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**Enhanced recovery pathways in pancreatic surgery: State of the art**

Pecorelli N *et al.* Enhanced recovery in pancreatic surgery

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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 pre-requisite 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 interventions 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 day 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 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 grams, 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 euvolemia 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 heplocked 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 intraperitoneal drain versus 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 perianastomotic 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 duodenojejunostomy 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 versus 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 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 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, withholding 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 and 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 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.

**REFERENCES**

1 **Cameron JL**, He J. Two thousand consecutive pancreaticoduodenectomies. *J Am Coll Surg* 2015; **220**: 530-536 [PMID: 25724606 DOI: 10.1016/j.jamcollsurg.2014.12.031]

2 **Herter FP**, Cooperman AM, Ahlborn TN, Antinori C. Surgical experience with pancreatic and periampullary cancer. *Ann Surg* 1982; **195**: 274-281 [PMID: 6277259]

3 **Gooiker GA**, Lemmens VE, Besselink MG, Busch OR, Bonsing BA, Molenaar IQ, Tollenaar RA, de Hingh IH, Wouters MW. Impact of centralization of pancreatic cancer surgery on resection rates and survival. *Br J Surg* 2014; **101**: 1000-1005 [PMID: 24844590 DOI: 10.1002/bjs.9468]

4 **Ghaferi AA**, Osborne NH, Birkmeyer JD, Dimick JB. Hospital characteristics associated with failure to rescue from complications after pancreatectomy. *J Am Coll Surg* 2010; **211**: 325-330 [PMID: 20800188 DOI: 10.1016/j.jamcollsurg.2010.04.025]

5 **Uzunoglu FG**, Reeh M, Vettorazzi E, Ruschke T, Hannah P, Nentwich MF, Vashist YK, Bogoevski D, König A, Janot M, Gavazzi F, Zerbi A, Todaro V, Malleo G, Uhl W, Montorsi M, Bassi C, Izbicki JR, Bockhorn M. Preoperative Pancreatic Resection (PREPARE) score: a prospective multicenter-based morbidity risk score. *Ann Surg* 2014; **260**: 857-63; discussion 863-4 [PMID: 25243549 DOI: 10.1097/sla.0000000000000946]

6 **Eaton AA**, Gonen M, Karanicolas P, Jarnagin WR, D'Angelica MI, DeMatteo R, Kingham TP, Allen PJ. Health-Related Quality of Life After Pancreatectomy: Results From a Randomized Controlled Trial. *Ann Surg Oncol* 2016 Jan 19; Epub ahead of print [PMID: 26786091 DOI: 10.1245/s10434-015-5077-z]

7 **Heerkens HD**, Tseng DS, Lips IM, van Santvoort HC, Vriens MR, Hagendoorn J, Meijer GJ, Borel Rinkes IH, van Vulpen M, Molenaar IQ. Health-related quality of life after pancreatic resection for malignancy. *Br J Surg* 2016; **103**: 257-266 [PMID: 26785646 DOI: 10.1002/bjs.10032]

8 **Bardram L**, Funch-Jensen P, Jensen P, Crawford ME, Kehlet H. Recovery after laparoscopic colonic surgery with epidural analgesia, and early oral nutrition and mobilisation. *Lancet* 1995; **345**: 763-764 [PMID: 7891489]

9 **Kehlet H**, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg* 2008; **248**: 189-198 [PMID: 18650627 DOI: 10.1097/SLA.0b013e31817f2c1a]

10 **Nicholson A**, Lowe MC, Parker J, Lewis SR, Alderson P, Smith AF. Systematic review and meta-analysis of enhanced recovery programmes in surgical patients. *Br J Surg* 2014; **101**: 172-188 [PMID: 24469618 DOI: 10.1002/bjs.9394]

11 **Lassen K**, Coolsen MM, Slim K, Carli F, de Aguilar-Nascimento JE, Schäfer M, Parks RW, Fearon KC, Lobo DN, Demartines N, Braga M, Ljungqvist O, Dejong CH. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *World J Surg* 2013; **37**: 240-258 [PMID: 22956014 DOI: 10.1007/s00268-012-1771-1]

12 **Guyatt GH**, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ. Going from evidence to recommendations. *BMJ* 2008; **336**: 1049-1051 [PMID: 18467413 DOI: 10.1136/bmj.39493.646875.AE]

13 **Kiecolt-Glaser JK**, Page GG, Marucha PT, MacCallum RC, Glaser R. Psychological influences on surgical recovery. Perspectives from psychoneuroimmunology. *Am Psychol* 1998; **53**: 1209-1218 [PMID: 9830373]

14 **Fredericks S**, Guruge S, Sidani S, Wan T. Postoperative patient education: a systematic review. *Clin Nurs Res* 2010; **19**: 144-164 [PMID: 20435785 DOI: 10.1177/1054773810365994]

15 **Snyder-Ramos SA**, Seintsch H, Böttiger BW, Motsch J, Martin E, Bauer M. Patient satisfaction and information gain after the preanesthetic visit: a comparison of face-to-face interview, brochure, and video. *Anesth Analg* 2005; **100**: 1753-1758 [PMID: 15920209 DOI: 10.1213/01.ane.0000153010.49776.e5]

16 **Glance LG**, Osler TM, Neuman MD. Redesigning surgical decision making for high-risk patients. *N Engl J Med* 2014; **370**: 1379-1381 [PMID: 24716679 DOI: 10.1056/NEJMp1315538]

17 **Li C**, Carli F, Lee L, Charlebois P, Stein B, Liberman AS, Kaneva P, Augustin B, Wongyingsinn M, Gamsa A, Kim do J, Vassiliou MC, Feldman LS. Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. *Surg Endosc* 2013; **27**: 1072-1082 [PMID: 23052535 DOI: 10.1007/s00464-012-2560-5]

18 **Fang Y**, Gurusamy KS, Wang Q, Davidson BR, Lin H, Xie X, Wang C. Pre-operative biliary drainage for obstructive jaundice. *Cochrane Database Syst Rev* 2012; **9**: CD005444 [PMID: 22972086 DOI: 10.1002/14651858.CD005444.pub3]

19 **van der Gaag NA**, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, Gerritsen JJ, Greve JW, Gerhards MF, de Hingh IH, Klinkenbijl JH, Nio CY, de Castro SM, Busch OR, van Gulik TM, Bossuyt PM, Gouma DJ. Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med* 2010; **362**: 129-137 [PMID: 20071702 DOI: 10.1056/NEJMoa0903230]

20 **Svanfeldt M**, Thorell A, Hausel J, Soop M, Rooyackers O, Nygren J, Ljungqvist O. Randomized clinical trial of the effect of preoperative oral carbohydrate treatment on postoperative whole-body protein and glucose kinetics. *Br J Surg* 2007; **94**: 1342-1350 [PMID: 17902094 DOI: 10.1002/bjs.5919]

21 **Ljungqvist O**. Insulin resistance and outcomes in surgery. *J Clin Endocrinol Metab* 2010; **95**: 4217-4219 [PMID: 20823470 DOI: 10.1210/jc.2010-1525]

22 **Ljungqvist O**, Søreide E. Preoperative fasting. *Br J Surg* 2003; **90**: 400-406 [PMID: 12673740 DOI: 10.1002/bjs.4066]

23 **Svanfeldt M**, Thorell A, Hausel J, Soop M, Nygren J, Ljungqvist O. Effect of "preoperative" oral carbohydrate treatment on insulin action--a randomised cross-over unblinded study in healthy subjects. *Clin Nutr* 2005; **24**: 815-821 [PMID: 15979768 DOI: 10.1016/j.clnu.2005.05.002]

24 **Smith MD**, McCall J, Plank L, Herbison GP, Soop M, Nygren J. Preoperative carbohydrate treatment for enhancing recovery after elective surgery. *Cochrane Database Syst Rev* 2014; **8**: CD009161 [PMID: 25121931 DOI: 10.1002/14651858.CD009161.pub2]

25 **Braga M**, Bissolati M, Rocchetti S, Beneduce A, Pecorelli N, Di Carlo V. Oral preoperative antioxidants in pancreatic surgery: a double-blind, randomized, clinical trial. *Nutrition* 2012; **28**: 160-164 [PMID: 21890323 DOI: 10.1016/j.nut.2011.05.014]

26 **Uchida I**, Asoh T, Shirasaka C, Tsuji H. Effect of epidural analgesia on postoperative insulin resistance as evaluated by insulin clamp technique. *Br J Surg* 1988; **75**: 557-562 [PMID: 3293693]

27 **Pöpping DM**, Elia N, Van Aken HK, Marret E, Schug SA, Kranke P, Wenk M, Tramèr MR. Impact of epidural analgesia on mortality and morbidity after surgery: systematic review and meta-analysis of randomized controlled trials. *Ann Surg* 2014; **259**: 1056-1067 [PMID: 24096762 DOI: 10.1097/sla.0000000000000237]

28 **Pratt WB**, Steinbrook RA, Maithel SK, Vanounou T, Callery MP, Vollmer CM. Epidural analgesia for pancreatoduodenectomy: a critical appraisal. *J Gastrointest Surg* 2008; **12**: 1207-1220 [PMID: 18264686 DOI: 10.1007/s11605-008-0467-1]

29 **Hiltebrand LB**, Koepfli E, Kimberger O, Sigurdsson GH, Brandt S. Hypotension during fluid-restricted abdominal surgery: effects of norepinephrine treatment on regional and microcirculatory blood flow in the intestinal tract. *Anesthesiology* 2011; **114**: 557-564 [PMID: 21307765 DOI: 10.1097/ALN.0b013e31820bfc81]

30 **Apfel CC**, Greim CA, Haubitz I, Goepfert C, Usadel J, Sefrin P, Roewer N. A risk score to predict the probability of postoperative vomiting in adults. *Acta Anaesthesiol Scand* 1998; **42**: 495-501 [PMID: 9605363]

31 **Gan TJ**, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, Watcha M, Chung F, Angus S, Apfel CC, Bergese SD, Candiotti KA, Chan MT, Davis PJ, Hooper VD, Lagoo-Deenadayalan S, Myles P, Nezat G, Philip BK, Tramèr MR. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2014; **118**: 85-113 [PMID: 24356162 DOI: 10.1213/ane.0000000000000002]

32 **Lobo DN**, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet* 2002; **359**: 1812-1818 [PMID: 12044376 DOI: 10.1016/s0140-6736(02)08711-1]

33 **Varadhan KK**, Lobo DN. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. *Proc Nutr Soc* 2010; **69**: 488-498 [PMID: 20515521 DOI: 10.1017/s0029665110001734]

34 **Miller TE**, Roche AM, Mythen M. Fluid management and goal-directed therapy as an adjunct to Enhanced Recovery After Surgery (ERAS). *Can J Anaesth* 2015; **62**: 158-168 [PMID: 25391735 DOI: 10.1007/s12630-014-0266-y]

35 **Navarro LH**, Bloomstone JA, Auler JO, Cannesson M, Rocca GD, Gan TJ, Kinsky M, Magder S, Miller TE, Mythen M, Perel A, Reuter DA, Pinsky MR, Kramer GC. Perioperative fluid therapy: a statement from the international Fluid Optimization Group. *Perioper Med (Lond)* 2015; **4**: 3 [PMID: 25897397 DOI: 10.1186/s13741-015-0014-z]

36 **Cannesson M**, Ramsingh D, Rinehart J, Demirjian A, Vu T, Vakharia S, Imagawa D, Yu Z, Greenfield S, Kain Z. Perioperative goal-directed therapy and postoperative outcomes in patients undergoing high-risk abdominal surgery: a historical-prospective, comparative effectiveness study. *Crit Care* 2015; **19**: 261 [PMID: 26088649 DOI: 10.1186/s13054-015-0945-2]

37 **Wang Z**, Chen J, Su K, Dong Z. Abdominal drainage versus no drainage post-gastrectomy for gastric cancer. *Cochrane Database Syst Rev* 2015; **5**: CD008788 [PMID: 25961741 DOI: 10.1002/14651858.CD008788.pub3]

38 **Peng S**, Cheng Y, Yang C, Lu J, Wu S, Zhou R, Cheng N. Prophylactic abdominal drainage for pancreatic surgery. *Cochrane Database Syst Rev* 2015; **8**: CD010583 [PMID: 26292656 DOI: 10.1002/14651858.CD010583.pub2]

39 **Van Buren G**, Bloomston M, Hughes SJ, Winter J, Behrman SW, Zyromski NJ, Vollmer C, Velanovich V, Riall T, Muscarella P, Trevino J, Nakeeb A, Schmidt CM, Behrns K, Ellison EC, Barakat O, Perry KA, Drebin J, House M, Abdel-Misih S, Silberfein EJ, Goldin S, Brown K, Mohammed S, Hodges SE, McElhany A, Issazadeh M, Jo E, Mo Q, Fisher WE. A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage. *Ann Surg* 2014; **259**: 605-612 [PMID: 24374513 DOI: 10.1097/SLA.0000000000000460]

40 **Bassi C**, Molinari E, Malleo G, Crippa S, Butturini G, Salvia R, Talamini G, Pederzoli P. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. *Ann Surg* 2010; **252**: 207-214 [PMID: 20622661 DOI: 10.1097/SLA.0b013e3181e61e88]

41 **Strobel O**, Büchler MW. Drainage after pancreaticoduodenectomy: controversy revitalized. *Ann Surg* 2014; **259**: 613-615 [PMID: 24603296 DOI: 10.1097/sla.0000000000000630]

42 **Berberat PO**, Ingold H, Gulbinas A, Kleeff J, Müller MW, Gutt C, Weigand M, Friess H, Büchler MW. Fast track--different implications in pancreatic surgery. *J Gastrointest Surg* 2007; **11**: 880-887 [PMID: 17440787 DOI: 10.1007/s11605-007-0167-2]

43 **Lassen K**, Kjaeve J, Fetveit T, Tranø G, Sigurdsson HK, Horn A, Revhaug A. Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. *Ann Surg* 2008; **247**: 721-729 [PMID: 18438106 DOI: 10.1097/SLA.0b013e31815cca68]

44 **Gerritsen A**, Wennink RA, Besselink MG, van Santvoort HC, Tseng DS, Steenhagen E, Borel Rinkes IH, Molenaar IQ. Early oral feeding after pancreatoduodenectomy enhances recovery without increasing morbidity. *HPB (Oxford)* 2014; **16**: 656-664 [PMID: 24308458 DOI: 10.1111/hpb.12197]

45 **Gianotti L**, Meier R, Lobo DN, Bassi C, Dejong CH, Ockenga J, Irtun O, MacFie J. ESPEN Guidelines on Parenteral Nutrition: pancreas. *Clin Nutr* 2009; **28**: 428-435 [PMID: 19464771 DOI: 10.1016/j.clnu.2009.04.003]

46 **Wente MN**, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Büchler MW. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2007; **142**: 761-768 [PMID: 17981197 DOI: 10.1016/j.surg.2007.05.005]

47 **Short V**, Herbert G, Perry R, Atkinson C, Ness AR, Penfold C, Thomas S, Andersen HK, Lewis SJ. Chewing gum for postoperative recovery of gastrointestinal function. *Cochrane Database Syst Rev* 2015; **2**: CD006506 [PMID: 25914904 DOI: 10.1002/14651858.CD006506.pub3]

48 **Andersson T**, Bjerså K, Falk K, Olsén MF. Effects of chewing gum against postoperative ileus after pancreaticoduodenectomy--a randomized controlled trial. *BMC Res Notes* 2015; **8**: 37 [PMID: 25886536 DOI: 10.1186/s13104-015-0996-0]

49 **Bell R**, Pandanaboyana S, Shah N, Bartlett A, Windsor JA, Smith AM. Meta-analysis of antecolic versus retrocolic gastric reconstruction after a pylorus-preserving pancreatoduodenectomy. *HPB (Oxford)* 2015; **17**: 202-208 [PMID: 25267428 DOI: 10.1111/hpb.12344]

50 **Convertino VA**. Cardiovascular consequences of bed rest: effect on maximal oxygen uptake. *Med Sci Sports Exerc* 1997; **29**: 191-196 [PMID: 9044222]

51 **Castelino T**, Fiore JF, Niculiseanu P, Landry T, Augustin B, Feldman LS. The effect of early mobilization protocols on postoperative outcomes following abdominal and thoracic surgery: A systematic review. *Surgery* 2016; **159**: 991-1003 [PMID: 26804821 DOI: 10.1016/j.surg.2015.11.029]

52 **Maessen J**, Dejong CH, Hausel J, Nygren J, Lassen K, Andersen J, Kessels AG, Revhaug A, Kehlet H, Ljungqvist O, Fearon KC, von Meyenfeldt MF. A protocol is not enough to implement an enhanced recovery programme for colorectal resection. *Br J Surg* 2007; **94**: 224-231 [PMID: 17205493 DOI: 10.1002/bjs.5468]

53 **Porter GA**, Pisters PW, Mansyur C, Bisanz A, Reyna K, Stanford P, Lee JE, Evans DB. Cost and utilization impact of a clinical pathway for patients undergoing pancreaticoduodenectomy. *Ann Surg Oncol* 2000; **7**: 484-489 [PMID: 10947015]

54 **Vanounou T**, Pratt W, Fischer JE, Vollmer CM, Callery MP. Deviation-based cost modeling: a novel model to evaluate the clinical and economic impact of clinical pathways. *J Am Coll Surg* 2007; **204**: 570-579 [PMID: 17382215 DOI: 10.1016/j.jamcollsurg.2007.01.025]

55 **Kennedy EP**, Rosato EL, Sauter PK, Rosenberg LM, Doria C, Marino IR, Chojnacki KA, Berger AC, Yeo CJ. Initiation of a critical pathway for pancreaticoduodenectomy at an academic institution--the first step in multidisciplinary team building. *J Am Coll Surg* 2007; **204**: 917-23; discussion 923-4 [PMID: 17481510 DOI: 10.1016/j.jamcollsurg.2007.01.057]

56 **Balzano G**, Zerbi A, Braga M, Rocchetti S, Beneduce AA, Di Carlo V. Fast-track recovery programme after pancreatico- duodenectomy reduces delayed gastric emptying. *Br J Surg* 2008; **95**: 1387-1393 [PMID: 18844251 DOI: 10.1002/bjs.6324]

57 **Kennedy EP**, Grenda TR, Sauter PK, Rosato EL, Chojnacki KA, Rosato FE, Profeta BC, Doria C, Berger AC, Yeo CJ. Implementation of a critical pathway for distal pancreatectomy at an academic institution. *J Gastrointest Surg* 2009; **13**: 938-944 [PMID: 19190968 DOI: 10.1007/s11605-009-0803-0]

58 **Nikfarjam M**, Weinberg L, Low N, Fink MA, Muralidharan V, Houli N, Starkey G, Jones R, Christophi C. A fast track recovery program significantly reduces hospital length of stay following uncomplicated pancreaticoduodenectomy. *JOP* 2013; **14**: 63-70 [PMID: 23306337 DOI: 10.6092/1590-8577/1223]

59 **Abu Hilal M**, Di Fabio F, Badran A, Alsaati H, Clarke H, Fecher I, Armstrong TH, Johnson CD, Pearce NW. Implementation of enhanced recovery programme after pancreatoduodenectomy: a single-centre UK pilot study. *Pancreatology* 2013; **13**: 58-62 [PMID: 23395571 DOI: 10.1016/j.pan.2012.11.312]

60 **Braga M**, Pecorelli N, Ariotti R, Capretti G, Greco M, Balzano G, Castoldi R, Beretta L. Enhanced recovery after surgery pathway in patients undergoing pancreaticoduodenectomy. *World J Surg* 2014; **38**: 2960-2966 [PMID: 24870390 DOI: 10.1007/s00268-014-2653-5]

61 **Kobayashi S**, Ooshima R, Koizumi S, Katayama M, Sakurai J, Watanabe T, Nakano H, Imaizumi T, Otsubo T. Perioperative care with fast-track management in patients undergoing pancreaticoduodenectomy. *World J Surg* 2014; **38**: 2430-2437 [PMID: 24692004 DOI: 10.1007/s00268-014-2548-5]

62 **Nussbaum DP**, Penne K, Speicher PJ, Stinnett SS, Perez A, White RR, Clary BM, Tyler DS, Blazer DG. The role of clinical care pathways: an experience with distal pancreatectomy. *J Surg Res* 2014; **190**: 64-71 [PMID: 24666986 DOI: 10.1016/j.jss.2014.02.026]

63 **Nussbaum DP**, Penne K, Stinnett SS, Speicher PJ, Cocieru A, Blazer DG, Zani S, Clary BM, Tyler DS, White RR. A standardized care plan is associated with shorter hospital length of stay in patients undergoing pancreaticoduodenectomy. *J Surg Res* 2015; **193**: 237-245 [PMID: 25062813 DOI: 10.1016/j.jss.2014.06.036]

64 **Coolsen MM**, van Dam RM, Chigharoe A, Olde Damink SW, Dejong CH. Improving outcome after pancreaticoduodenectomy: experiences with implementing an enhanced recovery after surgery (ERAS) program. *Dig Surg* 2014; **31**: 177-184 [PMID: 25097014 DOI: 10.1159/000363583]

65 **Shao Z**, Jin G, Ji W, Shen L, Hu X. The role of fast-track surgery in pancreaticoduodenectomy: a retrospective cohort study of 635 consecutive resections. *Int J Surg* 2015; **15**: 129-133 [PMID: 25615646 DOI: 10.1016/j.ijsu.2015.01.007]

66 **Sutcliffe RP**, Hamoui M, Isaac J, Marudanayagam R, Mirza DF, Muiesan P, Roberts JK. Implementation of an Enhanced Recovery Pathway After Pancreaticoduodenectomy in Patients with Low Drain Fluid Amylase. *World J Surg* 2015; **39**: 2023-2030 [PMID: 25809067 DOI: 10.1007/s00268-015-3051-3]

67 **Joliat GR**, Labgaa I, Petermann D, Hübner M, Griesser AC, Demartines N, Schäfer M. Cost-benefit analysis of an enhanced recovery protocol for pancreaticoduodenectomy. *Br J Surg* 2015; **102**: 1676-1683 [PMID: 26492489 DOI: 10.1002/bjs.9957]

68 **Morales Soriano R**, Esteve Pérez N, Tejada Gavela S, Cuadrado García Á, Rodríguez Pino JC, Morón Canis JM, Molina Romero X, Muñoz Pérez J, González Argente X. Outcomes of an enhanced recovery after surgery programme for pancreaticoduodenectomy. *Cir Esp* 2015; **93**: 509-515 [PMID: 26072690 DOI: 10.1016/j.ciresp.2015.04.009]

69 **Richardson J**, Di Fabio F, Clarke H, Bajalan M, Davids J, Abu Hilal M. Implementation of enhanced recovery programme for laparoscopic distal pancreatectomy: feasibility, safety and cost analysis. *Pancreatology* 2015; **15**: 185-190 [PMID: 25641674 DOI: 10.1016/j.pan.2015.01.002]

70 **Vlug MS**, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, Gerhards MF, van Wagensveld BA, van der Zaag ES, van Geloven AA, Sprangers MA, Cuesta MA, Bemelman WA. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). *Ann Surg* 2011; **254**: 868-875 [PMID: 21597360 DOI: 10.1097/SLA.0b013e31821fd1ce]

71 **Mehrabi A**, Hafezi M, Arvin J, Esmaeilzadeh M, Garoussi C, Emami G, Kössler-Ebs J, Müller-Stich BP, Büchler MW, Hackert T, Diener MK. A systematic review and meta-analysis of laparoscopic versus open distal pancreatectomy for benign and malignant lesions of the pancreas: it's time to randomize. *Surgery* 2015; **157**: 45-55 [PMID: 25482464 DOI: 10.1016/j.surg.2014.06.081]

72 **Tan CL**, Zhang H, Peng B, Li KZ. Outcome and costs of laparoscopic pancreaticoduodenectomy during the initial learning curve vs laparotomy. *World J Gastroenterol* 2015; **21**: 5311-5319 [PMID: 25954105 DOI: 10.3748/wjg.v21.i17.5311]

73 **Speicher PJ**, Nussbaum DP, White RR, Zani S, Mosca PJ, Blazer DG, Clary BM, Pappas TN, Tyler DS, Perez A. Defining the learning curve for team-based laparoscopic pancreaticoduodenectomy. *Ann Surg Oncol* 2014; **21**: 4014-4019 [PMID: 24923222 DOI: 10.1245/s10434-014-3839-7]

74 **Song KB**, Kim SC, Hwang DW, Lee JH, Lee DJ, Lee JW, Park KM, Lee YJ. Matched Case-Control Analysis Comparing Laparoscopic and Open Pylorus-preserving Pancreaticoduodenectomy in Patients With Periampullary Tumors. *Ann Surg* 2015; **262**: 146-155 [PMID: 25563866 DOI: 10.1097/sla.0000000000001079]

75 **Kendrick ML**, Cusati D. Total laparoscopic pancreaticoduodenectomy: feasibility and outcome in an early experience. *Arch Surg* 2010; **145**: 19-23 [PMID: 20083750 DOI: 10.1001/archsurg.2009.243]

76 **Asbun HJ**, Stauffer JA. Laparoscopic vs open pancreaticoduodenectomy: overall outcomes and severity of complications using the Accordion Severity Grading System. *J Am Coll Surg* 2012; **215**: 810-819 [PMID: 22999327 DOI: 10.1016/j.jamcollsurg.2012.08.006]

77 **de** **Rooij T**, Lu MZ, Steen MW, Gerhards MF, Dijkgraaf MG, Busch OR, Lips DJ, Festen S, Besselink MG. Minimally Invasive Versus Open Pancreatoduodenectomy: Systematic Review and Meta-analysis of Comparative Cohort and Registry Studies. *Ann Surg* 2016 Feb 10; Epub ahead of print [PMID: 26863398 DOI: 10.1097/sla.0000000000001660]

78 **Day RW**, Fielder S, Calhoun J, Kehlet H, Gottumukkala V, Aloia TA. Incomplete reporting of enhanced recovery elements and its impact on achieving quality improvement. *Br J Surg* 2015; **102**: 1594-1602 [PMID: 26364714 DOI: 10.1002/bjs.9918]

79 **Gustafsson UO**, Hausel J, Thorell A, Ljungqvist O, Soop M, Nygren J. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. *Arch Surg* 2011; **146**: 571-577 [PMID: 21242424 DOI: 10.1001/archsurg.2010.309]

80 **Nelson R**, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. *Cochrane Database Syst Rev* 2007; : CD004929 [PMID: 17636780 DOI: 10.1002/14651858.CD004929.pub3]

81 **di Sebastiano P**, Festa L, De Bonis A, Ciuffreda A, Valvano MR, Andriulli A, di Mola FF. A modified fast-track program for pancreatic surgery: a prospective single-center experience. *Langenbecks Arch Surg* 2011; **396**: 345-351 [PMID: 20703500 DOI: 10.1007/s00423-010-0707-1]

82 **Partelli S**, Crippa S, Castagnani R, Ruffo G, Marmorale C, Franconi AM, De Angelis C, Falconi M. Evaluation of an enhanced recovery protocol after pancreaticoduodenectomy in elderly patients. *HPB (Oxford)* 2016; **18**: 153-158 [PMID: 26902134 DOI: 10.1016/j.hpb.2015.09.009]

83 **Neville A**, Lee L, Antonescu I, Mayo NE, Vassiliou MC, Fried GM, Feldman LS. Systematic review of outcomes used to evaluate enhanced recovery after surgery. *Br J Surg* 2014; **101**: 159-170 [PMID: 24469616 DOI: 10.1002/bjs.9324]

84 **Wind J**, Hofland J, Preckel B, Hollmann MW, Bossuyt PM, Gouma DJ, van Berge Henegouwen MI, Fuhring JW, Dejong CH, van Dam RM, Cuesta MA, Noordhuis A, de Jong D, van Zalingen E, Engel AF, Goei TH, de Stoppelaar IE, van Tets WF, van Wagensveld BA, Swart A, van den Elsen MJ, Gerhards MF, de Wit LT, Siepel MA, van Geloven AA, Juttmann JW, Clevers W, Bemelman WA. Perioperative strategy in colonic surgery; LAparoscopy and/or FAst track multimodal management versus standard care (LAFA trial). *BMC Surg* 2006; **6**: 16 [PMID: 17134506 DOI: 10.1186/1471-2482-6-16]

85 **Greco M**, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials. *World J Surg* 2014; **38**: 1531-1541 [PMID: 24368573 DOI: 10.1007/s00268-013-2416-8]

86 **Braga M**, Capretti G, Pecorelli N, Balzano G, Doglioni C, Ariotti R, Di Carlo V. A prognostic score to predict major complications after pancreaticoduodenectomy. *Ann Surg* 2011; **254**: 702-77; discussion 702-77; [PMID: 22042466 DOI: 10.1097/SLA.0b013e31823598fb]

87 **Lee L**, Mata J, Ghitulescu GA, Boutros M, Charlebois P, Stein B, Liberman AS, Fried GM, Morin N, Carli F, Latimer E, Feldman LS. Cost-effectiveness of Enhanced Recovery Versus Conventional Perioperative Management for Colorectal Surgery. *Ann Surg* 2015; **262**: 1026-1033 [PMID: 25371130 DOI: 10.1097/sla.0000000000001019]

88 **Fiore JF**, Faragher IG, Bialocerkowski A, Browning L, Denehy L. Time to readiness for discharge is a valid and reliable measure of short-term recovery after colorectal surgery. *World J Surg* 2013; **37**: 2927-2934 [PMID: 24101012 DOI: 10.1007/s00268-013-2208-1]

89 **Selby JV**, Beal AC, Frank L. The Patient-Centered Outcomes Research Institute (PCORI) national priorities for research and initial research agenda. *JAMA* 2012; **307**: 1583-1584 [PMID: 22511682 DOI: 10.1001/jama.2012.500]

90 **Feldman LS**, Lee L, Fiore J. What outcomes are important in the assessment of Enhanced Recovery After Surgery (ERAS) pathways? *Can J Anaesth* 2015; **62**: 120-130 [PMID: 25391733 DOI: 10.1007/s12630-014-0263-1]

91 **Lassen K**, Hϕye A, Myrmel T. Randomised trials in surgery: the burden of evidence. *Rev Recent Clin Trials* 2012; **7**: 244-248 [PMID: 22621283]

92 **Jones C**, Kelliher L, Dickinson M, Riga A, Worthington T, Scott MJ, Vandrevala T, Fry CH, Karanjia N, Quiney N. Randomized clinical trial on enhanced recovery versus standard care following open liver resection. *Br J Surg* 2013; **100**: 1015-1024 [PMID: 23696477 DOI: 10.1002/bjs.9165]

93 **Pecorelli N**, Carrara G, De Cobelli F, Cristel G, Damascelli A, Balzano G, Beretta L, Braga M. Effect of sarcopenia and visceral obesity on mortality and pancreatic fistula following pancreatic cancer surgery. *Br J Surg* 2016; **103**: 434-442 [PMID: 26780231 DOI: 10.1002/bjs.10063]

94 **Kirihara Y**, Takahashi N, Hashimoto Y, Sclabas GM, Khan S, Moriya T, Sakagami J, Huebner M, Sarr MG, Farnell MB. Prediction of pancreatic anastomotic failure after pancreatoduodenectomy: the use of preoperative, quantitative computed tomography to measure remnant pancreatic volume and body composition. *Ann Surg* 2013; **257**: 512-519 [PMID: 23241871 DOI: 10.1097/SLA.0b013e31827827d0]

95 **Sutton JM**, Abbott DE. Neoadjuvant therapy for pancreas cancer: past lessons and future therapies. *World J Gastroenterol* 2014; **20**: 15564-15579 [PMID: 25400440 DOI: 10.3748/wjg.v20.i42.15564]

96 **Spitz FR**, Abbruzzese JL, Lee JE, Pisters PW, Lowy AM, Fenoglio CJ, Cleary KR, Janjan NA, Goswitz MS, Rich TA, Evans DB. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. *J Clin Oncol* 1997; **15**: 928-937 [PMID: 9060530]

97 **West MA**, Loughney L, Lythgoe D, Barben CP, Sripadam R, Kemp GJ, Grocott MP, Jack S. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. *Br J Anaesth* 2015; **114**: 244-251 [PMID: 25274049 DOI: 10.1093/bja/aeu318]

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**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 hours 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.

**Table 2 Study design and characteristics**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Year** | **Design** | **Sample size** | | **Type of resection** |
| **ERP** | **Control** |
| Porter *et al*[52] | 2000 | Retrospective cohort | 80 | 68 | PD, TP |
| Vanounou *et al*[53] | 2007 | Retrospective cohort | 145 | 64 | PD |
| Kennedy *et al*[54] | 2007 | Retrospective cohort | 92 | 44 | PD, TP |
| Balzano *et al*[55] | 2008 | Retrospective cohort | 252 | 252 | PD |
| Kennedy *et al*[56] | 2009 | Retrospective cohort | 71 | 40 | LP |
| Nikfarjam *et al*[57] | 2013 | Retrospective cohort | 20 | 21 | PD |
| Abu Hilal *et al*[58] | 2013 | Retrospective cohort | 24 | 20 | PD |
| Braga *et al*[59] | 2014 | Retrospective cohort | 115 | 115 | PD |
| Kobayashi *et al*[60] | 2014 | Retrospective cohort | 100 | 142 | PD |
| Nussbaum *et al*[61] | 2014 | Retrospective cohort | 50 | 100 | LP |
| Nussbaum *et al*[62] | 2014 | Retrospective cohort | 100 | 142 | PD |
| Coolsen *et al*[63] | 2014 | Retrospective cohort | 1441 | 86 | PD |
| Shao *et al*[64] | 2015 | Retrospective cohort | 325 | 310 | PD |
| Sutcliffe *et al*[65] | 2015 | Retrospective cohort | 65 | 65 | PD |
| Joliat *et al*[66] | 2015 | Prospective cohort2 | 74 | 87 | PD |
| Soriano *et al*[67] | 2015 | Retrospective cohort | 41 | 44 | PD |
| Richardson *et al*[68] | 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.

**Table 3 Enhanced recovery pathway elements used in comparative studies**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Preoperative** | | | |  | **Intraoperative** | | | | |  | **Postoperative** | | | | | | | |  |  |
| **Study** | Patient education and counselling | No mechanical bowel preparation | Shorter preoperative 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 | Stimulation of GI function |  | **Total number of ERP elements** |
| Porter *et al*[52] |  |  |  |  |  |  |  |  |  |  |  | ✓ | ✓ |  |  | ✓ | ✓ |  |  |  | 4 |
| Vanounou *et al*[53] | ✓ |  |  |  |  | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ |  |  | ✓ |  |  |  |  | 7 |
| Kennedy *et al*[54] |  |  |  |  |  | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ |  |  | 9 |
| Balzano *et al*[55] | ✓ |  |  |  |  | ✓ | ✓ | ✓ |  |  |  | ✓ |  |  |  | ✓ | ✓ | ✓ |  |  | 8 |
| Kennedy *et al*[56] |  |  |  |  |  | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ |  |  | 9 |
| Nikfarjam *et al*[57] | ✓ |  | ✓ |  |  | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  | 12 |
| Abu Hilal *et al*[58] |  |  | ✓ |  |  |  | ✓ |  |  |  |  |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  | 7 |
| Braga *et al*[59] | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ |  | ✓ |  | ✓ | ✓ | ✓ |  |  | 13 |
| Kobayashi *et al*[60] | ✓ | ✓ | ✓ |  |  |  |  |  |  |  |  | ✓ |  |  |  | ✓ | ✓ |  |  |  | 6 |
| Nussbaum *et al*[61] |  |  |  |  |  | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ |  |  | 8 |
| Nussbaum *et al*[62] |  |  |  |  |  | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ |  |  | 9 |
| Coolsen *et al*[63] | ✓ |  | ✓ | ✓ |  | ✓ | ✓ | ✓ |  | ✓ |  | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  | 14 |
| Shao *et al*[64] |  |  |  |  |  |  |  | ✓ |  |  |  | ✓ |  |  |  | ✓ | ✓ |  |  |  | 4 |
| Sutcliffe *et al*[65] | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ |  |  |  | ✓ | ✓ | ✓ |  |  | 13 |
| Joliat *et al*[66] | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | 17 |
| Soriano *et al*[67] |  | ✓ | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ |  | ✓ | ✓ |  |  | ✓ | ✓ | ✓ |  |  | 11 |
| Richardson *et al*[68] | ✓ |  | ✓ | ✓ |  |  | ✓ |  |  |  |  | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ |  |  | 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 *et al*[52] |  | 12 | 15 | 0.001 |  | 10 (15%) | 9 (11%) | 0.62 |
| Vanounou *et al*[53] |  | Median 8 | Median 8 | 0.357 |  | 13 (9%) | 4 (6%) | 0.508 |
| Kennedy *et al*[54] |  | Median 7 | Median 13 | < 0.001 |  | 7 (8%) | 3 (7%) | > 0.05 |
| Balzano *et al*[55] |  | 13 (7-110) | 15 (7-102) | < 0.001 |  | 18 (7%) | 16 (6%) | 0.865 |
| Kennedy *et al*[56] |  | Mean 7 | Mean 10 | 0.037 |  | 5 (7%) | 10 (25%) | 0.027 |
| Nikfarjam *et al*[57] |  | 8 (7-16) | 14 (8-29) | < 0.001 |  | 3 (15%) | 0 | 0.107 |
| Abu Hilal *et al*[58] |  | 8 (7-13) | 13 (10 - 20) | 0.015 |  | 1 (1%) | 2 (8%) | 0.583 |
| Braga *et al*[59] |  | 11 (5-51) | 13 (8-54) | 0.226 |  | 14 (12%) | 12 (10%) | 0.835 |
| Kobayashi *et al*[60] |  | 22 ± 12 | 36 ± 24 | < 0.001 |  | 2 (2%) | 2 (2%) | 0.689 |
| Nussbaum[61] |  | 6 (5-9) | 7 (5-9) | 0.026 |  | 15 (30%) | 20 (20%) | 0.219 |
| Nussbaum *et al*[62] |  | 11 (8-18) | 13 (10-18) | 0.015 |  | 31 (31%) | 36 (25%) | 0.85 |
| Coolsen *et al*[63] |  | 14 (7-83) | 20 (9-132) | < 0.05 |  | 11 (13%) | 14 (14%) | NR |
| Shao *et al*[64] |  | 14 ± 7 | 18 ± 8 | < 0.001 |  | 43 (13%) | 44 (14%) | 0.725 |
| Sutcliffe *et al*[65] |  | 9 (4-70) | 10 (4-114) | 0.16 |  | 9 (15%) | 5 (8%) | 0.26 |
| Joliat *et al*[66] |  | 15 (11-24) | 19 (14-29) | 0.029 |  | NR | NR | NR |
| Soriano *et al*[67] |  | 14 ± 1.3 | 19 ± 2 | 0.014 |  | 9 (10%) | 4 (9%) | > 0.05 |
| Richardson *et al*[68] |  | 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 ± standard deviation. Data for readmission are reported as number of patients (%). ERP: Enhanced recovery pathway.

**Table 5 Morbidity and mortality rates**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** |  | **Complication rates** | | |  | **Mortality rates** | | |
|  | **ERP** | **Usual care** | ***P* value** |  | **ERP** | **Usual care** | ***P* value** |
| Porter *et al*[52] |  | 56 (70%) | 52 (76%) | 0.21 |  | 2 (3%) | 1 (1%) | 0.87 |
| Vanounou *et al*[53] |  | 77 (54%) | 40 (62%) | 0.207 |  | 2 (1%) | 1 (2%) | 0.918 |
| Kennedy *et al*[54] |  | 34 (37%) | 19 (44%) | > 0.05 |  | 1(1%) | 1 (2%) | > 0.05 |
| Balzano *et al*[55] |  | 119 (47%) | 148 (59%) | 0.014 |  | 9 (4%) | 7 (3%) | 0.798 |
| Kennedy *et al*[56] |  | 11 (16%) | 15 (38%) | > 0.05 |  | 1 (1%) | 1 (2%) | > 0.05 |
| Nikfarjam *et al*[57] |  | NR | NR |  |  | NR | NR | - |
| Abu Hilal *et al*[58] |  | 8 (40%) | 6 (67%) | 0.077 |  | 0 | 0 | - |
| Braga *et al*[59] |  | 69 (60%) | 76 (66%) | 0.339 |  | 4 (4%) | 4 (4%) | 1.000 |
| Kobayashi *et al*[60] |  | 39 (39%) | 54 (60%) | 0.004 |  | 0 | 1.1 | 0.957 |
| Nussbaum *et al*[61] |  | 13 (26%) | 24 (24%) | 0.842 |  | 0 | 0 | - |
| Nussbaum *et al*[62] |  | 43 (43%) | 53 (41%) | 0.792 |  | 1 (1%) | 4 (3%) | 0.651 |
| Coolsen *et al*[63] |  | 46 (53%) | 48 (49%) | > 0.05 |  | 4 (5%) | 6 (6%) | > 0.05 |
| Shao *et al*[64] |  | 127 (39%) | 173 (55.8%) | < 0.001 |  | 40 (12%) | 53 (17%) | NR |
| Sutcliffe *et al*[65] |  | 15 (34%) | 15 (41%) | 0.65 |  | 2 (3%) | 2 (3%) | 1.000 |
| Joliat *et al*[66] |  | 50 (68%) | 71 (82%) | 0.046 |  | 3 (4%) | 4 (5%) | 1.000 |
| Soriano *et al*[67] |  | 12 (30%) | 24 (55%) | 0.029 |  | 0 | 2 (2%) | > 0.05 |
| Richardson *et al*[68] |  | 6 (27%) | 17 (39%) | 0.421 |  | 0 | 0 | - |

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