

Enhanced recovery pathways in pancreatic surgery: State of the art

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Abstract

Pancreatic surgery is being offered to an increasing number of patients every year. Although postoperative outcomes have significantly improved in the last decades, even in high-volume centers patients still experience significant postoperative morbidity and full recovery after surgery takes longer than we think. In recent years, enhanced recovery pathways incorporating a large number of evidence-based perioperative interventions have proved to be beneficial in terms of improved postoperative outcomes, and accelerated patient recovery in the context of gastrointestinal, genitourinary and orthopedic surgery. The role of these pathways for pancreatic surgery is still unclear as high-quality randomized controlled trials are lacking. To date, non-randomized studies have shown that care pathways for pancreaticoduodenectomy and distal pancreatectomy are safe with no difference in postoperative morbidity, leading to early discharge and no increase in hospital readmissions. Hospital costs are reduced due to better organization of care and resource utilization. However, further research is needed to clarify the effect of enhanced recovery pathways on patient recovery and post-discharge outcomes following pancreatic resection. Future studies should be prospective and follow recent recommendations for the design and reporting of enhanced recovery pathways.

Key words: Pancreas surgery; Perioperative care; Length of stay; Postoperative complications; Pancreatic neoplasms; Evidence-based medicine

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Core tip: In this study, we reviewed the available literature for enhanced recovery pathways in pancreatic surgery with a special focus on the evidence underlying specific perioperative interventions implemented in this surgical subspecialty and on postoperative outcomes. Although the quality of available studies is suboptimal, enhanced recovery proved to be safe and has the potential to reduce postoperative length of stay and costs after pancreatic resection. No evidence is available regarding post-discharge outcomes and patient functional recovery. Further research is needed to clarify the impact of care pathways on patient recovery after pancreatic surgery.

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INTRODUCTION

The number of patients undergoing pancreatic surgery has increased dramatically in the last decades^[1]. At the same time, outcomes have improved. Postoperative mortality rates have decreased from nearly 20% in the 1980s^[2] to 1%-2% thanks to centralization policies^[3], advances in surgical technique, perioperative care and multidisciplinary management of complications^[4]. However, even in high-volume centers (*i.e.*, institutions performing more than 15-20 pancreatic resections per year)^[3] patients still experience significant postoperative morbidity^[5] and full recovery after surgery takes longer than we think^[6]. Recent studies found that patients undergoing pancreatic cancer resection take around 6 mo to return to their preoperative quality of life^[7]. This finding suggests that an effort should be made to improve perioperative care and support patients in their recovery with the aim to reduce postoperative disability. In addition, considering that most of these patients receive surgery for cancer, it should be kept in mind that returning to a valid functional capacity status is also an essential prerequisite to face adjuvant chemotherapy, which is now a mainstay of pancreatic cancer treatment.

Around 20 years ago, a Danish group lead by Henrik Kehlet reported on a series of nine colonic surgery patients that were treated with a multimodal intervention program including epidural analgesia, early oral nutrition and mobilization^[8]. This represented the first step in the development of so-called fast-track programs, which later evolved in what are currently known as enhanced recovery pathways (ERPs). ERPs are standardized, multimodal, multidisciplinary care plans that integrate various evidence-based inter-

ventions in the perioperative period. Their main goal is to facilitate recovery by attenuating the metabolic surgical stress response and limiting postoperative organ dysfunction through multiple pharmacological, nutritional and physical approaches^[9]. Moreover, ERPs aim to better organize care for patients undergoing a particular procedure, and thereby contribute to reducing unwanted variability in care processes and outcomes. A meta-analysis of 38 randomized trials across multiple specialties concluded that ERPs reduced the risk of complications by about 30% and were associated with reduced hospital stay by about 1 d overall^[10]. The impact was consistent across specialties, which included colorectal, upper GI, genitourinary, thoracic and joint surgery.

In this review we will first discuss the specific elements included in ERPs for pancreatic surgery. We will then describe the evidence accumulated so far on the effect of enhanced recovery on postoperative outcomes following pancreatectomy, and finally we will suggest future directions in this field of research.

CHARACTERISTICS OF AN ENHANCED RECOVERY PATHWAY FOR PANCREATIC SURGERY

In 2012 the Enhanced Recovery After Surgery (ERAS[®]) Society drafted guidelines for perioperative care for patients undergoing pancreaticoduodenectomy (PD)^[11]. The body of evidence for many ERP interventions was in large part extrapolated from studies in other fields of gastrointestinal surgery, mainly colorectal. Following the GRADE Working Group guidelines^[12], recommendations were based on quality of evidence but also on the balance between desirable and undesirable effects; and on values and preferences. Accordingly, in certain cases, strong recommendations were reached from low-quality data and *vice versa*. Table 1 summarizes the specific elements that should be included in ERPs for PD according to the ERAS[®] Society guidelines. We will now provide an explanation for specific items of interest in the preoperative, intraoperative and postoperative settings.

Patient education and engagement

Preparing patients and their caregivers before surgery is fundamental. Patient should be informed about how they should get ready for surgery, what to expect on the day of surgery, and they should receive objectives for each postoperative day including instructions about their drains, infusions, diet and mobilization. Patients should be encouraged to play an active role in their recovery. In fact, patient knowledge and engagement have the potential to improve adherence to ERP elements, and it has been shown to reduce hospital stay, improve pain control and increase patient satisfaction^[13]. The format and the way education is delivered

Table 1 Enhanced recovery pathway interventions for pancreatic surgery

Element	Description
Preoperative	
Patient education	Dedicated counseling providing patients with information and goals for recovery
Optimization of organ dysfunction	Optimization of patient comorbidities and patient conditioning
Oral immunonutrition	Oral immunonutrients should be taken for 5-7 d prior to surgery
Selective biliary drainage	Endoscopic biliary drainage only indicated if serum bilirubin > 14.5 mg/dL, in case of cholangitis or planned neoadjuvant treatment
Avoid mechanical bowel preparation	Oral bowel preparation should not be used
Minimize fasting	Intake of clear fluids up to 2 h before anesthesia, and solid food until 6 h before.
Carbohydrate loading	A carbohydrate drink should be given the morning before surgery
Intraoperative	
Thromboembolic disease prophylaxis	Low molecular weight heparin should be administered
Antimicrobial prophylaxis	Antibiotic prophylaxis should start 30-60 min before incision
Epidural and opioid sparing analgesia	Avoid opioids. Multimodal analgesia including thoracic epidural analgesia, acetaminophen, NSAIDs. Early transition to oral analgesics
PONV prophylaxis	Multimodal nausea and vomit prophylaxis
Avoid hypothermia	Active cutaneous warming
Balanced intravenous infusions	Avoid fluid overload. Maintain near-zero fluid balance. Potential benefit in the use of goal directed fluid therapy.
Postoperative	
Avoid nasogastric intubation	Nasogastric tube should be removed at the end of surgery
Glycemic control	Avoid hyperglycemia with frequent blood sugar monitoring and insulin infusion when necessary
Early removal of urinary drainage	Bladder catheter should be removed within postoperative day 2
Early removal of perianastomotic drain	Early drain removal in patients at low risk for pancreatic fistula
Early oral feeding	Patients should be allowed a normal diet without restrictions as tolerated
Gastrointestinal stimulation	Oral laxative and chewing-gum should be started early after surgery
Early stop of intravenous infusions	Intravenous fluids should be stopped as soon as patients are able to tolerate oral liquids
Early mobilization	Scheduled active mobilization should start from postoperative day 1
Audit	Systematic audit on care processes and outcomes

NSAID: Non-steroidal anti-inflammatory drugs; PONV: Postoperative nausea and vomit.

can influence the patient's ability to retain information and act accordingly^[14]. Written or multimedia information have been shown to have a significant advantage on oral communication alone as information are often forgotten by patients^[15].

Optimization of organ dysfunction

Preoperative optimization aims at improving patient physiologic reserve to better tolerate the incoming stress of surgery. Patients at higher risk for postoperative morbidity such as elderly, frail and patients with severe comorbidities should be evaluated in a multidisciplinary setting^[16]. There is preliminary evidence in colorectal surgery that patients may benefit from prehabilitation programs focusing on improving co-existing morbid conditions and delivering effective nutritional therapy and physical exercise^[17]. A relevant proportion of patients undergoing pancreatic resection are elderly cancer patients with multiple comorbidities. Thus it can be speculated that this specific surgical population may particularly benefit from this approach.

Preoperative biliary drainage

Biliary drainage in patients with jaundice should not be routinely performed as it may increase the risk of serious adverse events, which are related to the drainage procedure^[18]. In a recent RCT including patients with serum bilirubin concentrations < 14.6 mg/dL, preoperative endoscopic biliary drainage

showed higher morbidity compared to patients undergoing upfront surgery^[19]. Patients candidate to neoadjuvant treatment or experiencing a cholangitis represent an exception. It is still unclear if patients with higher bilirubin levels actually benefit from preoperative drainage.

Preoperative fasting and carbohydrate loading

Traditionally patients have been kept fasting from midnight to prevent the risk of aspiration of gastric contents at induction of anesthesia. This leads to dehydration and increases insulin resistance triggering a catabolic state^[20], which is one of the main mechanisms responsible for poor surgical outcomes^[21]. It has been almost 20 years that anesthesia societies worldwide started to recommend a 6 h fast for solids, and allow oral intake of clear fluids up to 2 h before surgery, as it does not increase the risk of aspiration in healthy adults undergoing elective procedures^[22]. The administration of a carbohydrate-rich drink before surgery (50 g, 2-3 h preoperatively) can increase insulin sensitivity^[23], and shift cellular metabolism to a more anabolic state^[20]. A recent Cochrane review found only a slight reduction of postoperative hospital stay but no difference in complications or other outcomes when compared to placebo fluids^[24]. In patients undergoing PD, a double-blind placebo-controlled randomized clinical trial showed that carbohydrate-rich drinks can be safely administered,

as the residual gastric volume at anesthesia induction was similar between the carbohydrate drink and placebo groups^[25].

Multimodal analgesia

A multimodal approach for analgesia is the best strategy to obtain optimal pain control and enable patient recovery. A key element is neuraxial blockade *via* thoracic epidural analgesia, which provides excellent analgesia and is associated with reduced surgical stress response^[26]. Epidurals in major open surgery have been shown to reduce morbidity, especially respiratory complications, and facilitate recovery of bowel function compared to systemic opioids^[27]. A retrospective study by Pratt *et al.*^[28] raised concern that epidural in pancreatic surgery may be associated with increased major complications linked to the common occurrence of postoperative hypotension that may lead to anastomotic failure and increased fluid administration in response. No other study has confirmed these findings and epidurals are still considered the "gold standard". In the event of epidural-related hypotension due to vasodilatation, vasopressors should be considered to avoid fluid overload^[29]. In addition, acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) should be prescribed routinely to aid in epidural analgesia withdrawal and early transition to oral analgesics to promote patient mobilization. Opioids are given only if adequate analgesia (Visual Analogue Scale for pain < 4/10) is not obtained with all of the above.

Postoperative nausea and vomiting prophylaxis

Although no specific trial has specifically investigated postoperative nausea and vomiting (PONV) prophylaxis strategies in pancreatic surgery, it is evident that nausea and vomit early after surgery impair the return to oral nutrition, and mobilization. Ideally, patients should be screened for PONV risk factors using a simple risk calculator like the Apfel score^[30]. PONV prophylaxis begins during surgery and continues in the first hours postoperatively. A tailored strategy with multiple modalities and agents should be used in patients at high and moderate risk^[31]. Common prophylactic interventions during surgery include the use of total intravenous anesthesia (TIVA) with minimization of volatile anesthetics, and the use of loco-regional anesthesia techniques to spare systemic opioids. In addition, prophylaxis protocols include the administration of corticosteroids (*e.g.*, dexamethasone) after induction of general anesthesia, and 5-HT₃ receptor antagonists (*e.g.*, Ondansetron) or butyrophenones (*e.g.*, Droperidol) at the end of surgery.

Balanced intravenous infusions

Administering the optimal amount of fluids during and after surgery has the goal to maintain euolemia and avoid both organ hypo- and hyper-perfusion. Salt and

water overload significantly increase the complication rate and delay bowel function^[32]. However, it is not the restriction in fluid administration but the "near zero" fluid balance that should be achieved, as this has been showed to improve outcomes in major open abdominal surgery^[33]. Patients in ERPs usually require less maintenance fluids as they avoid prolonged fasting and bowel preparation thus have minimal deficits to be replaced^[34]. Pancreatectomy is usually associated with large volume depletion and considerable blood loss, which makes it more difficult to achieve a correct balance. Several noninvasive devices providing continuous cardiac performance measures are available and can be used to tailor fluid management. Overall, their use reduces complications after major surgery^[35]. Cannesson *et al.*^[36] recently implemented a goal directed fluid therapy (GDFT) algorithm in major surgery patients including 94 undergoing pancreatectomy, and found that GDFT significantly decreased complications and reduced length of hospital stay (LOS) by 18%. Although evidence for this approach is still preliminary, the use of monitoring devices to tailor fluid therapy should be encouraged particularly in high-risk patients (*e.g.*, patients with multiple comorbid diseases or candidate to multivisceral resection or complex vascular reconstructions).

Postoperatively, intravenous fluids should be discontinued when patients are able to drink enough liquids. After pancreatectomy in an ERP, oral fluid intake is usually started on the first day after surgery and the drip may be hepllocked within 48-72 h after surgery depending on patient symptoms and tolerance of oral intake.

Perianastomotic drain

The use of an abdominal drainage in pancreatic surgery has been traditionally advocated as it is thought to minimize the consequences of a pancreatic fistula and allow a conservative management of this complication. In contrast, in other abdominal surgery contexts, drains have been abandoned as they have been associated with increased risk of drain-related infectious complications and prolonged hospital stay^[37]. Currently, the routine use of a perianastomotic drain during pancreatic resection has been challenged^[38]. However, a recent multicenter randomized controlled trial investigating the use of a closed-suction intra-peritoneal drain vs no drain was stopped early because of an increase in 90-d mortality in the group of PD patients without drain^[39]. Thus, it clearly provided level I evidence that a concept of routine non-drainage in all cases after PD is not safe and should be abandoned. Nonetheless, further research is warranted to assess the possibility of selective drainage only in patients with a high-risk of developing pancreatic leak (*e.g.*, soft pancreatic texture and small duct). Evidence for distal pancreatectomy is currently lacking.

Concerning the timing of removal of the periana-

stomotic drain, a randomized trial supports its early removal (*i.e.*, on postoperative day 3) in patients at low risk of pancreatic fistula and low drain amylase value on postoperative day 1^[40]. In this subgroup of patients, early removal was associated with a significantly decreased rate of pancreatic fistula, abdominal and pulmonary complications compared to patients with prolonged drainage. Until further data are available, systematic postoperative drainage and early removal in patients at low risk of pancreatic fistula (firm pancreas, wide pancreatic duct) is recommended^[41].

Early oral nutrition

Allowing normal food at will from the first day after surgery has been shown to be feasible and safe after pancreatic surgery^[42]. A large RCT including nearly one hundred patients who underwent pancreatectomy found no advantage to withholding feeding compared to normal food^[43]. Furthermore, in 2014 Gerritsen *et al.*^[44] showed that allowing early oral feeding immediately after PD compared to prolonged naso-jejunal tube feeding is associated with reduced time to adequate oral intake and shortened LOS. Patients should be informed that early satiety, decreased appetite, and ultimately delayed gastric emptying (DGE) are common symptoms after pancreatic surgery. Thus they should be advised to gradually increase the amount of food intake as tolerated. Abdominal complications including pancreatic fistula are very common after pancreatic resection, and they may impair oral intake for long. In this event, enteral tube feeding through naso-jejunal catheters or jejunostomy should be preferred to parenteral nutrition^[45].

DGE prevention and gastrointestinal stimulation

No prokinetic agent has been shown to successfully prevent delayed gastric emptying, which is defined as a functional gastroparesis causing the inability to tolerate oral diet and requiring nasogastric tube decompression^[46]. Chewing sugar-free gum is a simple low cost intervention that decreases time to recovery of gastrointestinal function after colorectal surgery as part of an ERP^[47]. A recent small-size RCT carried out in PD patients found that chewing gum slightly accelerates the return to bowel function and to oral intake, but the data were not significant^[48]. Other authors have proposed the use of magnesium sulphate or lactulose in pancreatic surgery but few results other than safety have been reported^[42]. For pylorus-preserving PD, there is preliminary data suggesting that constructing the duodenojejunosomy in an antecolic (as opposed to a retrocolic) fashion reduces DGE^[49].

Early mobilization

It is well known that staying in bed leads to deconditioning that can largely be prevented by physical activity^[50]. However, there is little evidence that the

implementation of specific interventions to increase mobilization improves outcomes^[51]. In the context of ERPs for colorectal surgery, being out of bed on the first postoperative days is an independent predictor of shorter hospital stay^[52]. After pancreatic resection, due to the extent of surgical trauma, patients experience a prolonged recovery compared to other abdominal procedures. In addition, epidural-related hypotension is a common symptom limiting postoperative mobilization. However, mobilization out of bed should be scheduled early and adequate pain control provided to facilitate it.

OUTCOMES OF ENHANCED RECOVERY IN PANCREATIC SURGERY

In recent years, reporting of clinical pathways for patients undergoing pancreatic resection has progressively increased. Early reports included retrospective single cohort studies^[42] and retrospective studies comparing newly implemented ERPs with historical cohorts^[53-55]. They all focused on the feasibility and safety of implementing care pathways that included a limited number of perioperative interventions. Most of these studies only featured postoperative care elements such as multimodal analgesia, early return to oral diet and removal of tubes and drains, and scheduled mobilization. Compliance with the pathway seemed adequate, morbidity and readmission rates were low, and the authors concluded that this approach was safe, feasible, and promoted earlier discharge. In the following years, the number of publications on this topic, thus the number of patients and the experience with this type of approach increased but the quality of studies remained suboptimal. To date, there is still no report of a randomized clinical study, and no clinical study has been prospectively registered in an international trial registry.

Overall, seventeen trials^[53-69] comparing ERPs to usual perioperative care in pancreatic surgery were published between 2000 and 2015. Table 2 reports the study design and characteristics of studies analyzed in this review. Only one study by Joliat *et al.*^[67] included a prospective ERP cohort, while all others performed a retrospective review comparing patients treated with a recently implemented ERP to historical controls. In a study from the Netherlands^[64], the Authors also included an ERP-like group in which only a limited number of enhanced recovery elements were included.

The total number of patients included in the analyzed studies was 3220 (1576 ERP vs 1644 usual care). Study sample size ranged from 41 to 635 patients. Fourteen studies included PD patients, two of which also included total pancreatectomy patients. Only three studies investigated ERPs in the context of left pancreatectomy. This focus on PD is probably not only related to the greater proportion of patients who undergo this procedure compared

Table 2 Study design and characteristics

Study	Year	Design	Sample size		Type of resection
			ERP	Control	
Porter <i>et al</i> ^[53]	2000	Retrospective cohort	80	68	PD, TP
Vanounou <i>et al</i> ^[54]	2007	Retrospective cohort	145	64	PD
Kennedy <i>et al</i> ^[55]	2007	Retrospective cohort	92	44	PD, TP
Balzano <i>et al</i> ^[56]	2008	Retrospective cohort	252	252	PD
Kennedy <i>et al</i> ^[57]	2009	Retrospective cohort	71	40	LP
Nikfarjam <i>et al</i> ^[58]	2013	Retrospective cohort	20	21	PD
Abu Hilal <i>et al</i> ^[59]	2013	Retrospective cohort	24	20	PD
Braga <i>et al</i> ^[60]	2014	Retrospective cohort	115	115	PD
Kobayashi <i>et al</i> ^[61]	2014	Retrospective cohort	100	142	PD
Nussbaum <i>et al</i> ^[62]	2014	Retrospective cohort	50	100	LP
Nussbaum <i>et al</i> ^[63]	2014	Retrospective cohort	100	142	PD
Coolsen <i>et al</i> ^[64]	2014	Retrospective cohort	144 ¹	86	PD
Shao <i>et al</i> ^[65]	2015	Retrospective cohort	325	310	PD
Sutcliffe <i>et al</i> ^[66]	2015	Retrospective cohort	65	65	PD
Joliat <i>et al</i> ^[67]	2015	Prospective cohort ²	74	87	PD
Morales Soriano <i>et al</i> ^[68]	2015	Retrospective cohort	41	44	PD
Richardson <i>et al</i> ^[69]	2015	Retrospective cohort	22	44	LP

¹Includes 47 patients treated with an enhanced recovery-like pathway;

²Only the ERP group was prospective. PD: Pancreaticoduodenectomy; TP: Total pancreatectomy; LP: Left pancreatectomy.

to distal pancreatectomy, but also to the greater impact that this procedure has on patient recovery. In fact, PD is characterized by lengthy operative times, and extensive fluid and protein losses. At least three visceral anastomoses are fashioned leading to slower recovery of bowel function and obviously a greater chance of major complications compared to distal pancreatectomy. Laparoscopy was included in two out of three ERPs for patients undergoing distal pancreatectomy. In the context of enhanced recovery, laparoscopy has the potential to further accelerate recovery, as it has been shown for colorectal surgery^[70], but conclusive evidence is lacking on the outcomes following laparoscopic distal pancreatectomy compared to the open approach. However, several comparative nonrandomized studies have found that laparoscopy can shorten postoperative recovery compared to open surgery in terms of accelerated return to oral intake, recovery of bowel function and reduced LOS^[71]. The minimally invasive approach for PD, mainly laparoscopy, is slowly becoming more popular.

However, this procedure is technically demanding requiring long operative times and a steep learning curve^[72-74]. Single-centre studies from high-volume institutions have demonstrated that laparoscopic PD is feasible and safe in patients with benign and malignant pancreatic lesions^[75,76]. In their meta-analysis including only comparative cohort studies, de Rooij *et al*^[77] found no difference in postoperative mortality, morbidity and pancreatic fistula rates. They also reported quicker postoperative recovery resulting in reduced LOS. Nonetheless, the level of evidence supporting laparoscopic PD remains low and limited to small nonrandomized series. Even fewer evidence is available for robotic surgery, which may potentially facilitate the transition from open surgery and shorten the learning curve. In addition, to our knowledge there is no series evaluating the results of minimally invasive PD in the context of an ERP.

The role of adherence to ERP elements

In comparative studies analyzed in this review, a total of 17 individual elements aiming to enhance recovery after pancreatic resection were identified (Table 3). The number of elements used within each study ranged from 4 to 17 (median 9). The elements most frequently included were mostly part of postoperative care: standardized perianastomotic drain management ($n = 17$), omission or early removal of the nasogastric tube ($n = 16$), early oral feeding ($n = 16$), thromboembolic disease prophylaxis ($n = 13$), and early mobilization ($n = 13$).

Collecting information about adherence to the different care processes included in the ERP is important in order to understand outcomes and how to improve care. However, only a few studies reported the adherence to the individual ERP elements^[59,60,67]. This confirms recent findings from Day *et al*^[78] showing that the current standard of reporting in enhanced recovery trials is frequently incomplete, suggesting the need for guidelines for the design and reporting of such studies.

It is still unclear if there is an ideal combination of ERP items that should be implemented, what is the impact of overall adherence to the ERP and the relative contribution of each element included. Studies in colorectal surgery suggest that there is a dose-effect relationship between adherence and postoperative outcomes^[79]. In pancreatic surgery patients, Braga *et al*^[60] found that adherence was suboptimal for most of the postoperative interventions, especially perioperative fluid management and achievement of daily mobilization milestones. Notably, patients who experienced postoperative complications had a poor compliance early in the ERP pathway, suggesting that early low adherence may be associated with occurrence of postoperative complications. Sutcliffe *et al*^[66] used a drain amylase cutoff of 350 U/L on the first day after surgery to stratify high- from low-risk PD patients and chose to implement only a limited

Table 3 Enhanced recovery pathway elements used in comparative studies

Study	Preoperative			Intraoperative				Postoperative					Total number of ERP elements				
	Patient education and counselling	No mechanical bowel preparation	Shorter pre-operative fasting	Carbohydrate loading	Prophylactic antibiotics	Thromboembolic disease prophylaxis	Epidural/multimodal analgesia	Prevention of nausea and vomiting	Prevention of hypothermia	Early nasogastric tube removal	Early removal of urinary catheter	Early discontinuation of IV fluids		Glycemic control	Standardized perianastomotic drain management	Early oral feeding	Early mobilization
Porter <i>et al.</i> ^[53]										✓	✓		✓				4
Vanounou <i>et al.</i> ^[54]	✓				✓	✓				✓							7
Kennedy <i>et al.</i> ^[55]					✓	✓				✓		✓			✓		9
Balzano <i>et al.</i> ^[56]					✓	✓									✓		8
Kennedy <i>et al.</i> ^[57]					✓	✓				✓					✓		9
Nikfarjam <i>et al.</i> ^[58]			✓		✓	✓				✓		✓			✓		12
Abu Hilal <i>et al.</i> ^[59]			✓		✓	✓						✓			✓		7
Braga <i>et al.</i> ^[60]		✓			✓	✓			✓			✓			✓		13
Kobayashi <i>et al.</i> ^[61]		✓			✓	✓				✓					✓		6
Nussbaum <i>et al.</i> ^[62]					✓	✓						✓			✓		8
Nussbaum <i>et al.</i> ^[63]					✓	✓				✓		✓			✓		9
Coolsen <i>et al.</i> ^[64]			✓		✓	✓			✓			✓			✓		14
Shao <i>et al.</i> ^[65]					✓	✓				✓					✓		4
Sutcliffe <i>et al.</i> ^[66]		✓			✓	✓			✓						✓		13
Joliat <i>et al.</i> ^[67]		✓			✓	✓			✓			✓			✓		17
Morales Soriano <i>et al.</i> ^[68]		✓			✓	✓			✓			✓			✓		11
Richardson <i>et al.</i> ^[69]					✓	✓				✓					✓		10

Table 4 Postoperative length of stay and readmission rates

Study	Postoperative length of stay (d)			Readmission rates		
	ERP	Usual care	P value	ERP	Usual care	P value
Porter <i>et al.</i> ^[53]	12	15	0.001	10 (15)	9 (11)	0.620
Vanounou <i>et al.</i> ^[54]	8	8	0.357	13 (9)	4 (6)	0.508
Kennedy <i>et al.</i> ^[55]	7	13	< 0.001	7 (8)	3 (7)	> 0.05
Balzano <i>et al.</i> ^[56]	13 (7-110)	15 (7-102)	< 0.001	18 (7)	16 (6)	0.865
Kennedy <i>et al.</i> ^[57]	Mean 7	Mean 10	0.037	5 (7)	10 (25)	0.027
Nikfarjam <i>et al.</i> ^[58]	8 (7-16)	14 (8-29)	< 0.001	3 (15)	0	0.107
Abu Hilal <i>et al.</i> ^[59]	8 (7-13)	13 (10-20)	0.015	1 (1)	2 (8)	0.583
Braga <i>et al.</i> ^[60]	11 (5-51)	13 (8-54)	0.226	14 (12)	12 (10)	0.835
Kobayashi <i>et al.</i> ^[61]	22 ± 12	36 ± 24	< 0.001	2 (2)	2 (2)	0.689
Nussbaum <i>et al.</i> ^[62]	6 (5-9)	7 (5-9)	0.026	15 (30)	20 (20)	0.219
Nussbaum <i>et al.</i> ^[63]	11 (8-18)	13 (10-18)	0.015	31 (31)	36 (25)	0.850
Coolsen <i>et al.</i> ^[64]	14 (7-83)	20 (9-132)	< 0.050	11 (13)	14 (14)	NR
Shao <i>et al.</i> ^[65]	14 ± 7	18 ± 8	< 0.001	43 (13)	44 (14)	0.725
Sutcliffe <i>et al.</i> ^[66]	9 (4-70)	10 (4-114)	0.160	9 (15)	5 (8)	0.260
Joliat <i>et al.</i> ^[67]	15 (11-24)	19 (14-29)	0.029	NR	NR	NR
Morales Soriano <i>et al.</i> ^[68]	14 ± 1.3	19 ± 2	0.014	9 (10)	4 (9)	> 0.05
Richardson <i>et al.</i> ^[69]	3 (3-4)	6 (5-10)	< 0.001	2 (9)	8 (18)	0.476

Data for length of stay are reported as median (range or interquartile range) or mean ± SD. Data for readmission are reported as number of patients (%). ERP: Enhanced recovery pathway.

number of ERP elements in the high-risk group. Early oral intake, avoidance of nasogastric drainage, and early perianastomotic drain removal were only applied to low-risk patients. Although it is intuitive that high-risk patients will be more likely to develop postoperative morbidity and experience a slower recovery, with holding oral diet has been repeatedly shown to be unnecessary and to delay recovery after pancreatic surgery^[43,44], while prolonging postoperative nasogastric drainage after elective abdominal surgery is a known risk factor for pulmonary complications and delayed return to bowel function^[80]. Additionally, di Sebastiano *et al.*^[81] found that tolerating oral diet is an independent factor predicting early discharge within an ERP for PD. Studies published so far have shown that ERPs are safe and feasible in all elective patients undergoing pancreatic resection, including the elderly^[82]. Thus it is not recommended to select patients for being treated within an ERP. Further studies are warranted to clarify the impact of adherence to the pathway and identify key elements associated with improved outcomes.

Postoperative outcomes

The most common postoperative outcome considered in studies evaluating enhanced recovery in pancreatic surgery was LOS. Despite being influenced by many non-clinical factors such as surgeon's preference, social situation, caregiver availability as well as distance from the hospital^[83], LOS is an easy way to monitor outcomes within an institution as it relates to recovery, complications and costs. In addition, it is important to monitor hospital readmissions as discharging patients early may lead to misdiagnosed complications and increase the risk of patients returning to the emergency room and being readmitted early after

discharge^[84].

Table 4 shows LOS and readmissions for the studies analyzed in this review. The majority of the studies reported that primary LOS was significantly shorter when patients undergoing pancreatic resection were treated within an ERP with no increase in hospital readmissions. This corroborates with the results observed in other surgical populations^[10]. Differences in LOS between control and ERP groups varied from 1 to 14 d. It is important to observe that in studies where this difference was not significant^[60,66], subgroup analyses showed that in uncomplicated patients and patients experiencing minor complications, LOS was significantly shorter in the ERP compared to the usual care group.

Table 5 reports morbidity and mortality for the comparative studies analyzed. Complication rates ranged from 16% to 70%. Five of the sixteen studies reporting postoperative morbidity rates showed differences in overall complications when the control and ERP groups were compared. No difference was found in postoperative mortality. None of the studies reported differences in surgical complications between groups, while three studies^[56,61,65] found a significant reduction in the occurrence of delayed gastric emptying. A meta-analysis of randomized controlled trials in colorectal surgery found that ERPs had a protective effect only on medical complications whereas surgical complications were similar to the usual care^[85]. Compared to colectomy, pancreatectomy is associated with a higher rate of postoperative complications, often exceeding 50%. Most of these are surgical complications related to pancreatic fistula, which are unlikely to be influenced by the implementation of a care pathway as this does not modify relevant prognostic factors such as pancreatic

Table 5 Morbidity and mortality rates

Study	Complication rates			Mortality rates		
	ERP	Usual care	P value	ERP	Usual care	P value
Porter <i>et al</i> ^[53]	56 (70)	52 (76)	0.210	2 (3)	1 (1)	0.870
Vanounou <i>et al</i> ^[54]	77 (54)	40 (62)	0.207	2 (1)	1 (2)	0.918
Kennedy <i>et al</i> ^[55]	34 (37)	19 (44)	> 0.05	1 (1)	1 (2)	> 0.05
Balzano <i>et al</i> ^[56]	119 (47)	148 (59)	0.014	9 (4)	7 (3)	0.798
Kennedy <i>et al</i> ^[57]	11 (16)	15 (38)	> 0.05	1 (1)	1 (2)	> 0.05
Nikfarjam <i>et al</i> ^[58]	NR	NR		NR	NR	-
Abu Hilal <i>et al</i> ^[59]	8 (40)	6 (67)	0.077	0	0	-
Braga <i>et al</i> ^[60]	69 (60)	76 (66)	0.339	4 (4)	4 (4)	1
Kobayashi <i>et al</i> ^[61]	39 (39)	54 (60)	0.004	0	1.1	0.957
Nussbaum <i>et al</i> ^[62]	13 (26)	24 (24)	0.842	0	0	-
Nussbaum <i>et al</i> ^[63]	43 (43)	53 (41)	0.792	1 (1)	4 (3)	0.651
Coolsen <i>et al</i> ^[64]	46 (53)	48 (49)	> 0.05	4 (5)	6 (6)	> 0.05
Shao <i>et al</i> ^[65]	127 (39)	173 (55.8)	< 0.001	40 (12)	53 (17)	NR
Sutcliffe <i>et al</i> ^[66]	15 (34)	15 (41)	0.650	2 (3)	2 (3)	1
Joliat <i>et al</i> ^[67]	50 (68)	71 (82)	0.046	3 (4)	4 (5)	1
Morales Soriano <i>et al</i> ^[68]	12 (30)	24 (55)	0.029	0	2 (2)	> 0.05
Richardson <i>et al</i> ^[69]	6 (27)	17 (39)	0.421	0	0	-

Data are reported as number of patients (%). ERP: Enhanced recovery pathway.

texture and duct diameter, and intraoperative blood loss^[86].

Costs

Six studies analyzed hospital costs after the implementation of an ERP for pancreatic surgery^[53,55,57,67,69]. Three of them found a significant decrease in cost following the implementation of an ERP^[53,55,69]. All analyses were limited to in-hospital resources, and the most significant savings were due to a reduction in board and room costs because of reduction in LOS. Notably, Joliat *et al*^[67] performed a cost minimization analysis where they also took into account the fixed costs for the implementation of the pathway including a full-time dedicated ERP nurse manager and the use of a specific ERP database. No significant difference was found in overall costs but savings occurred for anesthesia, operating room, medication and laboratory costs. It should be noted that no study compared indirect costs between patients treated within an ERP and usual care. As care pathways aim at improving patient recovery and they result in reduced LOS, we may hypothesize that societal costs including time spent away from work and need for prolonged home support may be reduced as well. In colorectal surgery patients, a prospective study found that patients managed with an ERP incurred in lower societal costs compared to a conventional care strategy^[87]. After discharge, patients managed in the ERP experienced less productivity loss, had less caregiver burden and made fewer visits to outpatient health centers.

Other postoperative outcomes

In the context of ERPs for pancreatic surgery there is no study reporting recovery outcomes other than traditional short-term measures such as hospital LOS and complication rates, which are of interest for clinicians

but do not reflect the complexity of the recovery process and fail to capture patient's perspective. An alternative measure of in-hospital recovery may be obtained by assessing the time to achieve specific discharge criteria ("time to readiness for discharge")^[88]. The main advantage of this measure is that only factors related to physiological recovery are considered, without the influence of organizational and personal factors that affect LOS. Moreover, in line with the principles of patient-centered care^[89], recent literature has advocated that postoperative recovery be measured using patient-reported outcomes (reports of health coming directly from the patient without interpretation by others)^[90]. The main advantage of using patient reported outcomes in the context of recovery is that they allow a broad assessment of health across various domains, engaging patients as the key stakeholders in the recovery process.

FUTURE DIRECTIONS

We suggest that future research in this context should move in two directions: (1) designing studies with higher methodological quality to determine the impact of ERPs on postoperative outcomes and patient recovery after pancreatic resection; and (2) exploring the role of prehabilitation to optimize patients at high-risk of major complications.

Although non-randomized studies can yield relevant information when RCT data is not available, randomization is still the best approach to prevent selection bias in intervention studies. Therefore, it is our opinion that RCTs should be encouraged to provide convincing evidence about the role of ERPs in pancreatic resection patients. We do recognize that conducting RCTs to study complex interventions such as ERPs is challenging^[91], and that a relevant number of ERP

interventions are now considered standard of care even in institutions where a formal ERP has not been implemented, but examples of well-conducted trials in other surgical populations show that it is possible^[70,92]. In addition, all studies even if non-randomized, should be prospective and follow a structured reporting platform for enhanced recovery pathways as recently proposed^[78]. Moreover, more relevant recovery outcomes including physiological variables (e.g., postoperative stress response markers), long-term results and patient-reported outcomes should be investigated.

Recent literature reports scoring systems to predict patients at higher risk for major complications after pancreatic resection^[5,86]. In addition, research advocates the assessment of body composition measures such as abdominal muscle area and visceral adiposity in cancer patients undergoing PD, as sarcopenic and visceral obese patients are at higher risk for pancreatic fistula and postoperative mortality^[93,94]. High-risk patients could benefit from a prehabilitation program, which aims at improving patient's coexisting chronic disease therapy, nutritional status, and physical function through a multidisciplinary counseling involving multiple medical specialists, nutritionists and physiotherapists^[16,17]. Considering that systemic treatment with chemotherapy is virtually recommended at any stage of pancreatic cancer, patients at very high risk for postoperative mortality could even be shifted from upfront surgery to a tailored preoperative pathway including neoadjuvant chemotherapy^[95] and a prehabilitation program. This would allow a greater proportion of patients to receive treatment compared to an adjuvant setting where about a quarter of patients are unable to undergo chemotherapy due to surgical complications, poor performance status, or comorbidity^[96]. According to West *et al.*^[97], a structured preoperative exercise program in patients undergoing neoadjuvant treatment for rectal cancer can improve patient physical fitness and reduce surgical risk. In the context of pancreatic surgery, the use of neoadjuvant therapy would potentially buy the time needed to carry out prehabilitation eventually leading to improved surgical and oncologic outcomes. Future studies are needed to verify the clinical effectiveness of prehabilitation in pancreatic cancer patients at high risk for postoperative morbidity and mortality, and test the feasibility of a combination of neoadjuvant treatment and a physical intervention in this setting.

CONCLUSION

This review analyzed the state of the art of enhanced recovery pathways in pancreatic surgery. Although the amount of literature has grown exponentially in the last decade, the methodological quality of available studies is suboptimal. Most of the studies suggested that the use of ERP is safe and has the potential to reduce primary LOS and hospitalization costs. Well-designed trials are needed to provide conclusive evidence about

the role of ERPs in pancreatic surgery. Future studies should be prospective, follow recent recommendations for the reporting of enhanced recovery pathways and should also take into account more specific recovery outcomes such as physiological and patient reported outcomes.

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