disease remission.[72] Although TP removes the pancreatic parenchyma responsible for the pain, inflammation, and eventual cancer risk associated with CP, AIT prevents the

brittle pancreatogenic diabetes associated with loss of both insulin and counter-regulatory glucagon. However, the primary objective of TP-AIT is mitigation of pain; diabetes control is a secondary goal.[72]

The operation involves resection of the entire pancreas, duodenum, distal common bile duct, and spleen (typically). Complete pancreatic mobilization is undertaken before ligation of the major blood supply (ie, gastroduodenal artery, splenic artery) in order to minimize warm ischemia time to the pancreatic islet cells. Following resection, the specimen is placed in cold preservation solution before transportation to a Good Medical Practice facility for islet processing; biliary and enteric reconstruction is performed during islet processing. Islet isolates are typically infused through the portal vein with engraftment in the liver. If high portal pressures (>25 cm H_20) are detected, alternative sites of islet autotransplantation are sought (eg, intraperitoneal, gastric submucosa, beneath the renal capsule).[73,74]

The University of Minnesota experience of 409 consecutive patients with CP largely informs the growing understanding of the ramifications following TP-AIT. A majority (74%) of patients was female, almost all had narcotic-dependent pain before surgery, and 21% had undergone previous pancreatic resections. Following TP-AIT, actuarial survival was greater than 95% at 1 year and greater than 90% at 5 years. AIT function was achieved in 90% of patients, and 63% were independent of, or partially dependent on, exogenous insulin. Most importantly, 85% of patients experienced improvements in pain control postoperatively, with 59% ceasing narcotic use at 2 years. In Short Form 36 QOL surveys, significant improvements in all dimensions of physical and mental functioning were observed, whether patients were on narcotics or not.[74] Accumulating experience with TP-AIT is allowing optimization of patient selection and evidence-driven expansion of eligibility criteria for TP-IAT, which may improve recipients' endocrine function, pain relief, and QOL. Ongoing efforts to improve islet processing and engraftment, better understand the immunobiology of IAT, and optimize perioperative management will further contribute to enhanced postoperative outcomes for patients with CP in the future. Notwithstanding, it should be emphasized that this operation remains infrequently indicated and performed, with just a few centers in the United States performing more than 10 procedures a year. Its efficacy remains highly controversial.

SUMMARY

The ability to predict and prevent perioperative morbidity, gain access to the abdominal cavity and perform complex gastrointestinal reconstruction using endoscopic/laparoscopic techniques, and judiciously select patients with malignant and premalignant diseases who might benefit most from aggressive surgical resection are just a few of the major advances in pancreatic surgery that have taken the field to new levels. Technical advancements, as well as increasingly specialized training, have made pancreatic surgery safer, quicker, and more effective. Other technological advances being investigated are irreversible electroporation for pancreatic resection margin accentuation[75] and fluorescence-guided surgery to enhance intraoperative margin detection.[76,77] Centralization of multimodality pancreatic care to specialized centers of excellence allows a multidisciplinary approach to pancreatic diseases, resulting in improved outcomes with an emphasis on quality of delivered care. However, despite the aforementioned progress, there remains considerable room for improvement; for instance, 5-year survival for resectable PDAC remains approximately 20%. The growing understanding of the molecular and immunologic underpinnings of pancreatic disease, specifically cancer, will enable a more sophisticated approach to patient selection, disease detection, and surgical decision making in the near future.

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